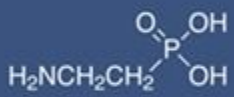
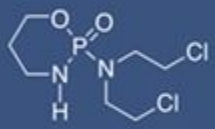
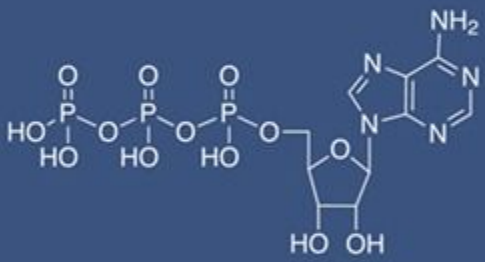
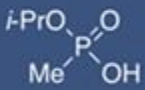
Best Synthetic Methods

ORGANOPHOSPHORUS (V) CHEMISTRY









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Best Synthetic Methods

Organophosphorus (V) Chemistry

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Best Synthetic Methods: ORGANOPHOSPHORUS (V) CHEMISTRY

Co-authored and edited by

CHRISTOPHER M. TIMPERLEY

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CONTRIBUTORS

Nicholas Cooper
Detection Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK

Catherine Gomez
Normandie Univ, COBRA, UMR 6014 & FR 3038, UNIV Rouen, INSA Rouen, CNRS, 1 Rue Tesnières, 76821 Mont-Saint-Aignan Cedex, France

Guoxiong Hua
EaStCHEM School of Chemistry, University of St Andrews, Fife, KY16 9ST, UK

Pierre-Yves Renard
Normandie Univ, COBRA, UMR 6014 & FR 3038, UNIV Rouen, INSA Rouen, CNRS, 1 Rue Tesnières, 76821 Mont-Saint-Aignan Cedex, France

James Riches
Detection Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK

John Tattersall
Biomedical Sciences Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK

Christopher M. Timperley
Detection Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK

Derek Woollins
EaStCHEM School of Chemistry, University of St Andrews, Fife, KY16 9ST, UK

PREFACE

The total chemical space of carbon-based molecules that can be prepared given enough ingenuity comprises more than 10^{60} small organic molecules and an even greater number of larger entities (*1*). So far, only a tiny proportion of these have been prepared and screened for useful properties, such as biological activity (*2*), and this drives chemists to develop novel reactions that can unlock new territories of chemical space. Methods of rapid generation of skeleton and decoration diversity are therefore in demand. Synthetic chemistry is a young science compared to mathematics and astronomy, for example, and has grown exponentially powerful over the last 150 years, yet many of the named reactions of organophosphorus chemistry were discovered a long time ago. For this reason organophosphorus chemistry might be considered an unfertile field, yet there is much left to harvest, and the discovery of new reactions is likely to reward chemists that can navigate the subject with agility.

Appointed in 1995 as a higher scientific officer in the synthetic chemistry team at the Chemical and Biological Defence Establishment, Porton Down, United Kingdom (*3,4*), under the direction of Dr Robin Black, I was set the challenge of learning organophosphorus chemistry for the first time. I needed to know about organophosphorus nerve agents to conduct defensive studies such as the synthesis of environmental degradation products and metabolites (in preparation for ratification of the Chemical Weapons Convention (*5*) that necessitated robust synthetic and analytical methods). I was surprised to find no modern textbook that collated synthetic recipes to all the structural permutations of phosphorus determined by its valency of three or five. No lecture course in the UK taught synthetic phosphorus chemistry in adequate detail. I had to learn the subject by studying research papers spanning the early days of the subject to those of the present, and supplement this with over 10 years of practical experience in the laboratory. Much of the primary literature was published in foreign languages, often German or Russia (where traditional schools of organophosphorus chemistry had been founded), and part of this I had to have translated. I decided to write a book one day to fill the gap perceived all those years ago. In doing so, it has been my ambition to provide researchers with an easy point of entry into practical methods used to form and transform organic compounds containing a phosphorus atom. This task has been made easier through collaboration with expert co-authors who have brought together many methods hidden in the literature or dispersed across publications in different languages.

This book follows the Best Synthetic Methods format. It contains practical methods, synthetic tips and short-cuts to form phosphorus (V) compounds, including phosphonyl, phosphoryl and various organophosphate species containing one or more sulfur or selenium atoms. Wherever relevant, sections also include toxicity data and historical data. The style and ordering of chapters are intended to allow researchers to move from one practical method to another to find new ways of charting unexplored chemical space.

To conclude this preface, I cannot beat the words of Gerhard Schrader, a master of organophosphorus chemistry; 'I cannot close without recalling the German chemist August Michaelis whose long years (1847–1916) of careful investigation created the framework of the organic chemistry of phosphorus. Without this basic work I could not have been successful'. Michaelis had foreseen that in the inorganic-organic phosphorus domain, still greater possibilities were to be expected. He wrote 'Even if at this present moment no special possibilities are apparent yet, there will, of that I am sure, be a future for this subject surpassing even its great past' (*6*).

EXEMPTION

The authors and publisher are not responsible for accidents that may arise from inappropriate handling of toxic organophosphorus compounds or for unlawful disregard of the Chemical Weapons Convention, which prohibits the synthesis of certain toxic organophosphorus substances and their precursor chemicals. Readers should familiarise themselves with this legal framework before conducting research in organophosphorus chemistry by accessing it through the website of the Organisation for the Prohibition of Chemical Weapons (OPCW) (www.opcw.org).

ACKNOWLEDGEMENTS

Organophosphorus chemistry is a complex subject, especially within chemical defence, and I have learned much through working with talented colleagues and friends: Herb Aaron, Eric Banks, Andy Bell, Robin Black, Mike Bird, Gradon Carter, Matt Chinn, Steve Eley, Fred Berg, Parker Ferguson, Chris Green, John Jenner, Rick Hall, John Harrison, Jim Manthei, James McGilly, Daan Noort, Robert Read, Helen Rice, Paul Rice, Mark Sambrook, Mark Sandford, Andy Smith, Horst Thiermann, David Upshall, Peter Watts, Franz Worek, and Colin Willis. My thanks go to all co-authors – their scholarship and professionalism has been an inspiration – and to senior management at the Defence Science and Technology Laboratory (Dstl) for their support: Jonathan Lyle, Simon Earwicker, Rebecca Hopkins, and Dean Payne. I also wish to thank Prof. Vernon Gibson FRS (Chief Scientific Advisor of the UK Ministry of Defence) for his encouragement. I am grateful to the Elsevier Science team of Adrian Shell, Louisa Hutchins, Katey Birtcher and Poulouse Joseph for their enthusiasm and help.

I thank my wife, Helen, and our sons, Edward and Jonny, and family, for their patience and support. I dedicate this book to my father, who bought me a chemistry set when I was a boy, and was diagnosed with cancer while I was writing this book.

Chris Timperley
Fellow (Chemistry), Defence Science and Technology Laboratory (Dstl), Porton Down, UK.

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CHAPTER 1

General Overview

Christopher M. Timperley[a] and John Tattersall[b]
[a] *Detection Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK*
[b] *Biomedical Sciences Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK*

1.1 INTRODUCTION

'Fifteen's for fitful Phosphorus.
On the head of every match,
From Boston to the Bosphorus
It flames at just a scratch' (*1*)

Phosphorus (symbol P; atomic number 15; atomic weight 30.97; electron configuration $1s^2 2s^2 2p^6 3s^2 3p^3$) is a nonmetallic element belonging to the same group of the periodic table as nitrogen (Group Va). Its name means 'light-bearing'. Although the Arabic alchemists and Paracelsus (1493–1541) (*2*) may have had access to phosphorus (*3*), the discovery of the element is attributed to the alchemist Hennig Brand, who isolated it in Hamburg in 1669 (*4*) from dried urine. Brand handled the element carelessly and was surprised to discover its hazardous nature, as he wrote in a letter to Gottfried Wilhelm von Liebniz on 30 April 1679: 'When in these days I had some of that very fire in my hand and did nothing more than blow on it with my breath, the fire ignited itself as God is my witness; the skin on my hand was burned truly into a hardened stone such that my children cried and declared that it was horrible to witness' (*5*).

Phosphorus exists in about 10 allotropes in three main catagories: white, red, and black. White phosphorus, the most reactive form, is a soft waxy solid that glows in the dark (phosphoresces) and burns in contact with air, forming dense white fumes of the oxide. White phosphorus melts at 44 °C and boils at 280 °C. It has two allotropes: an alpha form of cubic crystal structure stable at ordinary temperatures, and a beta form of hexagonal crystal structure stable below −78 °C. Both are poisonous. Exposure to sunlight or heat (250 °C) converts white phosphorus to red, which does not phosphoresce or ignite in air. Black phosphorus forms upon subjecting white phosphorus to high pressures. It is flaky like graphite and is the least reactive form. White phosphorus has been used for military purposes to produce smokes and as a fill for grenades and incendiary munitions. Red phosphorus is used to prepare the striking surface for safety matches.

All naturally occurring phosphorus is present as the stable isotope phosphorus-31. Radioactive phosphorus-32, a beta emitter, has a half-life of 14.3 days and is a useful tracer for studying the life cycles and metabolic processes of plants and animals (*6*).

1.2 NATURAL OCCURRENCE OF PHOSPHORUS

In view of its reactivity, phosphorus is not an element one expects to find free in nature, although traces have been reported to occur in some meteorites. Otherwise, phosphorus occurs in compounds that are

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widely distributed in many rocks, minerals, plants, and animals. Phosphorus normally ranks 12th in most tables of abundance of the elements in the Earth's crust: its average concentration approaches 0.12% by weight as phosphate ion (PO_4^{3-}) present in minerals. Over 200 species of phosphate minerals are recognised (7), all composed of tetrahedral PO_4 units, and they are grouped into three categories according to their origin:

1. Primary phosphates, crystallising from aqueous solution, occur in rocks of low silica content, and include apatite $Ca_5(F,Cl,OH)(PO_4)_3$, lithiophilite and triphylite $Li(Fe,Mn)PO_4$.
2. Secondary phosphates, from alteration of primary phosphates at low temperatures in the presence of water, often contain iron or manganese (II) or (III), and are usually brilliantly coloured. Examples include strengite $FePO_4 \cdot 2H_2O$ and vivianite $Fe_3(PO_4)_2 \cdot 8H_2O$.
3. Rock phosphates, from deposition of bones, shells and diatoms, are poorly characterised because of their fine grain.

The main commercial source of phosphorus is phosphate rock (phosphorite, mostly fluorapatite $Ca_5(PO_4)_3F$) (*8*), which is rich in phosphates derived from various sources, including marine invertebrates that secrete shells of calcium phosphate, and the bones and excrement of vertebrates. Phosphorite deposits are often associated with subsiding rock, such as carbonaceous shale and chert, and may be up to 1 m deep. Phosphorite also forms on stable planes of sandstone or shale. Typical phosphorite beds contain 30% phosphorus pentoxide (P_2O_5) and comprise the primary source of material for most of the world's production of phosphate fertilizers. Significant deposits of phosphorites are found in the USA (Idaho and California) and Peru (Sechura Desert) (*9*). Phosphate minerals are also found in mines in Cornwall (*10*) in the South West of England and include: bassetite $Fe(UO_2)_2(PO_4)_2 \cdot 8H_2O$; fluorapatite $Ca_5(PO_4)_3F$; metatorbernite $Cu(UO_2)_2(PO_4)_2 \cdot 8H_2O$; pseudomalachite $Cu_5(PO_4)_2(OH)_4$; pyromorphite $Pb_5(PO_4)_3Cl$; and turquoise (var. Henwoodite) $CuAl_6(PO_4)_4(OH)_8 \cdot 4H_2O$.

Phosphorus is a limiting mineral nutrient for plants (*11*). A large proportion of soil phosphorus is bound tightly to soil particles or fixed as organophosphorus compounds (*12*) and is relatively unavailable for plant uptake. Plant access to phosphate plays an important role in global food security. However, the phosphorus in fertilizers is derived from rock phosphate, a nonrenewable resource that could be depleted in 50–100 years (*13*), and this non-sustainability has prompted interest in crops that require less soil phosphorus and produce improved yields (*14*). The role of phosphorus in plants has featured in the novel *The Periodic Table* by Primo Levi (*15*).

1.3 PRINCIPAL COMPOUNDS OF PHOSPHORUS

Phosphorus is used almost entirely in the form of compounds usually of oxidation state −3, +3 or +5. It tends to prefer the +5 state unlike nitrogen and other members of its group. Hydrogen phosphide or phosphine gas (PH_3) is produced by treating white phosphorus with hot water or a strong base, or by the hydrolysis of a metal phosphide, and is of considerable economic

significance. It is employed as a starting material for the synthesis of various organophosphorus compounds and as a doping agent for solid-state electronics components. Other important phosphorus compounds include the oxides and acids. A large proportion of industrially produced white phosphorus is burned to form P_2O_5 that is obtained as a soft white powder or colourless crystalline solid. It is often used in organic chemistry as a drying or condensing agent due to its high affinity for water. Its controlled hydrolysis provides phosphoric acid (H_3PO_4), which is used industrially to produce salts containing the phosphate (PO_4^{3-}), hydrogen phosphate (HPO_4^{2-}) or dihydrogen phosphate ($H_2PO_4^-$) ion. Such salts are used in baking, as abrasives in toothpaste, and as additives in detergents. Calcium dihydrogen phosphate $Ca(H_2PO_4)_2$ – known as 'superphosphate' – is prepared by the action of phosphoric acid on phosphate rock and is the most widely employed phosphorus fertilizer. Phosphorus reacts with halogens to produce various halides that are used to manufacture many organophosphorus chemicals. It also reacts with sulfur to provide several sulfides that are used to make organic compounds and matches.

Elemental phosphorus is obtained industrially by reduction of phosphate rock with silica and carbon in an electric furnace (*16*). The furnace is charged continuously and the mixture heated to 1300–1400 °C, whereupon it transforms into calcium silicate slag, phosphorus vapour, and carbon monoxide. The overall reaction proceeds as follows: $Ca_3(PO_4)_2 + 3SiO_2 + 5C \rightarrow 3CaSiO_3 + 0.5P_4 + 5CO$ (*17*). The vapour is cooled to condense the phosphorus to the liquid and eventually the solid, which is stored underwater to prevent it from igniting. Elemental phosphorus can be purified by distillation (*18*).

Some industrial routes to key organophosphorus starting materials and reagents are shown in Fig. 1.3.1. Treatment with sulfur provides phosphorus pentasulfide (P_4S_{10}, vapour: P_2S_5). Molten white phosphorus reacts with chlorine to give phosphorus trichloride (PCl_3) and phosphorus pentachloride (PCl_5). During conversion to the former, phosphorus trichloride distills into receivers and is redistilled with white phosphorus to remove any pentachloride. Oxidation of phosphorus trichloride, controlled hydrolysis of phosphorus pentachloride, or treatment of it with P_2O_5, gives phosphorus oxychloride ($POCl_3$). Passage of phosphorus trichloride vapour over liquid sulfur of low viscosity at 140 °C, in the presence of catalysts (e.g. charcoal), produces continuously thiophosphoryl chloride ($PSCl_3$). However, this method of preparation is unsuitable for laboratory synthesis and other methods are preferred for small-scale production. Alkylphosphonous dichlorides ($RPCl_2$) can be prepared by several methods, such as heating phosphorus trichloride vapour and an alkane to high temperature, whereupon hydrogen chloride forms as the by-product. Physical properties for some organophosphorus compounds that are commonly used as starting materials for synthetic campaigns appear in Table 1.3.1.

Thiophosphoric, phosphoric, and phosphonic acid ester chlorides are obtained from sequences of quite straightforward reactions and many simple derivatives are available commercially and used as common starting materials. Chapters 2 to 6 cover many of the typical functional group interconversions that can be carried out from such materials by selection of appropriate experimental methods and conditions.

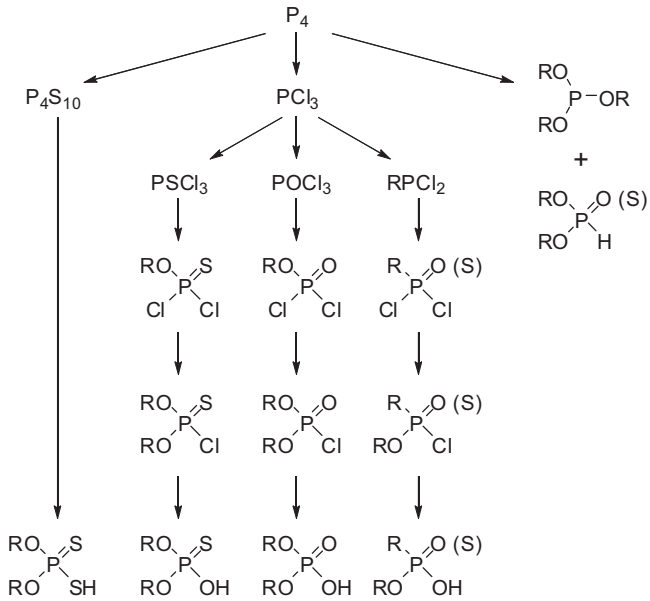


Figure 1.3.1 Key organophosphorus starting materials and intermediates.

1.4 PHOSPHORUS COMPOUNDS IN LIVING SYSTEMS

Living organisms comprise over 40 elements among which carbon, hydrogen, nitrogen and oxygen in addition to calcium, sulfur and phosphorus are the majority. There are theoretically many bonds possible between pairs of these seven elements, and although C—C, C—H, C—N, C—S and C—P bonds feature in nature, the C—P bonds are relatively rare. In biological molecules, oxygen or nitrogen often intervenes between carbon and phosphorus, so that C—O—P or P—N—C linkages predominate. Phosphorus is commonly found in biological systems in the highest oxidation state (P^V) most usually bonded to oxygen and in derivatives of phosphoric acid. Phosphoric acid, originating in the inorganic world during its incorporation into living systems, undergoes little chemical change apart from the formation of esters and salts.

The circulation of phosphorus in various forms throughout nature is known as the phosphorus cycle. Phosphorus is the scarcest of the elements recycled in the biosphere and is therefore one of the most limiting in any ecological system. Microorganisms secrete acids that dissolve phosphate rocks to produce soluble phosphates. These are consumed by algae and terrestrial green plants, which in turn are consumed by animals. Their death and decay releases the phosphates for recycling. The steady drain of phosphorus compounds into the oceans is the main reason for adding phosphorus-rich fertilizers to soils to maintain agricultural productivity.

The phosphate ion (PO_4^{3-}) is one of the most important mineral constituents for cellular function and is present in the fluids within living cells. The abundance of organic compounds of phosphorus on primitive Earth undoubtedly determined the course of evolution (*19*) as phosphate became

Table 1.3.1 Properties of some organophosphorus reagents (bp = boiling point, mp = melting point)

Name	Formula	Mass (amu)	Bp (°C/mmHg)	Mp (°C)	Density (g/ml, 25 °C)
Phosphorus trichloride	PCl_3	137.3	74–78	−112	1.574
Phosphorus pentachloride	PCl_5	208.2	S	180	-
Phosphorus pentoxide[a]	P_2O_5	141.9	S	340	2.300
Phosphorus pentasulfide	P_2S_5	222.3	S	282	2.090
Phosphorus oxychloride	$POCl_3$	153.3	106	1	1.645
Thiophosphoryl chloride	$PSCl_3$	169.4	125	−35	1.668
Methyl dichlorophosphite	$MeOPCl_2$	132.9	94	−91	1.376
Ethyl dichlorophosphite	$EtOPCl_2$	146.9	118	-	1.286
Dimethyl *H*-phosphonate	$(MeO)_2P(O)H$	110.1	170	-	1.200
Diethyl *H*-phosphonate	$(EtO)_2P(O)H$	138.1	50/2	-	1.072
Trimethyl phosphite	$(MeO)_3P$	124.1	111	−78	1.052
Triethyl phosphite	$(EtO)_3P$	166.2	156	-	0.969
Dimethyl chlorophosphite	$(MeO)_2PCl$	128.5		Not readily available*	
Diethyl chlorophosphite	$(EtO)_2PCl$	156.6	154	-	1.089
Methyl dichlorophosphate	$MeOP(O)Cl_2$	148.9	63/15	-	1.488
Ethyl dichlorophosphate[b]	$EtOP(O)Cl_2$	162.9	63/10	-	1.373
Dimethyl chlorophosphate	$(MeO)_2P(O)Cl$	144.5	80/25	-	1.340
Diethyl chlorophosphate	$(EtO)_2P(O)Cl$	172.6	60/2	-	1.194
Trimethyl phosphate	$(MeO)_3P{=}O$	140.1	197	−46	1.197
Triethyl phosphate	$(EtO)_3P{=}O$	182.1	215	-	1.072
Methyl dichlorothiophosphate	$MeOP(S)Cl_2$	165.0		Not readily available*	
Ethyl dichlorothiophosphate[c]	$EtOP(S)Cl_2$	179.0	55–68/10	-	1.353
Dimethyl chlorothiophosphate	$(MeO)_2P(S)Cl$	160.6	66/16	-	1.322
Diethyl chlorothiophosphate[d]	$(EtO)_2P(S)Cl$	188.6	45/3	-	1.200

S = Solid at room temperature.
[a]Alternative name for phosphoric anhydride.
[b]Alternative name for ethyl phosphorodichloridate.
[c]Alternative name for ethyl phosphorodichloridothionate.
[d]Alternative name for diethyl phosphorochloridothionate.
* Not readily available refers to the difficulty in obtaining samples commercially.

incorporated into deoxyribonucleic acid (DNA) (*20,21*) whose replication gave rise to life. Nucleotides are the building blocks of DNA and ribonucleic acid (RNA) (*22*). Each nucleotide is constructed from one phosphate group, a five-carbon sugar (pentose) and a nitrogenous base (a purine or a pyrimidine). Minus a phosphate group, the sugar and nucleobase comprise a nucleoside (a nucleotide is sometimes termed a nucleoside monophosphate). The phosphate groups are bonded to the 2′-, 3′- or 5′-carbon atom in the sugar; the most common bond is to the latter carbon atom. Ribonucleotides contain the sugar ribose and deoxyribonucleotides the sugar deoxyribose. Nucleic acids are large polymers made from nucleotide monomers (Fig. 1.4.1). In DNA the purine bases are adenine and guanine and the pyrimidine bases are cytosine and thymine. In RNA thymine is replaced by uracil. In DNA, adenine always pairs through two hydrogen bonds to thymine (A···T) and guanine with cytosine (G···C) through three hydrogen bonds.

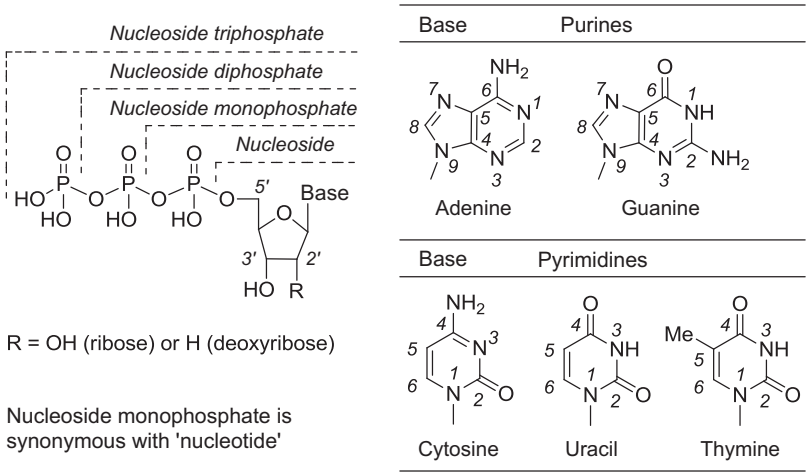


Figure 1.4.1 Structure of the most common nucleic acid constituents.

Cyclic nucleotides form when a phosphate group is bonded through the 3′- and 5′-carbon atoms of the pentose sugar forming a six-membered ring (Fig. 1.4.2). Earl W. Sutherland of Vanderbilt University won the Nobel Prize in Physiology and Medicine in 1971 for 'discoveries concerning the mechanisms of action of hormones,' especially epinephrine (adrenaline), via secondary messengers important in many biological processes, such as cyclic adenosine monophosphate (cAMP). The latter is derived from adenosine triphosphate and is used in intracellular signal transduction in many organisms. It is involved in the activation of protein kinases and in the regulation of function of specific ion channels. Cyclic guanosine monophosphate (cGMP) is the cyclic nucleotide derived from guanosine triphosphate. It also acts as a secondary messenger and is a common regulator of ion channel conductance and cell death. Its presence relaxes the smooth muscles of the vascular system and causes vasodilation and increased blood flow.

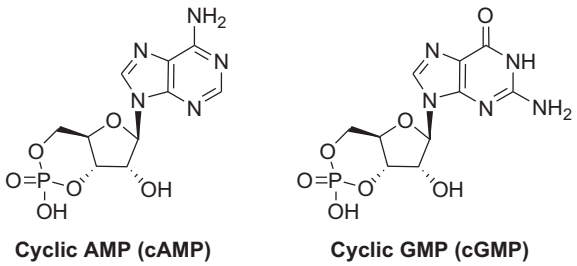


Figure 1.4.2 Biologically important cyclic nucleotides.

Living cells balance energy-demanding and energy-producing reactions. In 1941, Fritz A. Lipmann showed that cells store energy released from destructive reactions (catabolism) and provide it on demand for synthetic reactions (anabolism). The currency of energy transactions is

adenosine-5′-triphosphate (ATP) (*23*). Even the most inactive humans are thought to metabolise kilograms of ATP per day (*24*). The steps of hydrolysis to adenosine diphosphate (ADP) and then adenosine monophospate (AMP) are exergonic (they release energy), the last hydrolysis to adenosine is less exergonic (Figure 1.4.3). The di- and triphosphate bonds of ADP and ATP store the most energy. The synthesis of ADP and ATP is endergonic (it requires energy) and provides a method of utilising the energy from glucose oxidation.

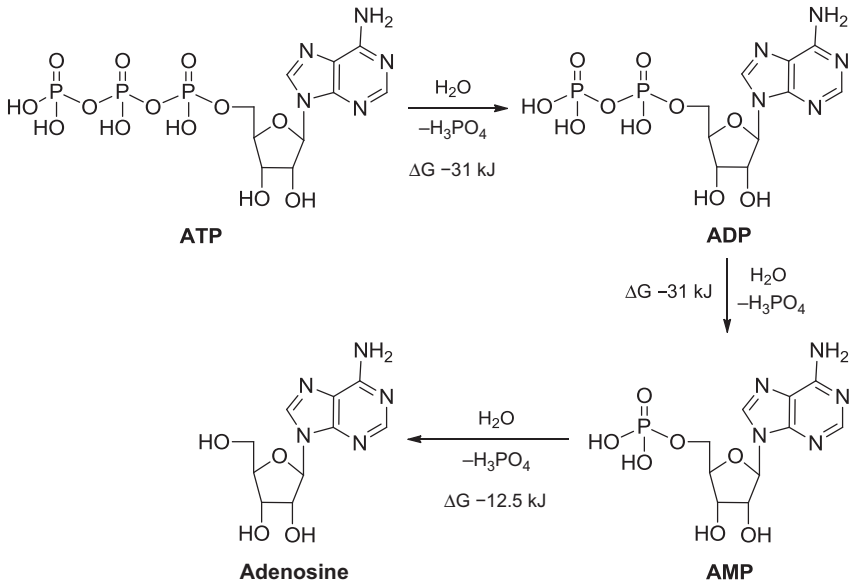


Figure 1.4.3 Adenosine triphosphate (ATP) metabolism to adenosine diphosphate (ADP), adenosine monophosphate (AMP), and adenosine, showing the free energies (ΔG) of each step.

Nicotinamide adenine dinucleotide (NAD), a coenzyme found in all living cells, was discovered in 1906 by the British biochemists Arthur Harden and William Youndin. Its main function is participation in electron-transfer reactions in which two hydrogen atoms are removed from a reactant (RH_2) to provide the oxidised reactant (R) (Fig. 1.4.4) (*23*). NAD accepts a hydrogen atom to give reduced nicotinamide adenine dinucleotide (NADH). Enzymes that make and use NAD and NADH are important in pharmacology and research into future treatments for disease. Nicotinamide adenine dinucleotide phosphate (NADP) differs from NAD by a phosphate group attached to the 2′-carbon atom of the ribose ring that bears the adenine base. It participates in plants in the photosynthetic pathway and in animals in anabolic reactions, such as lipid and nucleic acid synthesis that require its reduced form (NADPH) as a reducing agent.

Coenzyme A (CoA) plays a role in the synthesis and oxidation of fatty acids and in the oxidation of pyruvate in the citric acid cycle (*23*). Its structure (Fig. 1.4.5) was elucidated in the early 1950s at the Lister Institute in London in collaboration with workers at the Harvard Medical School and

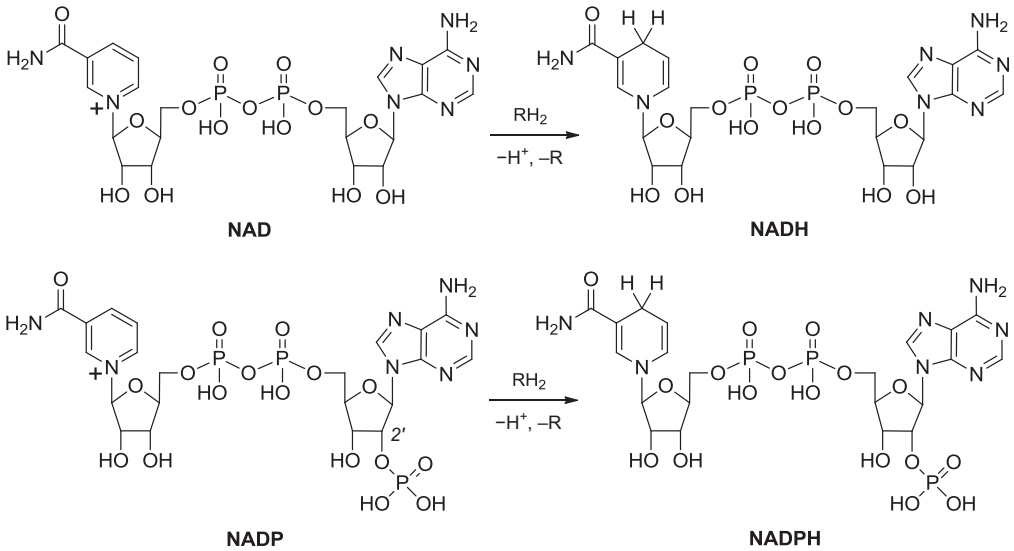


Figure 1.4.4 Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine phosphate (NADP) metabolism.

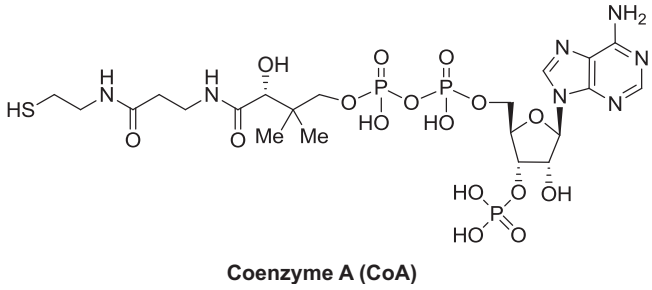


Figure 1.4.5 Structure of coenzyme A which contains three phosphoryl units.

Massachusetts General Hospital. All sequenced genomes encode enzymes that use CoA as a substrate; about 4% of these use it or a thioester, such as acetyl-CoA, as a substrate. It can form thioesters with fatty acids and aid their transfer from the mitochondria to the cytoplasm.

Flavin adenine dinucleotide (FAD) is a cofactor involved in metabolic redox reactions (*23*). The name is a misnomer as there is no dinucleotide segment; the molecule consists of a riboflavin moiety (vitamin B_2) bonded through the sugar-alcohol ribitol to the phosphate group of an adenosine diphosphate molecule. FAD can be reduced to $FADH_2$ by accepting two hydrogen atoms (Fig. 1.4.6).

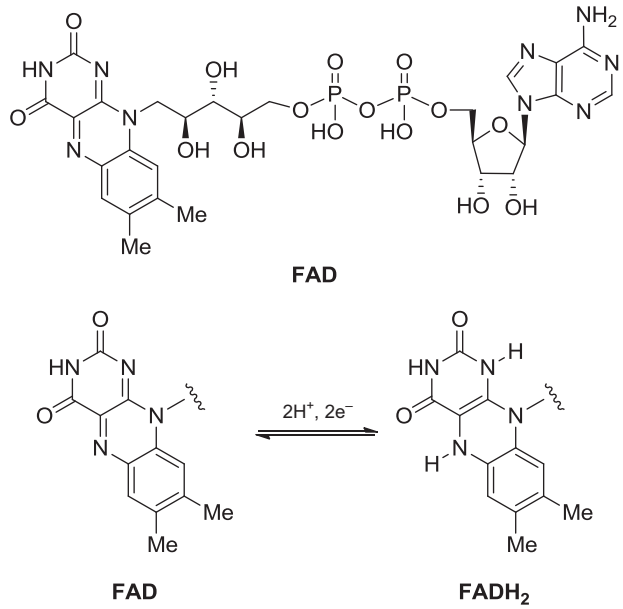


Figure 1.4.6 Flavin adenine dinucleotide (FAD) chemistry.

Creatine phosphate (phosphocreatine) is found in muscle tissue and, by virtue of its phosphate group, is a store of energy that can be used to convert ADP to ATP within seconds following intense muscular effort (Fig. 1.4.7) (*23*). Conversely, excess ATP can be converted to ADP during a period of low activity to transform creatine to creatine phosphate. The reversible phosphorylation of creatine is catalysed by creatine kinase enzymes.

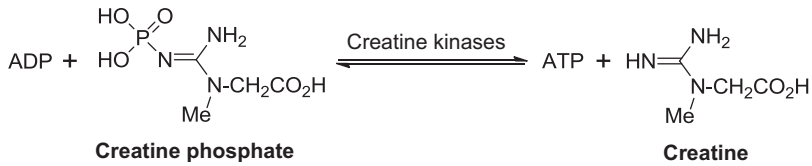


Figure 1.4.7 The energy-storage molecule creatine phosphate.

Phosphorylation, defined as the addition of a phosphoryl group to an organic compound, is universally important for life. Oxidative phosphorylation is the process whereby much of the energy in foods is conserved and made available to cells. Photophosphorylation is the process used by green plants to convert light energy to chemical energy. Nature uses phosphorylation and dephosphorylation of hydroxy-amino acids in peptides and proteins to regulate many cellular processes — for example, activating or deactivating enzymes for signal transduction and protein trafficking (*25*).

Protein kinases and protein phosphatases effect phosphorylation and dephosphorylation of serine, threonine and tyrosine residues in proteins. All organisms use this chemistry for regulating intracellular processes. Protein tyrosine kinase converts extracellular input (a ligand docking to a membrane-bound receptor) to an intracellular response (phosphorylation of one or more tyrosine residues on specific proteins).

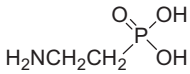
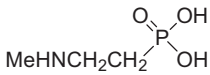
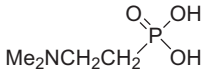
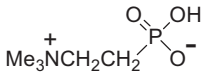
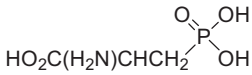
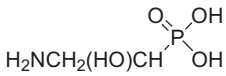
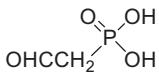
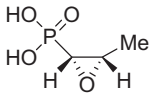
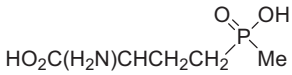
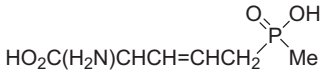
Protein phosphorylation is vital for controlling the cell cycle. Many receptors for hormones, neurotransmitters, peptide-based drugs, and growth factors are regulated by reversible phosphorylation. Phosphorylation of one serine residue is sometimes enough to regulate enzyme activity (e.g. glycogen synthase and glycogen phosphorylase). Phosphorylated tyrosine residues act as recognition sites for binding by signalling proteins. Pathological events can be driven by sequential protein tyrosine phosphorylation, recognition and binding of signalling proteins, and dephosphorylation. Inappropriate protein tyrosine phosphorylation is linked to disease states. Only 0.03% of protein-bound phosphate is bonded to tyrosine residues in normal cells; yet up to 0.6% can be present on tyrosine in malignant tumours (*25*). In view of the importance of protein phosphorylation, much effort has been devoted to the synthesis of phosphylated peptides (phosphopeptides) and their study, especially those derived from serine and tyrosine.

The phosphate group is a central feature of phospholipids, a large class of fat-like substances that play important metabolic and structural roles in cells. Phospholipids — sphingolipids, glycolipids and lipoproteins — are compound lipids distinguished from simple lipids (hydrocarbon fats and waxes) and other fat-soluble cellular constituents (isoprenoids and steroids). The term phosphoglyceride is sometimes used to refer to a phospholipid or a class of phospholipids. Usually phospholipids comprise a phosphate head, two alcohol and one or two fatty acid units. They are discussed in more detail in Chapter 7. Some phospholipids such as platelet-activating factor (*26*) are involved in inflammation responses, although their analogues may have medical value (*27*).

Phosphorus is also found in nature bonded to carbon. The first natural product confirmed to contain a C—P bond was 2-aminoethylphosphonic acid, which was obtained (63 mg) by Japanese researchers in 1958 from a ciliate protozoan (203 g) (*28*). Natural products having C—P bonds and their sources are listed in Table 1.4.1. Fosfomycin was obtained from *Streptomyces fradiae* isolated from soil samples in the 1960s and shown to kill bacteria. It is a broad-spectrum antibiotic effective against gastrointestinal and urinary tract infections. The phosphorus-bearing carbon atom reacts with the active-site cysteine of UDP-*N*-acetylglucosamine-3-*O*-enolpyruvyltransferase and inhibits bacterial cell wall biosynthesis.

The chemical and thermal stabilities of C—P bonds are remarkably high and comparable to C—C and C—S bonds; the C—P bond energies have been reported to be as high as 259—272 kJ/mol (*29*). Chemical reactions involving C—P bond cleavage are uncommon. Drastic hydrolytic procedures with strong mineral acids or alkalis do not usually split the C—P bond. Consequently, this portion of many organophosphorus compounds is normally unaffected by most reagents and chemical processes. However, if the carbon atom bonded to phosphorus is connected to certain electronegative elements, for example nitrogen (e.g. P—CN) or halogen atoms (e.g. P—CF_3), or within certain heteroatom-containing functional groups, for example carbonyl or carboxyl groups (e.g. P-acyl), the C—P bond is weakened and can often be cleaved upon treatment with hydroxide or other nucleophiles. The P—C(O)R group of acylphosphonates is particularly reactive and easily cleaved.

Table 1.4.1 Natural phosphonates and phosphinates isolated from various species

Name	Structure	Species isolated from
2-Aminoethylphosphonic acid		Aggregating sea anemone (*Anthopleura elegantissima*) from Pacific Ocean
2-Methylaminoethylphosphonic acid		Giant green sea anemone (*Anthopleura xanthogrammica*) from Pacific Ocean
2-Dimethylaminoethylphosphonic acid		Giant green sea anemone (*Anthopleura xanthogrammica*) from Pacific Ocean
2-Trimethylaminoethylphosphonic acid		Giant green sea anemone (*Anthopleura xanthogrammica*) from Pacific Ocean
2-Amino-3-phosphonoproprionic acid		Green sea mat or button polyp (*Zoanthus sociatus*) in tropical reefs from Japan, Central USA and the Carribean
1-Hydroxy-2-aminoethylphosphonic acid		Amoeba (*Acanthamoeba castellanii*) found in soil, freshwater and marine habitats, and an opportunistic parasite in humans
Phosphonoacetaldehyde		Gram-positive soil-dwelling bacterium (*Bacillus cereus*) that can cause foodborne illness in humans
Fosfomycin (phosphomycin)		Gram-positive actinobacterium (*Streptomyces fradiae*) found in soil and decaying vegetation
2-Amino-4-[hydroxy(methyl) phosphinyl]butyric acid (phosphinothricin)		Gram-positive actinobacterium (*Streptomyces viridochromogenes*) from soil
2-Amino-5-[hydroxy(methyl) phosphonyl]-3-pentenoic acid		Gram-positive actinobacterium (*Streptomyces plumbeus*) from soil

Some microbes have molecular machinery that can cleave normally inert C—P bonds. Most Gram-negative bacteria can use phosphonates as a nutritional source of phosphorus under conditions of phosphate starvation. This transformation is formally a hydrolytic cleavage of a C—P bond, although a general enzymatic mechanism for the activation and conversion of alkylphosphonates to phosphate and an alkane has not been elucidated, despite a search for over 20 years. In the bacterium *Escherichia coli* seven proteins have been shown to effect C—P bond cleavage and reactions for the conversion of methylphosphonic acid $MeP(O)(OH)_2$ to phosphoric acid have been identified (*30*). The marine archaeon *Nitrosopumilus maritimus* converts 2-hydroxyethylphosphonate $HOCH_2CH_2P(O)(OH)_2$ to methylphosphonic acid using an enzyme called methylphosphonate synthase (*31*). Other marine organisms convert methylphosphonic acid to methane, possibly explaining why the oceans produce some 4% of the Earth's methane.

1.5 A BRIEF HISTORY OF SYNTHETIC ORGANOPHOSPHORUS CHEMISTRY

The study of organophosphorus compounds began in the early part of the nineteenth century. Esterification of phosphoric acid with alcohols by I. L. Lassaigne in 1820 may represent the first research. Phosphine derivatives were prepared by P. E. Thénard in 1847, and that year M. Cloez also discovered a thiophosphoric acid ester (after suspecting sulfur derivatives of phosphorus existed by analogy to arsenic). P. de Clermont synthesised tetraethyl pyrophosphate $(EtO)_2P(O)OP(O)(OEt)_2$ in 1854 by alkylation of the silver salt of pyrophosphoric acid with ethyl iodide, but did not recognise its powerful toxic effect. The pyrophosphate was described in the following decades, yet 80 years elapsed before its insecticidal properties were recognised. A. W. Hofmann reported the oxidation of methyl and ethyl phosphine with nitric acid to provide methyl- and ethylphosphonic acids, $MeP(O)(OH)_2$ and $EtP(O)(OH)_2$, in 1872.

The literature contains the work of hundreds of chemists who have added to the present knowledge of the organic chemistry of phosphorus. The greatest contributions are those from relatively few investigators who remained loyal to this branch of chemistry for considerable lengths of time. Many view Carl Arnold August Michaelis in Germany and Alexandr Erminingel'dovich Arbuzov in Russia as the founders of organophosphorus chemistry. Michaelis and Th. Becker treated sodium diethyl phosphite $(EtO)_2P—ONa$ with ethyl iodide and isolated diethyl ethylphosphonate $(EtO)_2P(O)Et$ in 1897 (establishing the first instance of a process for the production of dialkyl alkylphosphonates, now known as the Michaelis—Becker reaction, which is discussed in Chapter 2).

In 1932, Willy Lange and Gerda von Krueger at the University of Berlin synthesised the first members of the dialkyl phosphorofluoridate class, namely $(MeO)_2P(O)F$ and $(EtO)_2P(O)F$, and experienced their highly toxic properties: 'Interesting is the strong effect of the monofluorophosphoric acid alkyl esters on the human organism. The vapours of these compounds have a pleasant strongly aromatic odour. But a few minutes after the inhalation, a strong force to the larynx, associated with dyspnoea, is felt. Then is experienced dimmed consciousness, and glare symptoms with painful hypersensitivity of the eye to light. These symptoms take several hours to subside. They are apparently not caused by acidic decomposition products of the esters and are likely to be attributed to the dialkyl phosphorofluoridates themselves' (*32*). The hypersensitivity of the eye caused by nerve agents is known as miosis (Fig. 1.5.1). The same clinical picture of toxicity was confirmed in the 1960s by two researchers at Glasgow University in Scotland, who

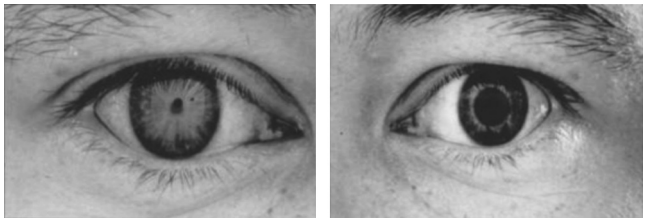


Figure 1.5.1 The eye on the left has developed miosis, in contrast with the eye on the right that is normal. Miosis is a constriction of the pupil to a pin-point size. The amount of light entering the eye and the powers of accommodation are greatly reduced. The condition results in photophobia, headaches and pain experienced in changing from bright to dull light. *(Source: Photograph reproduced courtesy of Dstl.)*

were admitted to Glasgow's Royal Infirmary with nerve agent symptoms, after preparing the phosphorofluoridates accidently while exploring the chemistry of phosphorus pentafluoride (*33*).

Probably aware of the findings of Lange and von Krueger (*32*), belligerent countries researched dialkyl phosphorofluoridates and related nerve agents during World War II (*34,35*). Much of this work had, and still has, limited interest. However, the studies on organic compounds containing P—F bonds initiated at Cambridge in the UK by Bernard Saunders (Biography 1.5.1) and colleagues, influenced studies in enzymology and clinical medicine, and achieved general importance in the field of pest control. The development of systemic insecticides stemmed from the independent wartime studies of Saunders in England and Gerhard Schrader in Germany.

During a search for insecticides among other organophosphorus compounds, Schrader prepared the nerve agent tabun in 1936 and experienced its miotic effect: he commented that 'the first symptom noticed is an inexplicable action causing the power of sight to be much weakened in artificial light. In the darkness of early January it was hardly possible to read by electric light, or after working hours to reach my home by car' (Biography 1.5.2) (*48*). His work during World War II led to the German Army stockpiling but not using tabun as a chemical warfare agent. Schrader discovered the more toxic nerve agent sarin (a name derived from those scientists involved in its discovery: *S*chrader, *A*mbros, *R*udriger and van der L*in*de) in 1938 (*34*). A chemist called Henkel working for Richard Kuhn, head of the Kaiser Wilhelm Institute for Medical Research in Berlin, and the 1938 recipient of the Nobel Prize for Chemistry (awarded in 1939) for work on carotenoids and vitamins, discovered an even more toxic variant in 1944, which was named soman (from the Greek word 'to sleep' or the Latin verb 'to bludgeon') (*34*). Tabun, sarin and soman (Fig 1.5.2) are collectively known as German or G agents, after the country that first recognised their weapons' potential, and during and after the Cold War some were stockpiled by several countries for military purposes (*49*).

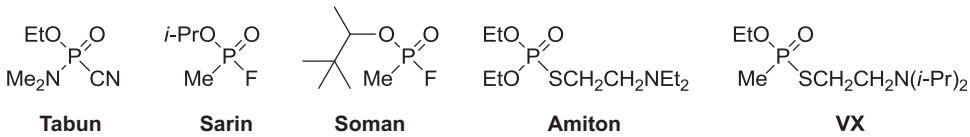


Figure 1.5.2 Some highly toxic organophosphorus compounds.

1.5.1 Biography

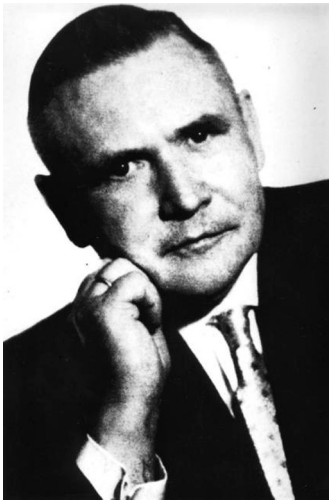
Bernard Charles Saunders (1903–1983) was born in the north west of England and educated at Manchester Grammar School and Burton-on-Trent Grammar School. He graduated from Pembroke College, Cambridge University, and then conducted PhD studies under W. H. Mills (*36*). He then worked for 2 years as a science master at Eton College before returning to Cambridge University, first to the Biochemistry Department and later to the Organic Chemistry Department. He wrote during the 1930s with F. G. Mann the first edition of the textbook 'Practical Organic Chemistry' (*37*), which emphasised preparative methods and characterisation. In an era when spectroscopic methods or purification by chromatography were unavailable, this book became the bible for many undergraduate courses after World War II. The direction of Saunder's research changed completely at the start of the war: from the mechanism of peroxidase action to organophosphorus chemistry (*38*). He was appointed as a director of a team of scientists working at the Extra-Mural Research Station of the British Ministry of Supply, based at Cambridge University, researching toxic compounds: organolead species, fluoroacetates and derivatives, and compounds containing phosphorus and fluorine atoms (*39–43*). Much of this research, especially on phosphorus compounds, paralleled that of Dr. Gerhard Schrader conducted under similar wartime restrictions in Germany. Fortunately, none of the chemicals researched was used during the war; however, some still pose a risk to world security. The end of the war saw publication of another book by Saunders, co-authored by R. E. D. Clark, and entitled 'Order and Chaos in the World of Atoms', which attempted to describe organic chemistry to the layperson (*44*).

The intensive research on toxic compounds containing phosphorus and fluorine carried out by G. Schrader in Germany and by H. McCombie and B. C. Saunders in Britain revealed biological properties of great importance, which were studied more fully during peacetime. The work of Saunders on phosphorus and fluorine compounds was described in a book published in 1957, entitled 'Some Aspects of the Chemistry and Toxic Action of Organic Compounds containing Phosphorus

and Fluorine' (*45*) in which he provided a personal account of his wartime and later work. The book was based on lectures (*46*) given in 1950 in the Netherlands and in 1954 in Canada and the USA. The book surveyed for the first time the British work on the synthesis and pharmacology of dialkyl phosphorofluoridates, systemic insecticides, and esterase activity. However, it neglected to acknowledge the earlier and significant contributions of F. Swarts and G. Schrader in the field of phosphorus–fluorine chemistry (*47*), most of which were pioneering. The book is still an interesting read and is recommended to those chemists and biologists that seek a comprehensive account of how wartime work on toxic compounds gave rise to a branch of phosphorus chemistry with distinct and important utility in agriculture and medicine.

After the war, Saunders returned to the Organic Chemistry Department of Cambridge University and served on various government committees. From 1967 to 1973 he was the President of Magdalene College where he welcomed visiting chemists from abroad, especially from the USA. After retirement, he became a Fellow of the Royal College of Pathologists, which reflected his major contribution to physiology as well as to chemistry. He died in December 1983 at the age of 80.

1.5.2 Biography



Dr. Gerhard Schrader (1903–1990) pioneered the chemistry of fluoroacetates and organophosphorus compounds that led to the discovery of many new pesticides. As a young scientist aged 25, he was assigned a laboratory at the Elberfeld factories of AG Bayer in autumn 1928 (these factories were then a subsidiary of the large chemical combine I.G. Farben that also included BASF and Hoechst) (*50*). In 1930, Schrader was posted to the main laboratory in Leverkusen to work on naphthalene dyes, and when Otto Bayer took over management of the research in 1934, he was assigned the task of synthesising new pesticides. At that time, the German Reich wanted to drop its reliance on foreign imports in the German food sector. To accomplish this, following the transfer of large areas in the East

after World War I, the harvest yields had to be increased. In the early 1930s, the German Reich spent 30 million deuschmarks on pesticides based mostly on plant extracts (mainly nicotine), but hoped for support from the German industry. At first, there were successes with some organic fluorides in the research laboratories of the Bayer factories, which were effective against beetles and moths.

Schrader worked on organophosphorus compounds at Leverkusen. He abandoned a series of experiments after he experienced severe disturbances of vision during trials with one particular substance in 1936. He stayed in hospital and afterwards spent time recuperating at the home of his parents. His father wrote 'In November Gerhard suffered a serious accident in the laboratory, which, had the Lord not shielded him, could have easily had severe consequences. He had to spend 14 days in hospital. After discharge he and Wiebke {his wife} spent almost 8 days with us. Thank God, he is now fully recovered' (*50*).

Back at work Schrader isolated the chemical and realised that he had discovered a highly poisonous new substance that was easy to manufacture. It was *O*-ethyl *N,N*-dimethyl phosphoramidocyanidate, a compound later named tabun. On 5 February 1937, Schrader informed Professor Gross of the Factory Hygiene Institute of Elberfeld of his new discovery in a letter. From here on, the development evidently followed its predestined path, and Dr. Hauptmann von Sicherer of the Army Weapons Office (Department Wa. Pruf. {Weapons Testing} 9) was alerted. Shortly afterwards, Schrader was called to Berlin to present his discovery. In recognition, Schrader and Professor Gross were awarded 50,000 deuschmarks. The Army Weapons Office took over everything to do with tabun research and its subsequent production. The Bayer management was keen to distance itself from the military development of chemical warfare agents and in autumn 1937 posted Schrader to a new, modestly equipped laboratory in Elberfeld. Schrader, a man with a genius for practical work, conducted further research on organophosphorus pesticides. In doing so, he accidentally discovered the nerve agent sarin, which was even more toxic than tabun. But he was also successful with pesticides. In 1942, he succeeded in producing an organophosphorus compound that could replace the imported nicotine used hitherto as a pesticide: this substance, tetraethyl pyrophosphate (TEPP), appeared on the German market in 1944 under the brand name Bladan. Towards the end of 1944, Schrader made a further discovery that would bring him world renown: under the codename E 605 he discovered an agent with high toxicity and stability. Tests on this product were incomplete when Allied troops occupied Leverkusen in March 1945 and Schrader was arrested. Along with other leading scientists in Germany, he was interned in Kransberg-Dustbin, but a charge against him was soon dropped.

The British were very interested in his research and took him to England for over a month for questioning. An investigating team that included Porton scientists S. A. Mumford and E. A. Perren (biography in Chapter 2), working for the British Intelligence Objectives Sub-Committee (B.I.O.S.), interviewed him in August 1945. The team requested an account of his research, including preparative details, his ideas on the relationship between chemical constitution and toxicity towards insects and mammals, and his suggestions for future work. In response, several voluminous reports were received. Schrader was handicapped in writing these by the destruction of many of his records by I.G. Farben, and there were certain gaps, especially in the insecticidal data and preparative methods. However, it was still possible after translation to piece together a coherent account of his work (*48*). English firms brought pesticide E 605 onto the market in February 1947 under the name of parathion.

On 6 August 1947, with regard to his previous writings, Schrader received offers from the British to continue his research in England. He declined because he wanted to join in the construction of a better community in Germany. By the end of 1946, he had resumed work in his completely destroyed laboratory, where his one aim was to improve upon product E 605 (*51*). His research team consisted of himself, Dr. Lorenz (chemist), Drs. Kükenthal, Unterstenhofer and Grefe (biologists), Dr. Hecht (toxicologist) and ample laboratory staff. These workers had been associated for a long time and constituted a well-balanced team capable of rapid output and test of chemical compounds.

On 21 November 1947 and 8 December 1948, a B.I.O.S. team that included the Porton Down experts Dr. E. A. Perren, Mr C. L. Wheeler and Mr A. H. Ford-Moore (biography in Chapter 2) interviewed Schrader at Spedan Towers, Hampstead, London, to discuss his work (*52*). He disclaimed any remaining interest in war gases and stated that his whole efforts were concentrated on the development of insecticides. In support of this, he remarked that all compounds he was now investigating had the P—O or P—S linkage and not the P—C linkage which, he considered, produced the most toxic substances (to warm blooded animals). Further questioning on his interests made it clear that he had little more wish to work on the more basic study of phosphorus compounds than to work on chemical warfare agents, and that he had applied insecticidal work nearest his heart. In a discussion on the scattered nature of the original literature of phosphorus compounds, Schrader mentioned that he had considered the possibility of writing a book on the organic chemistry of phosphorus. This was discussed with him in some detail, and he was strongly encouraged to persevere with this project, suggestions being made as to the form the book might take. He proposed to raise the subject with his employers at I.G. Farben and pointed out that the task, if undertaken, may take two or even more years. Sadly, such a book never materialised (and it was left to G. M. Kosolapoff — biography in Chapter 2 — to publish the first systematic survey of organophosphorus chemistry).

Schrader enjoyed his stay in England and made some useful contacts (*52*). Back in Germany, he enjoyed many successes in insecticide research: in February 1952, Bayer brought the product systox into production, which two years later was followed on the market by metasystox, which is less hazardous to humans. In a short time, Schrader and his team discovered some newer insecticides: dipterex, gusathion, folidol, etc (*53,54*). Schrader, who had worked in almost complete isolation during the war, now became world famous and received honours that included a silver commemorative plaque from the Bundesminister for Food, Agriculture and Forestry; the Otto-Appel commemorative coin; and the Adolf-von-Bayer medal of the Society of German Chemists. Highly honoured by his firm, Bayer AG, he passed the management of the plant protection laboratory to younger hands in 1967 and then retired. He enjoyed a long retirement and died in 1990 at the age of 87 (Photograph reproduced courtesy of Dstl.).

1.5.3 ORGANOPHOSPHORUS PESTICIDES

The discovery of militarily useful nerve agents has always been linked to pesticide research. The production of parathion (E 605) by the British company Albright & Wilson in 1947 prompted ICI Dyestuffs/General Chemicals Division Pest Control Research Committee to review in 1948 the

potential for further insecticide discoveries of this nature. This committee concluded, prematurely, that the discoveries made in Germany had 'closed the remaining gap in the insecticide field' (!) (*55*). Entomologists and chemists at ICI Plant Protection Division at Jealott's Hill, Bracknell, UK, however, argued that there was still scope for further products, and as a result, its Dyestuffs Division instructed one chemist, R. Ghosh, to carry out speculative work. Most of the compounds discovered up to then had been shown to be quite toxic to mammals and their toxicity had been linked to inhibition of acetylcholinesterase (AChE) (*56*), an enzyme involved in nerve impulse transmission. It was not known whether their insecticidal activity was due to this property, but it was a logical premise on which to proceed. Early in 1952, Ghosh prepared *O,O*-diethyl *S*-(diethylaminoethyl) phosphorothiolate (amiton) as the hydrogen oxalate salt (Fig. 1.5.2) (*57,58*). It was shown to be highly insecticidal and effective against spider mites. Interest in this compound and its close analogues was intense at Jealott's Hill and at the Industrial Hygiene Research Laboratories (IHRL) at Welwyn in Hertfordshire, UK. Tests by J. C. Gage at IHRL showed that amiton was highly toxic to mammals (*59*) and subsequent field trials in spider mite-infested orchards in the UK revealed that the farmers that had disseminated amiton using sprayers had experienced severe blood-AChE depression, sufficient to prevent amiton from being marketed. The decision was taken to abandon its development even though amiton was one of the most effective pesticides against spider mites: 'One farmer found spraying the chemical without any protective clothing, and warned that he could kill himself, was so alarmed that he asked for the remaining product to be removed from his farm. Later, having seen his trees clear of spider mites throughout the summer, he asked for a further supply!' (*55*). A sample of amiton was sent to the then Chemical Defence Experimental Establishment (C.D.E.E.) at Porton Down, UK, where it was discovered that this compound, unlike the G agents, had extremely high toxicity through the skin. Modification of the structure of amiton by A. H. Ford-Moore at Porton Down led to the discovery of the Venomous or V agents, of which VX (Fig. 1.5.2) is one of the most toxic and important from the standpoint of chemical defence (*60,61*). The history of amiton and tabun bear a curiously close resemblance. Both substances were discovered in the search for insecticides, both were found to be too toxic for the purpose, and both were modified by the services of the two countries of origin to give more potent war gases. Fortunately, both amiton and tabun are banned under the Chemical Weapons Convention (*62*), which prohibits the development, stockpiling and use of chemical weapons, of which most countries, including Germany and the UK, are signatories.

The researches of Schrader, Ghosh and others after World War II established structure-activity relationships for organophosphorus compounds, with small structural changes modulating mammalian toxicity often dramatically; for example, swapping the P—F group in sarin for P—OH produces a derivative of negligible toxicity (*63,64*). This knowledge paved the way for the systematic development of selective insecticides. Around 50 years ago, only 4% of phosphorus production was diverted to the manufacture of organophosphorus derivatives (*17*). However, this still constituted over 45,000 tons of chemicals, one-third of which were insecticides.

The publication in 1952 of Rachel Carson's book *Silent Spring* (*65*) highlighting the ecological effects of organochlorine insecticides triggered the modern enviromental movement, which resulted in better assessment of the risks associated with the use of organophosphorus pesticides and a drive

towards safer alternatives. The need for improved methods of analysis of pesticides and their residues, especially in trace amounts, prompted many advances in mass spectrometry and associated analytical methods (*66*) (Chapter 7). Unacceptable levels of residues of some organophosphorus pesticides in food led to the development of safer pesticides, and the role of phosphorus in modern crop protection (*67,68*) and the status of organophosphorus insecticides (*69*) have been reviewed.

The first textbook covering organophosphorus chemistry systematically was authored by G. M. Kosolapoff in 1950 and is a classic work (*70*). Since then, and until the present day, there have been many compilations, monographs and reviews published on specialist aspects of this expansive field (*29,71–167*). Particularly notable are *Topics in Phosphorus Chemistry* (*80–89*) and *Organic Phosphorus Compounds* (*90–96*). Chemists wanting to monitor developments in organophosphorus chemistry are encouraged to consult the Royal Society of Chemistry *Specialist Periodical Reports on Organophosphorus Chemistry* (*79*), published annually, which cover the literature in over 35 volumes from 1969 to the present. By scanning all volumes, it is possible to see how trends in organophosphorus chemistry have emerged and disappeared upon accrual of knowledge. Popular science books also cover some aspects of phosphorus chemistry (*168–171*).

Improved interpretation of the reactivities of organophosphorus compounds, especially those containing both sulfur and oxygen atoms, can be obtained by familiarisation with R. G. Pearson's Hard and Soft Acid and Base (HSAB) theory (*172,173*). Interpretation of many of the reactions of organophosphorus reagents using HSAB theory has been successful (*174*) and helpful – for example, in the synthesis of deuterated phosphorus compounds (*175*) for mass spectroscopic studies (*176,177*).

1.6 NOMENCLATURE OF ORGANOPHOSPHORUS COMPOUNDS

Considerable confusion in naming organophosphorus compounds was eliminated by a nomenclature system recommended in 1952 by a joint committee of the American Chemical Society and the London Chemical Society. It applied officially to compounds containing one phosphorus atom but there did not appear to be any difficulty in extending the same logic to the naming of simpler substances containing two phosphorus atoms. The system was supplemented by guidelines issued in 1973 by the International Union of Pure and Applied Chemistry (IUPAC) Commission on the nomenclature of inorganic and organic chemistry.

According to these systems, organophosphorus compounds arise from parent compounds having a P–H bond (Table 1.6.1) and are named as substitution products by replacing the hydrogen of the P–H bond by another group, for example an alkyl group. This is attached as a prefix to the name of the parent compound. Some examples are provided in the table. Names for trivalent oxy-acids end with the suffix 'ous' and names for pentavalent oxy-acids end with the suffix 'ic'. Corresponding esters and salts end with the suffix 'ite' and 'ate'. Alkoxy (or aryloxy) compounds are named as esters formed by replacement of the hydrogen of the O–H bond of the oxy-acid, and the organic group is denoted as a separate word before the name of the acid. Prefix names of phosphorus groups also appear in Table 1.6.1. The prefix 'phosphonato' may be used to indicate an ionic form of the phosphono group. Derivatives of the parent groups are also named by the replacement of the P–H bond by other groups.

Table 1.6.1 Parent phosphorus compounds and names of some example derivatives

Parent compound		Example derivatives	
Trivalent species			
PH_3	Phosphine	$MePH_2$	Methylphosphine
$(HO)PH_2$	Phosphinous acid	$(HO)PMeH$	Methylphosphinous acid
$(HO)_2PH$	Phosphonous acid	$(HO)_2PMe$	Methylphosphonous acid
$(HO)_3P$	Phosphorous acid	$(MeO)_3P$	Trimethyl phosphite
Pentavalent species			
PH_5	Phosphorane	$MePH_4$	Methylphosphorane
$H_3P{=}O$	Phosphine oxide	$Me_3P{=}O$	Trimethylphosphine oxide
$H_2P(O)OH$	Phosphinic acid	$Me_2P(O)OH$	Dimethylphosphinic acid
$HP(O)(OH)_2$	Phosphonic acid	$MeP(O)(OH)_2$	Methylphosphonic acid
$(HO)_3P{=}O$	Phosphoric acid	$(MeO)_3P{=}O$	Trimethyl phosphate
Prefixes of parent phosphorus groups			
$-PH_2$	Phosphino	$-P(OH)OMe$	Methyl hydrogen phosphinite
$=PH$	Phosphinidene		
$-P(O)H_2$	Phosphinyl	$-P(O)(OH)Me$	Hydrogen methylphosphinate
$=P(O)H$	Phosphinylidene		
$-P(O)(OH)_2$	Phosphono	$-P(O)(OH)OMe$	Methyl hydrogen phosphonate

To assist the reader, who may encounter difficulty in applying the system, the next paragraphs, containing specific examples, are devoted to its explanation. Its operation may be appreciated by a study of Table 1.6.2. Some concrete examples may help.

Tabun may first be examined. This substance on full hydrolysis gives phosphoric acid (**1**), ethanol, dimethylamine and hydrogen cyanide, and is an ethyl ester (Fig. 1.6.1). The acid moiety may first be regarded as a derivative of compound (**2**). This is an amide as well as an acid and reference to Table 1.6.1 shows that it is called phosphoramidic acid. It is also a derivative of phosphorocyanidic acid (**3**). If (**2**) and (**3**) are impacted to give (**4**), 'phosphoramidocyanidic acid' results. Note that the two different groups appear in alphabetical order. This rule holds throughout the whole system as will be seen in subsequent examples. The ethyl ester of (**4**) is naturally ethyl phosphoramidocyanidate, but as tabun has two methyl groups bonded to the amide-nitrogen, its name is *O*-ethyl *N,N*-dimethyl phosphoramidocyanidate.

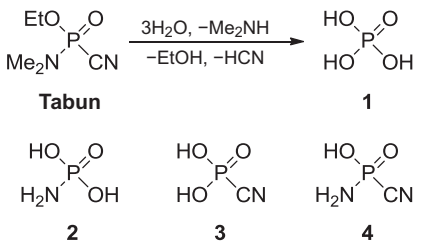
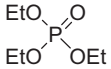
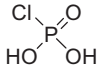


Figure 1.6.1 Tabun nomenclature.

Table 1.6.2 Handy reference guide to organophosphorus nomenclature

1	2	3	4	5	6
Parent acid	*From the ester*	*Substitute the hydrogen attached to the phosphorus atom*	*Operate to put chlorine in place of one hydroxyl*	*Operate to put chlorine in place of two hydroxyls*	*Operate to put chlorine in place of three hydroxyls*
		–			
Phosphoric acid	Triethyl phosphate		Phosphorochloridic acid	Phosphorodichloridic acid	Phosphorus oxychloride
					–
Phosphonic acid	Diethyl *H*-phosphonate	Diethyl ethylphosphonate	Phosphonochloridic acid	Phosphonodichloridic acid	
				–	–
Phosphinic acid	Ethyl *H*-phosphinate	Ethyl diethylphosphinate	Phosphinic chloride		

Removal of ═O alters the terminations to '-ou' and '-ite' throughout.
Replacement of ═O by ═S gives '-thionic acid.'
Replacement of —OH by —SH gives '-thiolic acid.'
Replacement of O by S, location unspecified, gives '-thioic acid.'
Analogous nomenclature can be used for selenium derivatives.

From esters as in column 2 (N.B. space between names of acid and alkyl groups). Substitute hydrogen attached to phosphorus as in column 3. Operating to put $—NH_2$, —CN, in place of hydroxyl gives "-amidic", "-cyanidic acid" as in columns 4 and 5. If operating twice with different groups, list in alphabetical order, e.g. 'phosphoramidocyanidic acid'.

When a substance contains a hydrocarbon or substituted hydrocarbon group attached directly to phosphorus, there is no gap between the name of the group and that of the phosphorus fragment. A simple case illustrates this: (**5**) is methylphosphonic acid, not methyl phosphonic acid (Fig. 1.6.2). A gap between words indicates the presence of one or more ester groups. Thus (**6**) is diethyl ethylphosphonate and (**7**) is ethyl diethylphosphinate.

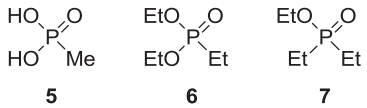


Figure 1.6.2 Phosphonate nomenclature.

Difficulties that might arise with the sulfur-containing phosphorus compounds will probably be concerned with the naming of structural isomers. Compound (**8**) and its isomers (**9**) and (**10**) may serve as an example (Fig. 1.6.3). Compound (**8**) is a mixed ester of phosphorothionic acid, $(HO)_3P{=}S$, whereas (**9**) and (**10**) are mixed esters of phosphorothiolic acid, $(HO)_2P(O)SH$. In the latter two derivatives the location of the sulfur atom is indicated by placing the prefix '*S*-' before the ester group bearing that atom. The name of (**9**) is therefore *O,S*-dimethyl *O*-ethyl phosphorothiolate, while that of (**10**) is *O,O*-dimethyl *S*-ethyl phosphorothiolate. No such prefixes are necessary for (**8**), which is simply dimethyl ethyl phosphorothionate (as the ending 'thionate' specifies the location of the sulfur atom, i.e. P═S). The same system extends to phosphorus—selenium compounds where the location of the selenium atom is indicated by the prefix '*Se*-' and the name reflects either the selenone (P═Se) or selenol (P—SeH) form. Thus, substances (**11**), (**12**) and (**13**) are dimethyl ethyl phosphoroselenonate, *O,Se*-dimethyl *O*-ethyl phosphoroselenolate and *O,O*-dimethyl *Se*-ethyl phosphoroselenolate.

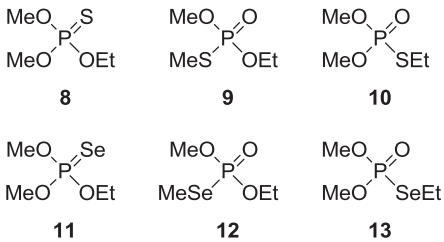
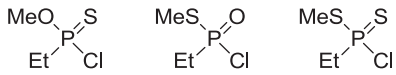


Figure 1.6.3 S and Se compounds.

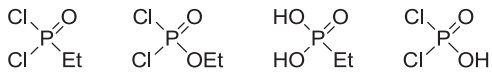
In cases where the precise position of the sulfur or selenium atom cannot be stated with certainty, especially for forms in tautomeric equilibria, the phrases 'phosphorothioate' or 'phosphoroselenoate' are used. When operating twice with different groups, the latter are placed in alphabetical order: for example, (**14**) is methyl ethylphosphonochloridothionate; (**15**) is *S*-methyl ethylphosphonochloridothiolate; and (**16**) is *S*-methyl ethylphosphonochloridothiolothionate (Fig. 1.6.4). In the last two compounds, it is permissible to omit the '*S*-' since the 'thiolo' sulfur atom can occupy only one position and no ambiguity can arise. However, in many cases, inclusion of such prefixes helps visualisation of the structure more easily.



14 **15** **16**

Figure 1.6.4 Some sulfur compounds.

One further point that may require an explanation is the apparent difference in nomenclature of (**17**) and the very similarly constituted (**18**) (Fig. 1.6.5). The former is ethylphosphonic dichloride and the latter ethyl phosphorodichloridate. The reason for this wide diversion is that the former is the dichloride corresponding to ethylphosphonic acid (**19**), but the latter is the ethyl ester of the hypothetical phosphorodichloridic acid (**20**) (see Column 5 of Table 1.6.2).



17 **18** **19** **20**

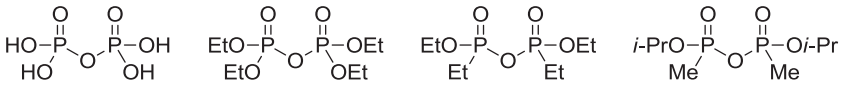
Figure 1.6.5 Some points of difference.

It is hoped that these few examples may help clear up any difficulty in naming correctly derivatives of pentavalent phosphorus. A few examples of trivalent phosphorus nomenclature may not be out of place. Ethyldichlorophosphine (**21**) is the acid chloride of ethylphosphonous acid (**22**) and is therefore also known as ethylphosphonous dichloride (Fig. 1.6.6). The corresponding pentavalent compound is ethylphosphonic dichloride and the sulfur adduct (**23**) is ethylphosphonothionic dichloride. Substance (**24**) is diethyl phosphorochloridite and the corresponding pentavalent compound is diethyl phosphorochloridate (**25**). The trivalent species (**26**) is *S*-ethyl ethylphosphonochloridothiolite (here also the prefix '*S*-' may be omitted without causing any ambiguity).

21 **22** **23** **24** **25** **26**

Figure 1.6.6 Examples illustrating trivalent nomenclature.

Some compounds containing two phosphorus atoms may now be considered, but, as mentioned previously, no international agreement on such compounds has been reached. Nevertheless, the simpler compounds present few difficulties. Just as the triethyl ester of phosphoric acid is triethyl phosphate, the full esterification of pyrophosphoric acid (**27**) with ethanol yields tetraethyl pyrophosphate (**28**) (Fig. 1.6.7). The symmetrical pyrophosphonates likewise present no difficulty: (**29**) is diethyl diethylpyrophosphonate and (**30**) is diisopropyl dimethylpyrophosphonate.



27 **28** **29** **30**

Figure 1.6.7 Symmetrical pyro-ester nomenclature.

Certain mixed pyrophosphonates are known and here the nomenclature remains uncertain. For example, (**31**) and (**32**) are mixed isopropyl and ethyl esters of mixed dialkylpyrophosphonic acids (Fig. 1.6.8). It is suggested that (**31**) is called ethyl isopropyl ethylmethylpyrophosphonate and (**32**) is ethyl isopropyl methylethylpyrophosphonate. A simpler case occurs when the compound contains no ester group. Here the compound is best described as the anhydride of the 'single-phosphorus' acid from which it is derived. Thus (**33**) is diethylphosphinic anhydride since it is obtained from two molecules of diethylphosphinic acid (Table 1.6.2) with loss of one molecule of water; (**34**) by the same reasoning is methylphosphonofluoridic anhydride.

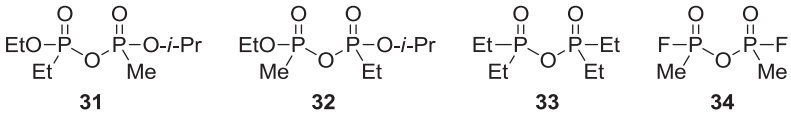


Figure 1.6.8 Unsymmetrical pyro-ester nomenclature.

Anhydrides of sulfur may be named by application of the rules in Table 1.6.2 and the scheme already outlined. Thus, (**35**) is tetraethyl pyrophosphorothionate, (**36**) is tetraethyl pyrophosphorodithionate and (**37**) is diisopropyl dimethylpyrophosphonothionate (Fig. 1.6.9).

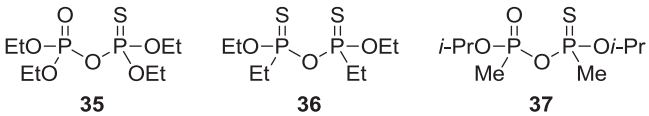


Figure 1.6.9 Unsymmetrical thio-pyroester examples.

Throughout this book, care has been taken to use a consistent and accurate nomenclature based on the rules outlined in this Section.

1.7 CHIRAL PHOSPHORUS COMPOUNDS AND BIOLOGICAL IMPLICATIONS

Tetracoordinate pentavalent phosphorus compounds have four σ-bonds arranged through sp^3 hybrid orbitals as in tetrahedral carbon compounds. Therefore, optically active forms where phosphorus serves as the asymmetric centre are possible when three different substituents are attached (*128*). The first enantiomeric phosphorus compound, ethylmethylphenylphosphine oxide, Et(Me)P(O)Ph, was isolated in 1911 by J. Meisenheimer. Many organophosphorus pesticides have an asymmetric phosphorus atom and several have been resolved into individual enantiomers (*128*). Although the enantiomers have identical properties, except for their ability to rotate a plane of polarised light in opposing directions, their biological activities depend greatly on their chirality. This is because their biological targets are chiral and discriminate between the enantiomers. H. O. Michel, observing a biphasic inhibition of AChE by sarin, realised this in 1955 (*178*). Since then, considerable progress has been made in the isolation and examination of biological activity of

Table 1.7.1 The effect of nerve agent stereochemistry on anticholinesterase activity and acute lethality of nerve agent stereoisomers *(179–182)*

Stereoisomer	Rate constant for AChE inhibition at 25 °C (/M/min)[a]	LD_{50} mouse (μg/kg)
(+)-tabun	4×10^5	837[b]
(−)-tabun	2×10^6	119[b]
(±)-tabun	–	208[b]
(+)-sarin	$<3 \times 10^3$ [e]	–
(−)-sarin	1×10^7	41[b]
(±)-sarin	–	83[b]
C(+)P(+)-soman	$<5 \times 10^3$	>5000[c]
C(−)P(+)-soman	$<5 \times 10^3$	>2000[c]
C(+)P(−)-soman	3×10^8	99[c]
C(−)P(−)-soman	2×10^8	38[c]
C(±)P(±)-soman	–	156[c]
(+)-VX	2×10^6	165[b]
(−)-VX	4×10^8	13[b]
(±)-VX	–	20[b]
(+)-BNM	6×10^4	>3720
(−)-BNM	3×10^6	699[d]
(±)-BNM	9×10^5	1210

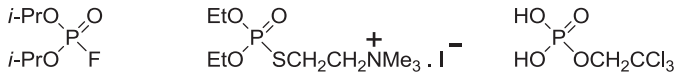
BMN = *S*-*n*-butyl *p*-nitrophenyl methylphosphonothiolate *n*-BuS(Me)P(O)$OC_6H_4NO_2$-*p* *(182)*. Note: the (−)-cyclosarin enantiomer, where the isopropyl group in sarin is replaced by a cyclohexyl group, inhibits AChE more strongly than (±)-cyclosarin and is the more toxic isomer *(183)*, in line with the trend revealed in the table.
[a]Rate constants for tabun and soman isomers were measured with electric eel AChE at pH 7.5 whereas those for sarin and VX enantiomers were obtained with bovine erythrocyte AChE at pH 7.7.
[b]Intravenous administration.
[c]Subcutaneous administration.
[d]Subcutaneous administration to rats.
[e]Estimated from an experiment with optically enriched (+)-sarin (64% enantiomeric excess).

organophosphorus enantiomers. Emphasis has been given to understanding the role of chirality in determining the toxicities of the nerve agents. Rate constants for inhibition of AChE and the lethal dose that kills half a group of mice (LD_{50}) after injection have been determined for the most important nerve agents and are listed in Table 1.7.1. The laevorotatory enantiomers generally react much faster with AChE, and are much more lethal, than the dextrorotatory enantiomers. This is particularly relevant to the design of medical countermeasures to nerve agents – for instance, the bioscavenger approach (Section 1.10.4.6), where enzyme bioscavengers ought to target the most toxic enantiomers preferentially.

Systematic work on the isolation, chemical reactions and biological activities of a variety of organophosphorus compounds was conducted at Porton Down over a fifteen-year period (1970s–1980s) by T. D. Inch et al. and provided many reliable synthetic methods for the isolation of pure enantiomers *(184–201)*. Modern strategies for the asymmetric synthesis of organophosphorus compounds have been reviewed *(202)*.

1.8 PHOSPHORUS-CONTAINING PHARMACEUTICALS

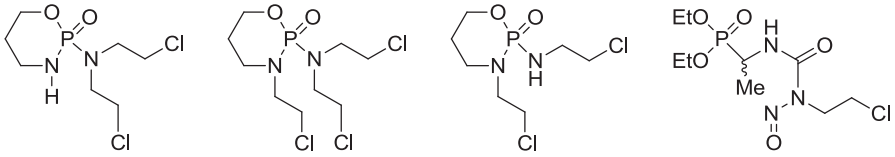
Toxicological properties and synthetic routes to some phosphorus-containing pharmaceuticals have been summarised (*203*) and an easily comprehensible guide of pharmacology for chemists is available (*204*). A review of the use of phosphate bioisosteres in medicinal chemistry and chemical biology is also worth consulting (*205*). The wartime research on anticholinesterase organophosphorus compounds provided the basis for the introduction into ophthalmology of isoflurophate and ecothiophate, two of the first organophosphorus drugs. Since then, many other organophosphorus compounds have been screened for medicinal properties, and some have entered mainstream medicine. The hypnotic drug, triclofos, is one such example (Fig. 1.8.1).



Isoflurophate (DFP) **Ecothiophate iodide** **Triclofos**

Figure 1.8.1 Phosphorus-based drugs related to pesticides.

Cyclophosphamide, trofosfamide and ifosfamide are nitrogen mustard alkylating agent prodrugs used to treat various cancers and autoimmune disorders (Fig. 1.8.2). They are metabolised by cytochrome P450 enzymes in the body to reactive aziridinium species. These react at the N^7-position of the guanine base in DNA forming inter- and intra-strand crosslinks. Fotemustine is a nitrosourea drug used to treat certain cancers. Nitrosourea drugs are useful for treating brain cancer (as they can cross the blood—brain barrier), melanoma, gastrointestinal cancer, lymphoma and myeloma. Fotemustine, like other nitrosourea drugs, is metabolised to an organic isocyanate (which reacts with proteins) and 2-chloroethyldiazonium hydroxide (which alkylates and crosslinks DNA).



Cyclophosphamide **Trofosfamide** **Ifosfamide** **Fotemustine**

Figure 1.8.2 Some anticancer drugs that contain phosphorus.

Phosphoryl compounds that contain *P*-aziridine groups are also potent alkylating agents. The nitrogen atom of the aziridine group can accept a proton under physiological conditions to generate a reactive aziridinium species that can alkylate DNA. Phosphazine and the less-toxic analogue mephosphazine have high anticancer activity in rodents (Fig. 1.8.3) (*206*). They are analogues of the structurally simpler tepa and metepa chemosterilants (used to sterilise insects through modification of their DNA by alkylation) (*120*). Thiotepa is used as an anticancer drug (*203*) and insect chemosterilant. Apholate is a chemosterilant having six aziridine groups. Alkyl *N*-[*bis*(1-aziridinyl)phosphinyl] carbamates (**38**) similar in structure to part of apholate also have anticancer and chemosterilant activity.

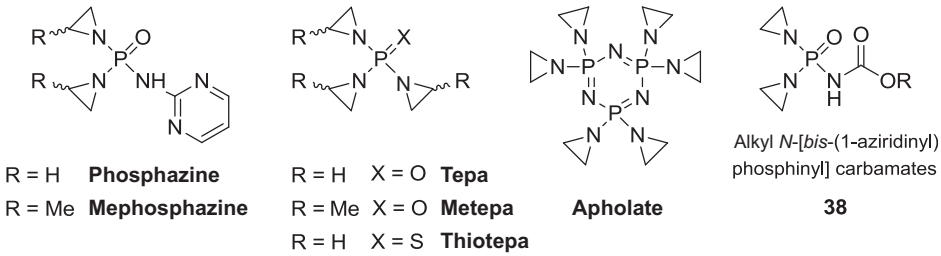


Figure 1.8.3 Anticancer drugs and chemosterilants that contain phosphorus.

Fosfestrol is a diphosphate drug that is also used to treat certain types of cancer (*203,207*) while monophosphate PD 113,271, from the bacterium *Streptomyces pulveraceus*, exhibits antitumour activity (*208*) (Fig. 1.8.4). It is an inhibitor of the enzyme topoisomerase II and also binds to the microtubule-associated protein 1B in human cells.

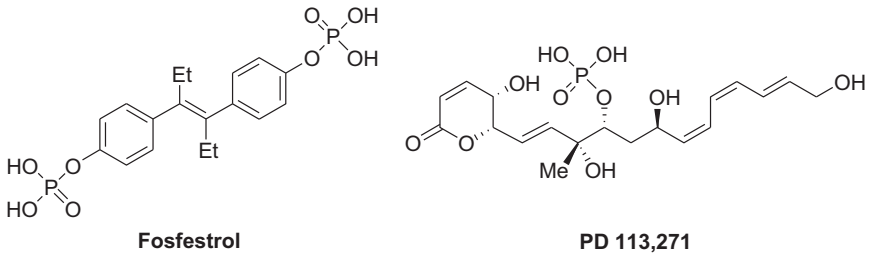


Figure 1.8.4 Fosfestrol and natural product PD 113,271 have anticancer activity.

The renin—angiotensin system exists in many tissues. Renin converts angiotensinogen into angiotensin I, which is then cleaved by angiotensin-converting enzyme (ACE) to give angiotensin II, a potent vasoconstrictor that causes increased blood pressure. The phosphorus-containing drug fosinopril inhibits ACE and prevents conversion of angiotensin I to angiotensin II, causing a fall in blood volume and blood pressure. ACE inhibitors therefore effectively treat hypertension. Fosinopril is the only phosphinate ACE inhibitor on the market and shares structural homology with other ACE-inhibiting drugs such as enalapril and lisinopril (Fig. 1.8.5) (*203*).

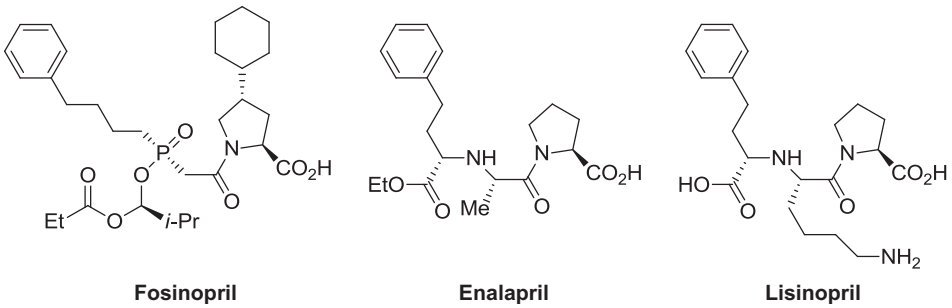
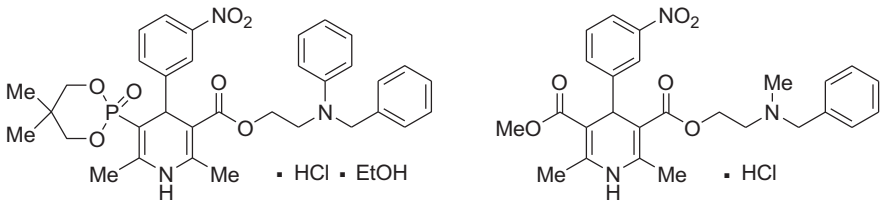


Figure 1.8.5 Fosinopril and some structurally related ACE inhibitors.

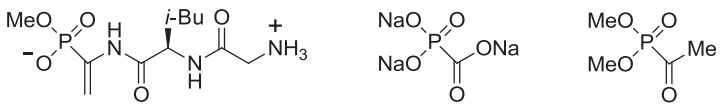
Efonidipine hydrochloride ethanol is a phosphonyl variant of nicardipine hydrochloride (Fig. 1.8.6) (*203*). Both drugs block slow calcium channels, decreasing contractile force and increasing vasodilation, which causes a fall in blood pressure. They are used to treat angina and cardiac arrhythmias.



Efonidipine hydrochloride ethanol **Nicardipine hydrochloride**

Figure 1.8.6 A phosphonyl Ca^{2+} channel blocker and analogue.

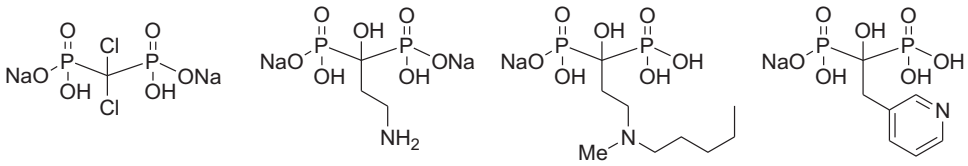
Dehydrophos is a Trojan horse antibiotic that upon uptake and proteolysis releases methyl acetylphosphonic acid that inactivates pyruvate oxidase and pyruvate dehydrogenase (*209*) (Fig. 1.8.7). Foscarnet sodium is an antiviral drug used to treat herpes virus infections. Dialkyl acetylphosphonates such as **39** inhibit the enzyme 1-deoxy-D-xylulose 5-phosphate synthase in *E. coli* and their modification may lead to new anti-infective agents (*210*).



Dehydrophos **Foscarnet sodium** **39**

Figure 1.8.7 Some phosphonates with antimicrobial properties.

Compounds from modification of the carbon-bridge of methylene-bisphosphonic acid are used to prevent and treat osteoporosis (bone resorption inhibitors) and to treat hypercalcaemia (raised blood calcium levels). They include the drugs clodronate, pamidronate, ibandronate, and risedronate (Fig. 1.8.8) (*203*).



Clodronate disodium **Pamidronate disodium** **Ibandronate sodium** **Risedronate sodium**

Figure 1.8.8 Examples of bisphosphonate bone resorption inhibitors.

Fosphenytoin sodium is a water-soluble phenytoin prodrug used to treat epileptic seizures, and prednisolone sodium phosphate is a glucocorticoid anti-inflammatory drug (Fig. 1.8.9) (*203*). DPO-1 inhibits the human K_v 1.5 potassium channel and thus blocks this novel pharmacophore (*211*).

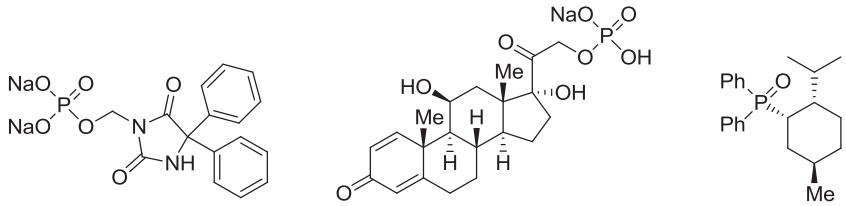


Figure 1.8.9 Miscellaneous phosphorus-containing drugs with different actions.

GS-9148 and GS-9219 have promising properties against human immunodeficiency virus (HIV) and leukaemia respectively. Several drugs based on the structure of acyclic nucleoside phosphonic acids (NMPc; R = adenine, cytosine, guanine, thymine, or uracil), for example, hepsera, viread and vistide are used to treat viral-induced retinitis, hepatitis B and HIV (*212,213*) (Fig. 1.8.10).

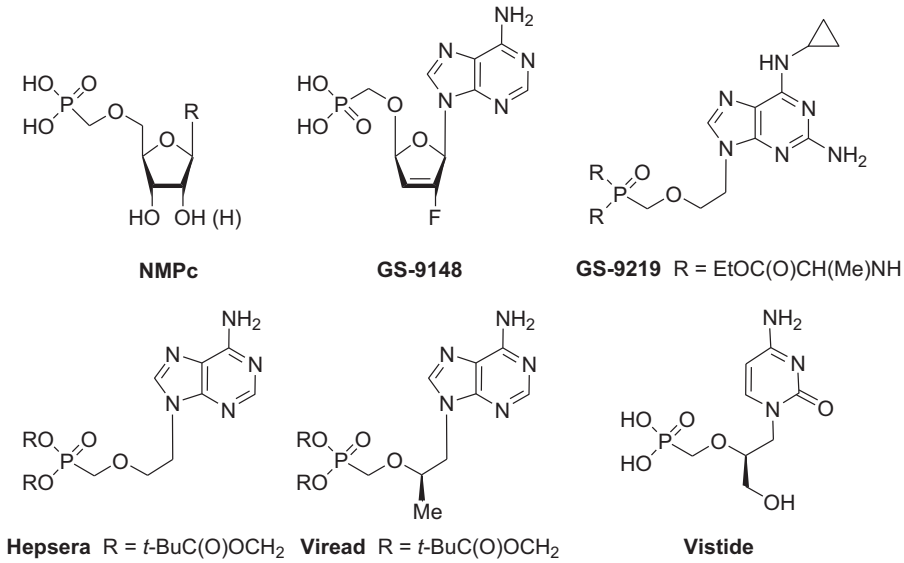


Figure 1.8.10 Nucleoside phosphonate analogues with antiviral properties.

Oxazolephosphonic acids such as compound (**40**), designed to mimic adenosine monophosphate (AMP), inhibit fructose 1,6-bisphosphatase (a drug discovery target for lowering glucose in type 2 diabetics) and have therapeutic potential (*214*) (Fig. 1.8.11). Bucladescine sodium is a cell-permeable

cyclic nucleotide compound that mimics the action of endogenous cyclic AMP (cAMP) (refer to Section 1.4).

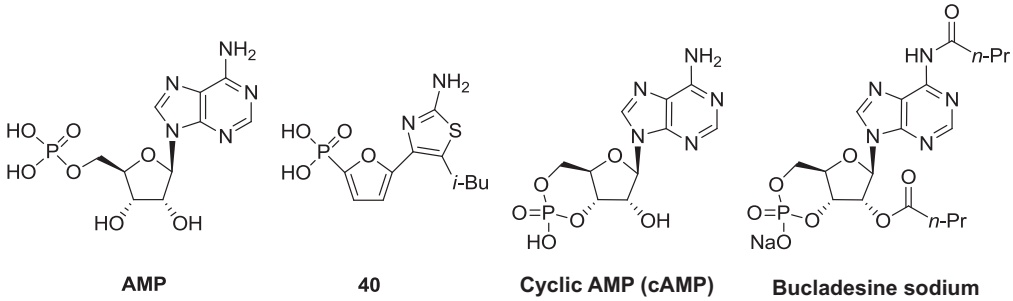


Figure 1.8.11 AMP and cAMP analogues with useful medicinal properties.

Several phosphorus species having a choline side-chain are useful medically; citicoline is used to treat Parkinson's disease and improve memory retention, while some synthetic phospholipids are beneficial for treating lung disease (Fig. 1.8.12). Lung surfactant is vital for respiration in air-breathing animals. Surfactant dysfunction contributes to clinical acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in humans and neonatal respiratory distress syndrome (NRDS) in infants. Lung inflammation in patients with ALI or ARDS can lead to a 30–50% mortality rate and NRDS can kill the young. Surfactant therapy using synthetic lung surfactants, such as colfosceril palmitate or DEPN-8, can decrease mortality and prolong life. In cases where lung injury is associated with phospholipase activity, which cleaves the natural lung surfactant, phospholipase-resistant synthetic surfactants, such as PG 1, may offer therapeutic benefit (*215*). In an anticancer application, edelfosine and less toxic analogues are able to partially inhibit the SK3 channel – a member of the small conductance calcium-dependent potassium channel family – which plays a central role in modulating the motility of highly metastatic cancerous cells (*216*). A phosphorus-based isostere of the anti-influenza drug Tamiflu™ called phosphaTamiflu is able via its methylthio tail to self-assemble on gold nanoparticles to provide a novel treatment for bird flu (*217*).

Other phosphorus-containing structural motifs possess antiviral activity. For example, alamifovir has entered phase II clinical trials as a potential therapy for hepatitis B virus infections (Fig. 1.8.13) (*218*). Unfortunately, though, clinical trials of BMS-986094, a nucleotide polymerase inhibitor for treating hepatitis C, stopped in 2012 when one patient suffered heart failure and died, and eight others were hospitalised (*219*). The diethyl phosphate **41** and *bis*(2,2,2-trifluoroethyl) phosphates **42–43** have selective anti-HIV activity in vitro (*220–223*).

There is much interest in fluorinated phosphonates (*224*) and fluorinated phosphates (*225*) in biomedical research. The potential for new discoveries in this field is high: fluoroalkyl groups are interesting isosteres for alkyl groups (*226*) and reliable methods for construction of a range of fluoroalkyl-substituted organophosphorus systems have become available (*227–241*).

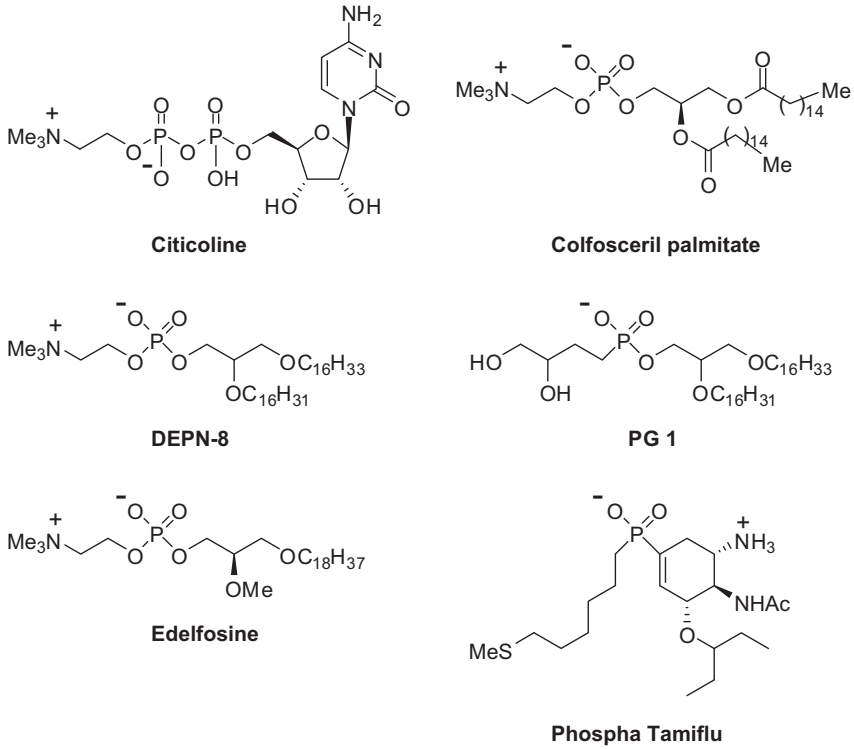


Figure 1.8.12 Phosphorus-based drugs with various beneficial actions.

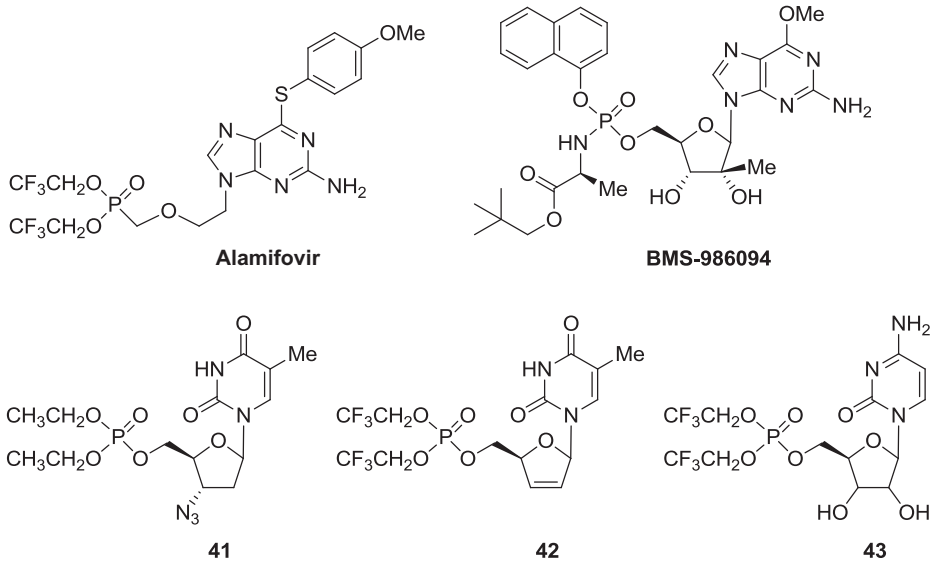


Figure 1.8.13 Some organophosphorus compounds with antiviral activity.

Some fluorinated oximes (*242*) and bis-pyridinium compounds (*243,244*) also show promise as nerve agent antidotes.

1.9 FIRE RETARDANTS AND FIRE-EXTINGUISHING COMPOUNDS

Fire retardants are added to materials to prevent combustion and to delay the spread of fire. Those added to plastics, polymeric foams and synthetic fibres include tris(2-chloroethyl) phosphate (TCEP), tris(1,3-dichloro-2-propyl) phosphate (TDCPP) and tetrakis(2-chloroethyl)dichloroisopentyl diphosphate (V6) (Fig. 1.9.1) (*245*), although health and environmental concerns may curtail their use in future (*246*).

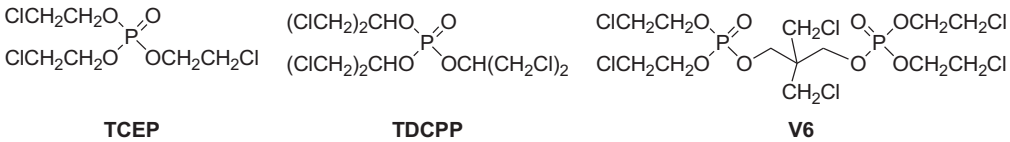


Figure 1.9.1 Chlorinated organophosphorus fire retardants.

The study and use of phosphorus fire retardants revived after the ban on brominated fire retardants, which comprised 20% of the European market in 2006 (*245*), and included triphenyl phosphate (TPP), tri(*ortho*-cresyl) phosphate (TOCP) and bisphenol-A diphenyl phosphate (BADP) (Fig. 1.9.2). These compounds have high boiling points, which limit their volatilisation and hence toxicity during combustion, and have favourable flame-suppressing properties. However, some are toxic to humans; TOCP exposure can cause delayed nerve damage, for example (see Section 1.10.2.3). Evaluation of their health and environmental effects must take place to ensure their safe use in antifire applications.

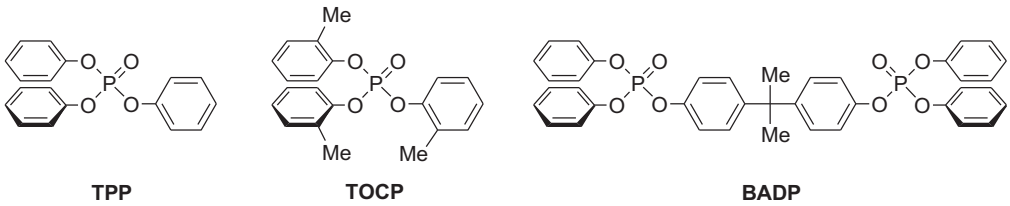


Figure 1.9.2 Aromatic organophosphorus fire retardants.

The search for fire-extinguishing alternatives to Halon gases, which deplete atmospheric ozone, has resulted in the synthesis (*227–241*) and screening of fluoroalkyl-phosphorus compounds as possible Halon replacements (*247*). These compounds, although much higher boiling (*233*) than common fire-extinguishing gases, extinguish flames more effectively (Table 1.9.1) (*248*). Tris(2,2,2-trifluoroethyl) phosphate does not inhibit AChE appreciably (*232*), hinting at low acute toxicity (at least by this mechanism), and is soluble in carbon dioxide and

Table 1.9.1 Extinguishing concentrations (% *v/v*) for some compounds measured using a cup burner or flame ionisation detector (FID) (*247–249*) (the lower the extinguishing concentration, the more effective the compound as a fire extinguishant)

Compound	Structure	Cup burner	FID
Nitrogen	N_2	28.0	26.9
Carbon dioxide	CO_2	20.4	18.8
Bromochlorodifluoromethane[a]	CF_2BrCl	3.2	3.5
Bromotrifluoromethane[b]	CF_3Br	2.9	3.0
Tris(2,2,2-trifluoroethyl) phosphate	$(CF_3CH_2O)_3P{=}O$	–	0.8
Diethyl 2,2,2-trifluoroethyl phosphate	$(EtO)_2P(O)OCH_2CF_3$	–	0.7

[a]Halon 1211.
[b]Halon 1301.

1,1,1,2-tetrafluoroethane (R134a) under supercritical conditions, suggesting the use of supercritical fluids as carrier and delivery media (*249*). Polymers made from polymerisation of the monomers $(R_FO)_2P(O)OCH_2CH_2OC(O)CR{=}CH_2$ (R_F = polyfluoroalkyl, R = H or Me) impart fire-resistance when impregnated onto fabrics (*250*).

Related data are also available; heats of hydrolysis and oxidation of organophosphorus compounds were measured at Porton Down in the 1950s to provide 'average bond-energies' to estimate the heats of formation or reaction of many such compounds (*251,252*). High-temperature decomposition pathways have been studied for amiton (*253*), dimethyl *H*-phosphonate (*254*), diethyl methylphosphonate (*255*), triethyl phosphate (*256*), and the nerve agent sarin and related species (*257*), and the chemistry of combustion of organophosphorus compounds has been reviewed (*258*).

1.10 TOXICOLOGY AND MEDICAL TREATMENT OF ORGANOPHOSPHORUS COMPOUNDS

Organophosphorus (OP) compounds can be toxic by ingestion, inhalation, absorption through the skin, or injection. OP pesticides and nerve agents act primarily by inhibiting the enzyme AChE. The nerve agents are designed to be more toxic to humans and therefore act more rapidly and have a greater lethality. Consequently, the potential use of such agents in warfare or in terrorism is of considerable concern (*259–262*). By far the majority of poisonings, however, are due to OP pesticides.

At least two million people are poisoned by OP pesticides each year in the developing world (*263,264*), mainly through self-poisoning. This results in an estimated 200,000 deaths per year (*265,266*), which accounts for nearly one-third of the world's suicides (*267*); however, estimating the number of individuals exposed to OP pesticides internationally is very difficult. For example, Gunnell and Eddleston estimated that there were around 300,000 pesticide suicides each year in China and South-East Asia alone (*264*). The World Health Organisation (WHO) has estimated that three million cases of pesticide poisoning occur every year worldwide, resulting in an excess of 250,000 deaths (*268,269*). Globally, there is a scarcity of information on the magnitude of both intentional and

unintentional poisoning, as well as on the relative importance of different pesticides, and the incidence of international OP pesticide-related human exposures appears to be underestimated (*270*). Information is particularly lacking from most of Africa, and detailed and accurate community-based data on pesticides responsible for fatal self-harm are not available for most of rural Asia (*271*). Pesticide poisoning is evidently as important in South America and Africa as it is in Asia (*272*).

Although there are many thousands of cases of OP pesticide poisoning each year, the majority of these are not well documented and the identity and amount of the OP compound involved is often unknown. In rural Asia, for example, a large variety of pesticides has been implicated in intentional or unintentional poisoning, reflecting the range of pesticides used in local agriculture (*271*). Studies from Sri Lanka suggest that less than 20% of pesticides used for self-harm are bought for the purpose; the majority are freely available in the home or nearby garden (*273*). The toxicity of different pesticides varies, but the case fatality of the commonly used varieties is at least 10 times higher than that for self-poisoning with medicines (*274*).

For nerve agents, in contrast, cases of human poisoning are rare. The most notable of these occurred during the Iran—Iraq war and the terrorist attacks in Japan, both of which involved sarin, as well as tabun in the case of Iran (*275,276*). There are even fewer examples for other nerve agents, such as soman and VX. Some studies of the effects of low doses have been conducted in volunteers (e.g. (*277,278*)) and there have been some reported cases of accidental poisoning (e.g. (*279—281*)), but these are rare.

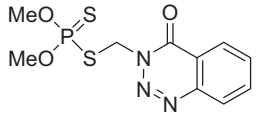
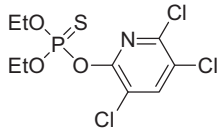
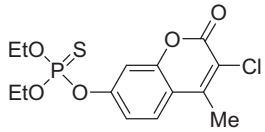
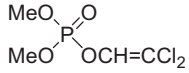
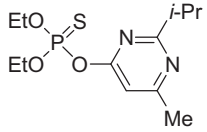
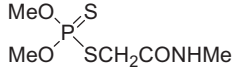
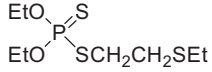
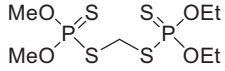
There were between 45,000 and 100,000 Iranian chemical casualties in the war with Iraq, of which the majority were apparently caused by the nerve agents (*282*). In the Matsumoto terrorist attack in Japan, seven people died and over 200 sought medical attention (*283*). Those critically and severely affected by sarin presented with loss of consciousness and generalised seizures (*284—290*). Following the later Tokyo subway attack, 12 people died and over 5000 civilians presented to medical facilities (*283,284*). Only 2.7% of patients admitted to hospital had seizures, compared with 99% who had miosis and 23% with muscle fasciculations (*284,285*). The concentration of sarin to which most victims were exposed was low, however, and the sarin was diluted with a variety of solvents, such as benzene, petroleum ether and hexane (*259*).

1.10.1 Toxicity

It is difficult to determine the toxicities of OP compounds from cases of human poisoning, since the dose of the compound and often its identity are not known. Additionally, many cases receive pharmaceutical therapy or other treatment, which is likely to affect the toxicity. Estimates of the human toxicity of OP anticholinesterases are therefore largely derived by extrapolation from data obtained using animals, usually rodents such as rats and mice.

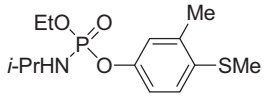
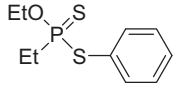
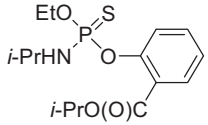
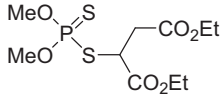
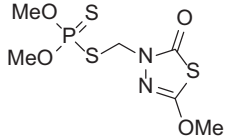
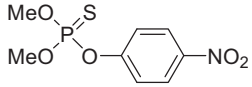
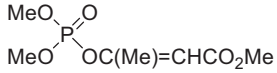
Toxicity for oral or cutaneous exposure is usually expressed as the Lethal Dose at which 50% of the exposed population die as a result of the poisoning (LD_{50}). A different measure is used for inhalation: LCt_{50}, the product of the concentration (C) and the duration of exposure (t) lethal for 50% of those exposed; sometimes expressed as the 50% lethal concentration (LC_{50}) for a fixed exposure time, usually 1 or 4 h. Table 1.10.1.1 shows LD_{50} and LC_{50} values for a range of OP pesticides in animals.

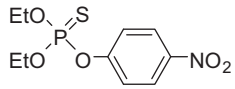
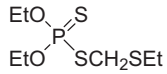
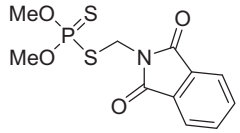
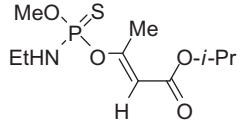
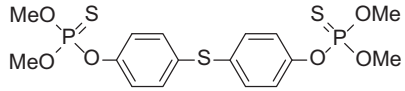
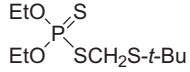
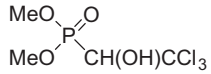
Table 1.10.1.1 Lethal dose of organophosphorus pesticides to rats (unless species otherwise specified)[a]

Pesticide (brand name/s)	Structure	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Inhalation LC_{50} (mg/m^3 in 1 or 4 h)
Azinphos-methyl (Guthion)		4.4–16	88–220	400 (1 h)
Chlorpyrifos (Dursban, Lorsban)		95–270	>2000	>200 (4 h)
Coumaphos (Co-Ral)		13–41	860	340 (1 h)
Dichlorvos (DDVP, Vapona)		25–80	70.4–250	>200 (1 h)
Diazinon (Spectracide)		300–400	3600 (rabbit)	350 (4 h)
Dimethoate (Cygon, De-Fend)		180–330	100–600	>200 (4 h)
Disulfoton (Di-Syston)		1.9–12.5	3.6–15.9	300 (1 h)
Ethion (Acithion, Commando)		21–191	62	864 (4 h)

(*Continued*)

Table 1.10.1.1 Lethal dose of organophosphorus pesticides to rats (unless species otherwise specified)[a]—cont'd

Pesticide (brand name/s)	Structure	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Inhalation LC_{50} (mg/m^3 in 1 or 4 h)
Fenamiphos (Nemacur)		2–19	72–154	110–170[b]
Fonofos (Dyfonate)		3.2–18.5	147	900 (4 h)
Isofenphos (Oftanol, Amaze)		28–38	188	130–144 (4 h)
Malathion (Cythion)		1000 to 10,000+	>4000	–
Methidathion (Supracide)		25–54	85–94	360 (4 h)
Methyl parathion (Metacide)		6–50	67	240 (1 h)
Mevinphos (Phosdrin)		3–12	4.2	125 (1 h)
Naled (Dibrom)		91–430	800	> 150 (6 h, mice)

Parathion (Alkron, Folidol)		2–30	6.8–50	84 (4 h)
Phorate (Rampart, Thimet)		1.1–3.7	2.5–6.2	60 (4 h)
Phosmet (Imidan, Prolate)		113–160	3160–4640	276 (1 h)
Propetamphos (Blotic, Safrotin)		75–119	2300–3100	204 (4 h, rabbit)
Temephos (Abate, Biothion)		1226–13,000	–	–
Terbufos (AC-92100, Counter)		1.3–1.74	1.1 (rabbit)	–
Trichlorfon (Dylox, Neguvon)		450–650	2000–5000	>500 (4 h)

[a]The information came from many studies which differed in some of their methods. A range of LD_{50} or LC_{50} values is presented to represent the different results.
[b]Time not specified but probably 4 h.
Source: Data compiled from the EXTOXNET website at http://ace.ace.orst.edu/info/extoxnet/pips/ghindex.html.

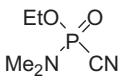
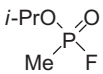
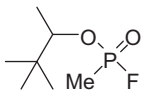
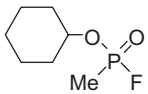
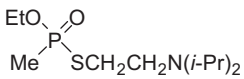
Table 1.10.1.2 The WHO-recommended classification of pesticides by hazard

Class		LD_{50} in the rat (mg/kg body weight)			
		Oral		Dermal	
		Solids	Liquids	Solids	Liquids
Ia	Extremely hazardous	≤5	≤20	≤10	≤40
Ib	Highly hazardous	5–50	20–200	10–100	40–400
II	Moderately hazardous	50–500	200–2000	100–1000	400–4000
III	Slightly hazardous	>500	>2000	>1000	>4000

Most OP pesticides are highly toxic. The WHO classifies the pesticides by hazards, based primarily on their oral and dermal toxicities in the rat (Table 1.10.1.2). The level of toxicity in humans ranges from an estimated oral lethal dose of <5 mg/kg to 0.5–5 g/kg (*291*). The estimated fatal dose of parathion for an adult by ingestion or inhalation is 10–200 mg, and children have died after ingesting only 2 mg, equivalent to a dose of about 0.1 mg/kg (*291*). For diazinon, the estimated fatal dose in humans is 25 g by oral ingestion (*292*). The mean fatal dose of malathion in humans has been estimated as 60 g (*292*), but may be as low as 250 mg/kg in an untreated adult (*291*); however, there are reports of a 34-month-old boy who survived a dose of malathion of about 190 mg/kg, and of a boy only 40-days old who survived after a dose of approximately 1750 mg (about 407 mg/kg) (*293*).

The nerve agents are considerably more toxic than the pesticides (*294*). Table 1.10.1.3 shows LD_{50} and LCt_{50} estimates for the most common nerve agents: the range of estimates by different groups

Table 1.10.1.3 Toxicity of some of the most important nerve agents in man

Nerve agent	Structure	LCt_{50} by inhalation (mg min/m^3)	LD_{50} on skin (mg/70 kg individual)
Tabun (GA)		200[a], 400[b,c], 135[d], 70[d]	4000[a], 1000[b,c], 1500[d]
Sarin (GB)		100[a,b,c], 70[d], 35[d]	1700[a,b,c,d]
Soman (GD)		100[a], 50[b], 70[c,d], 35[d]	300[a], 350[b,d], 50[c]
Cyclosarin (GF)		Unknown[c,d], 35[d]	30[c], 350[d]
VX		50[a,c], 10[b], 30[d], 15[d]	10[a,b,c,d], 5[d]

Sources: [a](*295*); [b](*296*); [c](*297*); [d](*298*) 'existing' and Chemical Defense Equipment Process Action Team (CDEPAT)-recommended values.

reflects the uncertainties in arriving at an estimate from the limited data available. Volatile agents, such as tabun and sarin, present an inhalation hazard but are much less toxic by the percutaneous route than less volatile agents such as VX. This is mainly due to the more volatile nerve agents evaporating from naked skin. If the evaporation is prevented, e.g. by clothing, the difference in percutaneous toxicity can be less.

Worldwide studies report mortality rates from OP pesticide poisoning of 3—25% (*299*). The compounds most frequently involved include malathion, dichlorvos, trichlorfon and fenitrothion/malathion. Mortality rates depend on the type of compound used, amount ingested, general health of the patient, delay in discovery and transport, insufficient respiratory management, delay in intubation and failure in weaning off ventilatory support. Complications include severe bronchorrhea, seizures, weakness and neuropathy. Respiratory failure is the most common cause of death.

The vast majority of deaths from OP pesticide poisoning are intentional (*271*); deaths from unintentional poisoning are less common than those from intentional poisoning and seem to be more common in regions where highly toxic OP pesticides (WHO Class I toxicity) are available (*300*). Unintentional oral or dermal exposure to WHO-Class I OP pesticides can cause severe poisoning, but the doses are usually smaller than with intentional poisoning, resulting in fewer deaths. WHO Class II OP pesticides are generally less toxic in unintentional poisoning. Where Class II OP pesticides are the most commonly used insecticides, unintentional poisoning is generally less likely to cause severe poisoning (*271*). Class II OP pesticides are highly toxic in intentional overdose. In a large cohort of Sri Lankan patients poisoned with WHO-Class II OP pesticides (*265*), no deaths resulted from unintentional poisoning (*301*).

The locally available pesticides will also determine how many poisoned people survive to hospital presentation. In areas where highly toxic fast-acting WHO Class I OP pesticides are used, the onset of poisoning can be so fast that many people die before they can be taken to hospital. In contrast, where slower acting pesticides are used, more patients will survive to reach hospital and medical care (*301*). The case fatality for different pesticides also varies markedly, from around 70% for both aluminium phosphide and paraquat (neither of them OP compounds), to close to 0% for many of the newer lower toxicity pesticides (*302,303*). Therefore, hospital statistics, whether from primary or secondary hospitals, must be interpreted in light of this difference.

1.10.2 Effects of OP poisoning

OP poisoning leads to three main clinical syndromes: (1) acute cholinergic syndrome; (2) intermediate syndrome (IMS); and (3) peripheral neuropathy (*268,304—308*). The acute cholinergic crisis develops within a period ranging from a few minutes to several hours after exposure, depending on the OP compound and the route of poisoning. Death can occur within a very short space of time if life-threatening conditions, such as respiratory failure, are not treated promptly and appropriately. OP-induced delayed neuropathy (OPIDN) occurs 2—3 weeks after acute exposure to certain OP insecticides. The clinical features primarily manifest as numbness and weakness of the lower extremities, followed by progressive ascending weakness of limb muscles. The IMS, which was first described by Senanayake and Karalliedde (*304*), arises in the interval between the end of the acute cholinergic crisis and the onset of OPIDN. It is marked by weakness and fatigue of skeletal muscles with fasciculation, leading to respiratory muscle paralysis, and is considered a major contributing factor to OP-related morbidity and mortality.

1.10.2.1 Acute cholinergic syndrome

The primary mechanism of action of OP pesticides and nerve agents is inhibition of carboxyl ester hydrolase enzymes, of which AChE is the most toxicologically important. AChE (EC 3.1.1.7), also known as true cholinesterase, is a serine protease enzyme that catalyses the hydrolysis of the neurotransmitter acetylcholine (ACh) to choline and acetic acid. Other enzymes inhibited by OP compounds include butyrylcholinesterase (BChE) (EC 3.1.1.8), also known as pseudocholinesterase, a nonspecific cholinesterase that hydrolyses many different choline esters (*309,310*), and carboxylesterases (EC 3.1.1.1). Mammalian carboxylesterases represent a multigene family whose gene products are localised in the endoplasmic reticulum of many tissues (*311*). These enzymes efficiently catalyse the hydrolysis of a variety of ester- and amide-containing chemicals as well as drugs (including prodrugs) to the respective free acids.

AChE is found in the central and peripheral nervous system, neuromuscular junctions and red blood cells (RBCs). OP inhibitors inactivate AChE by phosphylating the serine hydroxyl group located at the active site of the enzyme (phosphylation describes addition of a phosphoryl or phosphonyl moiety to the enzyme). Phosphylation occurs by loss of a suitable leaving group and formation of a covalent bond to AChE. Once the OP inhibitor binds to AChE, the enzyme undergoes one of the following (*312*):

1. spontaneous hydrolysis and restoration of function;
2. reactivation by a strong nucleophile such as an oxime;
3. dealkylation resulting in irreversible binding and permanent enzyme inactivation (aging).

The natural substrate for AChE, ACh, is a neurotransmitter that mediates chemical synaptic transmission at the neuromuscular junction, in the peripheral autonomic nervous system and in the central nervous system (CNS). The action of ACh is mediated by two main classes of receptors, muscarinic and nicotinic, named after the specific ligands, muscarine and nicotine, which were originally used to distinguish them. In contrast to the ionotropic nicotinic receptors (nAChRs), which contain a ligand-gated ion channel pore, the metabotropic muscarinic receptors (mAChRs) are G protein-coupled receptors that act through intracellular signal transduction pathways.

Following inhibition of AChE by an OP compound, ACh accumulates throughout the nervous system, resulting in overstimulation of muscarinic and nicotinic receptors. This leads to the classical muscarinic and nicotinic receptor-mediated signs of anticholinesterase intoxication including salivation, lacrimation, urination, miosis or mydriasis, diarrhoea, bronchospasm, bronchorrhoea, vomiting, muscle fasciculation, sweating, hypertension and tachycardia or bradycardia (*313,314*). This acute cholinergic crisis develops within a few minutes to several hours after exposure. In severe cases, death results from respiratory paralysis — both central and peripheral (*315*). Some authors have attributed the expression of overstimulation of ACh receptors as follows (*312*):

1. muscarinic overstimulation causes bradycardia, bronchorrhea, bronchospasm, diarrhoea, hypotension, lacrimation, miosis, salivation, urination and vomiting;
2. nicotinic overstimulation in the sympathetic system produces hypertension, mydriasis, sweating and tachycardia;

3. nicotinic overstimulation in the CNS results in agitation, coma, confusion and respiratory failure;
4. nicotinic overstimulation at the neuromuscular junction causes fasciculations, muscle weakness and paralysis.

Signs of CNS involvement are commonly observed in severe OP poisoning, including respiratory failure, depressed levels of consciousness and seizures (*316–318*). The seizures can lead to neuronal damage, contributing to mortality and, in the case of survivors, to neurological impairment. The onset of seizures has been attributed to a number of causes, including overstimulation of cholinergic pathways and hypoxia (*319*).

1.10.2.2 Intermediate syndrome

In 1987, Senanayake and Karalliedde described a syndrome of muscular paralysis that occurred in conscious patients 24–96 h following organophosphate ingestion, after their initial signs of poisoning had been treated with atropine (*304,320*). This syndrome usually followed an acute cholinergic syndrome and occurred earlier than a delayed neuropathy; hence, it was referred to as the intermediate syndrome (IMS). Muscle weakness affected predominantly the proximal limb muscles and those supplied by the cranial nerves, and IMS was often associated with respiratory failure. Later studies suggested that IMS could occur before 24 h and even after 96 h (*321–323*). Recent reviews of IMS include those by Yang and Deng (*268*) and by Abdollahi and Karami-Mohajeri (*324*).

The IMS is characterised by cranial and respiratory muscle weakness, which occurs 1–4 days after poisoning, following the cholinergic phase (*320*). IMS occurs in more than 60% of patients with acute OP poisoning (*321,325*) and is the chief cause of morbidity and mortality of the poisoning (*326*), which results largely from paralysis of the respiratory muscles (*324*). Respiratory insufficiency frequently draws medical attention to the onset of the syndrome (*268*). Complete recovery usually takes 4–15 days if adequate ventilatory support is provided (*327*). According to Senanayake and Karalliedde (*304*), the regression of toxic signs among patients who survived IMS followed a distinct pattern. Muscle power first resumed in cranial nerve-innervated muscles, followed by respiratory muscles, proximal muscles and neck flexors.

Because the definition of IMS has differed across studies, reports on its incidence have varied accordingly (*268*). In the first report of IMS, 10 out of 92 patients with OP poisoning developed IMS, an incidence of 11% (*304*). The reported incidence of IMS in subsequent reports ranges from 7.7% to as high as 84% (*268*). Findings on the risk factors of IMS also differed among studies. Although IMS generally occurred among patients with prolonged and severe inhibition of AChE (*328,329*), not every patient with severe inhibition of the enzyme developed IMS (*327,330*). Other risk factors included delayed metabolism of the OP compound due to toxicokinetic factors of the insecticides or impaired organ function, severity of poisoning, elevated muscle enzymes and inadequate or late oxime therapy (*325,327,328,330–332*).

IMS has been linked preferentially to specific organophosphates, namely fenthion, dimethoate and monocrotophos, all of which are dimethoxy compounds (*304*), but it is not limited to patients with exposure to these compounds. Parathion, combined ethyl parathion and methyl parathion, methamidophos, dichlorvos and other OP insecticides have all been implicated in the development of IMS (*268,307,328–330*).

In an earlier description of what appears to be the IMS (*333*), Wadia et al. divided paralytic signs in OP-poisoned patients into type 1 signs (present on admission) and type 2 signs (appearing later while on atropine treatment). Type 1 signs, chiefly impaired consciousness and bilateral pyramidal tract signs, responded to atropine. The most common type 2 signs were proximal limb weakness, areflexia and cranial nerve palsies. Electromyographic studies during type 2 paralysis showed a myasthenic response in some cases. Of 36 cases with type 2 signs, 15 died from respiratory paralysis after a variable period of artificial respiration. Wadia et al. speculated that type 2 signs were purely nicotinic and were distinct from OPIDN, since they appeared earlier and were distinct from the clinical characteristics of OPIDN. They postulated that IMS may be due to nicotinic signs manifesting later than muscarinic signs or the inhibition of serine esterases other than AChE.

The neurophysiological correlates of the IMS are well documented (*334–336*) and demonstrate that the syndrome is a disorder of the neuromuscular junction. Although the pathophysiology of IMS is not clearly understood (*321,327,328,330,337–340*), it is generally believed to result from a persistent excess of ACh at the neuromuscular junction (*307,321,327–330,341–345*). In their first description of the IMS (*304*), Senanayake and Karalliedde postulated that the syndrome might be caused by pathologic changes in the postsynaptic end-plate region of striated muscles, which had been described in experimental animals (hens and rats) that developed a similar pattern of paralysis after OP insecticide poisoning. It was subsequently proposed that myonecrosis was mediated by calcium mobilisation in the muscle fibres (*306*). In this scheme, the excess ACh seen in OP poisoning results in prolonged receptor-associated channel opening and influx of Ca^{2+} at the muscle endplate (*346,347*). In animals, this has been shown to lead to muscle necrosis (*348*), which is much more severe in the diaphragm than in other skeletal muscles (*333,346,349*). Oxidative damage to muscle membranes has been suggested as another possible mechanism of muscle necrosis (*325,330*).

The role of muscle injury in IMS has been supported by the demonstration of a clinical association between increased levels of muscle enzymes (creatinine phosphokinase and lactate dehydrogenase) in the blood and the development of IMS (*327*). In contrast, a prospective study of 19 patients with OP poisoning concluded that muscle fibre necrosis was unlikely to be the aetiology of IMS because muscle biopsy specimens in patients with IMS showed only a few necrotic fibres (*308,328,331*). This led to the proposition that IMS was a combined pre- and postsynaptic impairment of neuromuscular transmission as evidenced by electromyographic observations, and that IMS occurred after prolonged and severe AChE inhibition (*328,329*). Others disagreed and suggested that either different susceptibility of various cholinergic receptors or inadequate oxime therapy played a role in the development of IMS (*339*).

A single-fibre electromyographic study of patients voluntarily exposed to low doses of sarin found reversible subclinical changes compatible with the development of nondepolarizing neuromuscular block (*350*). The authors suggested that IMS could be explained by these findings, which were attributed to a reduction in the number of functioning ACh receptors at the postjunctional membrane or a failure of ACh release. It was further proposed that downregulation or desensitisation of post-synaptic ACh receptors after prolonged ACh stimulation could explain the occurrence of IMS (*337*).

In summary, IMS is a major cause of morbidity and mortality in patients with acute OP insecticide poisoning. Although IMS is well recognised as a disorder of neuromuscular junctions, its exact aetiology,

incidence and risk factors are not clearly defined, largely because existing studies are mainly small-scale case series and do not adhere to a consistent and rigorous definition of IMS. IMS carries a high risk of death among patients with respiratory failure: prompt recognition of the syndrome is therefore the key for medical management. Without a clear understanding of the pathophysiology of IMS, there are no specific antidotes available and therefore treatment is mainly supportive (*268*); however, although the syndrome has been considered a major contributing factor of OP-related morbidity and mortality, the prognosis of IMS is likely to be favourable if respiratory failure can be recognised and treated promptly. It has been recommended that future studies on IMS should focus on defining the mechanisms that underlie the syndrome and identifying clinical and/or laboratory predictors of IMS (*268,327*).

1.10.2.3 Delayed neuropathy

In addition to acute effects, OP poisoning can also result in OP-induced delayed neuropathy (OPIDN, also called OP-induced delayed polyneuropathy, OPIDP), which affects long axons in the spinal cord and peripheral nerves. OPIDN is characterised by sequential development of axonal degeneration, demyelination and flaccid paralysis after a latent period of 10—14 days, and is completely unrelated to the anticholinesterase action of these compounds (*351*). Of the thousands of OP agents on the market, relatively few have been associated with delayed onset of neuropathy (*352*). Those which have been associated with OPIDN include chlorpyrifos and dichlorvos (structures in Table 1.10.1.1), and *O*-ethyl *O*-(4-nitrophenyl) phenylphosphorothionate (EPN), leptophos, trichloronate, methamidophos, omethoate, parathion, trichlorfon (dipterex), TOCP, dimefox and mipafox (*353*) (Fig. 1.10.2.3.1). The clinical features are predominantly motor neuropathy and primarily manifest as numbness and weakness of the lower extremities, followed by progressive ascending weakness of limb muscles (*304,308*).

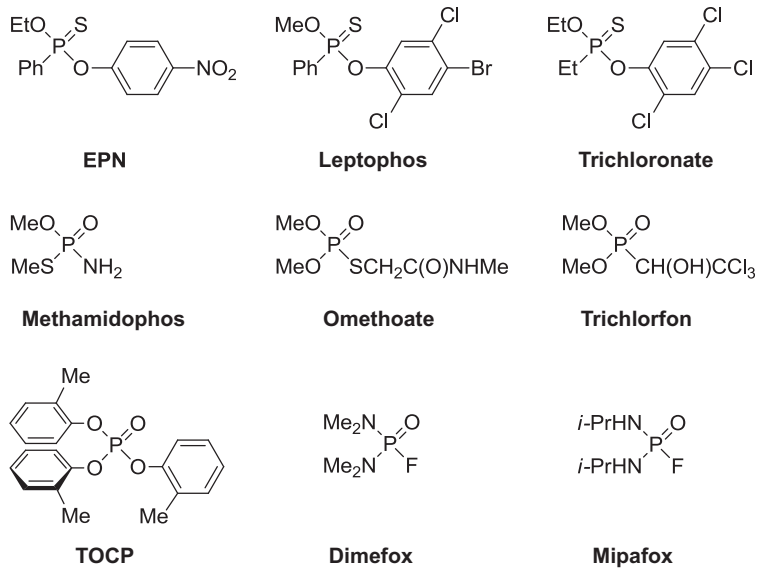


Figure 1.10.2.3.1 Structures of some OP compounds associated with OPIDN.

OPIDN may result from a single large dose or cumulative doses. The neuropathy takes at least 10 days to develop following a single acute exposure, while the effects of cumulative doses occur over a period of weeks following exposure (*352*). Histopathologic examination reveals central-peripheral distal axonopathy, in which swelling of the distal portion of the axon is followed by a 'dying-back' degeneration that progresses towards the neuronal cell body, although the latter is normally unaffected (*352,354*). The primary axonopathy is accompanied by secondary demyelination, and both sensory and motor fibres are involved. Typically, the spinal cord tracts and distal axons of the lower extremities are involved more than the upper extremities, resulting in clinical signs of ataxia and lower limb paralysis.

Although delayed neuropathy is relatively uncommon (*355*), several extensive outbreaks of human OPIDN have been reported, often resulting from the contamination of beverages or cooking oil with TOCP. The subject has been reviewed by Abou-Donia (*356,357*) and Zech and Chemnitius (*358*). During the twentieth century, thousands of people were paralysed by this form of organophosphate poisoning. In an epidemic in the USA during the 1930s Prohibition Era, as many as 50,000 men in the American South and Midwest developed arm and leg weakness and pain after drinking a patent medicine containing alcohol called 'Ginger Jake'. This contained an adulterated Jamaican ginger extract containing TOCP, which produced neurologic damage, often resulting in a characteristic limping gait ('Jake Walk', 'Jake Leg' or 'Jake Foot') (*359,360*). TOCP was also involved in the development of over 10,000 cases of OPIDN in Morocco in 1959. In this incident, imported cooking oil was found to be contaminated with high levels of TOCP. There were at least 16 other occurrences of OPIDN involving TOCP between 1925 and 1988. Worldwide, tens of thousands of people are thought to have been involved in these incidents (*359,361*). The insecticide methamidophos has been the most frequently reported cause of OPIDN in more recent years (*362,363*).

OPIDN is caused by phosphorylation and subsequent 'aging' (partial dealkylation) of neurotoxic esterase (NTE, EC 3.1.1.5) (*364,365*). The great majority of experimental studies on OPIDN have used adult chickens as a susceptible animal model. Chicken brain homogenates contain several esterases, which hydrolyse simple phenolic ester substrates, such as phenyl valerate (PV, PhOC(O)Bu-*n*) (*354*). NTE was originally identified by its ability to bind a radiolabelled OP inhibitor and to hydrolyse a (nonphysiological) ester substrate (*365,366*) and was defined empirically by Johnson (*364*) as the PV-hydrolysing esterase that is resistant to 40 μM paraoxon (E 600, a non-neuropathic OP pesticide) but is inactivated by 50 μM mipafox (a neuropathic OP pesticide). This definition forms the basis of an internationally accepted assay for NTE activity that can be used to screen OP compounds for neuropathic potential (*364,367*). An additional fraction of PV-hydrolysing activity is resistant to paraoxon and mipafox, but is largely inactivated by 50 μM diisopropyl phosphorofluoridate (DFP).

Inhibition of >70% of enzyme activity in brain is necessary to produce neuropathy in experimental hens (*367,368*). Johnson (*369*) showed that inhibition by OP compounds of NTE's esteratic activity did not itself initiate neuropathy; the latter required a rapid secondary intramolecular change in the neutrally charged covalently bound OP species, which left a negatively charged derivative of the OP compound attached to the active-site serine of NTE (*370–372*). This second step is essential for initiating the events which lead, much later, to axonal degeneration.

NTE activity was firmly associated with the membrane fractions of brain homogenates (*373*) and after covalent reaction with [^{3}H]DFP was shown to migrate on SDS-PAGE as a 155-kDa radiolabelled polypeptide (*374*). NTE was finally purified to homogeneity by using S9B (1-(saligenin cyclic phospho)-9-biotinyldiaminononane), a biotinylated OP compound that could be used for selective labelling of the active-site serine of NTE, and affinity purification by avidin—sepharose chromatography (*375*). These early studies have been reviewed by Glynn (*376*) and Johnson (*377*).

The cDNA for NTE has since been cloned (*367,372*) and this led to the generation of NTE-knock-out mice, which die by mid-gestation due to failed placenta formation, showing that global NTE deficiency is embryonically lethal (*378*); in particular, NTE is essential for formation of the labyrinth layer and for survival of the secondary giant cells of the placenta, but it is not required for cell division in the early embryo (*379*). Subsequently, mice were generated with a brain-specific deletion of NTE that survived beyond gestation. From about 6 weeks of age, the brains of these mice show signs of progressive neurodegeneration with disruption of the endoplasmic reticulum (ER), loss of neurons and spongiform vacuolation although, even by 5 months of age, neurological signs are quite mild with only moderate impairment of motor coordination (*380*).

NTE has been identified as patatin-like phospholipase domain containing protein 6 (PNPLA6) (*381*), which is an essential lysophospholipase in the brain (*382*). In humans, mutations near the catalytic site of NTE were found to cause the severe NTE-related motor neuron disease, which is characterised by progressive spastic paraplegia and distal muscle wasting (*383*). Thus, the lysophospholipase activity of NTE has a critical function in maintaining axonal integrity across species. NTE is not required by dividing cells, but is needed for survival of postmitotic cells such as placental secondary giant cells and brain neurons (*367*).

NTE is now known to play a crucial role in neuronal phospholipid deacylation, which is essential for axonal and synaptic integrity (*384*). The phospholipase-B activity of NTE reduces levels of phosphatidylcholine in the brain by degrading it to soluble products: glycerophosphocholine and two free fatty acids. The physiological substrate for NTE may be nascent phosphatidylcholine complexed with a phospholipid-binding protein (*384*). NTE-mediated phosphatidylcholine homeostasis facilitates membrane trafficking and export of materials from the neuronal soma. The main site of NTE activity is at the cytoplasmic face of neuronal ER, but it can also be detected in axons, where local phosphatidylcholine homeostasis is probably essential for efficient vesicular transport within the axon. Thus, NTE appears to be critical for the integrity of axon terminals in the spinal cord and hippocampus. Brain neurons and glia in *Drosophila* NTE-null mutants accumulate phosphatidylcholine, leading to abnormal membrane structures and finally cell death. In the nervous system of susceptible vertebrates, neuropathic OP compounds cause a transient loss of NTE activity, putatively disrupting membrane phospholipid homeostasis and ER functions including axonal transport and glial—axonal interaction: the distal parts of long axons are particularly vulnerable to a loss of these support functions (*367*). For maintenance of peripheral nerve axons, calcium-independent phospholipase A2-beta (iPLA2β) activity may be able to compensate for NTE deficiency but not vice versa (*384*).

1.10.3 Treatment of OP poisoning

Postexposure treatment for OP pesticides and nerve agents is essentially the same: a muscarinic receptor antagonist (usually atropine) combined with an oxime reactivator of OP-inhibited cholinesterase such as pralidoxime or obidoxime (*385–387*) (Fig. 1.10.3.1). A benzodiazepine anticonvulsant (usually diazepam) is the treatment currently indicated for control of seizures (*385,388–390*). Because nerve agents act so rapidly, military therapeutic approaches are based on immediate self or 'buddy' aid using autoinjection devices. In contrast, effective treatment of pesticide poisoning may be delayed because the range of nicotinic and muscarinic signs and symptoms is often incomplete, and may mimic a variety of other conditions, particularly in children (*314*).

For military medical countermeasures against the nerve agent poisoning (Fig. 1.10.3.2), the drugs are incorporated into autoinjection devices for immediate use by a casualty or a buddy (*297,390*). The benzodiazepine may be contained in a separate autoinjector or incorporated into the same device as the atropine and oxime. In the latter case, a water-soluble prodrug, avizafone, is used. This is a lysine conjugate of diazepam, which is rapidly hydrolysed in the body to release the active drug (*391–397*). Given sufficient warning, the therapy can be supported by a pretreatment using a reversible carbamate AChE inhibitor (pyridostigmine) – the aim being to shield a proportion of AChE from irreversible inhibition by nerve agents (*390*). In fact, however, in all recently reported exposures (which have involved civilian casualties), treatment – and usually diagnosis – of nerve agent poisoning has been delayed (*275,318*), resulting in a situation similar to that faced with pesticide poisoning (*397*).

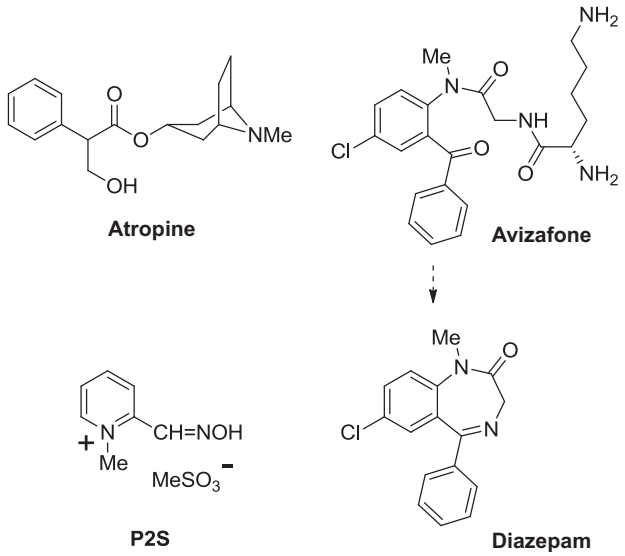


Figure 1.10.3.1 Drugs commonly used to treat OP poisoning. P2S is also known as pralidoxime mesylate. Avizafone is a water-soluble prodrug, which is rapidly converted to diazepam in the body.

Figure 1.10.3.2 Nerve agent medical countermeasures available to the UK Armed Forces. Left: the Combopen® autoinjector, which contains atropine, avizafone and P2S for intramuscular injection (centre). Right: the nerve agent pretreatment set (NAPS), which contains pyridostigime. (For a colour version of this figure the reader is referred to the online version of this book.)

It is not yet possible to establish the efficacy of most treatments for OP poisoning due to the lack of evidence-based data (*301,312,398*). Most research into treatments for OP poisoning is directed at chemical warfare agents such as sarin and VX (*397*) and is based around immediate first aid, whereas the vast majority of poisonings are due to pesticides, treatment of which is usually dependent on survival to hospital presentation (*271*). Some of the mainstay treatments were introduced long before it became mandatory to conduct controlled trials, and what is known about these treatments comes largely from animal studies and clinical experience (*301,312*).

1.10.3.1 Antimuscarinic drugs

Muscarinic antagonists (antimuscarinics) are competitive antagonists of ACh at muscarinic receptors. The best-known member of this group of drugs is atropine (Fig. 1.10.3.1), a naturally occurring tertiary amine, which was first isolated from the deadly nightshade plant (*Atropa belladonna*) by H. F. G. Mein in 1831 (*399*). Atropine is a specific antidote for the treatment of poisoning with OP and carbamate insecticides and OP nerve agents, acting by competitively blocking the action of excess ACh at muscarinic receptors, and is also used in resuscitation, anaesthesia and ophthalmology. While the effectiveness of oximes in human OP pesticide poisoning is still debated (*275,325,400,401*), atropine is regarded as the mainstay for treatment of OP poisoning.

Atropine is the drug of choice for the treatment of the muscarinic symptoms and signs of poisoning by anticholinesterase agents (OP or carbamate), particularly excessive salivation and lacrimation, bronchoconstriction and hypersecretion, pulmonary oedema and bradycardia. Animal studies have shown that atropine alone significantly reduces mortality and counteracts features of toxicity due to most anticholinesterase insecticides. In several clinical case reports, the administration of atropine is clearly associated with a reduction of cholinergic features and a favourable outcome (*402*).

The first recorded use of atropine as an antidote for AChE inhibition was by T. R. Fraser in 1870 (*403,404*), who used atropine to counteract the effect of a carbamate, physostigmine, on the pupil. Since then, the clinical efficacy of atropine in OP poisoning has been well established (*304,402,405–407*), although no controlled prospective studies have been published. Evaluation of

the efficacy of atropine is based mainly on case reports and retrospective case studies (*402*). Noncontrolled (i.e. all patients received atropine) clinical studies of OP-poisoned patients have consistently described beneficial effects of giving atropine (*400,408,409*).

Although other antimuscarinic agents may have advantages in animal models, none has been evaluated by high-quality randomised clinical trials (RCTs) and the role of atropine in the treatment of OP poisoning is essentially unchallenged; however, there has been controversy concerning the dose of atropine necessary for optimal therapy in OP poisoning (*402,409*). Overatropinisation may result in serious adverse effects (*409*), but few serious side effects are encountered in OP poisoning if the dose of atropine is titrated correctly; however, patients who are hypoxic (a frequent consequence of OP poisoning) are at risk of developing ventricular tachycardia or fibrillation if given atropine. It is important, therefore, to correct hypoxia by clearing airways, administering oxygen and, if necessary, mechanically ventilating the patient before giving atropine (*402*).

A monograph on the use of atropine in OP poisoning recommends giving atropine intravenously as bolus injections to dry the secretions as quickly as possible (*402*). In adults with unknown or mild poisoning, this requires a dose of 1–2 mg repeated every 5–10 min until the desired clinical response is achieved. In cases of severe OP poisoning, atropine must be given at much higher doses to dry the secretions. Atropine may then be repeated or increased in increments at 15–30 min intervals to maintain the signs of atropinisation. Since repeated dosing is required, a constant infusion of atropine to maintain atropinisation is more practical.

For diagnosis in children, an intravenous dose of 0.015 mg/kg can be administered, while watching for signs of atropinisation (mouth dryness, dilated pupils, tachycardia). For a therapeutic intravenous dose in symptomatic children, 0.015–0.05 mg/kg can be given every 15 min as needed (*402*).

A recent study in 34 patients with a severe OP pesticide poisoning suggested that, following initial atropinisation, the maintenance dosage of atropine can be usually kept low at 0.005 mg/kg/h and that doses of more than 0.06 mg/kg/h are only required when the RBC–AChE is completely inhibited (*409*). Effective reactivation of the enzyme was found greatly to reduce the atropine demand. If arrhythmia occurs and the plasma level of the pharmacologically active enantiomer of atropine (*S*-hyoscyamine) is low (<2.5 nmol/l), patients may benefit from further atropine therapy.

There are far fewer reports of the clinical use of atropine for poisoning by OP nerve agents, and those that are available tend to concentrate on the treatment given rather than the clinical outcome. Sarin was used in two terrorist incidents in Japan, at Matsumoto in 1994 and in the Tokyo subway in 1995 (*284*). Following the Matsumoto incident, severely affected subjects with loss of consciousness and generalised seizures recovered promptly after treatment with atropine sulfate, benzodiazepines, intravenous fluids and other systematic therapies (*284*). Muscarinic symptoms were reported to be generally resistant to treatment and atropine sulfate was used in large amounts. Victims of the later incident in the Tokyo subway in 1995 were assessed for serum cholinesterase (ChE) and RBC AChE levels before treatment with atropine sulfate or oximes (*284*). In severely affected patients in both incidents, consciousness recovered gradually within several hours after atropine sulfate, oximes, diazepam, intravenous fluid infusion and respiratory support were provided (*284,287,410*).

The only first-hand descriptions of battlefield nerve agent casualties in the world literature are available in a series of Farsi language articles published by Dr. Syed Abbas Foroutan, who ran an Iranian chemical casualty aid station during the war with Iraq and treated casualties of tabun and sarin poisoning. These articles have been reviewed by Col. Jonathan Newmark (*276*). There were between 45,000 and 100,000 Iranian chemical casualties in the war with Iraq, of which the majority were apparently caused by nerve agents (*282*). Iranian soldiers were each issued with three autoinjectors containing only atropine for intramuscular use. Further atropine, and some obidoxime, was available at the aid station for intravenous use. Due to limited supplies of oxime, Foroutan relied extensively and, at times, almost exclusively, on atropine to save patients. He titrated the atropine dose to the respiratory status of the patients: for patients with severe poisoning, he used 20–200 mg, commenting that there was a trade-off between over-atropinisation and insufficiently rapid atropinisation. Unfortunately, no data are included in Newmark's review regarding the clinical outcomes of treatment, although the discussion implies that this must have been successful.

1.10.3.2 Oximes

Oximes, such as pralidoxime and obidoxime chloride (toxogonin), can reactivate AChE, thus attempting a reversal of the pathological biochemical mechanism in addition to symptomatic relief in the poisoned patients. Oximes are especially useful for treating the nicotinic effects, for which atropine alone is ineffective (*333*). These compounds consist of an oxime moiety (–CH=NOH) attached to a quaternary nitrogen pyridinium ring and are able to reactivate OP-inhibited AChE by dephosphylating the enzyme active site (*411*). The quaternary nitrogen directs the antidote molecule to the proper location at the enzyme active site by interacting with a nearby anionic subsite. Reactivation occurs through nucleophilic attack by the oxime on the phosphorus atom, producing a phosphylated oxime (*412*) that leaves the active site, thus restoring normal enzymatic activity.

Some OP compounds produce enzyme–inhibitor complexes that are resistant to reactivation by oximes. Furthermore, the enzyme–inhibitor complex can undergo a dealkylation reaction, called aging, which results in an inhibited enzyme that resists nucleophilic attack. The half-time for this aging reaction ranges from approximately 2 min for the nerve agent soman to 72 h for some insecticides (*312*). Thus, each oxime has a characteristic profile of activity against different OP anticholinesterases and no single oxime has yet been found that is effective against all OP AChE inhibitors.

A substantial effort on medical therapies towards OP poisoning (largely in the military context) has focused for more than 50 years on identifying an ideal reactivator that is effective against all OP agents of concern: for example, Hagedorn and co-workers synthesised 500–700 oxime variations for in vivo evaluation in mice (*413*). Some of the most important compounds to emerge from this research are shown in Fig. 1.10.3.2.1. The basic structures are similar, differing only in the number of pyridinium rings (mono or bis) and the position of the oxime group on the pyridinium ring. As well as reactivating efficacy, an important property is the stability of the oxime in aqueous solution because of the necessity of storage in advance of possible clinical use. Pralidoxime, obidoxime and methoxime are relatively stable in water and can be stored in aqueous solution (*414*). HI-6 and HLö-7 are unstable in water and must be stored in solid form, such as a lyophilised powder (*415,416*).

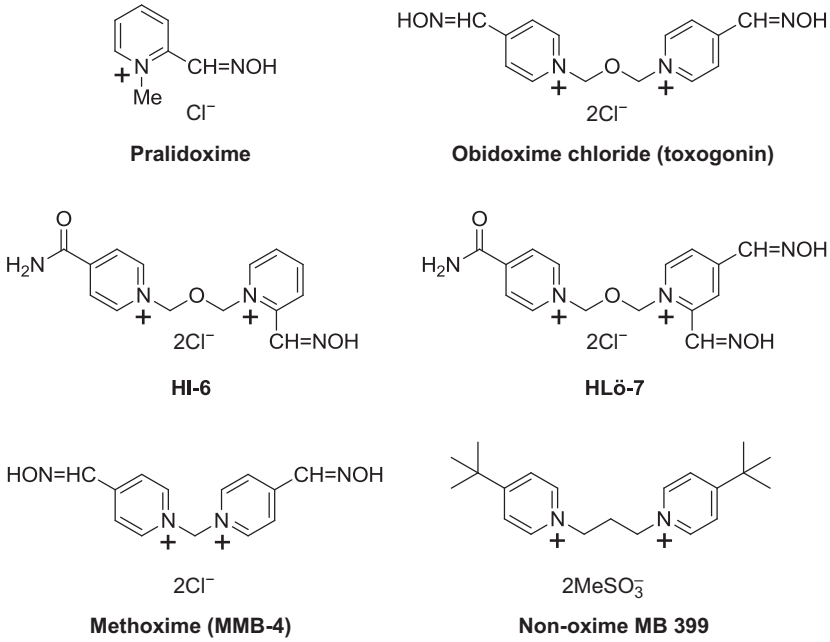


Figure 1.10.3.2.1 Structures of some important oximes and the non-oxime MB 399.

According to an early study on P2S (pralidoxime mesylate), plasma concentrations of about 4 μg/ml (2×10^{-5} M) were needed to counteract the toxic effects of the sarin derivative 37 S-N^+ (isopropyl methylphosphonyl thiocholine) in anaesthetised cats, measured as neuromuscular block, bradycardia, hypotension and respiratory failure (*417*). In many subsequent studies, this has been assumed to be the minimum effective antidotal plasma concentration in man of any oxime, regardless of its molecular weight or the OP AChE inhibitor being treated (*418*). Some studies, however, have disputed this plasma concentration as the presumed threshold of effectiveness in counteracting the toxic effects of OP poisoning. For example, Shiloff and Clement reported that an HI-6 plasma concentration of only 0.72 μg/ml, or a pralidoxime plasma concentration of only 2.56 μg/ml, was required to protect 50% of rats against a subsequent dose of sarin three times the LD_{50} when followed immediately by atropine. On the other hand, an obidoxime plasma concentration of 9.05 μg/ml was needed for comparable effectiveness in the same experiment (*419*). The threshold dose suggested by Sundwall (*417*) is unlikely to be valid in all cases and this assumption should therefore be re-evaluated.

The most widely used oxime is pralidoxime (*301,401*). In some countries, such as Israel, obidoxime chloride (toxogonin) and other oxime salts are available, but a thorough comparison between the different oximes in terms of clinical effect and outcome has not been performed (*312*). The WHO has published a recommendation to use oximes to treat all symptomatic patients who need atropine (*301*). To ensure a therapeutic concentration, a loading dose of pralidoxime chloride or obidoxime is recommended, followed by a continuous infusion. The loading dose of oxime should not

be given rapidly as a bolus because this method causes vomiting (risking aspiration), tachycardia and diastolic hypertension (*386*).

A recent review found seven RCTs of pralidoxime (*401*). Three RCTs including 366 patients studied pralidoxime versus placebo and four RCTs including 479 patients compared two or more different doses. These trials found quite disparate results, with treatment effects ranging from benefit to harm; however, many studies did not consider several issues important for outcomes. In particular, baseline characteristics were not balanced, oxime doses varied widely, there were substantial delays to treatment, and the type of OP poison was not taken into account.

Only one RCT compared the WHO-recommended doses with placebo (*420*). This trial showed no clinical benefits and a (statistically nonsignificant) trend towards harm in all subgroups, despite clear evidence that these doses reactivated AChE in the blood. Serious adverse effects occurring from pralidoxime were not clinically apparent. However, this study did not include the full number of patients originally planned. Discussion of the results of an earlier RCT (*421*), which suggested marked benefit from pralidoxime, resulted in loss of equipoise (the perception of treatments being of equal value) by clinicians, a fall-off in recruitment, and early termination of the trial (*420*). As a result, only 235 subjects were included in the study, well below the 1500 originally planned, and the sample size was thus much smaller than that calculated to have the planned statistical power to detect whether pralidoxime reduced the case fatality in symptomatic patients from 25% to 19% (two-sided significance level of 5%, power of 80%).

The authors of the review concluded that the current evidence is insufficient to indicate whether oximes are harmful or beneficial, and that the WHO-recommended regimen (30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/h infusion) is not supported by existing evidence (*401*). This result is surprising because oximes have been shown to effectively reactivate inhibited AChE, the widely accepted target of organophosphate toxicity (*386*). Most clinical studies have focused on clinical outcomes and duration of intensive care, but have generally lacked analytical identification of the causative poison and differentiation of outcomes according to the precise type of OP inhibitor. Only a few studies have aimed at assessing the course of the ChE status (*422*), of neuromuscular function and of OP inhibitor concentration in blood, and hardly any have controlled adherence to the oxime and atropine protocols and determined their plasma concentrations during the whole course of therapy (*422–425*).

Buckley et al. concluded that further RCTs are required to examine other strategies and regimens for oxime dosing (*401*). For example, it is possible that the maximum benefit from oximes occurs early on in the course of poisoning (animal studies generally involve only a short-term use of oximes). Since clinical effectiveness and required doses may depend on the type of OP compound, the authors made a number of recommendations for future studies, including that they should: screen specifically for patient subgroups that may benefit from oximes; explore different doses or incorporate flexible dosing strategies; stratify randomisation by baseline severity, time to presentation and class of OP pesticide taken (diethyl or dimethyl); be registered and use predefined subgroup hypotheses; measure the RBC–AChE activity and the potential for ex vivo reactivation (because of the importance of resistance and aging in determining the usefulness of oxime).

Worek et al. (*426*) considered that the determination of AChE and BChE activities in the whole blood and plasma, respectively, is a rapid, convenient and cheap screening method to establish

exposure to OP inhibitors, and may be a valuable tool for monitoring and optimisation of therapeutic use of oximes. This assumption is supported by clinical data from OP pesticide-poisoned patients (*427,428*). The repeated analysis of the ChE status, i.e. determination of the AChE and BChE activities, the reactivatability of AChE after incubation of patient's whole blood dilution with an oxime and the inhibitory activity of patient's plasma tested by incubation with donor AChE, provided meaningful parameters for the optimisation of antidotal treatment using oximes. In this respect, erythrocyte AChE proved to be a far more reliable parameter than BChE for the assessment of antidotal efficacy (*426*).

A clinical study of the effectiveness of obidoxime in 34 atropinised patients with severe parathion, oxydemeton-methyl and dimethoate self-poisoning found that the patients poisoned with parathion responded promptly to obidoxime (250 mg bolus followed by continuous infusion at 750 mg/day up to 1 week), as shown by improvement of neuromuscular transmission and increased AChE activity (*429*). The effects were transient only in cases with the other two poisons. The authors concluded that obidoxime appeared to be safe and reactivated AChE in parathion poisoning. There was a close correlation between the RBC−AChE activity and neuromuscular transmission (measured by ulnar nerve stimulation) in these patients (*430*). Atropine requirement of the patients was low (<0.01 mg/kg/h) when RBC−AChE was >10% but grew rapidly at RBC−AChE <10%. A steady-state plasma concentration of 11.4 μmol/l for a 70 kg person was targeted, using the kinetic parameters obtained in healthy volunteers. Substantial reactivation was achieved in 13 out of 14 patients poisoned with parathion (an *O,O′*-diethyl organophosphate) and was sustained in 10 of these patients. In contrast, obidoxime was found to be of little sustained benefit in most cases of *O,O′*-dimethyl OP poisoning, due to fast aging.

As is the case for atropine, there are very limited reports of the use of oximes in victims of nerve agent poisoning. Reports of the Matsumoto incident in Japan do not discuss the use of oximes; however, pralidoxime methiodide (PAM) was used in the Tokyo incident and was reported to be effective. It reversed serum ChE levels and miosis quickly if administered within 6 h of sarin inhalation; respiratory distress was also alleviated as the serum ChE level recovered (*284,410*).

For the Iranian tabun and sarin casualties, no oxime was available for immediate first aid, but small quantities of obidoxime were available at the aid station for intravenous administration (*276*). Since supplies were limited, use of the oxime was reserved for patients in critical condition and was restricted to emergency units and field hospitals. Although no data on clinical outcomes are provided, it is implied in the English language review of Foroutan's articles (in Farsi) that the treatment was successful: in patients who received oxime, 'reaction was generally immediate and complete' (*276*).

1.10.3.3 Anticonvulsants

Electrographic seizures are a feature of anticholinesterase intoxication (*388*). The seizures can rapidly progress to status epilepticus, contributing to mortality and, in the case of survivors, to neuronal damage and neurological impairment (*431*). Animal studies have indicated that only the early phase of seizure activity (0−5 min after seizure onset) is purely cholinergic, predominantly involving muscarinic mechanisms (*432*). Seizure activity subsequently progresses through a transitional phase of mixed cholinergic and noncholinergic modulation (5−40 min) into a final noncholinergic phase.

The neuropathology caused by the seizures is most likely to be associated with glutamatergic excitotoxicity (*433–435*). For a recent review of seizure mechanisms in OP poisoning, see Tattersall (*388*).

It is important to differentiate between 'seizures', the abnormal electrical activity of the brain, and 'convulsions', which are the outward manifestation of the electrical seizure activity. Many reports of OP poisoning in humans have relied on motor convulsions as the indicator of seizure activity; however, convulsions will only be observed if the electrographic seizure activity in the brain results in propagated electrical signals reaching the motor nerves and causing muscle stimulation. In many cases, 'silent' seizures can occur, in which the abnormal electrical activity remains confined to the CNS and does not cause muscle contraction. This is of particular concern in OP poisoning, in which one of the characteristic effects is flaccid paralysis, which can mask convulsions. The presence or absence of convulsions is therefore an unreliable indicator of seizures, which should be suspected in all cases presenting signs of severe CNS poisoning. The most reliable indicator of seizure activity is the electroencephalogram (EEG), but this has not been widely used in clinical studies.

Treatment with appropriate anticonvulsant drugs can significantly reduce the lethal and toxic effects of OP anticholinesterases; however, OP-induced seizures differ from other forms of status epilepticus in their response to anticonvulsant drugs (*282,436–438*). Animal experiments show that many common anticonvulsants, including carbamazepine, phenytoin, phenobarbital, lamotrigine or valproic acid, are ineffective against nerve agent-induced seizures (*439–442*). This may be due to the wide anatomic distribution of the cholinergic system within the brain, which could limit the effectiveness of drugs that depend on reducing the spread of seizure activity (*282,436–438*). Antimuscarinic drugs show anticonvulsant activity in animal models of nerve agent-induced seizures, but only during the cholinergic phase of seizures (~20 min), becoming ineffective as other neurotransmitter systems are recruited (*443,444*).

Benzodiazepines such as diazepam (Fig. 1.10.3.3.1) are the recommended anticonvulsants for patients presenting with seizures and other CNS symptoms (*301,385,445–450*). Studies in humans are lacking; however a review of clinical evidence (*301*) found no RCTs comparing a benzodiazepine with a placebo or another anticonvulsant, but concluded that there is sufficient evidence for efficacy that it would in fact be unethical to conduct a trial comparing a benzodiazepine with a placebo (*451*); see also (*452*).

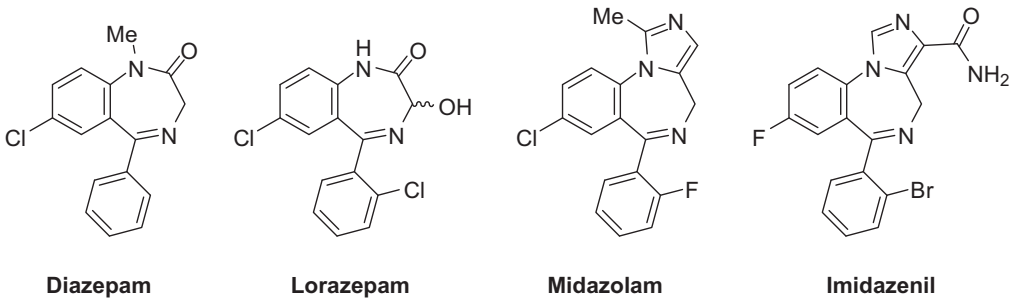


Figure 1.10.3.3.1 Some benzodiazepine anticonvulsants effective against OP poisoning. These all modulate $GABA_A$ receptors to enhance synaptic inhibition in the brain.

In the hospital setting, diazepam is recommended at initial doses of 5–10 mg intravenously for seizure control (*449,453*). It has been recommended that diazepam should be administered following all severe exposures, even in the absence of convulsions, in case nonconvulsive seizures are present (*453*). Alternative benzodiazepines include lorazepam and midazolam (*453*). These drugs act by modulating gamma-aminobutyric acid subtype A ($GABA_A$) receptor function to enhance synaptic inhibition in the brain (*454–456*). In the treatment of OP pesticide poisoning, diazepam (10 mg given by slow intravenous injection, repeated as necessary in an adult, up to 30–40 mg/24 h) is also recommended for sedation of agitated patients (*448*).

Due to the possibility that diazepam and other benzodiazepines may exacerbate OP-induced respiratory depression (*457*), it has been recommended that a patient's airway and mental status should be monitored carefully with this therapy (*458*); however, animal studies have suggested that diazepam can actually inhibit OP-induced central respiratory depression (*459*) as well as reducing neural damage (*460*).

A study of a range of benzodiazepines against soman in guinea pigs showed that midazolam stopped seizures most rapidly and at the lowest blood concentration (*443*). Nasally administered midazolam has been demonstrated to terminate seizure activity and prevent brain lesions and behavioural deficiencies in rats (*461*) and guinea pigs (*462*) poisoned with sarin. In Israel, the military changed its fielded benzodiazepine to midazolam in 2003 (*282,436–438,463*). An earlier retrospective study of 19,112 hospital in-patients who received injectable midazolam or diazepam found no increased risk of death for midazolam compared to diazepam for endoscopic, conscious sedative and general anaesthetic procedures (*464*). In fact, the overall death rate was significantly lower for midazolam than for diazepam (0.76% versus 1.93%, $p < 0.01$): this difference remained statistically significant after adjusting for age, sex, co-morbidity diagnosis, concomitant drug use, type of medical procedure and hospital size and teaching capability.

In his account of the treatment of Iranian casualties, Foroutan did not describe the incidence of seizures in these patients, but he did report using diazepam as an anticonvulsant as well as a muscle relaxant (*276*). He encountered a few patients who went into 'spastic stage' while recovering from severe sarin poisoning and speculated that this might be from central effects of the agent rather than from peripheral cholinergic effects. Since he did not mention using EEG to check these patients, the alternative explanation of nonconvulsive seizures remains a possibility.

Diazepam was used to treat victims of both the Matsumoto and Tokyo sarin attacks (*284*). A combination of atropine sulfate, oxime, diazepam, intravenous fluid infusion and respiratory support was successful in recovering consciousness in severely affected patients (*284,287,410*). It is difficult to dissect out the contribution of each individual component of this approach; however, one critically affected patient in Tokyo, who remained in a deep coma after spontaneous recovery of heart beat, was reported to show generalised convulsions that were controlled by intravenous diazepam (*284*). Two other patients had generalised convulsions, consciousness disturbance and respiratory failure. After diazepam and mechanical ventilation, both recovered quickly and were discharged 3 and 5 days later (*284*).

1.10.3.4 Carbamate pretreatment

In the case of OP inhibitors such as soman that undergo rapid aging, oxime treatment offers little advantage because AChE becomes refractory to reactivation within several minutes of exposure (*465,466*). To overcome this problem, military medical countermeasures have included a pretreatment approach. Given sufficient warning of potential exposure to such agents, a useful strategy is to protect a proportion of AChE from irreversible inhibition by pretreatment with reversible inhibitors such as the carbamate pyridostigmine bromide (PB) (*390,467–470*). Pretreatment by PB is feasible because of a large excess of AChE at cholinergic synapses, the relatively rapid rate of decarbamylation of PB-inhibited AChE and the ability of the organism to survive for brief periods with significant AChE inhibition (*470,471*). Although the pretreatment alone gives no protection, it has been shown to be effective in protecting against soman toxicity when followed by conventional therapy and to increase the AChE activity in diaphragm muscle in marmosets following soman poisoning and treatment with atropine and oxime (*472*). This would indicate that atropine is required to counteract the initial cholinergic crisis whilst decarbamylation occurs to regenerate the protected enzyme activity. Importantly for the military use of the pretreatment, protection occurs at doses of pyridostigmine that produce minimal signs of AChE inhibition (*473*).

1.10.4 Future treatments

As discussed earlier, the majority of studies to improve treatment of OP poisoning have been directed against nerve agents; relatively few studies have been carried out using pesticides. Due to the rarity of human cases of nerve agent poisoning, however, the study of antidotes for these compounds relies heavily on animal efficacy and safety data, and on pharmacokinetic studies in humans and animals; clinical data are largely lacking (*474*). In the absence of pretreatment, or in case of delayed diagnosis and treatment of nerve agent poisoning – as is likely to occur in a terrorist incident (*275,318*) – the situation may be considered to be similar to that faced with pesticide poisoning and the patients require much the same treatment as those poisoned with pesticides (*389*). This may be particularly true for percutaneous nerve agent poisoning, which leads to prolonged absorption of the OP compound. Much of the research on nerve agent antidotes is therefore relevant to OP pesticide poisoning; it has also been suggested that clinical trials in pesticide patients could benefit victims of both types of poisoning (*397*).

1.10.4.1 Antimuscarinics

Atropine is currently the antimuscarinic drug of choice for treatment of OP poisoning, with a long history of successful use, but animal studies have suggested that alternative antimuscarinics that have additional antagonistic activity at *N*-methyl-D-aspartate (NMDA) receptors (*475*), such as aprophen, azaprophen, benactyzine, biperiden, procyclidine and trihexyphenidyl (Fig. 1.10.4.1.1), are more effective in blocking OP-induced seizure activity (*391,432,476–479*). All of these compounds are antispasmodic and some (biperiden, procyclidine and trihexyphenidyl) are clinically used as anti-parkinsonian drugs (*432*). Biperiden and procyclidine have also been shown to prevent OP-induced seizures when given as pretreatments before DFP and soman (*480–483*). Egyptian troops in 1973

were reported to have been equipped with an antidote containing benactyzine (*484*), and benactyzine is a component of the Czech military pretreatment Panpal (*485*).

The antitussive drug caramiphen has been shown to protect against lethality, convulsions, electrographic seizure activity and brain damage in guinea pigs poisoned with soman (*486*). Two other antitussives, dextromethorphan and carbetapentane, were less effective against seizures and did not protect against the lethal effects of soman. The superior efficacy of caramiphen was attributed to its stronger anticholinergic properties, but it has since been suggested that its effects on NMDA receptors may be an important component of its protective efficacy (*487*). Thus, it appears that drugs that combine anticholinergic and antiglutamatergic properties have considerable potential as postexposure therapies against OP poisoning (*478*).

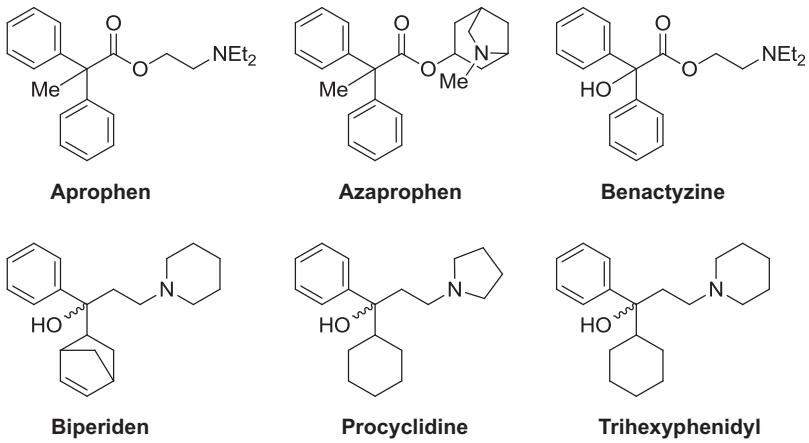


Figure 1.10.4.1.1 Some antimuscarinic drugs which also have antagonistic activity at NMDA receptors.

1.10.4.2 Oximes

There is no single, broad-spectrum oxime suitable for the antidotal treatment of poisoning with all OP agents. If more than one oxime is available, the choice depends primarily on the identity of the OP compound (*411*). For example, pralidoxime is effective against sarin and VX, whilst obidoxime is more effective against tabun (*411*). The Hagedorn oximes, such as HI-6 and HLö-7, emerged from the search for reactivators with a greater spectrum of activity, particularly against soman (*411*). HI-6 is currently fielded by some nations (e.g. Sweden) as a nerve agent antidote and is in development in the UK, Canada, Netherlands and France. A major consideration in this development is the requirement for a wet—dry autoinjector device, due to the poor stability of HI-6 in aqueous solution. Another bispyridinium oxime, methoxime (MMB-4), is currently in advanced development in the USA.

Currently available oximes are quaternary compounds that are poorly permeable through the blood—brain barrier and hence do not reactivate inhibited AChE in the CNS. Recent studies have

indicated that tertiary (nonquaternised) oximes can improve survival and prevent seizures if administered in high doses following nerve agent poisoning, and that this action is related to the reactivation of brain ChE (*488,489*). These studies show the benefit of centrally acting oximes, but the potency of these tertiary compounds is low and they are effective against a limited range of nerve agents (*490*). An alternative approach would be to increase the levels of oxime in the CNS by altering the penetration characteristics of the oxime or by influencing the properties of the blood–brain barrier. Recent studies have shown that administration of tariquidar, which inhibits the efflux transporter P-glycoprotein in the blood–brain barrier, to rats can result in a two-fold increase in the concentration of HI-6 in the brain, and that this leads to a comparable increase in ChE activity in the brain in rats pretreated with HI-6 and poisoned with soman (*490*). In vitro studies using primary porcine brain capillary endothelial cells as a model of the blood–brain barrier have demonstrated that human serum albumin nanoparticles can increase the transport of HI-6 by 1.5 to 2 times that of the free drug (*491*).

Despite these efforts, however, the reliance on oxime enzyme reactivators is a fundamental weakness in the search for an improved therapy. An ideal oxime would be capable of reactivating AChE inhibited by all OP compounds of concern. Despite this aspiration, researchers are no closer to discovering such an oxime, probably because it is unlikely to exist. Each AChE–OP complex differs chemically and some, after a period of time, undergo aging and cannot be reactivated. Whichever oxime is used will always be ineffective against one or more of the nerve agents, making a generic therapy based on this mechanism unlikely (*492*).

1.10.4.3 Antinicotinics

In contrast to the muscarinic effects of OP poisoning, which are directly treated by atropine, the nicotinic effects are treated indirectly, by the use of an oxime to reactivate inhibited AChE. As already discussed, however, currently available oximes have no broad-spectrum activity against structurally different OP anticholinesterases and it is highly unlikely that a generic therapy based on this mechanism will ever be discovered.

The effectiveness of an appropriate antinicotinic drug to treat the nicotinic effects of poisoning should be independent of the OP poison involved, in the same way as that of antimuscarinic drugs. Nicotinic antagonists are not currently used because it is very difficult to administer a dose of competitive nicotinic neuromuscular blocker sufficient to antagonise the effects of excessive ACh, but not so great that it paralyses the muscles (*493*).

An alternative approach would be to use a noncompetitive antagonist whose effects would not be overcome by increasing concentrations of ACh. Certain bispyridinium compounds, including some oximes, have a beneficial effect in OP poisoning through this type of action, which correlates with their ability to block the open ion channel of the nAChR (*494*). Open channel block, a form of noncompetitive antagonism, is attractive because the block is use-dependent: antagonism becomes greater as channel activation increases. This is the converse of what happens with a competitive antagonist and appears to be an ideal way of mitigating the effects of overstimulation of nAChRs.

A novel bispyridinium compound, 1,1′-(propane-1,3-diyl)*bis*(4-*tert*-butylpyridinium) di(methanesulphonate) (MB 399, Fig. 1.10.3.2.1), which blocks the open ion channel of the human muscle-type nAChR, has been synthesised and it has been demonstrated that this noncompetitive antagonism, as well as reversing the neuromuscular blocking action of the nerve agent soman in guinea pig and human muscle *in vitro*, can protect animals against poisoning by several nerve agents (tabun, soman or sarin) when used as part of a therapeutic drug combination (*495–497*). The results of these studies show that the nicotinic antagonist, unlike oximes, is effective against all three agents. Further studies are in progress in the authors' laboratory, including experiments to understand structure–activity relationships among related compounds.

1.10.4.4 Anticonvulsants

The efficacy of diazepam and other benzodiazepines against OP-induced seizures is well established, both clinically (*385*) and in animal studies (*498*); however, the depressant actions of benzodiazepines on central respiratory drive (*385,457*) are a potential cause for concern (but see (*459*)). Furthermore, some animal studies have suggested that OP-induced seizures can recur following apparently successful initial treatment with benzodiazepines (*499*). An effective anticonvulsant without the respiratory depressant effects would be a significant therapeutic improvement. Newer benzodiazepines, such as the partial agonist imidazenil (Fig. 1.10.3.3.1), may offer one possible solution. In mice and rats poisoned with DFP, imidazenil had comparable anticonvulsant efficacy to diazepam, but achieved this at doses 5 to 10 times lower than those that caused sedative and muscle relaxant effects (*500,501*).

The evidence for a key role of glutamatergic pathways in the later stages of OP-induced seizure activity, and in the subsequent neuropathology, has stimulated interest in antiglutamatergic drugs (Fig. 1.10.4.4.1) as potential therapies. Braitman and Sparenborg demonstrated the efficacy of the NMDA antagonist dizocilpine (MK-801) in attenuating or preventing soman-induced seizures in guinea pigs (*502*). Subsequent studies showed that treatment with MK-801 5 min after the onset of seizures prevented, arrested or reduced soman-induced seizure activity, convulsions and neuronal necrosis in a dose-dependent manner (*503,504*). Another NMDA antagonist, TCP (*N*-[l-(2-thienyl) cyclohexyl]piperidine, a thienyl analogue of phencyclidine), was also found to terminate soman-induced seizures in rats (*505,506*). The latency to seizure termination was shorter when TCP was given 30, 60 or 90 min after the seizure onset than when it was administered as a pretreatment or given 5 min after the seizure onset, a property that was also apparent with MK-801 and was consistent with the three-phase model (*503,507*).

NMDA antagonists have also been tested against the OP pesticide dichlorvos. Experiments in mice showed that both MK-801 and another NMDA antagonist, CPP (3-((*R,S*)-2-carboxypiperazin-4-yl) propyl-1-phosphonic acid), when administered alone, blocked convulsions induced by dichlorvos, but not by the carbamate physostigmine (*508*). When given together with atropine, both NMDA antagonists also increased protection against the lethal effects of dichlorvos, but not against physostigmine. The moderate affinity NMDA antagonist memantine has also been found to alleviate

dichlorvos toxicity in rats (*509*) and to protect against soman-induced seizures when given either prophylactically or 15 min after soman in that species (*510*). Memantine is approved by the US Food and Drug Administration and the European Medicines Agency for treatment of moderate-to-severe Alzheimer's disease.

Another noncompetitive NMDA antagonist gacyclidine (GK11), derived from phencyclidine, has been shown to prevent soman-induced seizures in cynomolgous monkeys when administered intravenously 30 or 45 min after soman (2 or $8 \times LD_{50}$) and to prevent the neuropathology observed 3 or 5 weeks later (*511–513*). Neuroprotection by gacyclidine was later demonstrated by magnetic resonance imaging in rats poisoned with soman (*514*). Gacyclidine underwent clinical trials for use in the treatment of acute spinal cord injury, but development was stopped because it failed to demonstrate a long-term benefit on neurological scores; however, there have been reports of the drug offering beneficial long-term effects in patients with traumatic brain injury (*515*).

There is also some evidence for the involvement of non-NMDA glutamate receptors in nerve agent-induced seizures (*516*). The AMPA (2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid) receptor antagonist NBQX (2,3-dihydroxy-6-nitro-7-sulphamoylbenzoquinoxaline) was found to block the neurotoxic effects of soman exposure in rats, although the animals experienced mild to moderate convulsions for around 90 min (*517*). When NBQX was given at the same time as soman, it blocked the seizure onset, and when given 5 min after the seizure onset, it greatly reduced the intensity of epileptic activity (*518*). Immediate treatment with atropine, followed by administration of NBQX and TCP at 5 or 50 min after the onset of soman-induced seizures, totally arrested seizure activity (*519*); if atropine treatment was delayed and given together with the other two drugs, then some epileptiform activity remained. These results suggest that AMPA receptor activation may be critical for the early propagation or maintenance of OP-induced seizure activity; however, a review by McDonough and Shih (*432*) reported unpublished data suggesting that NBQX and another AMPA antagonist, GYKI 52466, had minimal effects on soman-induced seizures in rats.

A later study of the relation between soman-induced neuropathology and subsequent spatial memory impairments in rats found that, without treatment, neuropathology and learning impairment were observed only in rats that experienced convulsions. When treatment consisting of atropine sulfate, and/or TCP and/or NBQX was administered to intoxicated animals, only treatment with all three drugs together was able to improve the different parameters of spatial learning, even though the doses given were too low to prevent convulsions of the animals (*520*). Although there is little information on the role of the metabotropic glutamate receptors in OP-induced seizures, one study has reported the involvement of these receptors in the inositol phosphate response after soman intoxication (*521*). Clearly, further work is needed to understand the roles of the different glutamate receptor subtypes in OP-induced seizures and neurotoxicity, and the therapeutic value of non-NMDA receptor blockade merits further investigation.

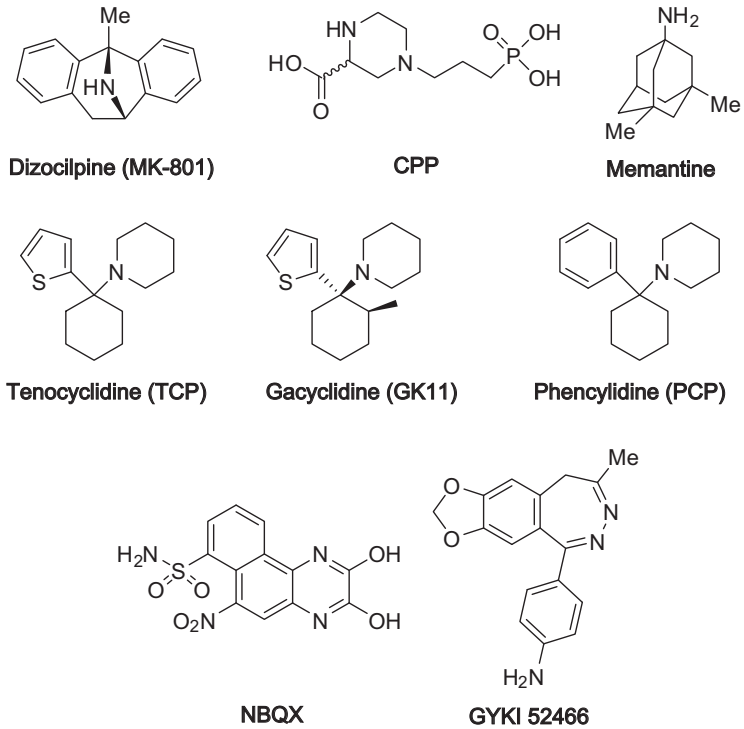


Figure 1.10.4.4.1 Some glutamate antagonists that have been tested against nerve agent poisoning.

1.10.4.5 Pretreatment with reversible AChE inhibitors

Pyridostigmine (Fig. 1.10.4.5.1) does not cross the blood–brain barrier and therefore does not protect AChE in the CNS (*522*). Physostigmine (eserine), a tertiary carbamate, does enter the CNS and, in combination with the antimuscarinic hyoscine (scopolamine), has been shown to provide better protection in animals against nerve agent poisoning than pyridostigmine (*523,524*) and to improve cognitive function (*525*). The faster elimination of physostigmine from the body requires a sustained release formulation to maintain the drug at effective plasma concentrations. A transdermal patch containing physostigmine and hyoscine (*526,527*) is currently in development for the UK Armed Forces.

Huperzine A, a selective and reversible inhibitor of AChE used in the treatment of Alzheimer's Disease, has also been shown to protect animals against nerve agent poisoning (*528,529*) and does not appear to have adverse behavioural effects (*530*). It also possesses a neuroprotective action through antagonism of NMDA receptors (*531*). Other drugs used for treatment of Alzheimer's Disease have been tested, including tacrine, donepezil, rivastigmine and galanthamine (structures not shown). Galanthamine, which is less toxic than huperzine and, as well as reversibly inhibiting AChE, is an

allosteric modulator of nicotinic receptors, has been demonstrated to protect guinea pigs challenged with 2 × LD_{50} of soman or sarin (*532*).

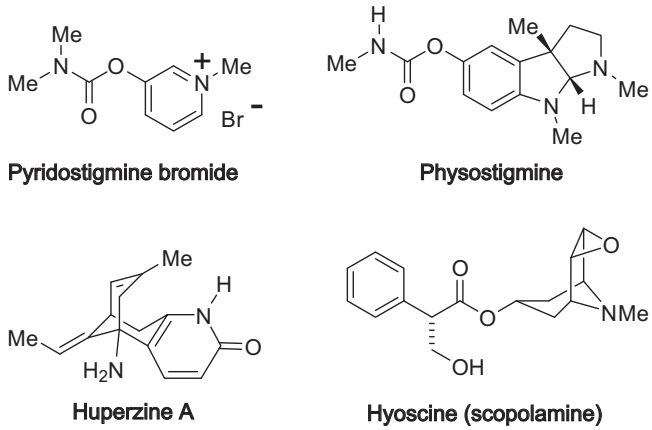


Figure 1.10.4.5.1 Some reversible AChE inhibitors that can be used as pretreatments to protect against the toxic effects of anticholinesterase agents.

1.10.4.6 Bioscavengers

The feasibility of using enzymes as bioscavengers for OP nerve agents has been studied for a number of years (*533–538*), the intention being to sequester the OP compound before it reaches its physiological targets and so prevent lethality and incapacitation (*539*). Significant advances have been made using ChEs and, of these, human butyrylcholineseterase (huBChE) has several advantages as an exogenously administered prophylactic for human use (*540*). It reacts rapidly with all highly toxic OP AChE inhibitors, offering a broad range of protection for nerve agents including soman, sarin, tabun and VX. It is readily absorbed from sites of injection and has a very long retention time in the human circulation. Finally, since the enzyme is from a human source, it should minimise the likelihood of any adverse immunological responses upon repeated administration to humans.

BChE purified from human plasma (huBuChE) (*541*) has been shown to provide significant protection against the lethal effects of nerve agents when administered as a pretreatment against a subcutaneous challenge of soman or VX (*535*) and against inhaled soman (*542*) or sarin vapour (*543*). This plasma-derived huBuChE has a long duration in the bloodstream and does not induce adverse or behavioural effects (*544*). More recently, it has been investigated as a postpoisoning therapy for percutaneous poisoning by the nerve agent VX (*545–548*).

Following percutaneous VX exposure, there is a slower rate of absorption, later onset and longer duration of signs of poisoning than for inhaled nerve agents (*549*). It has been shown that, following intramuscular administration to the guinea pig, the maximal plasma concentration of huBuChE was achieved at approximately 24 h with a long elimination half-time (65–75 h) (*535,550*). Given this protracted time profile, it was hypothesised that huBuChE may prove effective against percutaneous

nerve agent exposure. Treatment with huBuChE at 30 or 120 min following the percutaneous VX challenge (~2.5 LD_{50}) provided 100% protection from lethality; however, survival was greatly reduced when huBuChE administration was delayed until the onset of observable signs of poisoning (*547*). A subsequent study found that survival could be improved if huBuChE administration on signs of poisoning was combined with a single dose of conventional therapy (atropine, HI-6 and diazepam), which would not on its own have been effective (*545*).

From these studies, it appears that huBuChE may have utility both as a pretreatment and a post-exposure therapy for OP poisoning. Enzyme therapy for the prevention and treatment of poisoning depends on the availability of large amounts of ChEs. The enzyme used in most of these studies was isolated from human plasma that had exceeded its storage date for transfusion (*551*); however, since the amount of BuChE in human plasma is very low, its preparation is complicated and expensive. Possible alternatives are transgenic products such as Protexia™, a recombinant version of huBuChE from the milk of transgenic goats, developed by Nexia Biotechnologies, Canada (*552*). This required PEGylation to improve its pharmacokinetic properties, but this form has been shown to be effective in animal studies (*546*). Recombinant huBuChE has also been produced from other expression systems, including CHO cells (*553*), silkworm larvae (*554*) and plants (*555*).

In addition to enzymes like huBuChE that act solely as stoichiometric scavengers, a number of naturally occurring enzymes exist that are capable of catalysing the hydrolysis of OP nerve agents. Administration of a relatively small dose of a catalytic bioscavenger would be expected to provide better protection than a large dose of stoichiometric bioscavenger (*556*).

Mutation of human ChEs into OP-degrading enzymes has been attempted and more than 60 mutants of BuChE and AChE have been created (for reviews, see (*557,558*)). The first of these, the G117H mutant of BuChE (*559*), remains the most active, but its activity is too low to be of practical use. Future computational redesign based on the recently solved 3-D structure of this enzyme (*560*) may lead to more effective mutants (*522*). Monoclonal catalytic antibodies similarly lack sufficient catalytic activity and are too specific for certain nerve agents (*522*).

Several human enzymes with higher activity have been considered, including plasma paraoxonase-1 (PON1) (*561,562*). This enzyme hydrolyses numerous OP compounds at quite high rates (*563*) and intravenous administration has been shown to protect guinea pigs against sarin and soman (*564*). A 10- to 100-fold increase in its catalytic efficiency (k_{cat}/K_m) has been considered to be sufficient to afford protection against nerve agents (*522*). A knowledge of the 3-D structure and molecular dynamics of PON-1 would be required for computer-assisted design of more efficient mutants; an alternative approach would be directed evolution combined with high-throughput screening (*565*).

Phosphotriesterases from other species have been considered as potential bioscavengers, including squid (*Loligo vulgaris*) DFPase and several bacterial esterases (*522*). The phosphotriesterase from the bacterium *Pseudomonas diminuta* (*566*) has been shown to afford protection against soman lethality in mice and to protect against behavioural side effects (*567*), and to be effective against sarin, soman and VX poisoning (*568*). Encapsulation, PEGylation and other modifications may be required to improve immunocompatibility, stability and pharmacokinetic suitability of these nonhuman bioscavengers (*569*).

1.11 FLUOROGENIC NERVE AGENT MIMICS FOR SCREENING FOR IMPROVED BIOSCAVENGERS

Nerve agent mimics in which the fluoride or *N,N*-dialkylaminoethanethiolate leaving group of the nerve agent is replaced by a hydroxy-aromatic leaving group that upon hydrolysis produces a fluorescent signal are useful tools in the search for improved catalytic bioscavengers. Such nerve agent mimics are easily prepared by reaction of alkyl methylphosphonochloridates with the sodium salt of the aromatic alcohol, or the aromatic alcohol in the presence of triethylamine. For example, pinacolyl methylphosphonochloridate (**44**) can be derivatised with 3-chloro-4-methyl-7-hydroxycoumarin (*570*), 3-cyano-4-methyl-7-hydroxycoumarin (*571,572*) or 1,3-dichloro-7-hydroxy-9,9-dimethyl-9*H*-acridin-2-one (*571,572*) to provide the fluorogenic soman mimics (**45**—**47**) (Fig. 1.11.1). These compounds and close analogues (*573*) can be used to screen for bioscavengers, e.g. phosphotriesterase from the bacterium *P. diminuta* (*574,575*), mammalian serum paraxononase PON1 (*565,572,576*) or diisopropyl fluorophosphatase from the squid *L. vulgaris* (*577*). The nerve agent mimics are generally of lower acute toxicity than the parent nerve agents and safer to handle. Soman mimic **45** has been used to produce plasma carboxylesterase-knock-out mice for toxicity studies on nerve agents (*578*). The mimics (**45**—**47**) contain two chiral centres and are obtained as two diastereomers, hence their two ^{31}P NMR shifts.

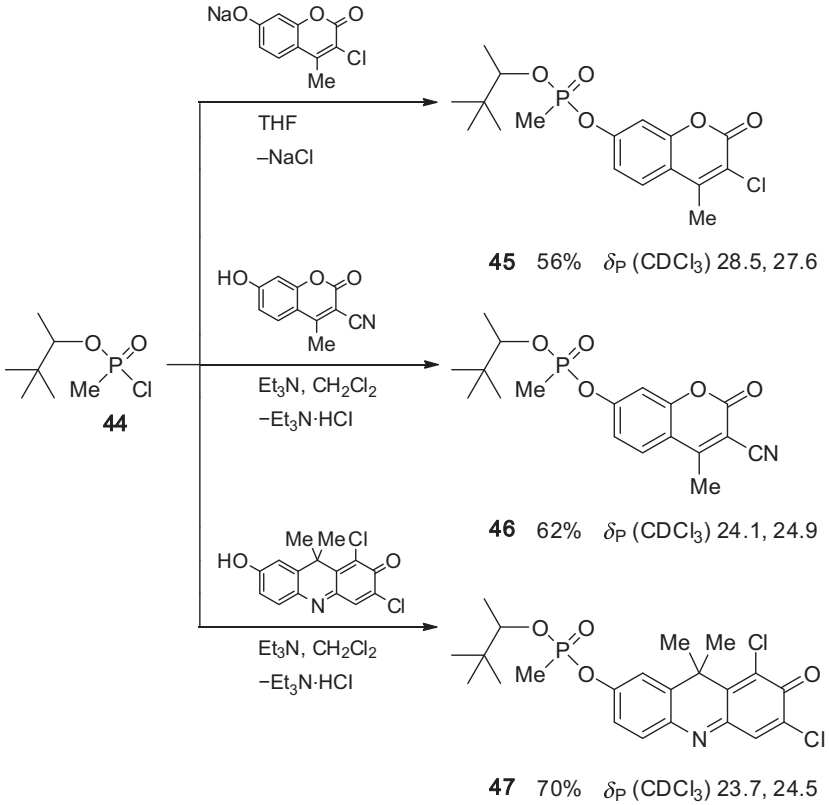


Figure 1.11.1 Synthesis of fluorogenic soman mimics used in enzyme studies.

Soman mimic **45** (*570*). A solution of 3-chloro-4-methyl-7-hydroxycoumarin (2.11 g, 10 mmol) in tetrahydrofuran (30 ml) was added dropwise to a stirred suspension of sodium hydride (0.24 g, 10 mmol) in tetrahydrofuran (20 ml). After addition, the mixture was heated under reflux for 30 min and then allowed to cool to room temperature. A solution of pinacolyl methylphosphonochloridate (1.99 g, 10 mmol) in tetrahydrofuran (5 ml) was added dropwise to the stirred sodium hydride suspension at 0–5 °C. After addition, the mixture was left at room temperature for 12 h. The solvent was removed to yield a liquid residue that was dissolved in chloroform (50 ml) and washed with 5% *w/v* aqueous potassium carbonate (100 ml). The aqueous layer instantly coloured yellow. The chloroform layer was separated and dried ($MgSO_4$). The drying agent was filtered off and the filtrate was concentrated to give a yellow liquid. Column chromatography on silica gel, eluting with chloroform, gave a solid product. Trituration of this with ether and drying gave the title compound as a white solid (2.09 g, 56%). Mp 97–98 °C. δ_P ($CDCl_3$) 28.5, 27.6 ppm.

Soman mimic **46** (*571*). A solution of pinacolyl methylphosphonochloridate (0.848 g, 4.27 mmol) in anhydrous dichloromethane (2 ml) was added dropwise to a stirred mixture of 3-cyano-4-methyl-7-hydroxycoumarin (0.616 g, 3.102 mmol) and triethylamine (0.431 g, 4.27 mmol) in anhydrous dichloromethane (25 ml) at 0 °C. The mixture was stirred at room temperature for 12 h. Ether was added and the obtained precipitate was filtered and washed with ether. The filtrate and washings were combined and evaporated to yield a yellow solid. Column chromatography on silica gel, eluting with 90:10 then 15:85 dichloromethane–ethyl acetate, gave after recrystallisation from ether–ethyl acetate, the pure product (0.690 g, 62%). Mp 135–136 °C. δ_P ($CDCl_3$) 24.1, 24.9 ppm.

Soman mimic **47** (*571*). A solution of pinacolyl methylphosphonochloridate (0.245 g, 1.23 mmol) in anhydrous dichloromethane (2 ml) was added dropwise to a stirred mixture of 1,3-dichloro-7-hydroxy-9,9-dimethyl-9*H*-acridin-2-one (0.251 g, 0.814 mmol) and triethylamine (0.131 g, 1.30 mmol) in anhydrous dichloromethane (8 ml) under nitrogen. The mixture was stirred at room temperature for 12 h. The solvent was removed, ether was added to the residue and the obtained precipitate was filtered and washed with ether. The filtrate and washings were combined and evaporated to give a yellow-brown liquid (0.5 g). It was purified by column chromatography on silica gel, eluting with 95:5 then 93:7 dichloromethane–ether, to give a pure product (267 mg, 70%). δ_P ($CDCl_3$) 23.7, 24.5 ppm.

1.12 BIOTINYLATED NERVE AGENT MIMICS FOR ACTIVITY-BASED ENZYME PROFILING

The availability in recent times of nerve agent analogues containing a reactive P–F bond and linker connected to a detection handle such as a fluorophore or biotin (*579–583*) (Fig. 1.12.1) has enabled activity-based profiling of multiple serine hydrolase targets in animals (*584*). This has allowed biological targets other than AChE and BChE to be identified, whose covalent modification presumably contributes to the toxicology of the nerve agents (and related pesticides (*585,586*)), but in ways that are not yet fully understood.

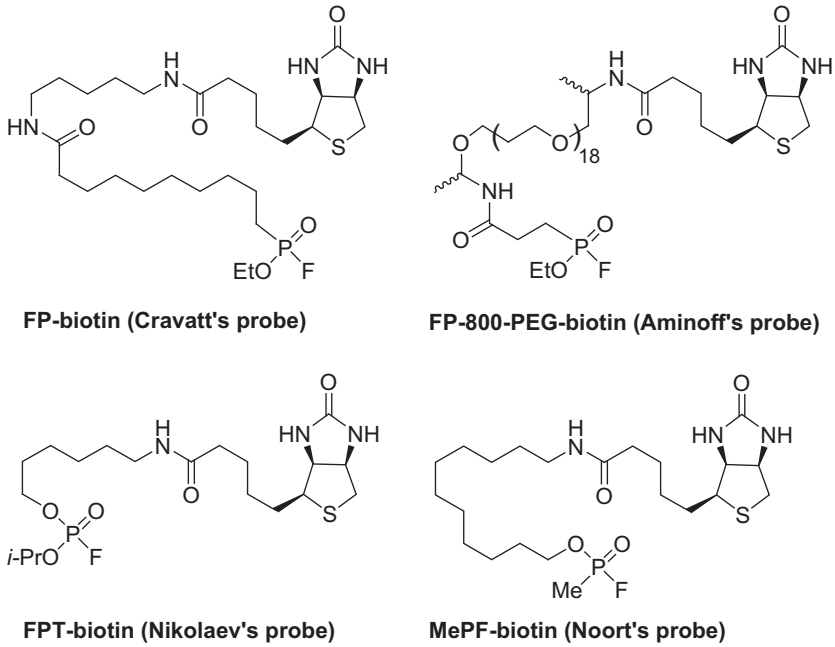


Figure 1.12.1 A selection of reactive P—F probes used for protein profiling.

Methyl arachidonyl phosphonofluoridate (MAFP, Fig. 1.12.2) is an irreversible site-directed inhibitor of nearly all serine hydrolases and serine proteases (*587*). It inhibits phospholipase A2 and fatty acid amide hydrolase with high potency. Methyl γ-linolenyl phosphonofluoridate (MLFP) also phosphorylates the active site serine residues of certain enzymes, such as human fatty acid synthase, and is a useful tool for enzyme profiling (*588*).

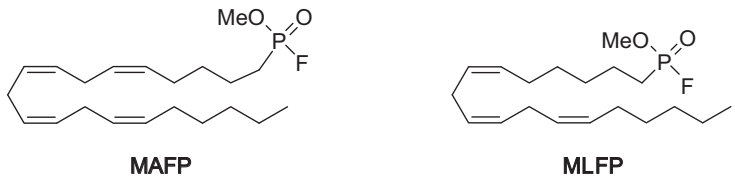


Figure 1.12.2 Phosphonofluoridates used to probe serine-containing proteins.

1.13 WORKING SAFELY WITH ORGANOPHOSPHORUS COMPOUNDS

As noted, many organophosphorus compounds are highly toxic and some are among the most lethal known. Throughout this book, every attempt has been made to report toxicity information where

these are available, but the absence of such information cannot be assumed as an indication of safety, and the authors and publisher are not responsible for any deficiencies in the hazard information provided in the synthetic procedures. Workers intending to handle and synthesise organophosphorus compounds are advised to acquaint themselves with the extensive literature on the biological activity of known representatives, so that they gain an awareness of the likely toxicological properties of newly synthesised substances. Clearly vigilance and adherence to safety procedures need to be practiced by all those who work with phosphorus and its compounds; above all, sensible adequate prior arrangements must be made for medical treatment in the event of an accident.

A suitable and sufficient risk assessment should be undertaken before starting synthetic work in organophosphorus chemistry. This document describing the process and control measures should be reviewed in-house by an independent technical reviewer, and by a health and safety specialist, before being authorised by the management. It is recommended that researchers have a baseline AChE measurement before starting any work with anticholinesterase compounds and have regular tests while working with these materials. If the AChE determination result is depressed >10% (indicative of exposure), the individual should be recalled for retesting and/or treatment, and their work process re-assessed. AChE levels recover naturally but only at the slow rate of 1% per day.

All synthetic work and handling of organophosphorus substances should be carried out in a fume cupboard (minimum flow rate of 0.5 m/s) equipped with a low flow-rate alarm. Anticholinesterase compounds should be kept in sealed containers over charcoal to absorb any spillages in a locked fume cupboard until required. It is best practice with such materials to use minimum amounts for each experiment; these are usually milligram to gram quantities. Staff working with these compounds should have attended an in-house safety awareness course and have been trained by an experienced mentor. All work with such compounds should be carried out in pairs; no one should work alone without an observer or buddy. With the more toxic compounds, it is best to have arranged medical support from a local medical team prior to starting work and have antidote autoinjectors nearby. Signs should be affixed to the laboratory doors while work is in progress, prohibiting entry to unauthorised personnel.

The fume-cupboard opening should always be treated as a clean-dirty line, with any item entering the cupboard considered contaminated with organophosphorus compounds. All contaminated items may leave the cupboard only after decontamination (aqueous bleach destroys most organophosphorus compounds safely and rapidly), or after being double-bagged securely with the outer bag denoted as clean. Waste should be disposed of according to recommended procedures such as incineration.

Work with biologically active organophosphorus compounds should be carried out in trays, with additional smaller trays containing charcoal for handling liquid substances over, to absorb spills. Decontamination baths are placed within the main tray, and it is good practice to check decontamination efficiencies towards the compounds in advance. The decontaminant in the bath should destroy the compounds usually through a combination of oxidation or hydrolysis. Swabbing and analysis, by gas chromatography—mass spectrometry (or another mass spectrometry technique), can be used to confirm that the equipment/apparatus has been decontaminated successfully.

Personal protective equipment is important while handling highly toxic organophosphorus compounds; gloves and eye protection must be worn at all times. In some instances, for example, during the handling of large amounts of toxic material, or while working with percutaneously toxic materials, it is also advisable to wear a protective cape and visor. The majority of organophosphorus compounds can be purified by vacuum distillation or by column chromatography on silica gel and these operations should be carried out with regard to the possible toxic properties of the products. Phosphorus compounds containing aromatic groups can be detected on thin-layer chromatography (TLC) plates often by illumination with ultraviolet (UV) light of wavelength 254 nm. Compounds containing sulfur are normally easily visualised by exposure of TLC plates to iodine vapour. For those compounds that do not show under UV light or in iodine vapour, TLC plates can be dipped into a dilute solution of potassium permanagante in acetone: the compounds show as white spots on a purple background (*250*). Phosphonic acids (*589–591*) and phosphonolipids (*592*) can be detected using specific reagents.

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110. Auflage, B. *Gmelins Handbuch der Anorganischen Chemie: Phosphor Teil C*, System-Nummer 16; Verlag Chemie: Weinheim, Germany, 1965; Contains 642 densely factual pages and chapters on phosphorus compounds (phosphorus and rare gases, and phosphorus and hydrogen, including phosphine); phosphorus and oxygen compounds (phosphorus pentoxide, hypophosphorous acid, phosphorous acid, polyphosphorous acid, orthophosphoric acid); condensed phosphoric acids (mixtures of condensed phosphoric acids, diphosphoric acid and its ions, triphosphoric acid and its ions, tetraphosphoric acid, polyphosphoric acids with 5 to 12 P atoms, higher polyphosphoric acids and their salts, and metaphosphoric acids); phosphorus and nitrogen compounds (imides and amides, oxide nitrides and other P—N—O compounds, oxonium acids and derivatives, hydrazidophosphoric acids, and nitrosylphosphoric acids); phosphorus and halogen compounds (phosphorus fluorides, fluorophosphoric acids, fluorine—phosphorus compounds containing nitrogen; phosphorus chlorides, compounds with perchloric acid, and chlorophosphoric acids; phosphorus bromides, and phosphorus iodides); phosphorus nitride halogenide derivatives; and compounds of phosphorus and sulfur, selenium, tellurium, boron, carbon and silicon.
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trivalent phosphorus; free radical reactions at phosphorus; four-centre rearrangements; reactions not involving a central phosphorus atom; nucleophilic attack on trivalent phosphorus; nucleophilic attack on phosphonium salts and pentacovalent phosphorus compounds; nucleophilic attack on tetrahedral P(V) compounds; and phosphorylation.

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120. O'Brian, R. D.; Yamamoto, I., Eds.; *Biochemical Toxicology of Insecticides;* Academic Press: London, UK, 1970, Chapters describing organophosphorus insecticides cover aspects of the metabolism of parathion and diazinon; acute and subacute toxicity of organophosphorus insecticides to mammals; the dealkylation of organophosphorus triesters by liver enzymes; and the biological significance of alkylation reactions of organophosphorus pesticides.
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140. Holmes, R. R. *Pentacoordinated Phosphorus. Vol. 1: Structure and Spectroscopy,* ACS Monograph 175; American Chemical Society: Washington, DC, 1980, Chapters on the pentacovalent state; geometry and bond parameters; structure and exchange phenomena from NMR spectroscopy; potential functions and intramolecular exchange; including an appendix of vibrational spectra of trigonal bipyramidal and square pyramidal pentacoordinated molecules.
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142. Goldwhite, H. *Introduction to Phosphorus Chemistry*; Cambridge University Press: Cambridge, UK, 1981; A survey of structural types, geometries, and reactions; physical methods in organophosphorus chemistry; phosphorus compounds of coordination numbers 3, 4 and 5; and phosphorus reagents in chemistry. Two appendices summarise physical and spectroscopic data.
143. Quin, L. D. *The Heterocyclic Chemistry of Phosphorus*; John Wiley & Sons Inc.: New York, 1981.
144. Quin, L. D.; Verkade, J. G. *Phosphorus Chemistry,* Proceedings of the International Conference on Phosphorus Chemistry at Duke University, Durham NC, on 1—5 June 1981, ACS Symposium Series 171. Contains lecture material on new organic synthetic methods based on reagents containing phosphorus; biochemistry of phosphorus compounds; new synthetic methods for phosphorus compounds; biologically important phosphorus compounds (natural and synthetic); phosphorus heterocycles; phosphazenes; new organophosphorus compounds of commercial interest; inorganic phosphates; compounds with mono-, di-, penta- and hexa-coordinated phosphorus; phosphorus ligands and complexes (including catalytic properties); reaction mechanisms involving organic and inorganic phosphorus compounds; photochemistry with phosphorus compounds; and bonding and theory of phosphorus compounds.
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151. Pudovik, A. N. *Chemistry of Organophosphorus Compounds* (translated from the Russian by S K Sarkar); MIR Publishers: Moscow, 1989; Chapters on the reaction of esters of some phosphorus acids with α,β-unsaturated ketones; kinetics and mechanism of the Pudovik reaction; acid catalysis in reactions of derivatives of trivalent phosphorus acids; substitution and addition reactions in the series of thioderivatives of trivalent phosphorus acids; reactions of phosphorus acid derivatives with α- and β-oxides, and thiooxides of alkylenes; steric aspects of coordination of polyphosphoryl ligands and selectivity of complexation with metals; analysis of dual reactivity of alkali metal monothiophosphorus salts; reactions of organohalides of Group V, IV, and III elements with organophosphorus nucleophiles containing ambident dyads and triads (kinetic and thermodynamic control of reaction); tri-coordinated pentavalent phosphorus derivatives; and phosphorus-containing heterocumulenes (ketenes, thioketenes, and ketenimines).
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role in catalyst stability in homogeneous transition-metal-catalysed processes; crystalline chloro-trisodium orthophosphate; and the development of functional organophosphorus compounds.
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163. Murphy, P. J., Ed.; *Organophosphorus Reagents – A Practical Approach in Chemistry;* Oxford University Press: Oxford, UK, 2004, Chapters on the synthesis and applications of phosphines; application of phosphorus (III) and (V) compounds as reagents in synthesis; the Wittig and related reactions; applications of the Wittig reaction in the synthesis of heterocyclic and carbocyclic compounds; preparation and reactions of iminophosphoranes and their synthetic applications in the aza-Wittig reaction; phospho-transfer processes leading to P–C bond formation; low-coordinated phosphorus compounds; and phosphorus methods in nucleotide chemistry.
164. Engel, R.; Cohen, J. I. *Synthesis of Carbon–Phosphorus Bonds*, 2nd ed., CRC Press: Cleveland, Ohio, USA, 2004; Update of an earlier version covering approaches to P–C bond formation with chapters on the synthesis of organophosphorus compounds from elemental phosphorus, P–C bond formation using nucleophilic trivalent phosphorus reagents; P–C bond formation via displacement, addition, or rearrangement; pentacoordinate phosphorus; and aromatic and vinylic P–C bonds.
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171. Gratzer, W. Boyle on the Boil. In *Eurekas and Euphorias – The Oxford Book of Scientific Anecdotes*; Oxford University Press: Oxford, UK, 2002; pp 277–280; A delightful essay describing Robert Boyle's lurid adventures with white phosphorus.
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CHAPTER 2

Phosphonyl Compounds

Christopher M. Timperley
Detection Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK

2.1 INTRODUCTION

Organophosphonates have a variety of biological activities and span a range of toxicities (Chapter 1). Some members are potent inhibitors of human acetylcholinesterase and tiny quantities can cause severe poisoning or death, e.g. as with the military nerve agent sarin (*1*), which has been used in conflict, including in Syria in 2013 (*2–6*), and the even more toxic nerve agent VX (*O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate) (*7–12*). Syntheses of such compounds should not be attempted by inexperienced chemists without suitable protective equipment, specialist training, or access to specific medical countermeasures, outside laboratories declared under the Chemical Weapons Convention (CWC) (*13*). Methods of synthesis of compounds related to these substances, such as hydrolysis products (*14–16*), which are important environmental (*17,18*) and biomedical markers (*19–21*), are covered here. However, some organophosphonates are controlled under the CWC and pursuing their synthesis may be unlawful.

Fortunately the majority of organophosphonates are not of military or terrorist interest. They include several compounds that have beneficial properties to humans and have been used in medicine and agriculture to improve heath and crop production, respectively. A selection of such compounds appears in Fig. 2.1.1 (*22*). Ethyl *p*-nitrophenyl ethylphosphonate (armine) has been used to treat the eye disease glaucoma. The related compound H6034 has been used as a fungicide. Trichlorfon is an insecticide: it is converted in the insect body to the more potent anticholinesterase dichlorvos, $(MeO)_2P(O)OCH{=}CCl_2$, through metabolic dehydrochlorination. Ethyl hydrogen *n*-propylphosphonate (NIA10637), a plant growth regulator (PGR), retards the growth of plants by reducing internode elongation; *n*-propylphosphonic acid, $n\text{-}PrP(O)(OH)_2$, has a similar effect. Ethephon is also used as a PGR but has a different mechanism of action. It hydrolyses rapidly in plants to yield phosphoric acid, hydrochloric acid, and ethene. Ethene is a 'plant hormone' and induces fruit ripening, flowering, and other physiological effects. Glyphosate is a commonly used weedkiller that was introduced as a herbicide by Monsanto in 1971. It has low mammalian toxicity and kills annual and perennial weeds by interfering with phenylalanine biosynthesis. Note that in all these compounds except ethephon the stable P–C bond remains intact in derivatives found as residues in the environment or after metabolism, which highlights its chemical inertness.

The increasing importance of phosphorus compounds in organic synthesis, materials science, and biological applications has stimulated advances in P–C bond formation. Phosphonate synthetic methods published up to 1958 have been summarised (*23,24*). Books covering modern phosphonate

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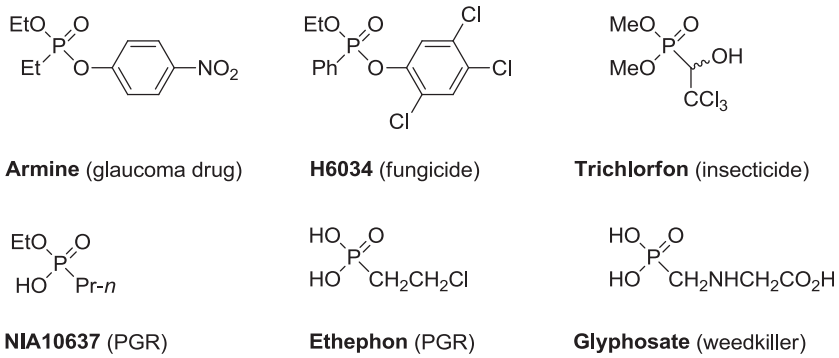


Figure 2.1.1 Some useful organophosphonates.

chemistry (*25*) and the synthesis of P—C bonds (*26*) are available. Specialist reviews describe the Arbuzov reaction (*27*), the synthesis and uses of 2-chloroethylphosphonic dichloride (*28*), the oxidative phosphonylation of aromatic compounds (*29*), the synthesis of dialkyl α-halogenated methylphosphonates (*30*), the synthesis of phosphonates by nucleophilic substitution at phosphorus (*31*), the preparations and uses of phosphylated aldehydes (*32*), the preparation and properties of phosphonic acids (*33*), catalytic methods for constructing P—C bonds (*34*), the anionic phospho-Fries rearrangement (conversion of dialkyl aryl phosphates to dialkyl *o*-hydroxyarylphosphonates) (*35*), modern advances in chemical methods for the introduction of a phosphonic acid group (*36*), surface modification using phosphonic acids and esters (*37*), and the synthesis and biomedical applications of fluorinated phosphonates (*38*).

2.2 ALKYL ALKYL-*H*-PHOSPHINATES R(R′O)P(O)H

It might be supposed that since phosphorus trichloride and an alcohol, in the absence of a tertiary amine base, give a dialkyl *H*-phosphonate, an alkylphosphonous dichloride, under similar conditions would give an alkyl alkyl-*H*-phosphinate. When this reaction is carried out, however, the yield of the expected product under ordinary conditions is always poor and variable, and sometimes nil. This failure is due to the presence of traces of free hydrogen chloride that at only slightly elevated temperatures cause profound decomposition of the product. If, however, they are entirely eliminated by the introduction of anhydrous ammonia gas, good to excellent yields of product may be obtained (*39*). Like dialkyl *H*-phosphonates, the infrared absorption spectra of the alkyl alkyl-*H*-phosphinates show the presence of RO—P, R′—P, P═O, and P—H bonds. Therefore they have the *H*-phosphinate structure. Sufficiently strong bases convert such compounds into the trivalent anion RO(R′)P—O$^-$, which is a nucleophile, and usually reacts through the phosphorus atom. The neutral compounds may also show nucleophilic reactivity towards strong electrophiles, and these reactions are often catalysed by acids or bases. The facts are interpreted in terms of an equilibrium between pentavalent P(O)H (**A**) and trivalent P—OH (**B**) forms, the reaction occurring exclusively through the trivalent form (Fig. 2.2.1).

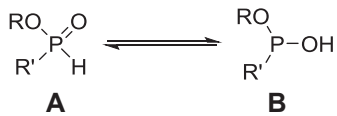


Figure 2.2.1

Many spectroscopic studies have failed to produce evidence for the existence of the trivalent form, but it has now become clear that it is not present in high enough concentration to be detected spectroscopically. Acceptable evidence comes from kinetic investigations (*40,41*) supporting the thesis that the reactive form is normally present only in extremely low concentration ($\leq 10^{-4}$ %).

The earliest method for the synthesis of the lower alkyl *H*-methylphosphinates relied on the reaction of methylphosphonous dichloride with at least two molar equivalents of an alcohol (Fig. 2.2.2). In several cases this procedure was unsuitable due to the tendency of the alkyl *H*-methylphosphinates, especially the lower members, to dealkylate according to the equation RO(Me)P(O)H + HCl → HO(Me)P(O)H + RCl, thus reducing product yields (*42*).

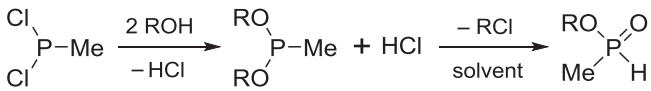
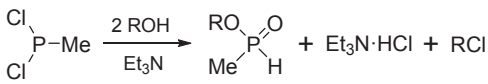


Figure 2.2.2

An alternative and sometimes better synthetic procedure in terms of product yield involves the reaction of alkylphosphonous dichlorides with alcohols in the presence of tertiary amines (usually triethylamine) in a 1:2:1 molar ratio (Fig. 2.2.3) (*43*). The role of the hydrogen chloride acceptor is taken not only by the tertiary amine but also by the neutral phosphonite formed, which is converted to the monoester and alkyl chloride according to the process $MeP(OR)_2$ + HCl → RO(Me)P(O)H + RCl.



Alkyl *H*-methylphosphinates

R'	Bp (°C/mmHg)
Et	70/15
n-Pr	84/15
i-Pr	69–70/11
n-Bu	88–89/10
i-Bu	75–76/8
i-Pentyl	106–107/15
n-Hexyl	103–104/6
c-Hexyl	102–103/4

Figure 2.2.3

The possibility of dealkylation can be suppressed by bubbling carbon dioxide, or any other inert gas, through the reaction mixture. In this case, alkyl ethyl-*H*-phosphinates can be prepared from ethylphosphonous dichloride in moderate yields (up to 64%) (*26*). Short-chain ester groups are generally dealkylated more readily than longer ester groups. These preparative methods are generally superior to alternatives that involve the isolation of dialkyl alkylphosphonites, $RP(OR')_2$, which are prone to hydrolytic decomposition, and their subsequent reaction with hydrogen chloride.

Alkyl methyl-*H*-phosphinates are colourless mobile liquids, readily soluble in organic solvents, and, for the lower members of the series, in water. They are stable to storage: when carefully protected from moisture and air, they do not change after standing for a year (*44*). Like dialkyl *H*-phosphonates, they react with sodium to give the alkali salt that has the trivalent structure. The same type of 'back-isomerisation' to the trivalent state takes place in the presence of triethylamine. Sulfur can then be added and the product on acidification in this case gives in good yield the alkyl hydrogen alkylphosphonothioate, RO(R′)P(S)OH.

▶ *Ethyl H-methylphosphinate EtO(Me)P(O)H* (*39*). A solution of methylphosphonous dichloride (175.5 g, 1.5 mol) in anhydrous ether (300 ml) was added gradually with stirring to absolute ethanol (138 g, 3.0 mol) contained in a 1-litre three-necked flask fitted with a gas inlet delivering a stream of nitrogen, a mechanical stirrer, a dropping funnel, and a thermometer (the bulb in the reaction mixture). The temperature was kept at 0 °C during the addition. Afterwards, the nitrogen stream was replaced by one of dry ammonia gas until the reaction mixture was alkaline, the temperature being maintained at 0 °C during passage of the gas (the temperature must not be allowed to rise until all the hydrogen chloride has been removed). The ammonium chloride was filtered off and the ether recovered from the filtrate. Distillation of the residue under reduced pressure gave the title compound as a colourless mobile liquid (116 g, 72%). Bp 66 °C/13 mmHg. This is a general method of preparing alkyl alkyl-*H*-phosphinates. Ethyl ethyl-*H*-phosphinate, EtO(Et)P(O)H (*39*), was prepared similarly from ethylphosphonous dichloride (131 g, 1.0 mol) in ether (300 ml) and ethanol (92 g, 2.0 mol). Yield 99.5 g (82%). Bp 99.5 °C/42 mmHg.

▶ *Isopropyl H-methylphosphinate i-PrO(Me)P(O)H* (*39*). Methylphosphonous dichloride (117 g, 1 mol) in anhydrous ether (300 ml) was added with stirring to isopropanol (120 g, 2 mol) under nitrogen over 90 min, the temperature being maintained at 0–5 °C. Ammonia gas was then passed into the mixture at 0–10 °C until it was alkaline. Removal of the ammonium chloride by filtration, recovery of the ether, and fractionation of the residue gave the product (86 g, 71%). Bp 70 °C/14 mmHg. The following were prepared similarly: *n*-PrO(Me)P(O)H (75%, bp 50.5 °C/2 mmHg), *n*-BuO(Me)P(O)H (77%, bp 93 °C/12 mmHg), and *n*-C_5H_{11}O(Me)P(O)H (68%, bp 59 °C/0.5 mmHg). During the fractionation of the last of these compounds, unreacted *n*-pentanol was recovered, together with slightly impure *n*-pentyl *H*-methylphosphinate *n*-C_5H_{11}O(Me)P(O)H (bp 98 °C/0.2 mmHg).

▶ *Isobutyl H-methylphosphinate i-BuO(Me)P(O)H* (*39*). A solution of methylphosphonous dichloride (175.5 g, 1.5 mol) in anhydrous ether (900 ml) was added dropwise with stirring to a solution of triethylamine (151.5 g, 1.5 mol) and isobutanol (244.2 g, 3.3 mol) in anhydrous ether

(300 ml) maintained at 0 °C under a nitrogen atmosphere. After addition, the solution was gently refluxed for 40 min, and then allowed to cool overnight. The triethylamine hydrochloride was filtered off and the volatiles removed from the filtrate by rotary evaporation at 40–50 °C. Vacuum distillation of the residue afforded isobutyl *H*-methylphosphinate (146.9 g, 72%). Bp 76–78 °C/8 mmHg.

▶ *Cyclohexyl H-methylphosphinate* $C_6H_{11}O(Me)P(O)H$ (*44*). A solution of cyclohexanol (41.07 g, 0.41 mol) in ether (100 ml) was added dropwise to a stirred solution of methylphosphonous dichloride (24.00 g, 0.205 mol) in ether (200 ml) at 0 °C under argon. After addition, the mixture was allowed to warm to room temperature and was left for 12 h. The solvent was removed and the residue distilled under reduced pressure to afford the title compound as a mobile colourless liquid (23.2 g, 70%). Bp 102–103 °C/4 mmHg and δ_P (202 MHz) 30.9 ppm.

Rather than start with alkylphosphonous dichlorides, which are difficult to acquire and handle in pure form, it is possible to use the more readily available and easily handled trialkyl phosphites to derive the required dialkyl alkylphosphonites through reaction with a Grignard reagent (*45*). Dealkylation of the dialkyl alkylphosphonites with hydrochloric acid then provides the alkyl alkyl-*H*-phosphinates. Unfortunately the reaction between trimethyl phosphite and alkylmagnesium halides is complicated, as the dimethyl alkylphosphonite formed enters into an Arbuzov reaction, providing an unwanted alkyl alkylmethylphosphinite (e.g. **1**) (Fig. 2.2.4).

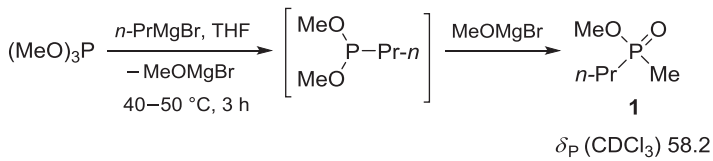
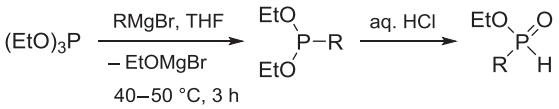


Figure 2.2.4

However, although this route is unsatisfactory for methyl *H*-methylphosphinates, it is useful for higher homologues, e.g. the ethyl alkyl(or aryl)-*H*-phosphinates (Fig. 2.2.5) starting from triethyl phosphite (δ_P $CDCl_3$ 140.8 ppm) and using tetrahydrofuran (THF) as the solvent. These



Ethyl alkyl-*H*-phosphinates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
Et	56	78–80/10	40.6
n-Pr	73	88/10	38.4
i-Pr	84	88–90/10	43.9
n-Bu	85	106/20	38.9
Ph	82	108–110/0.9	26.5

a. Measured in $CDCl_3$ with 85% H_3PO_4 external standard.

Figure 2.2.5

H-phosphinates can be isolated by vacuum distillation from the reaction mixtures in purities exceeding >95%. Contaminants identifiable by ^{31}P-nuclear magnetic resonance (NMR) spectroscopy include diethyl *H*-phosphonate (δ_P $CDCl_3$ 7.2 ppm) and the diethyl alkylphosphonates (δ_P 33–35 ppm) or diethyl phenylphosphonate (δ_P ~21 ppm) depending on the nature of the R group (alkyl or phenyl).

▶ *Ethyl alkyl-H-phosphinates EtO(R)P(O)H (general procedure)* (*45*). The first stage involves the synthesis of the diethyl alkyl(or aryl) phosphonite $(EtO)_2P{-}R$, starting with the generation of the Grignard reagent: thus, the alkyl or aryl bromide (0.15 mol) was added dropwise to a stirred mixture of magnesium (3.6 g, 0.15 mol) and anhydrous THF (40 ml) under nitrogen at 50 °C. After addition, the reaction mixture was stirred at 50 °C for an additional 1–2 h to complete the reaction. It was then added dropwise to a solution of triethyl phosphite (16.6 g, 0.1 mol) in anhydrous THF (25 ml) under nitrogen at 40–50 °C, and then stirred at 50 °C for 3 h. The mixture was concentrated by rotary evaporation to half its volume, and diluted with hydrochloric acid (1:1 *v*/*v* conc. acid-water) with stirring at room temperature, until the pH reached 2. The solvent (aqueous THF) was removed and chloroform (60 ml) was added to the colourless semisolid residue. The mixture was extracted with water (3 × 30 ml) and the organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent and distillation under reduced pressure gave the pure title compounds. (The diethyl alkylphosphonite can be isolated if necessary by avoidance of the acidolysis step and removal of the solvent under reduced pressure and vacuum distillation from the semisolid residue; yield 50–82%.)

2.3 ALKYLPHOSPHONIC DICHLORIDES $RP(O)Cl_2$

The alkylphosphonic dichlorides are of great importance since they are essential starting materials for a diverse range of organophosphorus compounds. Usually they are instantly decomposed by water, with much heat being liberated, and the alkylphosphonic acid and hydrogen chloride are formed. Alkylphosphonic dichlorides (**2**) can be converted into alkyl alkylphosphonochloridates (**3**) by treatment with 1 mol of an alcohol and one of a tertiary base (e.g. triethylamine) (Fig. 2.3.1). Two moles of an alcohol and two of a tertiary amine give the dialkyl alkylphosphonates (**4**). The latter reaction, for example, provides a convenient method for preparing pure diethyl methylphosphonate (from ethanol and methylphosphonic dichloride) free from diethyl ethylphosphonate that always accompanies it when it is prepared by the Arbuzov reaction of triethyl phosphite with methyl iodide (such reactions are discussed later in this chapter, Section 2.13.3).

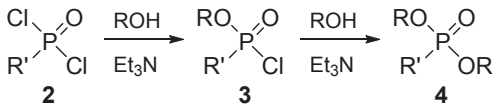


Figure 2.3.1

An exception to this high degree of reactivity is to be found in *tert*-butylphosphonic dichloride *t*-BuP(O)Cl_2. This compound behaves quite differently from the other alkylphosphonic dichlorides in that the chlorine atoms are remarkably unreactive. Whereas the other compounds are decomposed more or less violently by cold water, the *tert*-butyl compound requires prolonged boiling to convert it into *tert*-butylphosphonic acid, *t*-BuP(O)$(OH)_2$. *Tert*-butylphosphonic dichloride is also unreactive towards isopropanol, and isopropyl *tert*-butylphosphonochloridate, *i*-PrO(*t*-Bu)P(O)Cl, cannot be obtained by the action of isopropanol and triethylamine on the dichloride. The reason for the divergence of this dichloride from the usual pattern of the others is twofold: the *tert*-butyl group is strongly electropositive and decreases the electrophilicity of the phosphorus atom to attack by nucleophiles, and the *tert*-butyl group is bulky, and blocks the approach of the nucleophile. Only under forcing conditions, therefore, it is possible to replace both chlorine atoms in this particular phosphonic dichloride by hydroxy or alkoxy groups.

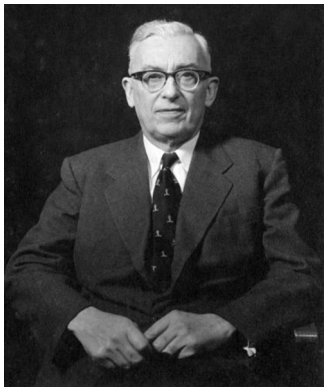
The preparation of alkylphosphonic dichlorides can be accomplished in several ways:

- Through the interaction of phosphorus trichloride, alkyl chloride, and aluminium trichloride — a process known as the Kinnear—Perren (KP) reaction, named after the two chemists who discovered it.
- Through the action of certain inorganic halides such as thionyl chloride or phosphorus pentachloride (or phosphorus trichloride and chlorine) on dialkyl alkylphosphonates or on the rearranged material from pyrolysis of dimethyl *H*-phosphonate.

2.3.1 Reaction of phosphorus trichloride and an alkyl halide (KP reaction)

Alkylphosphonic dichlorides were first reported in 1873 by A. W. Hoffman (*46*) and A. Michaelis (*47*). Their synthesis was improved in 1952 by A. M. Kinnear and E. A. Perren working at the then Chemical Defence Experimental Establishment (CDEE) at Porton Down near Salisbury, Wiltshire, UK. The alkylphosphonic dichlorides were produced by reaction of an alkyl halide, phosphorus trichloride and aluminium trichloride, and hydrolysis of the resulting complex. Five classified technical papers by Kinnear and Perren deposited in the Porton Down Archive between 1948 and 1950 were condensed into a single paper that appeared in the open literature slightly later, in 1952 (*48*). This paper entered into print a year after a similar publication by J. P. Clay of Hunter College in New York described the same process (*49*). It appears that the priority of discovery must go to Kinnear and Perren, with Clay undoubtedly contributing to the development of the process and confirming its validity (for this reason some chemists refer to it as the Clay—Kinnear—Perren reaction). Unfortunately the Porton Down Archive offers no hint of the character of Kinnear, but does provide some interesting background to that of Perren, who enjoyed a colourful and distinguished career working for the British Government. Previously unpublished biographical details appear next.

2.3.1.1 Biography



Dr E A Perren (1900–date of death unknown). Dr E.A. Perren was a research chemist of high calibre who enjoyed a successful career working on chemical defence for over 40 years for the British Government. Born on 13 June 1900 (*50*) and after gaining qualifications – Diploma of Imperial College and Diploma of Associateship of the Royal College of Science from Imperial College in London UK (*51*), Perren joined the Ministry of Supply – probably then the CDEE at Porton Down (*52*) – on 5 December 1922. Four years later he was a temporary assistant in the offensive munitions department – later the Technical Chemistry Department (TCD). In 1940 the TCD divided into TCD and TCD2. Perren became the head of the TCD in 1941 and a year later this division was renamed the Technical Chemistry Section. Perren was appointed Assistant Superintendent of the Development Division at Porton in 1942 and Head of the Planning and Reporting Section in 1944. In August–September 1945, with CDEE renamed the Chemical Defence Experimental Station (CDES), Perren worked for the British Intelligence Objectives Subcommittee (BIOS) located at 32 Bryanston Square, London W1H 2DU, and participated in Trip No. 1103 to Germany to report on German chemical warfare developments.

Perren interviewed amongst others at Kransberg-Dustbin, the research chemist Dr Gerhard Schrader, who had worked at the I. G. Works Elberfeld (a biography of Schrader appears in Chapter 1, Section 1.5.2). A brief account was obtained of the history of Schrader's important researches on organic fluorine and phosphorus compounds, embracing the discovery of the nerve gases tabun and sarin, and of a number of potent insecticides. This account was included in BIOS Final Report No. 44 Item No. 8. At the conclusion of this interrogation, the team requested Schrader to prepare a fuller account of his work, including preparative details, his ideas on the relationship between chemical constitution and toxicity towards insects and mammals, and his suggestions for future work. In response, several voluminous reports were received. Schrader was handicapped in writing these by the destruction or inaccessibility of his records and notes, so that there were certain gaps, especially in the insecticidal data and the preparative methods. Despite this it was still possible after translation to piece together a coherent account of his work (*53*).

Perren was appointed Superintendent of the Chemistry Section at Porton Down in 1946 and proceeded, with other chemists including Arthur Henry Ford-Moore (biography in this Chapter, Section 2.24.1), to exploit in the laboratory the new German revelations, especially in connection with organophosphorus nerve agents. He focused his attention on the preparation of alkylphosphonic dichlorides. These were German nerve agent precursors and presented the British scientists with a difficult manufacturing problem. One of the most attractive suggestions for their synthesis was that it might be possible to condense phosphorus trichloride with an alkyl chloride, and convert the resulting addition product to the desired intermediate, according to this equation: $PCl_3 + RCl \rightarrow RPCl_4$ $(+SO_2) \rightarrow RP(O)Cl_2 + SOCl_2$. The German workers had considered this possibility but it was doubtful whether they had succeeded in effecting the reaction, despite a statement to this effect by Dr Hoyer, Technical Director of a factory in Dyhernfurth that had produced the nerve agent sarin. Schrader had stated that after many experiments he was of the opinion that the reaction could not be made to occur. Seeking alkylphosphonic dichlorides by other means, Perren made the interesting observation that carbon tetrachloride reacted rapidly with aluminium chloride and phosphorus trichloride to give a complex that produced a relatively stable acid chloride after cautious decomposition with water. The acid chloride contained besides carbon and phosphorus, such a high proportion of chlorine that it seemed clear that a reaction according to the following equation had occurred: $CCl_4 + PCl_3 \rightarrow CCl_3PCl_4$ $(+H_2O) \rightarrow CCl_3P(O)Cl_2 + 2HCl$. Systematic exploration of this Friedel-Crafts-inspired chemistry at CDES Porton Down by Perren and Kinnear in the period 1948–1949 led to the discovery of the general method of synthesis of alkylphosphonic dichlorides that now bears their names.

At the end of these researches Perren emigrated to Canada to take up a 2-year post as the director of the Experimental Station Suffield, a military research facility located 5 km north of Suffield, Alberta, from autumn 1949 to 1951 (*52*). He returned to the defence establishment at Porton Down and became its Chief Superintendent in 1955. This post was replaced by that of Director in 1956 in which Perren remained until his retirement in 1961, whereupon he returned to the laboratory within the Chemistry Division and spent several years studying a range of highly toxic chemicals. He was very much a pure and practical scientist. He was elected a Fellow of the Royal Institute of Chemistry (Photograph reproduced courtesy of Dstl.).

2.3.1.2 The KP reaction

The KP reaction involves the combination of an alkyl chloride, phosphorus trichloride, and aluminium chloride (Fig. 2.3.1.2.1). This gives an aluminium complex that on careful treatment with a controlled amount of water provides the alkylphosphonic dichloride and hydrated aluminium salt byproduct. Success depends on the reactivity of the starting alkyl chloride, the quality of the

$$RCl + PCl_3 + AlCl_3 \longrightarrow [RPCl_3 \cdot AlCl_4] \xrightarrow[-2\,HCl]{7\,H_2O} RP(O)Cl_2 + AlCl_3 \cdot 6\,H_2O$$

Figure 2.3.1.2.1

aluminium chloride used, and the susceptibility of the formed alkylphosphonic dichloride to hydrolysis during the last step. Alkylphosphonic dichlorides that are the least vulnerable to hydrolysis are usually isolated in the greatest yields. The recipes given in this section are those that are known to work consistently rather than ones that have been optimised. Note that the KP reaction on a large scale is complicated due to the difficulty of stirring the viscous/solid reaction mixture. Also, the voluminous solid product formed in the last stage tends to block large apparatus and make isolation of the alkylphosphonic dichloride far from trivial.

Different complexes form depending upon whether 1 or 2 mol of aluminium chloride are employed, e.g. $[MePCl_3]^+[AlCl_4]^-$ or $[MePCl_3]^+[Al_2Cl_7]^-$. The former is a solid that is probably ionic: it has a high melting point (mp 275–280 °C) and solutions in dichloromethane (*48*) or nitromethane (*49,54*) conduct electricity. The complexes do not form readily when phosphorus trichloride is added to a mixture of the alkyl chloride and aluminium chloride. The order of addition is crucial and optimal yields result when the alkyl chloride is added to premixed phosphorus trichloride and aluminium trichloride. The reaction is exothermic and when using equimolar amounts of reagents overheating can transform the complex $[MePCl_3]^+[AlCl_4]^-$ (δ_P 118) into $[MePCl_3]^+[Al_2Cl_7]^-$ (δ_P 117.5), lowering the conversion of PCl_3 (δ_P 220, CH_2Cl_2) (*55*). The complexes react with water to release the alkylphosphonic dichloride. Dichloromethane is added and water in excess of the stoichiometric amount (i.e. >7 mol equiv.) is introduced into the cooled mixture with stirring. An excess of water (up to 11 mol equiv.) is required to form a granular precipitate of aluminium chloride hydrate (*56,57*) that can be easily removed.

Different hydrolysis methods – H_2O (*48,57*) or aq. HCl (*49,54,58*) – have been employed at different temperatures: −20 °C (dry ice, water) or 0 °C (crushed ice). Use of excess water is a necessary complication, since water uncoordinated to aluminium chloride hydrolyses the alkylphosphonic dichloride, a side reaction suppressed at lower temperature. After all the water has been added, the aluminium chloride hydrate must be removed immediately to prevent serious falls in yield, especially when preparing primary alkylphosphonic dichlorides (secondary and tertiary ones hydrolyse less readily). Conductivity experiments show that with efficient stirring the stoichiometric 7 mol of water suffice to hydrolyse 1 mol of complex, but produce a difficult-to-separate mixture, whereas 8 mol of water cause the hydrated aluminium chloride to flocculate, simplifying filtration. The first stage involves the formation of an 'intermediate complex' (Fig. 2.3.1.2.2).

$$[MePCl_3]^+[AlCl_4]^- \xrightarrow[-\,HCl]{H_2O} MeP(O)Cl_2 \cdot AlCl_3$$

Figure 2.3.1.2.2

The liberated hydrochloric acid contributes to a better yield by suppressing the hydrolysis of the methylphosphonic dichloride. This has been verified by the synthesis of $MeP(O)Cl_2 \cdot AlCl_3$ (mp 166–167 °C) from methylphosphonic dichloride and aluminium trichloride in dichloromethane (*59,60*). Its hydrolysis with concentrated hydrochloric acid instead of water produced more

methylphosphonic dichloride (average yields 78% vs 58%). Other phosphorus (V) halides form similar complexes with aluminium trichloride: phosphorus oxychloride gives $Cl_3P{=}O \cdot AlCl_3$ (mp 181 °C) when heated in equimolar ratio with aluminium trichloride in dichloromethane (*61*).

Alkyl chlorides are the preferred alkyl halides for KP reactions and various ones react, although the alkyl structure does not always transpose unchanged into the alkylphosphonic dichloride. Primary alkyl chlorides with one or two carbon atoms react straightforwardly (Table 2.3.1.2.1, *entries 1 and 2*), while those with three or more carbon atoms yield secondary (*entries 3–6*) or tertiary alkylphosphonic

Table 2.3.1.2.1 Data for selected alkylphosphonic dichlorides made using the KP reaction

No.	Alkyl halide	Molar proportions			Reaction conditions		Product	Bp	Yield	Ref.
		RCl	PCl_3	$AlCl_3$	Time [a]	Hydrolysis [b]		(°C/mmHg)	(%)	
1	MeCl	1.50	1.00	1.10	64 h	14 mol	$MeP(O)Cl_2$	162/760 [c]	68%	(*48*)
2	EtCl	0.35	0.25	0.27	1 h	2.8 mol	$EtP(O)Cl_2$	34/3	82%	(*48*)
3	*n*-PrCl	0.25	0.25	0.50	2 h	2.5 mol	*i*-$PrP(O)Cl_2$	35/0.5	90%	(*48*)
4	*i*-PrCl	0.30	0.25	0.50	1 h	- [d]	*i*-$PrP(O)Cl_2$	36/1.5	70%	(*48*)
5	*s*-BuCl [e]	0.25	0.25	0.50	12 h	4.5 mol	*s*-$BuP(O)Cl_2$	59/3	83%	(*48*)
6	*n*-BuCl	0.25	0.25	0.50	12 h	4.5 mol	*s*-$BuP(O)Cl_2$	57/2	93%	(*48*)
7	*t*-BuCl	0.32	0.25	0.25	10 min	3.5 mol	*t*-$BuP(O)Cl_2$	mp 110 °C	81%	(*48*)
8	*i*-BuCl	0.25	0.25	0.50	1 h	5.5 mol	*t*-$BuP(O)Cl_2$	mp 110 °C	92%	(*48*)
9	Me-*i*-PrCHBr	1.00	1.00	1.00	12 h	- [f]	$EtMe_2CP(O)Cl_2$	~55/0.2	32%	(*70*)
10	*t*-$BuCH_2Cl$	0.48	0.50	0.50	1 h	4.4 mol	$EtMe_2CP(O)Cl_2$	77/5	51%	(*64*)
11	Et-*i*-PrCHBr	1.00	1.00	1.00	12 h	- [f]	$Et_2MeCP(O)Cl_2$	~70/0.2	40%	(*70*)
12	*c*-$C_6H_{11}Cl$	0.25	0.50	0.50	15 min	5.0 mol	*c*-$HexP(O)Cl_2$	90/1	82%	(*48*)
13	$CH_2{=}CHCl$	-	1.10	0.50	1.5 h [g]	5.0 mol	$ClCH_2CH_2P(O)Cl_2$	80–84/15	trace	(*48*)
14	$CH_2{=}CHCH_2Cl$	0.25	1.00	0.50	0.5 h [g]	4.5 mol	$CH_2{=}CHCH_2P(O)Cl_2$	55/3	53%	(*48*)
15	$CHCl{=}CCl_2$	0.25	0.25	0.25	12 h	2.0 mol	$CCl_3CH_2P(O)Cl_2$	65–66/1	20%	(*48*)
16	$ClCH_2CH_2Cl$	0.25	0.50	0.50	45 min	3.5 mol	$ClCH_2CH_2P(O)Cl_2$ [h]	77/6	58%	(*48*)
17	CH_2Cl_2	1.00	1.00	1.00	24 h	11 mol	$ClCH_2P(O)Cl_2$	50/0.5	85%	(*48*)
18	$CHCl_3$	0.50	0.25	0.50	10 h	3.0 mol	$Cl_2CHP(O)Cl_2$	79/9	63%	(*48*)
19	CCl_4	0.35	0.25	0.25	1 h	3 mol	$Cl_3CP(O)Cl_2$ [i]	mp 156 °C	85%	(*48*)
20	$PhCH_2Cl$	0.25	1.10	0.50	30 min [j]	4.5 mol	$PhCH_2P(O)Cl_2$	130/2 [k]	62%	(*48*)
21	$PhCHCl_2$	0.25	1.00	0.50	30 min [l]	3.5 mol	$PhCHClP(O)Cl_2$	132/2 [m]	40%	(*48*)
22	$PhCCl_3$	0.25	1.00	0.50	90 min	4.5 mol	$PhCCl_2P(O)Cl_2$	114–120/2	10%	(*48*)
23	Me_3SiCH_2Cl	1.00	1.00	1.00	2 h	9 mol	$Me_3SiCH_2P(O)Cl_2$	64/1.4	31%	(*64*)

a. Reaction time. *b*. Molar amount of water. *c*. Mp 33 °C. *d*. Product stirred vigorously with CCl_4 and suspension poured onto crushed ice. *e*. Alternatively *s*-BuBr gave *s*-$BuP(O)Cl_2$ in 78% yield (*58*). *f*. Added to crushed ice. *g*. Heated to 40–50 °C. *h*. This (61%) and the isomer $CH_3CH(Cl)P(O)Cl_2$ (39%) were produced in a different study (*62*). *i*. Mp 155–156°C (*65,94*). *j*. Heated to 40 °C. *k*. Mp 58 °C. *l*. Heated under reflux. *m*. Mp 48 °C.

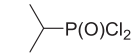
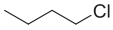
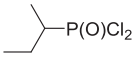
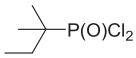
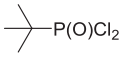
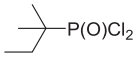
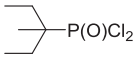
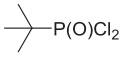
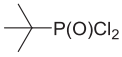
dichlorides (*entries 7–11*). Primary chlorides containing three or more carbon atoms yield derivatives of the corresponding secondary or tertiary chlorides, to the exclusion of primary derivatives. Cyclohexyl chloride gives cyclohexylphosphonic dichloride (*entry 12*). Vinyl chloride reacts inappreciably (*entry 13*), allyl chloride yields allylphosphonic dichloride (*entry 14*) and 1,1,2-trichloroethene gives 2,2,2-trichloroethylphosphonic dichloride (*entry 15*).

α,ω-Dihaloalkanes yield only monophosphonates: e.g. $ClCH_2CH_2Cl \rightarrow ClCH_2CH_2P(O)Cl_2 + CH_3CH(Cl)P(O)Cl_2$ (*28,48,62,63*). Attempts to make *bis*-phosphonyl derivatives from PCl_3 and $AlCl_3$ (1:2 mol equiv.) and 1,2-dichloroethane (4 mol equiv.) or 2-chloroethylphosphonic dichloride (2 equiv.) failed (*48*). 1,5-Dichloropentane gave only $Cl(CH_2)_3CHMeP(O)Cl_2$ in 15% yield with no trace of higher boiling material (*48*). Dichloromethane, chloroform and carbon tetrachloride provide mono-, di- and tri-chloromethylphosphonic dichloride, respectively (*entries 17–19*) and reactivity decreases in the order $CCl_4 > CHCl_3 > CH_2Cl_2$. Carbon tetrachloride is almost as reactive as the alkyl monochlorides, chloroform requires refluxing for several hours for complete reaction, and dichloromethane requires heating to 100 °C under pressure for 24 h (its inertness, and ability to dissolve the aluminium complexes, makes it the preferred KP reaction solvent) (*48*). Benzyl chloride and α-chlorinated derivatives react analogously (*entries 20–22*) under conditions that minimise Friedel–Crafts ring alkylation: adding benzyl chloride to PCl_3 and $AlCl_3$ in the cold prompts hydrogen chloride release and gives a resinous material, but adding it slowly to a warm mixture of PCl_3 and $AlCl_3$ gives benzylphosphonic dichloride in satisfactory yield. Chlorotrimethylsilane does not react with PCl_3 and $AlCl_3$ at room temperature to give the expected product (*64,66*), yet chloromethyltrimethylsilane provides $Me_3SiCH_2P(O)Cl_2$ (*entry 23*) (*64*), a useful precursor to silicon-containing phosphonates (*67*) (Me_3SiCH_2Cl rearranges to $EtMe_2SiCl$ when warmed with aluminium chloride in the absence of PCl_3 (*68*)). Neopentyl chloride (Me_3CCH_2Cl) in contrast isomerises during KP reaction to give the tertiary product $EtMe_2CP(O)Cl_2$ (*entry 10*).

The KP reaction mechanism is not understood fully (*59,60,66*). Alkyl rearrangement (primary 1° → secondary 2° → tertiary 3°) suggests a similarity to the Friedel–Crafts reaction ($RCl + AlCl_3 \rightarrow R^+AlCl_4^-$) (*24*). However, there are important differences. Adding phosphorus trichloride to a mixture of the alkyl halide and aluminium chloride gives a lower product yield than mixing the reactants in any other order (*66*). Thermal measurements indicate that methyl chloride reacts quickly, yet inappreciable Me^+ ions form in the presence of $AlCl_3$ (*59,60*). The Friedel–Crafts reaction produces isomerised and non-isomerised products (e.g. *n*-PrCl + C_6H_6 → *n*- and *i*-PrC_6H_5) (*69*), whereas in the KP reaction the alkyl groups isomerise completely (*48*) and tertiary alkyl chlorides having over four carbon atoms degrade to *tert*-butylphosphonic dichloride (*58,70,71*) and higher boiling products (Table 2.3.1.2.2).

That an alkyl chloride must be added to premixed PCl_3 and $AlCl_3$ for effective reaction, and that the outcome differs from that of the Friedel–Crafts reaction, suggests a reactive intermediate other than $[R]^+[AlCl_4]^-$. The complex $[PCl_2]^+[AlCl_4]^-$ has been suggested (*59,60*) but no evidence exists for stable compound formation from PCl_3 and $AlCl_3$ (*72,73*). Aluminium trichloride is insoluble in PCl_3 (2:1 mol ratio) at room temperature, although at 130 °C about 5 mol% dissolves, and most

Table 2.3.1.2.2 Some skeletal changes known to occur in the KP reaction

No.	Alkyl halide	Product	Yield (%) [a]	Outcome	Ref.
1			90%	isomerisation 1°→2°	(*48*)
2			93%	isomerisation 1°→2°	(*48*)
3			51%	isomerisation 1°→3°	(*64*)
4			92%	isomerisation 1°→3°	(*48*)
5			32%	isomerisation 1°→3°	(*70*)
6			40%	isomerisation 1°→3°	(*70*)
7			- [b]	degradation 3°→3°	(*58,70*)
8			47% [c]	degradation 3°→3°	(*71*)

a. Isolated yield. *b*. Not given. *c*. Unidentified high-boiling P-compounds also produced.

precipitates out upon cooling to 25 °C (*73*). Consequently, PCl_3 and $AlCl_3$ produce only a weak donor—acceptor complex rather than the ion $^{+}PCl_2$. This has been identified as the most abundant cation in the mass spectrum of PCl_3 (*74*), but ^{31}P-NMR studies give no indication of it in the $PCl_3/AlCl_3/CH_2Cl_2$ system (*75*). A KP mechanism consistent with experimental data (**5**→**6**→**7**) (*76*) appears in Fig. 2.3.1.2.3.

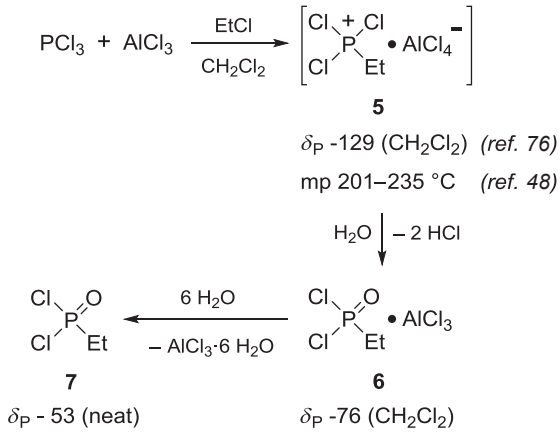


Figure 2.3.1.2.3

The transformations in Table 2.3.1.2.2 may result from equilibration of $[RPCl_3]^+$ with R^+ and PCl_3 (Fig. 2.3.1.2.4). The equilibrium position might move to the right when the starting alkyl group can produce a stable carbocation (2° or 3°). Its rearrangement to a more stable form, and recombination with PCl_3 might return the equilibrium position to the left, producing a more stable $RPCl_3^+$ ion (stabilised by the rearranged alkyl group, correlating with alkyl group electron donor ability: 3° > 2° > 1°). The alternative, rearrangement of $RPCl_3^+$ without P—R bond dissociation, fails to account for the skeletal changes observed with some tertiary alkyl halide starting materials. If R^+ ions are involved, then alkyl halide reactivity and structural changes should mirror those known for the corresponding carbocations.

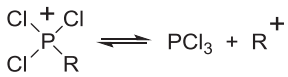


Figure 2.3.1.2.4

Stabilities of the suggested carbocation intermediates and the structures of the resulting alkylphosphonic dichlorides appear to correlate. Normal to secondary alkyl $[CH_3CH_2CH_2^+ \rightarrow (CH_3)_2CH^+]$ and isobutyl to *tert*-butyl arrangements $[(CH_3)_2CHCH_2^+ \rightarrow (CH_3)_3C^+]$ are a prime example (Table 2.3.1.2.1, *entries 3—8*). The *tert*-butyl cation (77) and the *tert*-pentyl cation (78) are particularly stable, in the latter case explaining the conversions Me-*i*-PrCHBr or *t*-$BuCH_2Cl \rightarrow EtMe_2CPOCl_2$ (Table 2.3.1.2.1, *entries 9 and 10*). The vinyl cation is unstable, unlike the allyl cation which is stabilised because of resonance delocalisation — the positive charge is spread over two atoms ($CH_2{=}CHCH_2^+ \leftrightarrow {}^+CH_2CH{=}CH_2$) (79) — and this may explain why vinyl chloride barely participates in the KP reaction, but allyl chloride does (Table 2.3.1.2.1, *entries 13 and 14*). Lack of *bis*-phosphonic products from $ClCH_2CH_2Cl$ and $ClCH_2Cl$ may reflect the difficulty of dication formation (24) (Table 2.3.1.2.1, *entries 16 and 17*). The reactivity order $CCl_4 > CHCl_3 > CH_2Cl_2$ parallels the stabilities of the respective cations ($CCl_3^+ > CHCl_2^+ > CH_2Cl^+$ (80,81)). The benzyl cation, for which canonical forms similar to those for the allyl cation can be drawn, is stable (82) and benzyl chloride, and di- and tri-chloromethylbenzene, provide benzylic phosphonic dichlorides (Table 2.3.1.2.1, *entries 20—22*). Trimethylsilyl chloride does not react (unlike *tert*-butyl chloride); often siliconium ions do not form under conditions favouring carbonium ions (64). The absence of rearrangement observed with chloromethyltrimethylsilane ($Me_3SiCH_2Cl \rightarrow Me_3SiCH_2POCl_2$, Table 2.3.1.2.1, *entry 23*), contrasting with that observed for neopentyl chloride ($Me_3CCH_2Cl \rightarrow EtMe_2CPOCl_2$, *entry 10*), may reflect the greater stabilisation of $Me_3SiCH_2^+$ versus $Me_3CCH_2^+$. The more electropositive silicon atom stabilises a neighbouring positive charge better than a carbon atom (83).

Involvement of carbocations accords with the carbon chain degradation observed for tertiary alkyl derivatives with over four carbon atoms (Table 2.3.1.2.2, *entries 7 and 8*). The carbocations $EtMe_2C^+$ and *i*-$PrMe_2C^+$ from $EtMe_2CCl$ and *i*-$PrMe_2CCl$, respectively, are expected to fragment to the most stable carbocation (*t*-Bu^+), explaining the production of *tert*-$BuPOCl_2$. *Tert*-pentyl and *tert*-hexyl cations fragment to give the *tert*-butyl cation, as do other alkyl cations with four or more carbon atoms (77). Participation of carbocations also accounts for the facile reaction of

7,7-dichlorobicyclo[4.1.0]heptane (**8**) with equimolar amounts of phosphorus trichloride and aluminium trichloride (Fig. 2.3.1.2.5). Two phosphonic dichlorides (**9**) and (**10**), presumably from an 'allylic' carbocation, were formed in a 1:1 ratio after hydrolysis of the intermediate complex (*84*).

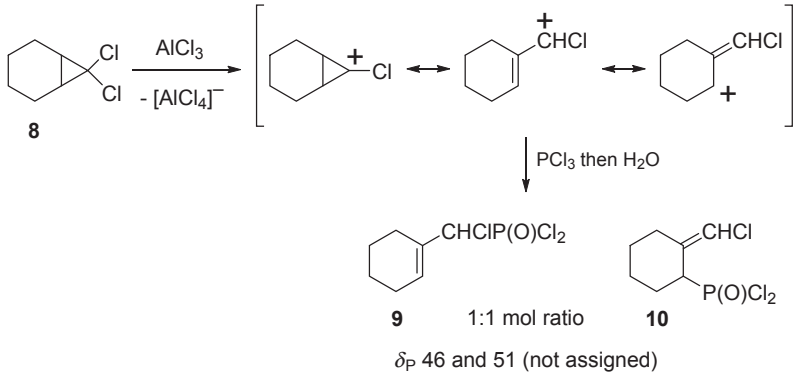


Figure 2.3.1.2.5

Modifications to the KP reaction have involved replacing alkyl chlorides with alkyl bromides or polyhaloalkanes, substituting phosphorus trichloride with phosphorus chlorofluorides or alkyl phosphorodichloridites, the use of dialkyl ethers instead of alkyl halides, and nonaqueous decomposition of the aluminium complex:

1. **Use of alkyl bromides.** Alkyl bromides can be advantageous (*70*) as substitutes for lower boiling alkyl chlorides (EtCl and EtBr: bp 12 vs 38 °C). They form the complex $[RPCl_3]^+[AlCl_3Br]^-$ which hydrolyses to give the same products as those from alkyl chlorides. Ethyl bromide and $[^{32}P]$-labelled PCl_3 give $[^{32}P]$-$EtP(O)Cl_2$ (*85*).
2. **Use of polyhaloalkanes.** As noted already, dichloromethane and 1,2-dichloroethane give monosubstituted phosphonic dichlorides. *Sym*-tetrachloroethane reacts little (if at all) even if heated under pressure with phosphorus trichloride and aluminium trichloride at 100 °C for 24 h (*48*). Penta- and hexa-chloroethane, although appearing to form complexes, yield no phosphonic dichloride (*48,86*); phosphorus oxychloride is produced instead. Haloalkanes containing chlorine and other halogen atoms, or halogens other than chlorine, undergo halogen exchange, e.g. $[CHX_2PCl_3]^+[AlCl_4]^- \rightarrow [CHCl_2PCl_3]^+[AlCl_2X_2]^-$, and hydrolysis gives only the chloroalkylphosphonic dichlorides (*48,87*) (Table 2.3.1.2.3).
   Bromochloromethane reacts more readily than dichloromethane, although a longer period of refluxing is necessary; the product appears to be entirely chloromethylphosphonic dichloride (*48*). An experiment using dibromomethane gave the same product in the same moderate yield (35%) (*48*). Behaviours of fluorocarbon systems vary and appear to reflect carbocation stabilities. Trifluorochloromethane is unreactive (CF_3^+ is difficult to form in solution (*80,81*)). Other relatives participate, giving the corresponding polychlorinated monosubstituted products (Table 2.3.1.2.3, *entries 1–6*). 1,1-Difluoro-1,2,2-trichloroethane gave two products (Table 2.3.1.2.3, *entry* 7)

Table 2.3.1.2.3 Data for selected alkylphosphonic dichlorides derived from polychloroalkanes

No.	Alkyl halide	Molar proportions RHal	PCl_3	$AlCl_3$	Reaction conditions T (°C) [a]	Hydrolysis [b]	Product	Bp (°C/mmHg)	Yield (%)	Ref.
1	$CHClF_2$	xs.	0.25	0.50	60 °C	4.5 mol	$CHCl_2P(O)Cl_2$	67–70/1	40%	(*48*)
2	CF_2Cl_2	xs.	0.50	0.50	60 °C.	4.5 mol	$CCl_3P(O)Cl_2$	mp 158 °C	50%	(*48*)
3	$ClCH_2CH_2F$	0.21	0.50	0.50	reflux 1 h	3.5 mol	$ClCH_2CH_2P(O)Cl_2$	63/3	35%	(*48*)
4	CH_3CHF_2	- [c]	2.50	1.00	30 °C [d]	6.5 mol	$CH_3CHClP(O)Cl_2$	50/0.5	15%	(*87*)
5	CH_3CFCl_2	0.25	0.25	0.50	sv 1.5 h	4.5 mol	$CH_3CCl_2P(O)Cl_2$	mp 149 °C	nr	(*48*)
6	CH_3CF_2Cl	- [c]	1.00	0.50	60 °C [e]	3.5 mol	$CH_3CCl_2P(O)Cl_2$	mp 150 °C	nr	(*87*)
7	$CHCl_2CF_2Cl$	0.50	0.60	0.75	reflux [f]	5.3 mol	$CHCl_2CCl_2P(O)Cl_2$ / $CH_2ClCCl_2P(O)Cl_2$	59–62/0.02	- [g]	(*87*)
8	$CHCl_2CF_2Cl$	0.50	1.00	0.50	reflux [h]	6.5 mol	$CHCl{=}CClP(O)Cl_2$ [i]	44/0.02	- [j]	(*87*)

xs = excess gaseous alkyl halide was passed slowly through heated reaction mixture. sv = sealed vessel at room temp. *a*. reaction time. *b*. molar amount of water. *c*. haloalkane bubbled in. *d*. 2.5 h. *e*. 2.0 h. *f*. 1.5 h. *g*. the mixture gave: 85% $CHCl_2CCl_2P(O)Cl_2$ and 15% $CH_2ClCCl_2P(O)Cl_2$; also $CHCl_2CCl_3$, CCl_3CCl_3 and $Cl_2C{=}CCl_2$. *h*. 1.0 h. *i*. (*E*)-isomer only. *j*. $CHCl_2CCl_3$, CCl_3CCl_3 and pentachlorobutadiene by-products. nr = the yield was not reported in the reference quoted.

thought to arise from chloride—hydride exchange between the intermediate complex and $CHCl_2CCl_3$ (from halex reaction of the starting fluoroalkane and $AlCl_3$) (Fig. 2.3.1.2.6) (*87*):

$$[CHCl_2CCl_2PCl_3]^+ + CHCl_2CCl_3 \longrightarrow [CH_2ClCCl_2PCl_3]^+ + CCl_3CCl_3$$

Figure 2.3.1.2.6

A mixture of $CHCl_2CF_2Cl$, PCl_3 and $AlCl_3$ (1:2:1 molar ratio) generates a complex that fragments to give *trans*-1,2-dichlorovinylphosphonic dichloride (Table 2.3.1.2.3, *entry 8*) in addition to penta- and hexachloroethane and pentachlorobutadiene (*87*). A hypothesis to account for these changes has not been advanced. Chlorine atoms replace fluorine atoms at the ends of the alkyl chain via the mechanism already discussed: $CF_2ClCFCl_2$ or CF_3CCl_3 convert to hexachloroethane (CCl_3CCl_3) and $CFCl_2CF_2CCl_3$ converts to 1,1,1,3,3,3-hexachloropropane ($CCl_3CF_2CCl_3$). These products, having terminal trichloromethyl groups like hexachloroethane, do not participate in the KP reaction. Alkylphosphonic dichlorides obtained from chlorodifluoromethane, dichlorodifluoromethane and 1-chloro-2-fluoroethane are the same as those from chloroform, carbon tetrachloride and 1,2-dichloroethane. Different polyhaloalkanes that give common chloroalkylphosphonic dichlorides are listed in Table 2.3.1.2.4.

3. **Use of phosphorus chlorofluorides**. Ethyl chloride reacts with PCl_3, $FPCl_2$ and F_2PCl to give ethylphosphonic dichloride in 82%, 22% and 15% yield, respectively, although slightly different reactant ratios were used each time (*48*). Alkylphosphonic chlorofluorides RP(O)ClF or

Table 2.3.1.2.4 Summary of polyhaloalkanes that transform into identical products

No.	Starting materials				Product	Intermediate
1	$CHClCF_2$	or	$CHCl_3$	→	$CHCl_2P(O)Cl_2$	$CHCl_2^+$
2	CCl_2F_2, CCl_3Br	or	CCl_4	→	$CCl_3P(O)Cl_2$	CCl_3^+
3	$ClCH_2CH_2F$	or	$ClCH_2CH_2Cl$	→	$ClCH_2CH_2P(O)Cl_2$	$ClCH_2CH_2^+$
4	CH_3CF_2Cl	or	CH_3CFCl_2	→	$CH_3CCl_2P(O)Cl_2$	$CH_3CCl_2^+$
5	$ClCH_2Cl$, $ClCH_2Br$	or	$BrCH_2Br$	→	$ClCH_2P(O)Cl_2$	$ClCH_2^+$

difluorides $RP(O)F_2$ are inaccessible using this approach because of halogen redistribution, e.g. $[EtPClF_2]^+[AlCl_4]^- \rightarrow [EtPCl_3]^+[AlCl_2F_2]^-$, prior to hydrolysis.

4. **Use of alkyl phosphorodichloridites**. Alkyl chlorides, alkyl phosphorodichloridites and aluminium trichloride react when mixed to give alkylphosphonic dichlorides (*48*). The assumed mechanism is shown in Fig. 2.3.1.2.7. It is proposed that in the intermediate **11**, chloride ion dealkylates the alkoxy group, forming the alkyl chloride and $RP(O)Cl_2 \cdot AlCl_3$ (*48*).

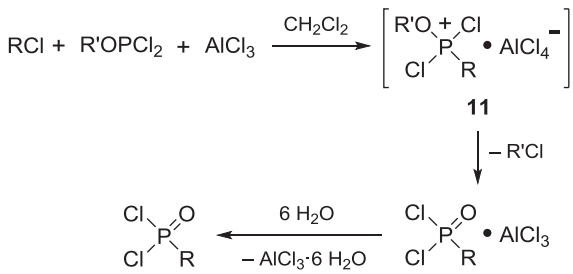


Figure 2.3.1.2.7

The salt (**11**) resembles the Arbuzov reaction intermediate $(RO)_3PR^+Cl^-$. *n*-Alkyl chlorides participating in the latter reaction do not usually isomerise, so it is interesting that in the KP reaction *n*-propyl chloride and $EtOPCl_2$ give *iso*propylphosphonic dichloride (45% yield vs. 90% from PCl_3). *Tert*-butyl chloride reacts similarly with *i*-$PrOPCl_2$ to give *tert*-butylphosphonic dichloride (75% yield vs 81% from PCl_3) (*48*).

5. **Use of dialkyl ethers instead of alkyl chlorides**. Dialkyl ethers react with a mixture of phosphorus trichloride and aluminium trichloride, the ether presumably cleaving to give the alkyl chloride and alkyl phosphorodichloridite, which transforms as described in the previous subsection. Diethyl ether, di-*n*-butyl ether, and *bis*(2-chloroethyl) ether yield ethylphosphonic dichloride, *s*-butylphosphonic dichloride, and 2-chloroethylphosphonic dichloride, respectively (Fig. 2.3.1.2.8) (*48*).

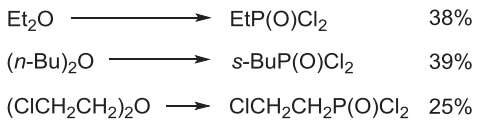


Figure 2.3.1.2.8

6. **Nonaqueous decomposition of the aluminium complex**. Treatment of $[MePCl_3]^+[AlCl_4]^-$ with dimethoxytetraglycol or diethyl phthalate [DEP: C_6H_4-1,2-$(CO_2Et)_2$] gives $MeO(CH_2CH_2O)_4Me \cdot AlCl_3$ or $DEP \cdot AlCl_3$ (*88*) and $MePCl_4$. The latter reacts with sulfur dioxide to furnish $MeP(O)Cl_2$ in 80–85% yield after vacuum distillation; cf. $MePF_4 + SO_2 \rightarrow MeP(O)F_2 + S(O)F_2$ (*89*). The process avoids aqueous workup, but has not been adopted widely. In contrast to compounds of the type $RPCl_4$, the aluminium complexes $[RPCl_3]^+[AlCl_4]^-$ and $[RPCl_3]^+[Al_2Cl_7]^-$ do not react readily with sulfur dioxide; prolonged treatment of the ethyl chloride derivatives with SO_2 at temperatures up to 100 °C failed to effect decomposition (*90*).

Synthetic procedures to selected alkylphosphonic dichlorides, some of whose ^{1}H-NMR spectroscopic properties have been studied (*91*), are now described:

▶ *Methylphosphonic dichloride MeP(O)Cl₂* (*55*). Powdered $AlCl_3$ (18.7 g, 0.137 mol) and PCl_3 (11 ml, 0.125 mol) were added to a 250-ml pressure glass bottle. A 2-cm-long magnetic stirrer bar was placed on the surface of the mixture (solid soaked with PCl_3) and pressurised MeCl (4.5 atm at 25 °C) was introduced. Starting the rotation of the stirrer bar on the surface of the mixture and maintaining the temperature at 25 °C caused the gradual formation of a viscous liquid. After 2 h, 96% of the initial PCl_3 charge had been consumed. Dichloromethane (225 ml) was added to dissolve the complex. A white precipitate formed instantly. The suspension was transferred to a 500-ml three-necked flask equipped with a condenser, an addition funnel and a mechanical stirrer, immersed in an ice bath at 0 °C. Water (25 ml) was added dropwise (1 ml/min) with vigorous stirring (1000 rpm) until the milky suspension suddenly coagulated to form granules (3–4 mm in diameter). The solution was filtered, and the filtrate was rotary evaporated under reduced pressure to give the product as a colourless solid (10.1 g, 61%, 98% pure), with δ_P ($CDCl_3$) 44.0 ppm (q, $^2J_{PH}$ 15 Hz).

▶ *Ethylphosphonic dichloride EtP(O)Cl₂* (*48*). Powdered $AlCl_3$ (66.8 g, 0.5 mol) and PCl_3 (34.3 g, 0.25 mol) were mixed in a flask and cooled to 0 °C. Ethyl chloride (16.1 g, 0.25 mol) was added and the flask securely stoppered. On standing with occasional stirring the $AlCl_3$ soon began to liquefy and the mixture was warmed to about 30 °C. The contents of the flask were shaken in intervals for about an hour, after which all solid material had disappeared. The flask was then cooled and opened, with little sign of pressure formation, and the liquid contents dissolved in CH_2Cl_2 (800 ml). The solution was cooled to −30 °C by the addition of solid carbon dioxide. Water (100 ml) was added a small quantity at a time, with vigorous stirring and venting. Stirring was continued until the gelatinous suspension first formed coagulated sufficiently to allow filtration. The solution was decanted through a filter, dried ($CaCl_2$) and the solvent removed. Distillation under reduced pressure gave the product as a colourless liquid (30.1 g, 82%). Bp 34 °C/3 mmHg.

▷ *Isopropylphosphonic dichloride i-PrP(O)Cl_2 (48)*. Powdered $AlCl_3$ (66.8 g, 0.5 mol) and PCl_3 (34.3 g, 0.25 mol) and isopropyl chloride (23.6 g, 0.30 mol) were mixed in this order and shaken in a stoppered flask at room temperature for about 1 h, during which time the mixture warmed slightly and liquefied. The product was stirred vigorously with CH_2Cl_2 (800 ml) and the suspension poured onto several litres of crushed ice. The organic layer was separated, dried ($CaCl_2$) and the volatile matter evaporated. Distillation under reduced pressure gave the product as a colourless liquid (28.2 g, 70%). Bp 35.5 °C/1.5 mmHg (bp 69.5 °C/12 mmHg and density 1.290 g/ml, 20 °C (*92*)).

▷ *Sec-butylphosphonyl dichloride s-BuP(O)Cl_2 (90)*. Anhydrous aluminium chloride (133 g, 1.0 mol) and phosphorus trichloride (250 ml, 1.2 mol) were placed in a 1-liter flask fitted with a reflux condenser. Butyl chloride (93 g, 1.0 mol; Note 1) was added in portions down the condenser, the flask being shaken after each addition to mix the reactants. The mixture was heated on an oil bath for 30 min, so that the trichloride refluxed gently, and was then allowed to cool. The excess phosphorus trichloride (Note 2) was carefully poured off and the solid residue after degassing at the water pump, was dissolved in dichloromethane (1000 ml), cooled to −20 °C by addition of solid carbon dioxide and hydrolysed at that temperature by dropwise addition of water (150 ml, ∼8.5 mol; Note 3) to the vigorously stirred solution. The resulting suspension was filtered, and the solid residue was washed with dichloromethane (2 × 200 ml). The filtrate and washings were distilled to low bulk and the residue after degassing at the water pump was distilled, and the fraction boiling between 80 and 100 °C was collected. Redistillation gave pure *sec*-butylphosphonyl dichloride (158–167 g, 90–95%). Bp 57 °C/2 mmHg. Notes: (1) Either *n*- or *s*-butyl chloride may be used. (2) The recovered trichloride can be used in subsequent runs. Where the nature of the alkyl halide is such that the aluminium chloride–alkyl chloride-phosphorus trichloride complex is a liquid, the excess trichloride must be removed by distillation. (3) The addition of 8–9 g mol of water per g mole of aluminium chloride used is recommended.

▷ *Tert-butylphosphonic dichloride t-BuP(O)Cl_2 (48)*. A mixture of *tert*-butyl chloride (29.6 g, 0.32 mol) and PCl_3 (34.4 g, 0.25 mol) was added gradually to powdered $AlCl_3$ (33.4 g, 0.25 mol). The temperature was not allowed to rise above 30 °C. The $AlCl_3$ dissolved within a few minutes and the complex was worked up in the usual way, 65 ml of water being used. Purification by vacuum sublimation gave the product as a colourless solid (35.2 g, 81%). Mp ∼ 110 °C. Sublimation at 90–100 °C/10 mmHg gave a product of mp 111–112 °C (*93*).

▷ *Tert-pentylphosphonic dichloride $EtMe_2CP(O)Cl_2$ (64)*. Neopentyl chloride (51 g, 0.48 mol) was added over 1 h to a mixture of PCl_3 (69 g, 0.5 mol) and anhydrous $AlCl_3$ (67 g, 0.5 mol) in anhydrous CH_2Cl_2 (200 ml). The temperature was held at −5 to −10 °C during this time. After addition, more CH_2Cl_2 (100 ml) was added to dissolve the complex. The solution was then cooled to −30 °C and hydrolysed by careful addition of water (80 ml), keeping the temperature below −20 °C. The reaction mixture was worked up as before. Vacuum fractionation gave the pure product (48 g, 51%). Bp 76.5 °C/5 mmHg.

▷ *Cyclohexylphosphonic dichloride c-$C_6H_{11}P(O)Cl_2$ (48)*. Cyclohexyl chloride (30 g, 0.25 mol) was added to a mixture of PCl_3 (69 g, 0.5 mol) and powdered $AlCl_3$ (67 g, 0.5 mol) at room temperature. Reaction commenced immediately, accompanied by a rise in temperature, and all solid material

dissolved within about 15 min. The product, hydrolysed in the normal manner (90 ml of water), yielded the product after distillation (41 g, 82% from cyclohexyl chloride). Bp 90 °C/1 mmHg.

▶ *Benzylphosphonic dichloride* $PhCH_2P(O)Cl_2$ (48). Phosphorus trichloride (151.3 g, 1.1 mol) and powdered $AlCl_3$ (66.8 g, 0.5 mol) were placed in a flask fitted with a mechanical stirrer, a reflux condenser and a dropping funnel. The temperature was raised to 40 °C and benzyl chloride (31.6 g, 0.25 mol) was added over 30 min, maintaining the temperature between 40 °C and 50 °C. Hydrogen chloride was evolved and all the $AlCl_3$, with the exception of a few granules, liquefied to form a brown lower layer. After removing the excess PCl_3 by distillation under reduced pressure, the complex in dichloromethane was hydrolysed, using 81 ml of water. The precipitated solid was brown and resinous. After filtration, drying ($CaCl_2$) and removal of solvent, the residue was distilled to give the product (32.4 g, 62% from benzyl chloride). Bp 130 °C/2 mmHg; mp 57.5 °C.

▶ *Allylphosphonic dichloride* $CH_2{=}CHCH_2P(O)Cl_2$ (48). Allyl chloride (19.1 g, 0.25 mol) was added to a stirred mixture of powdered anhydrous $AlCl_3$ (66.8 g, 0.5 mol) and PCl_3 (137.5 g, 1.0 mol) maintained for 30 min at 40–50 °C. The usual workup using water (81 ml) and vacuum fractionation gave the title compound (21 g, 53% from allyl chloride, bp 55 °C/3 mmHg), a higher boiling portion (2.5 g, bp 60–70 °C/3 mmHg) and an undistillable residue (2.5 g).

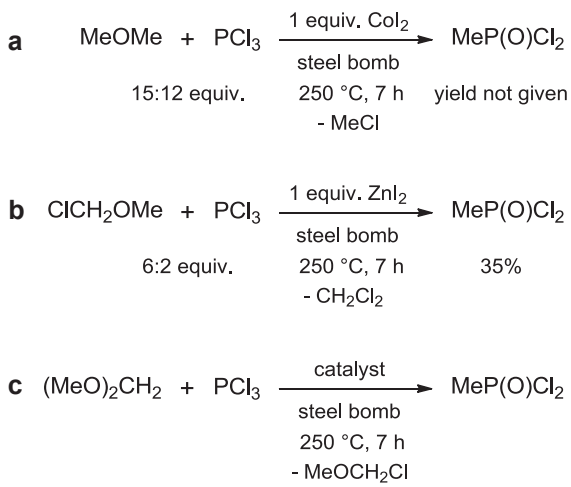
▶ *Trimethylsilylmethylphosphonic dichloride* $Me_3SiCH_2P(O)Cl_2$ (64). A mixture of PCl_3 (137.4 g, 1.0 mol) and anhydrous $AlCl_3$ (133.4 g, 1.0 mol) in anhydrous CH_2Cl_2 (300 ml) was prepared under nitrogen. Chloromethyltrimethylsilane (122.7 g, 1.0 mol) was added dropwise with stirring over 1 h while the reaction temperature was kept at 25–28 °C with external cooling. The mixture was stirred for an additional 1 h at 25 °C to give a clear solution of the complex. More CH_2Cl_2 (300 ml) was added and the solution was cooled to −30 °C (dry ice–acetone). Water (162 ml) was added dropwise with rapid stirring over 1 h. The temperature was kept below −20 °C to minimise hydrolysis of the phosphonic dichloride. Precipitated aluminium salt was removed on a filter and washed with CH_2Cl_2. The filtrate was dried over calcium chloride at 0 °C. Removal of solvent and distillation of the residue through an efficient column gave the pure product (64 g, 31%). Bp 64 °C/1.4 mmHg.

▶ *Trichloromethylphosphonic dichloride* $CCl_3P(O)Cl_2$ (94). Anhydrous powdered $AlCl_3$ (133.3 g, 1 mol), PCl_3 (137.4 g, 1 mol) and CCl_4 (184.6 g, 1.2 mol) were placed in a 2-litre round-bottomed three-necked flask fitted with an efficient reflux condenser, a mechanical stirrer and a dropping funnel (the equipment was dried beforehand and during the experiment was protected from moisture by calcium chloride guard tubes). The reactants were stirred slowly until thoroughly mixed, and then heat was applied carefully until the reaction began. At this point the liquid boiled vigorously and the reaction mixture thickened, so that faster stirring was required. The stirrer was stopped when the mixture solidified. After the mixture had cooled for 30 min, dichloromethane (1 l, distilled from $AlCl_3$ to prevent colouration of the product) was run into the flask, and the solvent was stirred vigorously until the solid was finely suspended. The reflux condenser was replaced by a low-temperature thermometer which dipped into the reaction mixture, the suspension was cooled (dry ice–acetone bath) and the temperature kept at −10 to −20 °C as distilled water (180 g, 10 mol) was added dropwise with vigorous stirring over a period of ∼25 min (vigorous stirring prevented caking of $AlCl_3 \cdot 6H_2O$ and unwanted localised hydrolysis of the product). After the addition, stirring was continued for 15 min

without the cold bath. The apparatus was dismantled. The reaction mixture was filtered quickly by suction through a 1.5-cm layer of filter aid on a 11-cm Büchner funnel placed on a 2-litre flask. The filter cake was pressed down well and washed with CH_2Cl_2 (3 × 50 ml). The filtrate was immediately protected from moisture by calcium chloride guard tubes, and the solvent was removed by distillation from the 2-litre flask. After the solution had been concentrated to about 225 ml, the hot liquid was poured into a suitable container (e.g. a 500-ml round-bottomed wide-mouthed flask) and the remaining solvent was removed under reduced pressure (the product may be warmed to aid solvent removal, but decomposes upon prolonged heating above 60 °C). The product was obtained as a white crystalline solid (192–199 g, 81–84%). Mp 155–156 °C.

2.3.2 Lewis-acid-catalysed alkylation of phosphorus trichloride

Prolonged heating of dimethyl ether, chloromethyl methyl ether or formaldehyde dimethyl acetal, with phosphorus trichloride and Lewis acid catalysts in autoclaves provides an industrial route to methylphosphonic dichloride (Fig. 2.3.2.1(a–c)) *(95–104)*. Nickel(II) iodide catalyst gave the highest yield of methylphosphonic dichloride (Fig. 2.3.2.1(c), *entry 1*).



No.	Mol.	Mol.	Catalyst	Yield (%)
1	6	2	1 mol NiI_2	61 [a]
2	15	5	1 mol MnI_2	51
3	18	6	1 mol PI_3	47
4	15	5	1 mol I_2	29

a. 225 °C, 7 h.

Figure 2.3.2.1 Pilot-scale routes to methylphosphonic dichloride *(97,100)*.

Alkyl chloromethyl ethers (e.g. made from ROH + paraformaldehyde + HCl) react with methyl phosphorodichloridite and iron(III) chloride to give alkoxymethylphosphonic dichlorides (Fig. 2.3.2.2) (*103,104*). Short-path distillations at temperatures below 80 °C and pressures below 0.2 mmHg are necessary to prevent their decomposition. Only methoxymethylphosphonic dichloride (**12**) appears to have been isolated pure using this route (*103,105*). The mechanism has not been proved but may resemble the one proposed for alkyl halides reacting with alkyl phosphorodichloridites in the presence of $AlCl_3$. Analogous complex formation, followed by chloride-promoted dealkylation of the methyl group, might regenerate $FeCl_3$ (phosphorus oxychloride yields $Cl_3P{=}O \cdot FeCl_3$ when mixed with an equimolar amount of ferric chloride in dichloromethane, and exists in nitromethane solution as the ionic species $[Cl_3P{=}O]_2 \cdot FeCl_2^{+} \cdot FeCl_4^{-}$ (*61*)).

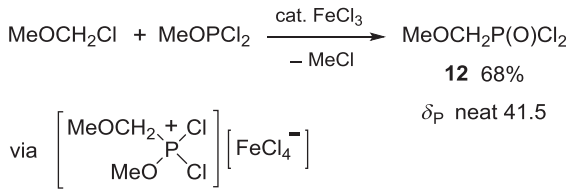


Figure 2.3.2.2

Phosphorus trichloride undergoes formaldehyde insertion and oxidation when heated strongly with paraformaldehyde in a sealed tube, providing chloromethylphosphonic dichloride (**13**) in acceptable yield (Fig. 2.3.2.3) (*106*).

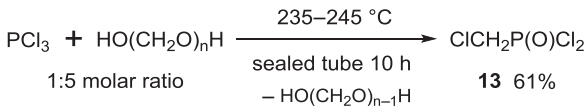


Figure 2.3.2.3

▶ *Methoxymethylphosphonic dichloride $MeOCH_2P(O)Cl_2$* (**12**) (*103*). Methyl phosphorodichloridite (199.4 g, 1.5 mol) and anhydrous $FeCl_3$ (4.9 g, 0.03 mol) were added to a three-necked flask fitted with a reflux condenser, a stirrer and a cooled trap (dry ice—acetone). Chloromethyl methyl ether (137.0 g, 1.7 mol) was added dropwise from a dropping funnel attached to the condenser over 30 min. During addition the temperature rose to 65 °C and the gas evolved was collected in the cooled trap and found to be methyl chloride. The reaction mixture was fractionated under reduced pressure (1—2 mmHg) to provide a portion boiling between 40 and 46 °C. Redistillation gave the pure product (166.3 g, 68%). Bp 40 °C/0.07 mmHg.

▶ *Chloromethylphosphonic dichloride* $ClCH_2P(O)Cl_2$ (**13**) (*106*). Phosphorus trichloride (35 g, 0.25 mol) and paraformaldehyde (5 g, 0.17 mol) were heated together in a sealed tube at 235–245 °C for 10 h. Phosphorus trichloride was distilled first from the reaction mixture at slightly reduced pressure, and then the residue was distilled at a lower pressure. Two distillations furnished the title compound (17.1 g, 61%). Bp 84–85 °C/13 mmHg. To prepare large amounts of chloromethylphosphonic dichloride the experiment can be conducted in an autoclave under the same conditions. Thus phosphorus trichloride (1.5 mol) and paraformaldehyde (1 mol) yielded the dichloride (0.6 mol) and in this way the compound could be prepared in any quantity. Chloromethylphosphonic dichloride is a colourless, mobile liquid that fumes slightly in air; it is insoluble in water, but reacts violently with it with evolution of heat. Bp 87–88 °C/15 mmHg, 78–79 °C/10 mmHg and 52–53 °C/2 mmHg.

2.3.3 Lewis-acid catalysed dichlorophosphonylation of alkanes

A reaction similar to the KP one was reported in 1990 by G.A. Olah and colleagues (*75*). Adding phosphorus trichloride to secondary or tertiary hydrocarbons and aluminium trichloride in dichloromethane, followed by acidic hydrolysis, yields the alkylphosphonic dichlorides (Fig. 2.3.3.1).

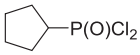
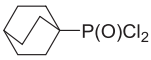
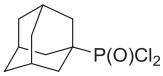
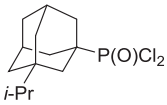
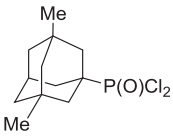
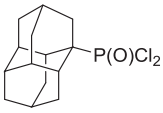
$$RH + PCl_3 + AlCl_3 \xrightarrow[-\,CH_3Cl]{CH_2Cl_2} [RPCl_3 \cdot AlCl_4] \xrightarrow[-\,2\,HCl]{10\%\ HCl\ aq.} RP(O)Cl_2 + AlCl_3 \cdot 6\,H_2O$$

Figure 2.3.3.1

The mechanism proposed involves interaction of the weak complex between aluminium trichloride and dichloromethane interacting with the alkane C–H bond, generating an alkyl chloride that then reacts with phosphorus trichloride (*75*). Replacing dichloromethane with other solvents reduces the yields substantially. Polycyclic alkanes best suit the method (Table 2.3.3.1).

▶ *(3,5-Dimethyladamantyl)phosphonic dichloride (aluminium trichloride method)* (*75*). Phosphorus trichloride (5.5 ml, 2 M solution in CH_2Cl_2, 11.0 mmol) was added dropwise over 10 min to a stirred suspension of 1,3-dimethyladamantane (1.64 g, 10.0 mmol), anhydrous $AlCl_3$ (1.72 g, 13.0 mmol) and anhydrous CH_2Cl_2 (25 ml) at 0 °C under nitrogen. After addition the reaction mixture was refluxed for 18 h and cooled. Hydrochloric acid (10% aq.) was added and the mixture was stirred for 30 min. Extraction was carried out with CH_2Cl_2 (3 × 5 ml) and the organic layers were combined and dried ($MgSO_4$). Removal of the drying agent, evaporation of solvent and column chromatography on silica gel, eluting with dichloromethane-hexane, gave colourless crystals (1.29 g, 46%). Mp 79–80 °C.

Table 2.3.3.1 Data for selected alkylphosphonic dichlorides derived from alkanes (*75,107*)

No.	Alkane	Reaction conditions Time (h)	Reaction conditions Temp. (°C)	Product	Bp (°C/mmHg)	Yield (%)	δ_P (neat)	$\nu_{P=O}$ (/cm)
1	*t*-butane	24	rt	*t*-BuP(O)Cl_2	45/30	10	65.0	1270
2	cyclopentane	22	reflux		nr	18	55.1	1260
3	bicyclo[2.2.2] octane	21	reflux		69/1	20	62.2	1250
4	adamantane	16	reflux		135/2 *	64	65.1	1265
5	1-isopropyl adamatane	20	rt		141/1	40	61.6	1270
6	1,3-dimethyl adamantane	18	reflux		mp 79 °C	46	61.2	1275
7	diamantane	17	reflux		mp 288 °C	60	62.3	1280

rt = room temperature. nr = not reported. * mp 102 °C (the purification procedure is given in reference 107)

Dichlorophosphonylation can also be effected by refluxing adamantane-based alcohols with phosphorus trichloride (*108*). Trifluoroacetic acid (TFA) can be added to increase product yields. 1- and 2-adamantanols (**14a—b**) react to yield the 1- and 2-substituted phosphonic dichlorides (**15a—b**) (Fig. 2.3.3.2). 1-Adamantylmethanol (**16**) gave the ring-expanded 3-homoadamantyl product (**17**). The mass spectral fragmentations of the products of such reactions are characteristic (*109*).

▶ *2-Adamantylphosphonic dichloride* (**15b**) (*108*). A solution of 2-adamantanol (0.30 g, 2 mmol) in a stirred mixture of phosphorus trichloride (0.39 ml, 4.4 mmol), TFA (1.50 ml, 20 mmol) and CF_3SO_3H (0.09 ml, 1 mmol) was maintained at 45 °C for 4 h. The volatile material was removed by rotary evaporation. Chromatography of the residue on silica gel, eluting with 1:1 chloroform:hexane, gave the title compound (0.47 g, 88%). Mp 80—82 °C. δ_P (121 MHz, $CDCl_3$) 54.1 ppm.

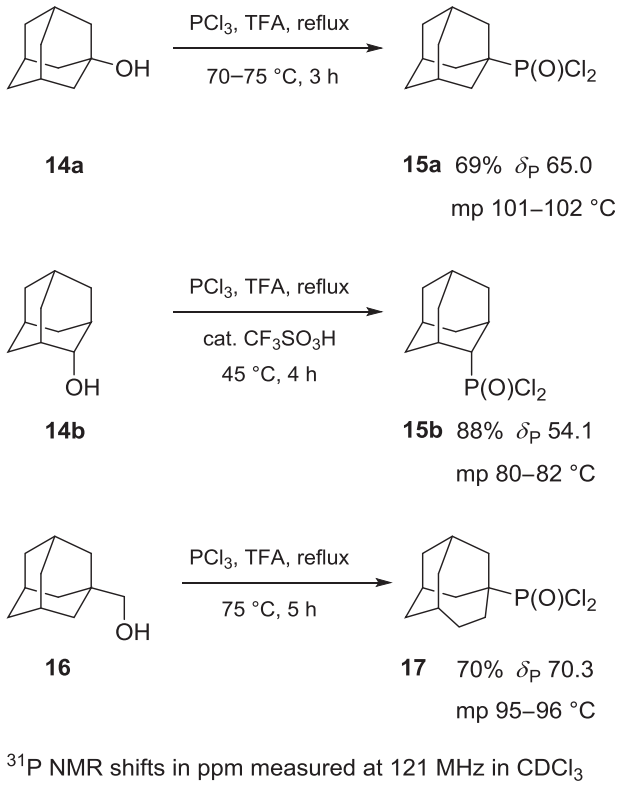


Figure 2.3.3.2

2.3.4 Oxidation of alkylphosphonous dichlorides

Alkylphosphonous dichlorides are oxidised by oxygen to alkylphosphonic dichlorides (Fig. 2.3.4.1) (*110*). The reaction is exothermic, allowing progress to be monitored by thermometer, although cooling to maintain a constant temperature of 35 °C is recommended. Alkylphosphonic dichlorides are also oxidised smoothly by sulfuryl chloride in benzene (*39*). This method often provides the

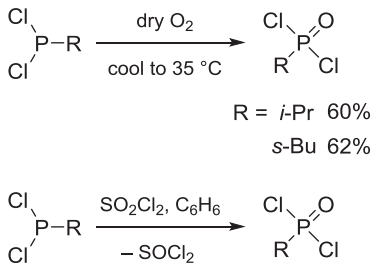


Figure 2.3.4.1

alkylphosphonic dichlorides in quantitative yield. Note that the starting alkylphosphonous dichlorides are not trivial to prepare and often transform slowly on exposure to air to amorphous yellow solids of unknown constitution.

Phenylphosphonous dichloride (**18**) adds chlorine to produce the tetrachlorophosphorane (**19**) whose oxidation can be accomplished using phosphorus pentoxide (*106,111*) or sulfur dioxide (*106*), giving phenylphosphonic dichloride (**20**) (Fig. 2.3.4.2). The yields are excellent and this approach can be used to prepare kilogram amounts of arylphosphonic dichlorides in a single run.

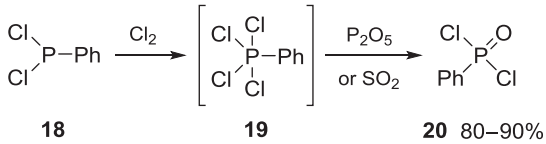


Figure 2.3.4.2

▶ *Isopropylphosphonic dichloride i-PrP(O)Cl$_2$* (*110*). Isopropylphosphonous dichloride (68.4 g, 0.47 mol) was weighed into a 200-ml three-necked flask fitted with a condenser, a thermometer, a gas inlet tube, and a magnetic stirrer bar. A slow stream of dry oxygen was passed through the stirred liquid with external water-cooling to maintain the temperature at 35 °C in the early stages. Oxygenation was continued for 8 h, by which time the temperature of the reaction mixture had dropped to room temperature. The reaction product was fractionated to give the title compound (45.5 g, 60%). Bp 37 °C/1.5 mmHg or 60 °C/5.6 mmHg. Using the same method, *s*-butylphosphonous dichloride (25.0 g, 0.16 mol) gave *s*-butylphosphonic dichloride (16.9 g, 62%). Bp 56 °C/2 mmHg.

▶ *Phenylphosphonic dichloride PhP(O)Cl$_2$* (**20**) *(phosphorus pentoxide method)* (*106,111*). A four-necked 3-litre flask equipped with a reflux condenser (topped with a calcium chloride drying tube), a mechanical stirrer, a thermometer and an inlet tube for the introduction of chlorine, was charged with phenylphosphonous dichloride (1611 g, 9 mol). Finely ground phosphorus pentoxide (511 g, 3.6 mol) was added and chlorine was passed, with stirring, into the liquid mixture that formed. The exotherm that was observed reached initially 150 °C, but dripping of phosphorus oxychloride from the condenser soon lowered the liquid temperature to 130 °C. The chlorine was passed at a rate sufficient to ensure a steady refluxing of the phosphorus oxychloride. After 4 h the temperature began to fall, indicating that the reaction was over. The flow of chlorine was stopped and the reaction mixture was fractionated. Most of the phosphorus oxychloride was distilled off at atmospheric pressure. Subsequent fractionation under reduced pressure gave the title compound (1550 g, 88%). Bp 258 °C/760 mmHg, 137–138 °C/15 mmHg, 104 °C/4 mmHg.

▶ *Phenylphosphonic dichloride PhP(O)Cl$_2$* (**20**) *(sulfur dioxide method)* (*106*). The apparatus was composed of a four-necked 4-litre flask equipped with a reflux condenser (topped with a calcium chloride drying tube), a mechanical stirrer, a thermometer and a T-piece; gas could be introduced through the side tube of the T-piece, and a glass rod fitted through a sleeve of pressure tubing (lubricated with glycerine) was inserted through the upper tube. The flask was charged with phenylphosphonous dichloride (1720 g, 9.6 mol) and carbon tetrachloride (1400 ml). The gas inlet tube

was adjusted so that it remained just above the surface of the liquid and dry chlorine was passed, with efficient stirring, into the flask for 6–8 h, while the internal temperature was maintained at 10–20 °C by exterior cooling (ice–salt mixture). Tetrachlorophenylphosphorane separated out as yellow-white crystals. The vertical section of the T-piece was periodically freed from crystals with the glass rod. After the exothermic reaction had ceased, chlorine was passed for a further 5–10 min, and then the end of the gas inlet tube was pushed below the surface of the semiliquid mass and dry sulfur dioxide gas was introduced (also with stirring and exterior cooling) until the crystals had dissolved completely and the reaction mixture had transformed into a homogeneous liquid. This was distilled to yield a highly volatile fraction (SO_2, $SOCl_2$, SO_2Cl_2, CCl_4) after which the residue was distilled under reduced pressure to give phenylphosphonic dichloride (1620–1650 g, 88–90%). Bp 83–84 °C/1 mmHg.

2.3.5 From dimethyl *H*-phosphonate and phosphorus pentachloride

Treatment of dimethyl *H*-phosphonate with sodium methoxide at low temperature yields dimethyl ether and a solid product, presumed to be disodium dimethylpyrophosphonate (**21**) (Fig. 2.3.5.1) (*112*). Acidification of this with methanolic hydrogen chloride liberates the diacid, HO(Me)P(O)OP(O)(Me)OH, which an excess of phosphorus pentachloride converts into methylphosphonic dichloride (**22**).

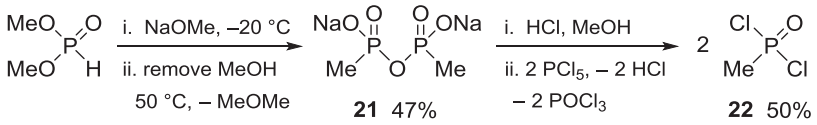


Figure 2.3.5.1

On exposure to relatively high temperature, dimethyl *H*-phosphonate (**23**) isomerises to methyl methylphosphonic acid (**24**), and at the same time, formation of the anhydride (**25**) occurs (Fig. 2.3.5.2). These various products can then be converted into methylphosphonic dichloride (*23*,*39*). The 'heat isomerisation' process, as this reaction has been called, has to be carried out in an inert atmosphere and requires careful control on a large scale. Nujol, a hydrocarbon of high molecular weight, can be used as a heat transfer medium, though small quantities of isomerised material are equally effective. Isomerisation is confined to dimethyl *H*-phosphonate and does not take place with the higher dialkyl *H*-phosphonates. Several side reactions occur, however, since quantities of dimethyl ether are evolved, and along with the products already mentioned, the free pyro-acid (**26**) and polymeric methylphosphonic anhydride (**27**) are also formed. The presence of all these products is of no concern since all of them on treatment with phosphorus pentachloride give methylphosphonic dichloride.

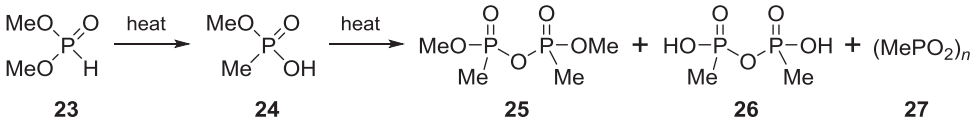


Figure 2.3.5.2

▶ *Methylphosphonic dichloride MeP(O)Cl$_2$* (**22**) (*112*). Dimethyl *H*-phosphonate (110 g, 1 mol) was added to a solution of sodium (23 g, 1 mol) in anhydrous methanol (400 ml) at −20 °C. After addition, the excess of methanol was removed in vacuo at ∼50 °C. A lively exothermic reaction occurred and a gas was liberated that was trapped at −78 °C. The reaction was moderated by cooling; when it subsided the product was slowly heated to 150 °C. A white, water-soluble salt was obtained. The low-temperature condensate was saturated with gaseous BF_3 with cooling, and $Me_2O \cdot BF_3$ (bp 127 °C, 10.7 g) was obtained, corresponding to a 47% yield of disodium dimethylpyrophosphonate (**21**) in the solid product. The latter was treated with an excess of methanolic HCl and the filtered solution concentrated. The residual viscous oil was added slowly to PCl_5 (400 g). When the exothermic reaction had ceased, the product was refluxed for 2 h, and volatile material (up to 108 °C) was removed. Distillation of the residue gave methylphosphonic dichloride (66 g, 50%). Bp 163 °C, mp 32 °C, δ_P (40.5 MHz, $CDCl_3$) −42.6 ppm (*113*).

2.3.6 From dialkyl alkylphosphonates and phosphorus pentachloride

Dialkyl alkylphosphonates react with two (or more) molar equivalents of phosphorus pentachloride to yield alkylphosphonic dichlorides, which are separated from the volatile byproducts — an alkyl chloride and phosphorus oxychloride — by vacuum fractionation (Fig. 2.3.6.1). An excess of

$$(R'O)_2P(O)R + 2\ PCl_5 \longrightarrow RP(O)Cl_2 + 2\ POCl_3 + 2\ R'Cl$$

Alkylphosphonic dichlorides

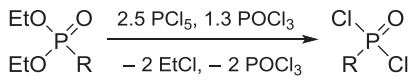
No.	Reactant	Molar proportions $(R'O)_2P(O)R$	PCl_5	Conditions	Product	Bp (°C/mmHg)	Yield (%)	Ref.
1	$(MeO)_2P(O)CH_2OMe$	1.0	2.0	55° C (2¾ h)	$MeOCH_2P(O)Cl_2$	95/12	43	(*105*)
2	$(EtO)_2P(O)Et$	1.0	2.4	reflux (1 h)	$EtP(O)Cl_2$	75/25	70	(*112*)
3	$(EtO)_2P(O)CH_2CH(Me)$*i*-Pr	1.0	2.7	reflux (1 h)	*i*-$PrCH(Me)CH_2P(O)Cl_2$	108/12	52	(*118*)
4	$(n\text{-}PrO)_2P(O)n\text{-}Pr$	1.0	2.8	reflux (1 h)	*n*-$PrP(O)Cl_2$	90/28	68	(*112*)
5	$(n\text{-}PrO)_2P(O)n\text{-}Pr$	1.0	2.1 [a]	reflux (2 h)	*n*-$PrP(O)Cl_2$	75/15	80	(*39*)
6	$(n\text{-}BuO)_2P(O)n\text{-}Pr$	1.0	2.0	150° C	*n*-$PrP(O)Cl_2$	78/14	75	(*92*)
7	$(n\text{-}BuO)_2P(O)n\text{-}Bu$	1.0	2.0	150° C	*n*-$BuP(O)Cl_2$	96/14	94	(*92*)
8	$(n\text{-}BuO)_2P(O)n\text{-}Bu$	1.0	2.4	reflux (1 h)	*n*-$BuP(O)Cl_2$	102/24	56	(*112*)
9	$(n\text{-}BuO)_2P(O)i\text{-}Bu$	1.0	2.0	150° C	*i*-$BuP(O)Cl_2$	86/12	70	(*92*)
10	$(n\text{-}BuO)_2P(O)C_{12}H_{25}\text{-}n$	1.0	2.0	100 °C (10 h)	*n*-$C_{12}H_{25}P(O)Cl_2$	145/1	65	(*92*)
11	$(n\text{-}BuO)_2P(O)CH(Me)C_{10}H_{21}$	1.0	2.0	100 °C (10 h)	$C_{10}H_{21}(Me)CHP(O)Cl_2$	153/1	65	(*92*)
12	$(EtO)_2P(O)C_8H_{17}\text{-}n$	1.0	2.0	reflux (1 h)	*n*-$C_8H_{17}P(O)Cl_2$	90/28	68	(*106*)
13	$(EtO)_2P(O)CH{=}CH_2$	1.0	2.0	25 °C (1 h)	$CH_2{=}CHP(O)Cl_2$	75/18	69	(*39*)
14	$(i\text{-}PrO)_2P(O)CH{=}CHMe$	1.0	2.0	100 °C (1 h)	$MeCH{=}CHP(O)Cl_2$	60/3	83	(*39*)

a. PCl_5 was prepared *in situ* by bubbling chlorine through a mixture of di-*n*-propyl *n*-propylphosphonate and phosphorus trichloride.

Figure 2.3.6.1

phosphorus pentachloride, used only if necessary, is usually removed prior to distillation by bubbling sulfur dioxide into the mixture ($PCl_5 + SO_2 \rightarrow POCl_3 + SOCl_2$). The phosphorus pentachloride reagent can be prepared *in situ* if necessary by bubbling chlorine into a mixture of the dialkyl alkylphosphonate and phosphorus trichloride.

Diethyl alkylphosphonates are converted readily into alkylphosphonic dichlorides when heated with a mixture of phosphorus pentachloride (2.5 mol equiv.) and phosphorus oxychloride (1.3 mol equiv.) (Fig. 2.3.6.2) (*114*). A temperature in the range 25—100 °C and a reaction time of 4—24 h needs to be employed, depending on the structure of the starting phosphonate.



Alkylphosphonic dichlorides

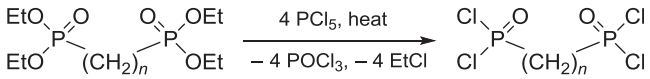
No.	R	Temp. (°C)	Time (h)	Yield (%) [a]	Bp (°C/mmHg)	δ_P (ppm) [b]
1	Et	25	24	90	110–115/16	54.4
2	*i*-Pr	110	4	84	130–135/16	61.9
3	*n*-Bu	110	4	86	160–165/16	51.9
4	*i*-Bu	110	4	83	150–155/16	49.9
5	Bn	110	4	82	185–190/16	46.0
6	CH(Cl)Me	110	4	88	150–155/16	46.1
7	CH(Br)Me	110	4	84	160–165/16	44.1
8	CH_2CO_2Et	60	24	95	220–225/16	33.9

a. Isolated yield. *b*. Measured at 81 MHz in $CDCl_3$.

Figure 2.3.6.2

With an increase in steric hindrance at the carbon atom a longer reaction time is required to obtain good yields. In the absence of PCl_5 monochlorination occurs exclusively, even after a prolonged reaction time. It is apparent that PCl_5 and $POCl_3$ synergistically promote the dichlorination. Two successive reactions occur as evidenced by monitoring by ^{31}P NMR spectroscopy. Examination of the crude mixture at the start shows signals for $POCl_3$ (δ_P 4.5 ppm), the starting diethyl alkylphosphonate, the monochlorinated product (one signal for a nonasymmetric α-carbon atom and two signals for two diastereoisomers for an unsymmetrically disubstituted α-carbon atom) and the expected dichloride in the range δ_P 34—62 ppm. After a few hours, the signals for the diethyl alkylphosphonates and monochlorinated products (ethyl alkylphosphonochloridates) disappear successively: nonetheless, if the reaction mixture is overheated, byproducts can be detected in the ^{31}P NMR spectrum. The method permits easy preparation of alkylphosphonic dichlorides and is widely applicable. However, the reproducibility relies on the use of freshly purified diethyl alkylphosphonate starting material.

Alkylene bisphosphonic tetraesters react with 4 molar equivalents of phosphorus pentachloride to provide the corresponding bisphosphonic dichlorides in acceptable yield (*115*,*116*) (Fig. 2.3.6.3).



Alkylenebisphosphonic dichlorides

n	Yield (%)	Mp (°C)	Bp (°C/mmHg)
1	52	104–105	-
2	64	167–170	-
3	49	60–62	-
4	85	110–112	-
5	37	60–62	165/0.3
6	39	60–62	166/0.2
7	80	32–34	178/0.2
8	65	63–65	184/0.3
9	59	39–40	191/0.2
10	51	70–72	196/0.3

Figure 2.3.6.3

The product of the Arbuzov reaction of 2 molar equivalents of triethyl phosphite and 1,2-dichloro-3,3,4,4,5,5-hexafluorocyclobutene (**28**) reacts with an excess of phosphorus pentachloride to provide the trichloride (**29**) (Fig. 2.3.6.4) (*117*). One of the diethyl phosphonyl groups is replaced by chlorine, representing an unusual P—C bond cleavage. This also occurs upon similar treatment of the diphosphonic acid (**30**). However, in this case, it is possible to isolate the diphosphonic tetrachloride (**31**) as the major component.

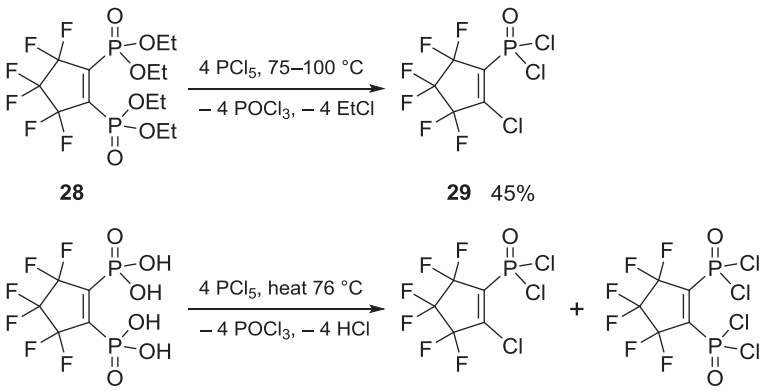


Figure 2.3.6.4

There are two options available for the synthesis of vinylphosphonic dichloride: chlorination of diethyl vinylphosphonate (**32**) with 2 molar equivalents of phosphorus pentachloride (*39*) or dehydrochlorination of 2-chloroethylphosphonic dichloride (**33**) by passing its vapour through a heated quartz tube packed with anhydrous barium chloride (*106*) (Fig. 2.3.6.5). In both cases the yield of the vinyl product (**34**) is high.

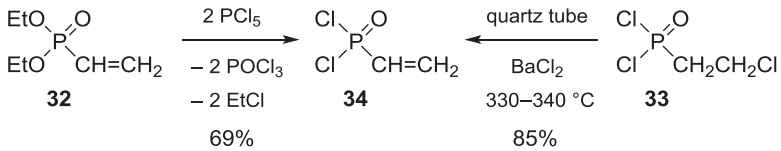


Figure 2.3.6.5

The related species, 2-chlorobuta-1,3-dienylphosphonic dichloride (**35**), can be prepared by treating phosphorus trichloride with vinylacetylene at low temperature (Fig. 2.3.6.6) (*106*). In this particular case the yield of product is low. The derivative from hydrogenation of this product at the double bond attached to the phosphorus atom, namely, 2-chlorobut-3-enylphosphonic dichloride (**36**), is obtained by addition of phosphorus pentachloride to butadiene in benzene, followed by oxidation of the obtained pentachlorophosphorane with sulfur dioxide (*106*). In this instance distillation furnishes the product in excellent yield.

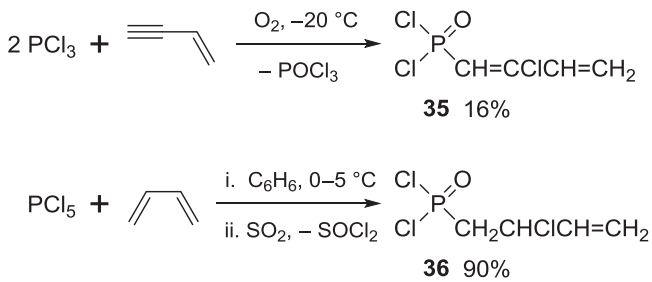


Figure 2.3.6.6

▶ *n-Propylphosphonic dichloride n-PrP(O)Cl$_2$* (*112*). Di-*n*-propyl *n*-propylphosphonate (104 g, 0.5 mol) was added dropwise to PCl_5 (300 g, 1.4 mol). After addition the mixture was refluxed for 1 h. Volatile material (*n*-propyl chloride and phosphorus oxychloride) was removed and the product was isolated after distillation (55 g, 68%). Bp 90—91 °C/28 mmHg.

▶ *n-Butylphosphonic dichloride n-BuP(O)Cl$_2$* (*92*). Phosphorus pentachloride (417 g, 2 mol) was added in small portions with stirring to di-*n*-butyl *n*-butylphosphonate (250 g, 1 mol) heated to 150 °C. At the end of a lively reaction a vacuum was applied and low-boiling products (*n*-BuCl and $POCl_3$) were removed. Fractionation of the residue gave *n*-butylphosphonic dichloride (165 g, 94%). Bp 96 °C/14 mmHg. Density 1.238 g/ml at 20 °C.

▶ *2,3-Dimethylbutylphosphonic dichloride i-PrCH(Me)CH$_2$P(O)Cl$_2$* (*118*). Phosphorus pentachloride (25.4 g, 122 mmol) was added slowly to diethyl 2,3-dimethylbutylphosphonate (10.2 g, 45.8 mmol)

contained in a 100-ml flask protected from moisture. There appeared to be no reaction at room temperature, but on heating to 60–70 °C a vigorous reaction occurred, which was complete after refluxing for 1 h. Excess PCl_5 was destroyed by passing sulfur dioxide through the mixture. The product was isolated by distillation (4.8 g, 52%). Bp 107–109 °C/12 mmHg. Density 1.174 g/ml at 20 °C.

▶ *n-Propylphosphonic dichloride n-PrP(O)Cl_2 (39)*. Di-*n*-propyl *n*-propylphosphonate (bp 96 °C/1 mmHg from tri-*n*-propyl phosphite and *n*-propyl iodide by the Arbuzov reaction) (68 g, 0.33 mol) and phosphorus trichloride (60 ml, 0.69 mol) were placed in a three-necked flask fitted with a fractionating column attached to a condenser set for distillation, a sealed stirrer and a gas inlet tube. Stirring was started and chlorine introduced at such a rate that *n*-propyl chloride distilled steadily through the column. When a yellow colour persisted in the reaction mixture, the column was replaced by a reflux condenser and the mixture heated to gentle boiling for 2 h. The phosphorus oxychloride formed was then removed and the residue distilled under vacuum to give a colourless liquid (42 g, 80%). Bp 74–75 °C/15 mmHg.

▶ *n-Octylphosphonic dichloride n-C_8H_{17}P(O)Cl_2 (39)*. Phosphorus pentachloride (124 g, 0.6 mol) was placed in a flask equipped with a stirrer, a dropping funnel and a reflux condenser. The flask was placed in a bath heated to 60–70 °C and diethyl *n*-octylphosphonate (bp 135–137 °C/4 mmHg in 78% yield from triethyl phosphite and *n*-octyl bromide by the Arbuzov reaction) (about 15 g, 60 mmol) added. As soon as the reaction had moderated, more of the ester was added dropwise until a total of 75.5 g (0.3 mol) had been introduced. After heating for 2 h at 100 °C, the phosphorus oxychloride was recovered and the residue fractionated under reduced pressure to provide the title compound as a colourless liquid (51 g, 75%). Bp 148–150 °C/13 mmHg. Other *n*-alkylphosphonic dichlorides can be prepared by a similar procedure. These include *n*-butylphosphonic dichloride (74% yield, bp 68–70 °C/4 mmHg), *n*-pentylphosphonic dichloride (75% yield, bp 80 °C/4 mmHg), *n*-hexylphosphonic dichloride (73% yield, bp 105 °C/6 mmHg) and *n*-heptylphosphonic dichloride (71% yield, bp 112–113 °C/5 mmHg).

▶ *Alkylphosphonic dichlorides RP(O)Cl_2 (from diethyl alkylphosphonates, phosphorus pentachloride and phosphorus oxychloride) (114)*. A 1-litre oven-dried pressure bottle equipped with a magnetic stirring bar, and filled with freshly distilled diethyl alkylphosphonate (30 mmol), phosphorus pentachloride (15.6 g, 75 mmol) and phosphorus oxychloride (6.0 g, 39 mmol), was closed with a rubber stopper. The mixture was heated in an oil bath for a set time (refer to Fig. 2.3.6.2). During this period the mixture rapidly became homogeneous. The mixture was allowed to cool to room temperature. It was transferred into a distillation flask and the excess of PCl_5 and $POCl_3$ was removed by rotary evaporation at 35–40 °C for about 1 h. Kugelrohr distillation under reduced pressure gave pure specimens of the alkylphosphonic dichlorides.

▶ *2-Chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-ylphosphonic dichloride* (**29**) *(117)*. Phosphorus pentachloride (876 g, 4.2 mol) was added in portions to tetraethyl-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1,2-ylenediphosphonate (448 g, 1.0 mol) at 75–100 °C at a rate sufficient to maintain a vigorous evolution of ethyl chloride. Once the evolution of gas subsided, after 14 h, the mixture was distilled at atmospheric pressure until most of the $POCl_3$ was removed. The temperature was raised to

140 °C and more phosphorus pentachloride was added periodically until either no more ethyl chloride evolution could be induced or phosphorus oxychloride distilled. The reaction mixture was cooled to 70 °C, purged with sulfur dioxide and then nitrogen, and distilled to provide the title compound (140.5 g, 45%). Bp 49–50 °C/0.6 mmHg.

▷ *3,3,4,4,5,5-Hexafluoro-1-cyclopenten-1,2-ylenediphosphonic tetrachloride* (**31**) (*117*). A solution of 3,3,4,4,5,5-hexafluoro-1-cyclopenten-1,2-ylenediphosphonic acid (114.0 g, 0.34 mol) in phosphorus oxychloride (500 ml) was treated with phosphorus pentachloride (298.0 g, 1.43 mol) in portions over 30 min at 30–40 °C. Gas evolution was brisk. The temperature was raised gradually to 76 °C, and when the gas evolution subsided, after 3.5 h, the solvent was removed under vacuum while keeping the pot temperature below 70 °C. Vacuum fractionation of the partly solid residue (139.5 g) gave three fractions: (1) 11.6 g, bp 52–55 °C/1.3 mmHg; (2) 16.6 g, bp 53–58 °C/1.3–0.8 mmHg; and (3) 90.2 g, bp 89–90 °C/0.45 mmHg. The first fraction was composed of the trichloride **29** (11.6 g, 25%) and the third fraction contained the title compound (90.2 g, 65%) which crystallised on cooling. Mp 79–82 °C.

▷ *Vinylphosphonic dichloride* $CH_2{=}CHP(O)Cl_2$ (**34**) (*39*). Phosphorus pentachloride (41.6 g, 200 mmol) was added gradually to diethyl vinylphosphonate (16.4 g, 100 mmol), the mixture being cooled during the addition. On fractionating, vinylphosphonic dichloride (10 g, 69%, bp 65 °C/18 mmHg) was obtained together with a small amount of ethyl vinylphosphonochloridate (2.0 g, bp 75 °C/18 mmHg). The latter was also obtained in poor yield by the action of phosgene on diethyl vinylphosphonate.

▷ *Vinylphosphonic dichloride* $CH_2{=}CHP(O)Cl_2$ (**34**) (*106*). 2-Chloroethylphosphonic dichloride (45.4 g, 0.25 mol) was passed in an inert gas stream over 4 h into a quartz tube packed with anhydrous barium chloride (small pieces about 1–2 mm in size) heated to 330–340 °C. The reaction product was condensed and twice fractionated under reduced pressure to give the title compound as a colourless liquid (30.8 g, 85%). Bp 69–71 °C/21 mmHg. Dehydrochlorination at a lower temperature led to a reduction in yield.

▷ *Propenylphosphonic dichloride* $CH_3CH{=}CHP(O)Cl_2$ (*39*). Diisopropyl propenylphosphonate (49 g, 0.24 mol) was added to stirred phosphorus pentachloride (100 g, 0.48 mol) suspended in phosphorus oxychloride (50 ml). The reaction was completed by warming to 100 °C for 1 h. After recovery of the phosphorus oxychloride, the product was obtained by distillation under reduced pressure (31.5 g, 83%; bp 81–83 °C/14 mmHg). An analytically pure specimen was isolated by a second distillation. Bp 59.5 °C/3 mmHg. The preparation proceeds much more smoothly with the diisopropyl ester than with the diethyl ester.

▷ *2-Chlorobuta-1,3-dienylphosphonic dichloride* $CH_2{=}CHCCl{=}CHP(O)Cl_2$ (**35**) (*106*). Oxygen was passed into a mixture of vinylacetylene (26.0 g, 0.5 mol) and phosphorus trichloride (137.5 g, 1 mol) at a rate of 4 l/h at −20 °C. A total of 36 l of oxygen was introduced. After evaporation of the phosphorus oxychloride, the residue was distilled to furnish the title compound (15.5 g, 16%; bp 70–75 °C/2.5 mmHg) and then redistilled to give a pure specimen. Bp 71–73 °C/4 mmHg.

▷ *2-Chlorobut-3-enylphosphonic dichloride* $CH_2{=}CHCHClCH_2P(O)Cl_2$ (**36**) (*106*). Phosphorus pentachloride (208 g, 1.0 mol) and dry benzene (250 ml) were placed in a three-necked flask equipped

with a condenser, a mechanical stirrer and a gas inlet tube. Butadiene (85–90 g, 1.6–1.7 mol) was passed into the stirred and ice-cooled mixture. After the passage of butadiene a pale yellow crystalline mass formed and the reaction mixture was left overnight. On the following day it was treated with sulfur dioxide gas until the crystalline mass dissolved. After evaporation of the solvent, phosphorus oxychloride and thionyl chloride, the title compound was obtained by distillation under reduced pressure (114 g, 90%). Bp 103–105 °C/2 mmHg.

2.3.7 Oxidative chlorophosphonylation of alkenes with phosphorus trichloride

The oxidative chlorophosphonylation of alkenes using phosphorus trichloride and oxygen often yields mixtures of products that are difficult to separate, and is therefore of limited synthetic utility (unlike the oxidative chlorophosphonylation of vinylacetylene, see the previous section). The reaction of allyl chloride provides three products that co-distil during attempted fractionation under reduced pressure (Fig. 2.3.7.1) (*119*). The products are 1,3-dichloropropyl-2-phosphonic dichloride (**37**), 1,3-dichloro-2-propyl phosphorodichloridate (**38**) and 2,3-dichloropropyl-1-phosphonic dichloride (**39**).

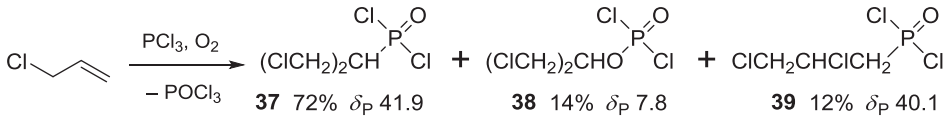


Figure 2.3.7.1

2.3.8 Chlorination of *bis*(trimethylsilyl) alkylphosphonates with oxalyl chloride

A convenient method of conversion of dialkyl alkylphosphonates to alkylphosphonic dichlorides involves the use of intermediate *bis*(trimethylsilyl) alkylphosphonates, and their treatment with oxalyl chloride and *N*,*N*-dimethylformamide (DMF) catalyst (*120*). A sequence where diisopropyl d_3-methylphosphonate (**40**) is converted to *bis*(trimethylsilyl) d_3-methylphosphonate (**41**), and then to d_3-methylphosphonic dichloride (**42**) is provided as an illustrative example (Fig. 2.3.8.1).

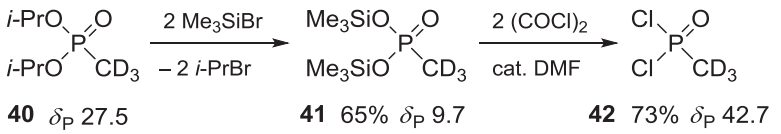


Figure 2.3.8.1

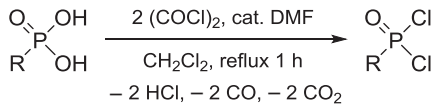
▶ *Bis(trimethylsilyl) d_3-methylphosphonate $(Me_3SiO)_2P(O)CD_3$* (**41**) (*121*). Bromotrimethylsilane (TMSBr) (27.4 g, 179 mmol) was added in one portion to diisopropyl d_3-methylphosphonate (14.4 g, 79 mmol) in anhydrous dichloromethane (90 ml). A slight warming of the flask was observed and the dark orange solution paled in colour. The reaction mixture was stirred for 12 h. Volatile material was

removed on a rotary evaporator, and the residue was distilled under reduced pressure to give a colourless liquid (12.5 g, 65%). Bp 80 °C/10 mmHg. δ_P ($CDCl_3$) 9.7 ppm.

▶ *d_3-Methylphosphonic dichloride $CD_3P(O)Cl_2$* (**42**) (*121*). Oxalyl chloride (19.0 g, 150 mmol) was added over 10 min to a stirred solution of *bis*(trimethylsilyl) d_3-methylphosphonate (36.5 g, 150 mmol) in anhydrous dichloromethane (70 ml) containing DMF (250 µl). After the addition, stirring was continued for 1 h. The solvent was removed and the residue was distilled under reduced pressure to afford a colourless liquid (14.8 g, 73%). Bp 59 °C/12 mmHg. δ_P ($CDCl_3$) 42.7 ppm.

2.3.9 Chlorination of alkyl/arylphosphonic acids with oxalyl chloride

The DMF-catalysed reaction of alkyl/arylphosphonic acids with oxalyl chloride is strongly endothermic and liberates large quantities of gas (hydrogen chloride, carbon monoxide and carbon dioxide) (Fig. 2.3.9.1) (*122*). The pure alkyl/arylphosphonic dichlorides are obtained in high purity after solvent removal and distillation under vacuum.



Alkyl/arylphosphonic dichlorides

R	Yield (%) [a]	Bp (°C/mmHg)	δ_P (ppm) [b]
c-C_6H_{11}	92	178/21	59.6
$H_2C{=}CHCH_2$	85	127/8	33.1
Ph	89	107/4	37.3

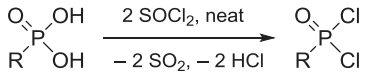
a. Isolated yield after distillation. *b.* 81 MHz measured in $CDCl_3$.

Figure 2.3.9.1

▶ *Phenylphosphonic dichloride* (*122*). A solution of phenylphosphonic acid (2.0 g, 12.7 mmol; δ_P 20.9 ppm in $CDCl_3$) and anhydrous DMF (10 µl) in anhydrous dichloromethane (30 ml) was refluxed gently under nitrogen. A solution of oxalyl chloride (2.4 ml, 3.6 g, 28.4 mmol) in anhydrous dichloromethane (20 ml) was added via a pressure-equalising addition funnel whose drip tube, extended with Teflon tubing, reached into the reaction mixture. Copious effervescence occurred and heat was applied to maintain the temperature at 35 °C. After addition, the mixture was refluxed for 1 h. The condenser was replaced by a still head and volatile material removed (distillation temperature less than 70 °C at 763 mmHg). Analysis of the residual brown liquid (2.3 g, 93%) by ^{31}P-NMR spectroscopy revealed a single peak consistent with clean formation of phenylphosphonic dichloride. The product could be used for transformations without further purification, although, if necessary, pure material could be obtained by distillation. Bp 107 °C/4 mmHg. δ_P (81 MHz, $CDCl_3$) 37.3 ppm.

2.3.10 Chlorination of alkyl/arylphosphonic acids with thionyl chloride

Heating alkylphosphonic acids with 2 molar equivalents of thionyl chloride provides after distillation the alkylphosphonic dichloride in typically high yields (60–80%) (Fig. 2.3.10.1) (*123*). Infrared vibrations for many of the products have been documented (*124*).



Alkylphosphonic dichlorides

R	(°C/mmHg)	R	(°C/mmHg)
Me	102/760	1-Hexyl	82/2
Et	91/31	2-Hexyl	70/2
n-Pr	70/10	3-Hexyl	73/2
i-Pr	81/20	1-Heptyl	82/0.1
n-Bu	88/10	1-Octyl	78/0.2
i-Bu	82/11	1-Nonyl	98/0.1
1-Pentyl	76/5	1-Decyl	115/1
2-Pentyl	70/2	2-Decyl	47/0.02

Figure 2.3.10.1

▶ *d_3-Methylphosphonic dichloride $CD_3P(O)Cl_2$* (*125*). Diisopropyl d_3-methylphosphonate (2.82 g, 15.4 mmol) was heated to 145 °C with concentrated hydrochloric acid (2.5 mol equiv.) to produce d_3-methylphosphonic acid (1.50 g, 99%). The dried acid was then chlorinated with thionyl chloride at 105 °C until the evolution of HCl gas stopped. Fractionation gave the title compound (yield not stated). Bp 85–90 °C/20 mmHg.

▶ *Ethylphosphonic dichloride $EtP(O)Cl_2$* (*126*). Ethylphosphonic acid (110 g, 1 mol) and thionyl chloride (600 g, 5 mol) were stirred and heated to 70 °C for 14 h. Distillation of the mixture gave the dichloride (yield not stated). Bp 91 °C/31 mmHg.

▶ *n-Butylphosphonic dichloride $n\text{-}BuP(O)Cl_2$* (*126*). *n*-Butylphosphonic acid (138 g, 1 mol) and thionyl chloride (600 g, 5 mol) were stirred and heated to 70 °C for 16 h. Distillation of the mixture gave the dichloride (yield not stated). Bp 97–105 °C/40 mmHg.

2.4 ALKYLPHOSPHONIC DIBROMIDES $RP(O)Br_2$

Alkylphosphonic dibromides are encountered far less commonly than alkylphosphonic dichlorides and have been studied in less detail. This is because alkylphosphonic dihalides are generally used as intermediates to other compounds and the less reactive and often more easily synthesised dichlorides often suffice for this purpose. Alkylphosphonic dibromides can be obtained by heating the

corresponding dichlorides with phosphorus tribromide (e.g. **22** → **43**) and removal of the formed phosphorus trichloride by distillation (Fig. 2.4.1) (*127*). The optimum reaction temperature is 170–190 °C. The rate of reaction falls at a lower temperature, while at a higher temperature the yield decreases due to tarring. Dibromophosphonylation of 1-adamantanol (**14a**) by phosphorus tribromide in refluxing TFA gives after chromatography on silica gel the solid 1-adamantylphosphonic dibromide (**44**) (Fig. 2.4.1) (*108*).

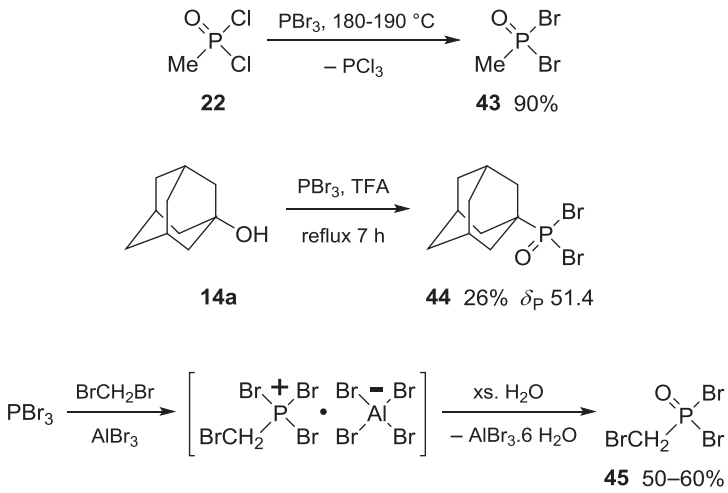


Figure 2.4.1

Phosphorus tribromide, alkyl bromides and aluminium tribromide when mixed permit preparation of the phosphonic dibromides $BrCH_2P(O)Br_2$ (Fig. 2.4.1) (*128,129*), $Br_2CHP(O)Br_2$ and $BrCH_2CH_2P(O)Br_2$ (bp 94 °C/4 mmHg) (*130,131*). The use of $AlBr_3$ does not cause isomerisation of the carbon chain of the alkyl halide (*131*). Alkylphosphonic dibromides participate in many of the reactions typical of alkylphosphonic dichlorides.

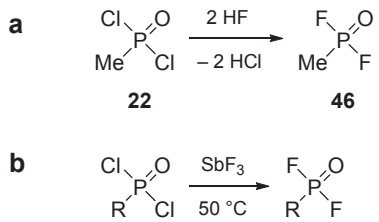
▶ *Methylphosphonic dibromide MeP(O)Br₂* (**43**) (*127*). Methylphosphonic dichloride (26.6 g, 0.20 mol) and phosphorus tribromide (35.6 g, 0.13 mol) were heated with stirring in a flask fitted with a Vigreux column and distillation system. Phosphorus trichloride distilled over at a bath temperature of 180–190 °C. Fractionation of the residue gave methylphosphonic dibromide (39 g, 90%). Bp 65–66 °C/9 mmHg.

▶ *1-Adamantylphosphonic dibromide* (**44**) (*108*). A mixture of 1-adamantanol (0.30 g, 2 mmol), phosphorus tribromide (0.46 ml, 4.4 mmol) and TFA (1.5 ml, 20 mmol) was heated under reflux for 7 h. The mixture was cooled and water (5 ml) was added carefully. The mixture was extracted with chloroform (30 ml) and the organic layer was washed with water (20 ml), dried ($MgSO_4$) and concentrated under vacuum. Chromatography of the residue on silica gel, eluting with 1:1 chloroform-hexane, gave the title compound (0.16 g, 26%). Mp 114–116 °C. δ_P (121 MHz, $CDCl_3$) 51.4 ppm.

▶ *Bromomethylphosphonic dibromide* $BrCH_2P(O)Br_2$ (**45**) (*128*). Anhydrous aluminium bromide (280 g, ~1 mol) and phosphorus tribromide (272 g, 1 mol) were placed in a 1-litre flask fitted with an efficient reflux condenser, and dibromomethane (500 ml, excess) was added in portions down the condenser, while the flask was cooled under running water. The mixture was heated cautiously to reflux, and then boiled for 2 h when it became a homogeneous deep red liquid. The bulk (350 ml) of the dibromomethane was removed by distillation, and the residual syrup was poured into a large evaporating basin which was placed in a dessicator while the product was allowed to solidify. The solid was quickly broken into coarse lumps and then transferred to a 3-litre beaker containing dichloromethane (1200 ml) cooled to −20 °C by the addition of solid carbon dioxide. The suspension was stirred rapidly with a metal-bladed stirrer until the solid thoroughly disintegrated, and then water (160 ml, 8.5 mol) was added dropwise from a funnel while the mixture was kept at −20 °C by adding more carbon dioxide. After the hydrolysis had been performed, the stirrer was removed and the mixture was filtered through a sintered glass funnel. The precipitate was washed with dichloromethane (2 × 200 ml), and the filtrate and washings were distilled to low bulk, and degassed at the water pump. The residue was distilled and the fraction (154−180 g, 50−60%) boiling between 130 and 138 °C/12−14 mmHg was collected. Redistillation afforded bromomethylphosphonic dibromide. Bp 118−120 °C/7 mmHg.

2.5 ALKYLPHOSPHONIC DIFLUORIDES $RP(O)F_2$

Alkylphosphonic difluorides can be obtained from the dichlorides (with the exception of the *tert*-butylphosphonic compound) by the action of anhydrous hydrogen fluoride (e.g. **22**→**46**) (Fig. 2.5.1(a)) (*132*). With *tert*-butylphosphonic dichloride, it is necessary to use a powerful



Alkylphosphonic difluorides

R	Bp (°C/mmHg)	Yield (%)	Ref.
Et	100–111/760	73	(*133*)
n-Pr	68–70/15	75	(*133*)
t-Bu	116/760	nr	(*39*)
MeCH=CH	113/760	42	(*39*)
CCl_3	96/760	68	(*138*)
$PhCH_2$ [a]	64/0.2	60	(*138*)
Ph	78/15	nr	(*133*)

a. Fluorinated by ZnF_2 at 70 °C for 1 h.
nr = not reported in the original reference.

Figure 2.5.1

fluorinating agent such as antimony trifluoride (Fig. 2.5.1(b)); even so, the reaction can be made to stop halfway at the chlorofluoride stage (*39*). 1,2-Alkenylphosphonic dichlorides are also somewhat resistant to fluorination but this may be carried out with antimony trifluoride in the absence of solvent (Fig. 2.5.1(b)) (*133*), the reaction being somewhat vigorous. The low-boiling difluorides are obtained by distillation from the reaction mixture either at atmospheric pressure or under partial vacuum. Normally, the reaction between hydrogen fluoride and the alkylphosphonic dichloride is so rapid that it can be performed in the laboratory in glass apparatus. The introduction of 1 mol of hydrogen fluoride does not provide the chlorofluoride RP(O)ClF, but instead a mixture of the dichloride and difluoride that can be separated into its components by careful distillation.

Methyltetrafluorophosphorane (**47**) reacts with anhydrides of acetic, propionic and butyric acids to form methylphosphonic difluoride and the acid fluorides (Fig. 2.5.2). The acid anhydride is heated to 80 °C and passed slowly into the methyltetrafluorophosphorane. The products are distilled twice to obtain them in a pure state (*134*).

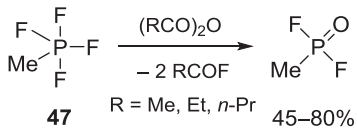


Figure 2.5.2

An unusual reaction takes place when isobutyl phosphorodifluoridite (**48**) is allowed to react with a catalytic amount of xenon difluoride (10 mol%). The major product is *tert*-butylphosphonic difluoride (**49**) (>85% as indicated by ^{31}P-NMR spectroscopy) (Fig. 2.5.3). The difluoride is easily obtained from the reaction mixture by distillation (*135*).

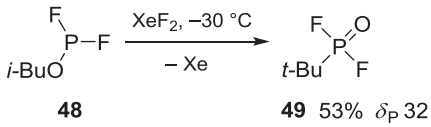


Figure 2.5.3

Methyl methylphosphonic acid (**24**) reacts with 2 mol of anhydrous hydrogen fluoride at high temperature and pressure in a silver-lined steel autoclave to furnish methylphosphonic difluoride (**46**) in modest yield (*136*). A route more suitable for industrial rather than laboratory-scale production of alkyl/arylphosphonic difluorides involves fluorination of alkyl/arylphosphonic acids with 2 molar equivalents of sulfur tetrachloride (bp −40 °C) in an autoclave (Fig. 2.5.4) (*137*). The volatile byproducts, thionyl fluoride and hydrogen fluoride, are easily removed and the target compounds (e.g. **50** and **51**) are isolated by fractionation under vacuum.

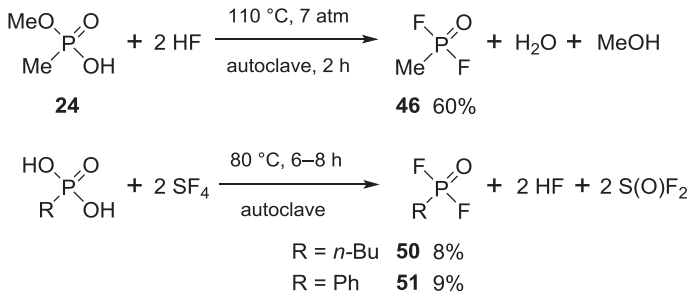


Figure 2.5.4

Alkylphosphonic difluorides are decomposed by water but the reaction is not as violent as the comparable reaction of the alkylphosphonic dichlorides. The lower members, especially methylphosphonic difluoride, fume in moist air and hydrolyse to the more hydrolytically stable alkylphosphonofluoridic acids.

▷ *Methylphosphonic difluoride MeP(O)F$_2$* (**46**) *(from methylphosphonic dichloride and hydrogen fluoride)* (*132*). Methylphosphonic dichloride was melted at about 35 °C and treated with anhydrous hydrogen fluoride at such a rate that the temperature rose to 75 °C. Hydrogen chloride was evolved steadily. If the system was completely dry, this reaction could be carried out in Pyrex glass, the supply line from the gas cylinder being composed of polythene tubing, with a copper dip pipe. The product was degassed under reduced pressure and the residue heated under reflux for 30 min. The difluoride was isolated by fractionation (90%). Bp 98 °C. Ethylphosphonic difluoride (bp 109 °C) and isopropylphosphonic difluoride (bp 114 °C) were prepared similarly (*39*).

▷ *Methylphosphonic difluoride MeP(O)F$_2$* (**46**) *(from methyl methylphosphonic acid and hydrogen fluoride)* (*136*). Methyl methylphosphonic acid (110 g, 1 mol) and anhydrous hydrogen fluoride (400 g, 20 mol) were heated in a silver-lined steel autoclave to 110 °C, at a pressure of ~7 atm, for 2 h. The resultant mixture was separated from the aqueous hydrogen fluoride. Fractional distillation of the organic material removed the methanol byproduct and gave the title compound (60 g, 60%). Bp 98 °C.

▷ *Tert-butylphosphonic difluoride t-BuP(O)F$_2$* (**49**) *(from isobutyl phosphorodifluoridite and xenon difluoride)* (*135*). Xenon difluoride (0.24 g, 1.4 mmol) was added to isobutyl phosphorodifluoridite (2.00 g, 14 mmol) at −30 °C (no reaction occurred at this temperature) and the cooling bath was heated slowly. When the bath temperature reached −10 to −12 °C, a vigorous reaction occurred accompanied by gas evolution. After completion of the reaction, ^{31}P-NMR spectroscopy of a sample of the mixture showed it to be composed of traces of the starting difluoridite (δ_P −19 ppm), 10% hexafluorophosphate anion, and ~90% of the *tert*-butylphosphonic difluoride. Distillation of this gave the pure title compound (1.05 g, 53%). Bp 120 °C. δ_P 32.0 ppm.

▷ *n-Butylphosphonic difluoride n-BuP(O)F$_2$* (**50**) *(from n-butylphosphonic acid and hydrogen fluoride)* (*137*). A reaction vessel (capacity 145 ml), capable of withstanding pressure and lined with stainless

steel, was flushed with nitrogen and charged with *n*-butylphosphonic acid (20.7 g, 0.15 mol). It was then cooled in ice and evacuated to approximately 1 mmHg pressure. Sulfur tetrafluoride (66.0 g, 0.61 mol) was introduced. The vessel was heated with mechanical shaking to 80 °C for 6 h, then at 100 °C for a further 6 h, and then opened to reveal a liquid product (20.8 g). This was treated with sodium fluoride (20.0 g, 0.48 mol) suspended in petroleum ether (100 ml) to remove hydrogen fluoride, if present. The solution was filtered and the ether removed. Fractionation of the residue under reduced pressure gave the title compound as a colourless liquid (1.8 g, 8%). Bp 68–70 °C/56 mmHg.

▷ *Phenylphosphonic difluoride $PhP(O)F_2$* (**51**) *(from phenylphosphonic acid and hydrogen fluoride)* (*137*). A reactor similar to the one described in the previous method was charged with phenylphosphonic acid (31.6 g, 0.20 mol) and sulfur tetrachloride (33.0 g, 0.31 mol) and the same protocol followed. It was heated with mechanical agitation to 80 °C for 8 h to give a liquid product (39.9 g). This was treated with sodium fluoride (20.0 g, 0.48 mol) suspended in petroleum ether (100 ml). The solution was filtered and the ether removed. Fractionation of the residue under reduced pressure gave the title compound as a colourless liquid (3.0 g, 9%). Bp 172–173 °C.

▷ *Benzylphosphonic difluoride $PhCH_2P(O)F_2$ (from benzylphosphonic dichloride and zinc fluoride)* (*138*). Zinc(II) fluoride (2.7 g, 26 mmol) was added portionwise to benzylphosphonic dichloride (4.2 g, 22 mmol) with stirring at 70 °C. The mixture was heated for 1 h at this temperature and vacuum fractionated to give the product (2.1 g, 60%). Bp 64 °C/0.2 mmHg.

▷ *Propenylphosphonic difluoride $MeCH{=}CHP(O)F_2$ (from propenylphosphonic dichloride and antimony trifluoride)* (*39*). Propenylphosphonic dichloride (30.0 g, 0.19 mol) was treated with antimony trifluoride (21.5 g, 0.12 mol). After a brief induction period, a violent reaction set in. It was necessary to provide the reaction flask with a long and efficient water-cooled condenser to avoid loss of product. On distillation at ordinary pressure, the product was obtained (10.0 g, 42%). Bp 113 °C.

▷ *Trichloromethylphosphonic difluoride $CCl_3P(O)F_2$ (from trichloromethylphosphonic dichloride and antimony trifluoride)* (*138*). Antimony trifluoride (4.45 g, 25 mmol) was added in portions to a stirred mixture of trichloromethylphosphonic dichloride (5.91 g, 25 mmol) and antimony pentachloride (0.05 ml). The mixture was heated to 60 °C for 1 h. Vacuum fractionation gave the title compound (3.4 g, 68%). Bp 96 °C.

2.6 ALKYLPHOSPHONOFLUORIDIC ACIDS RP(O)(OH)F

It is well known that alkyl alkylphosphonofluoridate nerve agents such as sarin cannot be distilled at ordinary pressure. Decomposition occurs and may become uncontrollable if the initial substance is of a low order of purity; it is strongly catalysed by H^+ ions and since the process is mainly one of dealkylation, one of the products must be the free acid. The decomposition is therefore autocatalytic. When alkyl alkylphosphonofluoridates are heated to an appropriate temperature, a gas or low-boiling liquid is evolved. This has been shown to consist mainly of the alkene corresponding to the ester group. In the case of sarin, this is of course propene, the other product being methylphosphonofluoridic acid (**52**) (Fig. 2.6.1) (*39,139–143*). The latter is not only a thermal degradation product of sarin, but is the

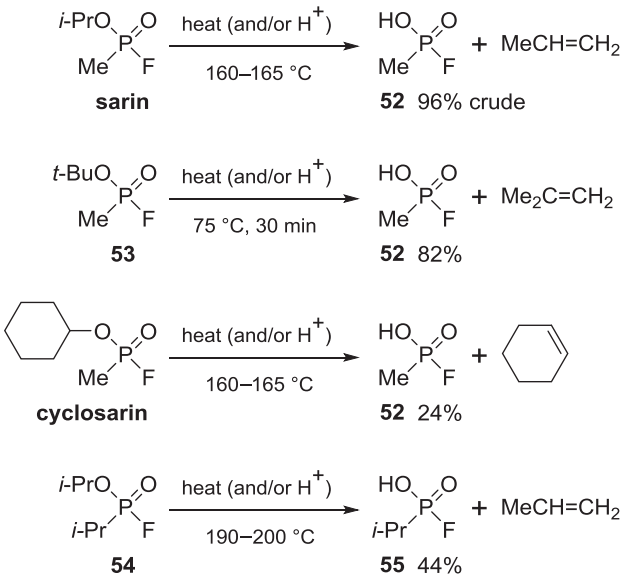


Figure 2.6.1

first product of hydrolysis of methylphosphonic difluoride (*16*), a precursor to binary sarin. It does not occur naturally in the environment and is therefore an important reference compound during investigations of alleged use of sarin.

Cyclohexyl methylphosphonofluoridate (cyclosarin) is a convenient substance to use for studying pyrolysis chemistry. The pure substance pyrolyses quietly and smoothly at 160—165 °C and a quantity of liquid distils between 74 and 82 °C. This distillate comprises two immiscible liquids, the lighter being identified as cyclohexene and the heavier as methylphosphonic difluoride (**46**). The residue, which was distillable at low pressure, consisted of the expected methylphosphonofluoridic acid (**52**), leaving a small amount of methylphosphonic acid (**56**). The presence of the latter and of the difluoride in the original distillate indicates that disproportionation to some extent occurred (Fig. 2.6.2).

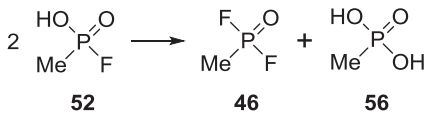


Figure 2.6.2

A convenient method of preparing the alkylphosphonofluoridic acids and one that does not involve the handling of relatively large amounts of highly toxic material consists of heating the alkylphosphonic difluoride (e.g. **46**) with an alcohol that splits with ease into an alkene. *Tert*-butanol is suitable for this purpose. When catalysed with a trace of free hydrogen chloride, evolution of isobutylene is brisk at 45 °C and a good yield of the alkylphosphonofluoridic acid (e.g. **52**) results (Fig. 2.6.3).

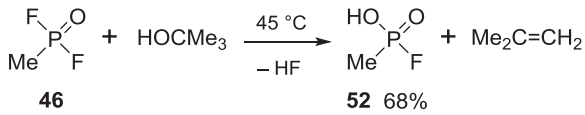


Figure 2.6.3

Some reactions of methylphosphonofluoridic acid are worthy of comment. When this acid is treated with an excess of thionyl chloride, methylphosphonic dichloride can be obtained in acceptable yield. The use of a smaller amount of thionyl chloride in this process yields methylphosphonofluoridic anhydride (see Section 2.7). The reaction of methylphosphonofluoridic acid (**52**) with isopropyl methylphosphonochloridate (**57**) in the presence of a tertiary base (e.g. *N,N*-diethylaniline), in an attempt to prepare methylphosphonofluoridic-isopropyl methylphosphonic anhydride (**58**), although appearing to proceed smoothly, on working up was found to consist of a mixture of diisopropyl dimethylpyrophosphonate (**59**) and methylphosphonofluoridic anhydride (**60**) (Fig. 2.6.4) (*39*). This reaction furnishes another example of a symmetrical disproportionation akin to that shown in Fig. 2.6.2. Methylphosphonofluoridic acid (**52**) and related compounds, although strongly corrosive, are practically without toxicity. Methylphosphonofluoridic anhydride (**60**) is rapidly hydrolysed by water with evolution of heat, the anhydride and P—F linkages both breaking and methylphosphonic acid forming.

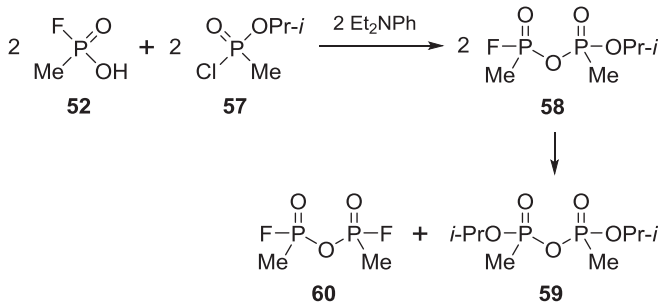


Figure 2.6.4

▶ *Methylphosphonofluoridic acid MeP(O)F(OH)* (**52**) *(from pyrolysis of sarin)* (*140*). Sarin (46.7 g, 0.33 mol; supertoxic!) in a 100-ml round-bottomed flask, equipped with a reflux condenser and an attached dry ice—acetone trap, was immersed into an oil bath at 160—165 °C. After an induction period of about 30 min, the decomposition of sarin began with the evolution of a gas. During this decomposition the pot temperature fell to 141 °C and remained steady until the gas evolution ceased after a total heating period of 50 min. The condensate in the attached cold trap was composed of propene (14.1 g, theoretical quantitative yield 14.0 g) which was identified by its conversion to 1,2-dibromopropane (bp 139—140 °C). After removal of a small forerun at 30—33 °C/5 mmHg, fractionation of the viscous liquid residue of crude methylphosphonofluoridic acid (31.0 g; 96%) gave the bulk of the pure title compound as a colourless oily liquid (bp 69—72 °C/2 mmHg). A small

amount of solid distillation residue was recrystallised from 1:5 *v/v* absolute ethanol—acetone to give methylphosphonic acid (mp 105 °C).

▶ *Methylphosphonofluoridic acid MeP(O)F(OH)* (**52**) *(from pyrolysis of cyclosarin)* (*39*). Cyclosarin (47.0 g, 0.26 mol; supertoxic!) contained in a round-bottomed flask equipped with a jacketed column attached to a condenser and receiver, and a thermometer, the bulb of which was immersed in the substance, was heated in an oil bath to 160—165 °C (bath temperature). The receiver was protected by a calcium chloride guard tube. After an induction period of about 40 min, during which a slight evolution of gas took place, decomposition set in fairly briskly and a mixture of two liquids started distilling, the temperature at the head of the column rising from 74 °C to 82 °C during the process, which lasted for about 2.5 h. Though the bath was maintained at 165 °C, the temperature of the decomposing material fell to about 120—125 °C. After this period, when the reaction appeared to have ceased, the heating was continued until the residue in the reaction flask had reached 160 °C, at which temperature it was kept for 15 min. The receiver was then changed and when the bath temperature had fallen to 100 °C, the residue was degassed completely with the aid of a water pump. The residue was then distilled under reduced pressure. A slightly cloudy liquid (11.7 g) was collected at 45—47 °C/0.05 mmHg leaving about 13 g of high-boiling residue. The distillate on refractionation gave pure methylphosphonofluoridic acid (6.0 g, 24%; bp 48 °C/0.05 mmHg). During the refractionation 1.5 g of material collected in the trap, immersed in cardice—acetone, interposed between the apparatus and the pump. Its boiling point, refractive index, and infrared absorption spectrum confirmed its identity as methylphosphonic difluoride. The two immiscible liquids from the initial decomposition were shown to be cyclohexene (bp 83 °C/761 mmHg) and slightly impure methylphosphonic difluoride (bp 98 °C). Its identity was confirmed by infrared spectroscopy.

▶ *Methylphosphonofluoridic acid MeP(O)F(OH)* (**52**) *(from the action of tert-butyl alcohol on methylphosphonic difluoride)* (*39*). Anhydrous *tert*-butyl alcohol (37.0 g, 0.5 mol) and methylphosphonic difluoride (50.0 g, 0.5 mol) were warmed to 45 °C in a round-bottomed flask fitted with a reflux condenser and take-off connected to two bubblers. The first of these contained potassium hydroxide solution (to remove hydrogen fluoride) and the second a solution of bromine in carbon tetrachloride (to absorb unsaturated hydrocarbons). Both bubblers were kept cool. The reaction was slow until 5 ml of a solution of dry hydrogen chloride in dichloromethane (obtained by bubbling the gas through the solvent) was introduced whereupon it proceeded smoothly and appeared to be complete in about 2.5 h. The product was degassed and fractionated under high vacuum to give pure methylphosphonofluoridic acid (33.5 g, 68%). Bp 44 °C/0.07 mmHg. The potassium hydroxide bubbler gave a strong positive reaction for ionic fluorine. The bromine—carbon tetrachloride solution was completely decolourised and, after warming with dilute sodium carbonate solution and water, it was dried and fractionated giving 1,2-dibromo-2-methylpropane (bp 149 °C/762 mmHg), thus confirming the evolution of isobutene during the reaction. If the reaction is performed at a temperature of 65—70 °C, it proceeds, after a short induction period, in the absence of hydrogen chloride. It is complete in about 1.5 h and on working up as described above, methylphosphonofluoridic acid is obtained in approximately the same yield. Note that methylphosphonofluoridic acid tends to disproportionate into methylphosphonic difluoride and methylphosphonic acid. For this reason it

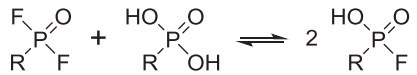
should be distilled at as low a temperature as possible. Disproportionation also takes place slowly at laboratory temperature. If required very pure, it should be used as soon as possible after it has been prepared. Ethylphosphonofluoridic acid EtP(O)F(OH) was prepared similarly, by replacing methyl- with ethylphosphonic difluoride. Yield 70%. Bp 53 °C/0.07 mmHg.

▶ *Methylphosphonofluoridic acid dicyclohexylamine salt (from pyrolysis of tert-butyl methylphosphonofluoridate)* (*141*). *Tert*-butyl methylphosphonofluoridate (3.08 g, 20 mmol) was added to a round-bottomed flask equipped with a magnetic stirrer and a reflux condenser; the latter was connected to a trap cooled to −80 °C, whilst a slow stream of nitrogen was passed through the apparatus. The contents of the flask were warmed slowly with an oil bath. At 75 °C decomposition of the liquid commenced suddenly as indicated by vigorous gas evolution. After 10 min no more gas was evolved and a viscous residue remained. This was heated at 75 °C for 30 min, cooled and dissolved in anhydrous ether (5 ml). A white precipitate formed immediately when a solution of dicyclohexylamine (3.63, 20 mmol) in ether (10 ml) was added dropwise with stirring. The precipitate was filtered off, washed with ether and dried. The crude material (5.19 g, 93%; mp 160−164.5 °C) was recrystallised from acetone (350 ml) yielding the dicyclohexylamine salt of methylphosphonofluoridic acid (4.58 g, 82%). Mp 164−166 °C.

▶ *Isopropylphosphonofluoridic acid i-PrP(O)F(OH)* (**55**) *(from pyrolysis of isopropyl isopropylphosphonofluoridate)* (*142*). Crude isopropyl isopropylphosphonofluoridate (100.8 g, 0.6 mol) was heated at 190−200 °C until no more propene was evolved (2 h). Distillation of the liquid gave the product (33.3 g, 44%). Bp 85−87 °C/3 mmHg.

▶ *Disproportionation of methylphosphonofluoridic acid* (*39*). After standing for 10 days at room temperature, the bulked product from an aforementioned preparation was subjected to high vacuum without heating. Approximately 5% of the material collected in the dry ice−acetone trap and was shown to be methylphosphonic difluoride by its boiling point and refractive index. The residue after this treatment was fractionated to give a further quantity of the difluoride.

Redistribution reactions, especially when the mixed species are strongly favoured at equilibrium, can be used to prepare certain organophosphorus compounds. The redistribution of fluorine atoms and hydroxy groups on the methylphosphonyl moiety, according to the equation given in Fig. 2.6.5 (R = Me), was established when mixtures of methylphosphonic difluoride and methylphosphonic acid were heated to 120 °C and monitored by ^{1}H-NMR spectroscopy (*138*). The doublet of doublets at 1.66 ppm corresponding to the methyl group ($^{2}J_{PH}$ 18 Hz and $^{3}J_{HF}$ 6 Hz) of the fluoridic acid appeared after approximately 1 h and equilibrium was attained after about 48 h at this temperature. At equilibrium the only species detected from an equimolar starting mixture of the difluoride and the diacid was the fluoridic acid: side reactions, such as exchange of methyl groups or dehydrofluorination and concomitant condensation to pyro- or polyphosphonic acids, were not observed even after heating to 120 °C for 4 weeks. Favour of the equilibrium towards the fluoridic acid was also observed for the phosphonyl centres where R = ethyl, phenyl, benzyl or trichloromethyl, although the reaction rates differed significantly. Thus, for example, 1 week at room temperature is sufficient to achieve complete redistribution of the PhP(O) moiety, while 1 day at 120 °C is required for the $CCl_3P(O)$ centre (Fig. 2.6.5).



Alkyl/arylphosphonofluoridic acids

R	Temp. (°C)	Time (h)	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)[a]
Me	120	48	95	48/0.15	–30.2
Et	120	48	95	72/0.2	–33.3
Ph	20	168	100	mp 50	–17.6
Bn	120	24	85	mp 74 [b]	–26.0
CCl_3	120	24	95	115/0.25 [c]	–0.5

a. Measured neat referenced to 85% H_3PO_4, taken postively towards increasing fields. *b*. Recrystallised from 1:1 pentane-chloroform. *c*. Melting point is 53 °C.

Figure 2.6.5

▶ *Alkylphosphonofluoridic acids RP(O)(OH)F (redistribution method)* (*138*). Equimolar amounts of the alkylphosphonic acid and its difluoride were sealed in glass tubes under nitrogen and heated for the time specified in Fig. 2.6.5. The contents of the tubes were then distilled under reduced pressure or recrystallised.

2.7 ALKYLPHOSPHONIC CHLOROFLUORIDES RP(O)CIF

Few alkylphosphonic chlorofluorides have been prepared. The most commonly encountered is methylphosphonic chlorofluoride (**61**) which can be obtained by heating methylphosphonofluoridic acid (**52**) with a moderate excess of thionyl chloride; smaller amounts of thionyl chloride result in formation of methylphosphonofluoridic anhydride (**60**) (Fig. 2.7.1) (*39*). In an analogous way, isopropylphosphonofluoridic acid (**55**) yields the corresponding chlorofluoride (**62**) but in higher yield (*142*).

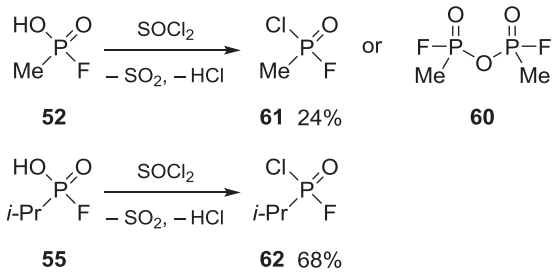


Figure 2.7.1

Alkylphosphonic chlorofluorides can also be prepared by other routes. The first relies on the action of phosphorus pentachloride on alkyl alkylphosphonofluoridates at 30–40 °C (Fig. 2.7.2; Method A) (*142*). It is inadvisable to heat the reaction mixture beyond this temperature range; at 80 °C the desired product reacts with the phosphorus oxychloride produced to give the alkylphosphonic dichloride together with phosphorus oxydichlorofluoride (bp 54 °C) (*144,145*).

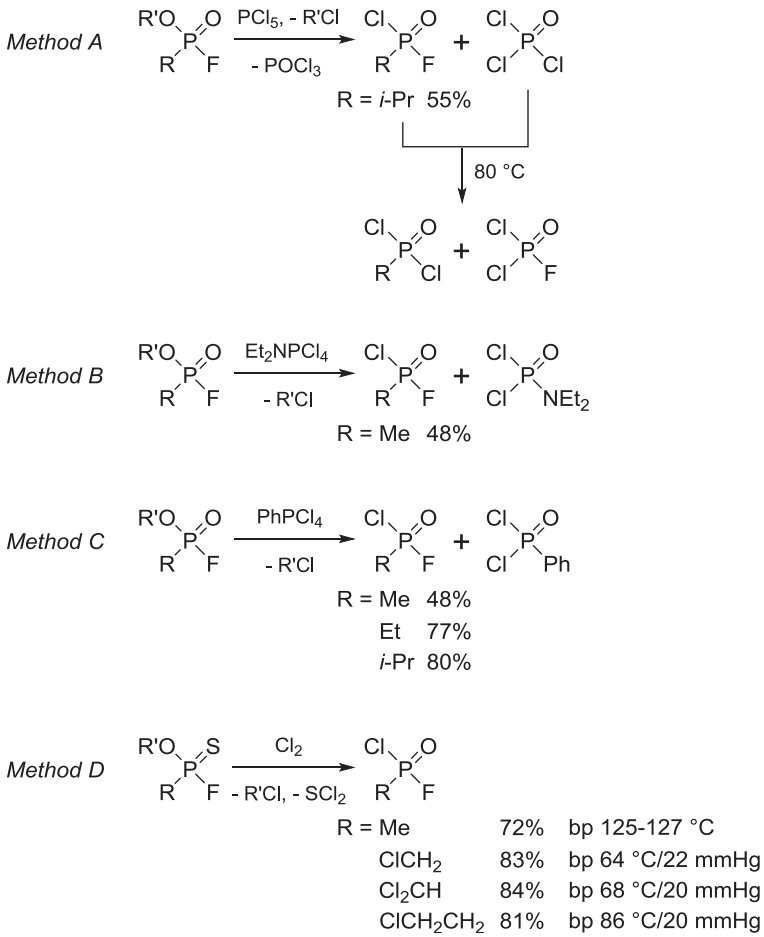


Figure 2.7.2

The boiling points of methyl- and ethylphosphonic chlorofluorides are close to the boiling point of phosphorus oxychloride (bp 106 °C) and for the preparation of these chlorofluorides it is better to use not phosphorus pentachloride, but (diethylamino)tetrachlorophosphorane or phenyltetrachlorophosphorane (Fig. 2.7.2, Methods B and C). Alkylphosphonic chlorofluorides are also formed by treating a mixture of undistilled alkyl alkylphosphonofluoridate and phenylphosphonous dichloride ($PhPCl_2$) with chlorine (to generate $PhPCl_4$ *in situ*). Alkyl alkylphosphonofluoridates react with phosphorus pentachloride at

70–80 °C and are converted into the alkylphosphonic dichlorides. Hence, methyl-, chloromethyl-, dichloromethyl- and 2-chloroethylphosphonic chlorofluorides are prepared instead by chlorination of alkyl alkylphosphonofluoridothionates (Fig. 2.7.2, Method D).

Alkylphosphonic chlorofluorides are colourless mobile liquids that fume in moist air and can be hydrolysed by water. The chloride atom is displaced initially, followed by the fluorine atom (Fig. 2.7.3). The first reaction is quick and the second slow. The chlorine atom of alkylphosphonic chlorofluorides is replaced selectively by various functional groups upon treatment with nucleophiles under mild conditions.

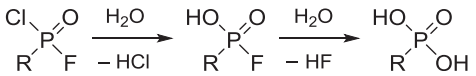


Figure 2.7.3

▶ *Methylphosphonic chlorofluoride MeP(O)ClF* (**61**) *(from methylphosphonofluoridic acid and thionyl chloride)* (*140*). Crude undistilled methylphosphonofluoridic acid (438.5 g, 4.5 mol) from the thermal decomposition of sarin was mixed in a 2-l round-bottomed flask with thionyl chloride (500 g, 4.2 mol) and the mixture refluxed for 6 h until the pot temperature rose to 80 °C. Additional thionyl chloride (50 g) was then added and the mixture heated for another 3 h during which the pot temperature finally reached 127 °C. Fractionation of the crude reaction mixture through a 15-cm column packed with glass helices at a pressure of 68 mmHg yielded the crude chlorofluoride (389 g, bp 52–67 °C). The product was redistilled through a 30-cm helix-packed column to provide a constant boiling fraction (240 g, bp 41 °C/30 mmHg) comprising a 9:1 chlorofluoride-difluoride mixture by fluoride ion analysis. A portion this material (230 g) was solidified by cooling it with a dry ice–acetone bath and then thawed slowly. The portion that was liquid at −23 °C was filtered from the crystal sludge, and the filter residue melting between −23 and −19 °C separated by filtration (any residue melting above −19 °C was discarded). Fluoride ion analysis showed the fraction melting between −23 and −19 °C to contain less of the difluoride impurity, and as further fractional crystallisation did not lower the difluoride content, this fraction (190 g) was redistilled through a 30-cm helix-packed column to yield title compound (127 g, 24%) of 98% purity. Bp 34–35 °C/14 mmHg. Methylphosphonic chlorofluoride is a relatively stable compound that boils at 126.0–126.5 °C at atmospheric pressure. About 10% of it disproportionates to methylphosphonic difluoride and presumably methylphosphonic acid when heated for 70 h in a sealed glass bulbs.

▶ *Isopropylphosphonic chlorofluoride i-PrP(O)ClF* (**62**) *(from isopropylphosphonofluoridic acid and thionyl chloride)* (*142*). A stirred mixture of isopropylphosphonofluoridic acid (12.6 g, 0.10 mol) and freshly distilled thionyl chloride (14.3 g, 0.12 mol) was boiled until no more gas was liberated. Distillation of the residue gave the chlorofluoride (9.8 g, 68%). Bp 36–37 °C/8 mmHg.

▶ *Alkylphosphonic chlorofluorides RP(O)ClF (from the alkyl alkylphosphonofluoridate and phosphorus pentachloride;* Fig. 2.7.2*, Method A)* (*142*). Phosphorus pentachloride (0.6 mol) was added in portions to the crude alkyl alkylphosphonofluoridate (0.5 mol) with stirring at a temperature not above 30–40 °C. When no more alkyl chloride was formed, sulfur dioxide was passed into the reaction

mixture to decompose traces of unchanged phosphorus pentachloride. The alkylphosphonic chlorofluoride was distilled.

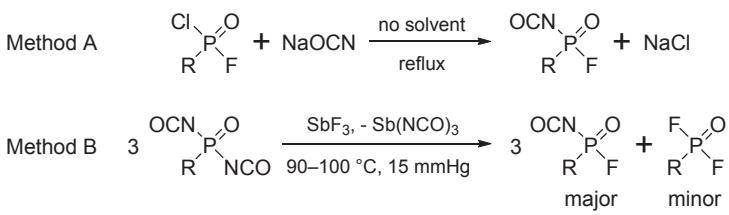
▶ *Alkylphosphonic chlorofluorides RP(O)ClF (from the alkyl alkylphosphonofluoridate and (diethylamino) tetrachlorophosphorane;* Fig. 2.7.2*, Method B)* (*142*). The crude alkyl alkylphosphonofluoridate (0.5 mol) was added dropwise to vigorously stirred (diethylamino)tetrachlorophosphorane (0.5 mol) heated to 70 °C. After addition the reaction mixture was stirred for 3 h at 60 °C and then cooled. Sulfur dioxide was passed through the liquid and the alkylphosphonic chlorofluoride was distilled off.

▶ *Alkylphosphonic chlorofluorides RP(O)ClF (from the alkyl alkylphosphonofluoridate and phenyltetrachlorophosphorane;* Fig. 2.7.2*, Method C)* (*142*). Phenylphosphonous dichloride (0.5 mol) was added to the crude alkyl alkylphosphonofluoridate (0.5 mol) and dry chlorine was passed at such a rate that the temperature of the stirred reaction mixture did not rise above 50–60 °C. Sulfur dioxide was then passed into the mixture and the alkylphosphonic chlorofluoride was subsequently distilled off.

▶ *Alkylphosphonic chlorofluorides RP(O)ClF (from the alkyl alkylphosphonofluoridothionate and chlorine;* Fig. 2.7.2*, Method D)* (*142*). An excess of dry chlorine was passed into an alkyl alkylphosphonofluoridothionate (0.2 mol) with vigorous stirring and external cooling to 0–5 °C. Sulfur dichloride was driven off and the alkylphosphonic chlorofluoride was obtained by distillation.

2.8 ALKYLPHOSPHONIC ISOCYANATOFLUORIDES RP(O)(NCO)F

Alkylphosphonic chlorofluorides react with sodium cyanate in the absence of solvent to yield alkylphosphonic isocyanatofluorides (Fig. 2.8.1) (*142*). These are colourless liquids that are hydrolysed readily by atmospheric moisture. Careful heating of a 3:1 molar ratio of alkylphosphonic diisocyanates with antimony trifluoride also provides the same products, plus a small quantity of the alkylphosphonic difluoride. The reaction products are easily separated by distillation. When a 2:1 molar ratio is used, the difluoride can be isolated in low yield (*146*).



Alkylphosphonic isocyanatofluorides

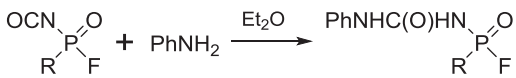
R	Yield (%)	Bp (°C/mmHg)	Method
Et	67	66–67/20	A
CH_2CH_2Cl	73	80–81/7	A
i-Pr	51	56–57/8	A
i-Pr	39	56–57/8	B
EtOCH=CH	40	54–56/3	B

Figure 2.8.1

▶ *Alkylphosphonic isocyanatofluorides RP(O)F(NCO) (Method A)* (*142*). A mixture of the alkylphosphonic chlorofluoride (0.20 mol) and sodium cyanate (0.28 mol) in anhydrous benzene (50 ml) was boiled with vigorous stirring for 4 h. The precipitate was filtered off, the benzene was evaporated, and the alkylphosphonic isocyanatofluoride was obtained by distillation.

▶ *Alkylphosphonic isocyanatofluorides RP(O)F(NCO) (Method B)* (*146*). Antimony trifluoride (0.1 mol) was added in portions to the stirred alkylphosphonic diisocyanate (0.3 mol) heated to 60–70 °C. The mixture was maintained at 90–100 °C for 15 min, and then the alkylphosphonic isocyanatofluoride and alkylphosphonic difluoride were separated by distillation under vacuum. Isolated yields of the alkylphosphonic difluorides were 10–15%.

Hardly any disproportionation with formation of the alkylphosphonic isocyanatofluoride occurs on prolonged boiling of a mixture of the alkylphosphonic difluoride and the alkylphosphonic diisocyanate (*146*). Partial fluorination of alkylphosphonic diisocyanates is the most convenient method of preparing alkylphosphonic isocyanatofluorides. These compounds react with aromatic amines to give *P*-alkyl-*N*-(arylcarbamoyl)phosphonamidic fluorides (Fig. 2.8.2) (*142*).



P-alkyl-*N*-(phenylcarbamoyl)phosphonamidic fluorides

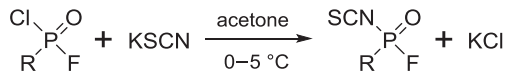
R	Yield (%)	Mp (°C)
Et	84	127–128
$ClCH_2CH_2$	76	123–125
i-Pr	90	140–141

Figure 2.8.2

▶ *P-alkyl-N-(phenylcarbamoyl)phosphonamidic fluorides PhNHCONH(R)P(O)F* (*142*). A solution of aniline (1.86 g, 20 mmol) in anhydrous ether (50 ml) was added dropwise to a stirred solution of the alkylphosphonic isocyanatofluoride (20 mmol) in anhydrous ether (50 ml). The precipitated crystals were filtered off and washed with ether. Isolated yields and melting points of the title compounds are given in Fig. 2.8.2.

2.9 ALKYLPHOSPHONIC ISOTHIOCYANATOFLUORIDES RP(O)(NCS)F

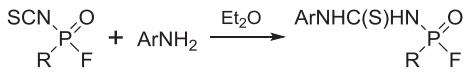
Alkylphosphonic chlorofluorides react with potassium thiocyanate to give alkylphosphonic isothiocyanatofluorides (Fig. 2.9.1) (*142*). These are colourless pleasant-smelling liquids that are readily hydrolysed by water. They are very unstable and after distillation soon become dark coloured, and after a few days are partially converted into orange crystalline masses.



R = Me **63** 10%
R = *i*-Pr **64** 48%

Figure 2.9.1

Methylphosphonic isothiocyanatofluoride was obtained in low yield after several distillations, but isopropylphosphonic isothiocyanatofluoride could be isolated more easily and in acceptable yield. For the identification of the crude alkylphosphonic isothiocyanatofluorides the reaction with aromatic amines to yield crystalline products is convenient (Fig. 2.9.2) *(142)*.



P-Alkyl-*N*-(arylthiocarbamoyl)phosphonamidic fluorides

R	Ar	Yield (%)	Mp (°C)
Me	C_6H_5	68	105–107
Me	*p*-ClC_6H_4	74	106–108
i-Pr	*p*-ClC_6H_4	56	119–120

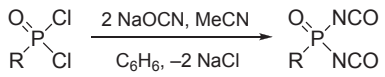
Figure 2.9.2

▶ *Alkylphosphonic isothiocyanatofluorides RP(O)F(NCS) (R = Me* **63** *or i-Pr* **64**) *(142)*. A solution of potassium thiocyanate (0.1 mol) in anhydrous acetone (100 ml) was added dropwise to a stirred solution of the alkylphosphonic chlorofluoride (0.1 mol) in anhydrous acetone (20 ml). After 24 h the precipitate was separated by centrifugation, the acetone was evaporated and the alkylphosphonic isothiocyanatofluoride was distilled. The method gave methylphosphonic isothiocyanatofluoride (**63**) (10%, bp 40–43 °C/0.05 mmHg) and isopropylphosphonic isothiocyanatofluoride (**64**) (48%, bp 64–65 °C/0.55 mmHg).

▶ *P-alkyl-N-(arylthiocarbamoyl)phosphonamidic fluorides ArNHCSNH(R)P(O)F (142)*. A solution of the appropriate amine (20 mmol) in anhydrous ether (30 ml) was added to a stirred solution of the alkylphosphonic isothiocyanatofluoride (20 mmol) in anhydrous ether (20 ml). After 24 h, the *P*-alkyl-*N*-(arylthiocarbamoyl)phosphoramidic fluoride was filtered off, washed several times with ether, and dried in a vacuum desiccator. Products, isolated yields and melting points appear in Fig. 2.9.2.

2.10 ALKYLPHOSPHONIC DIISOCYANATES $RP(O)(NCO)_2$

These compounds are readily prepared by treating alkylphosphonic dichlorides with 2 molar equivalents of sodium cyanate in acetonitrile–benzene (Fig. 2.10.1) *(131,146)*. They are colourless mobile liquids, soluble in the usual organic solvents, and are rapidly hydrolysed by moist air, e.g.



Alkylphosphonic diisocyanates

R	Yield (%)	Bp (°C/mmHg)
Me	–	71/2
Et	–	80–81/7
i-Pr	56	60–61/4
$ClCH_2CH_2$	15	62–67/0.1
$H_2C{=}CH$	44	71–72/6
EtOCH=CH	45	117–118/5
$H_2C{=}C{=}CH$	34	76–77/3
Ph	–	123/2[a]

a. Melting point approximately –5 °C.

Figure 2.10.1

$RP(O)(NCO)_2 + H_2O \rightarrow RP(O)NH_2(NCO) + CO_2$ and then through the same process to $RP(O)(NH_2)_2$. Isopropylphosphonic diisocyanate and 2-chloroethylphosphonic diisocyanate are unchanged upon storage in a closed vessel. The other diisocyanates listed in Fig. 2.10.1 darken rapidly after distillation (*146*). The alkylphosphonic diisocyanates easily add alcohols, aromatic amines, phenylhydrazine or acetoxime to the carbon atoms of the two isocyanate groups, to generate derivatives **65**–**68** (Fig. 2.10.2).

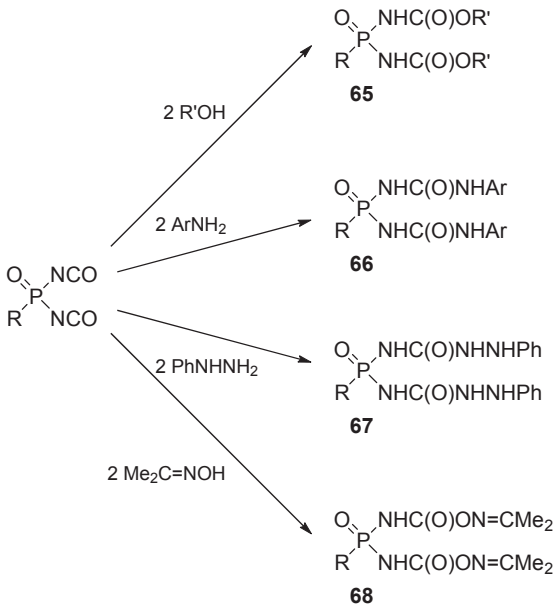


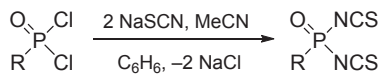
Figure 2.10.2

▶ *Alkylphosphonic diisocyanates RP(O)(NCO)$_2$ (146)*. A stirred mixture of the alkylphosphonic dichloride (0.2 mol), sodium cyanate (0.4 mol), anhydrous benzene (500 ml) and anhydrous acetonitrile (30 ml) was heated under reflux for 6–8 h. The precipitate was separated by centrifugation, the benzene and acetonitrile were evaporated and the diisocyanates were distilled under vacuum. Yields and boiling points are given in Fig. 2.10.1.

▶ *Alkylphosphonic bis-carboxyamides RP(O)(NHCO$_2$R′)$_2$* (**65**) *(146)*. Absolute alcohol (10 mmol) was added dropwise to a stirred solution of alkylphosphonic diisocyanate (10 mmol) in anhydrous ether (30 ml) at 0–5 °C. After several hours the alkylphosphonic *bis*-carboxyamide was filtered off and washed with ether. A similar reaction of aromatic amines, phenylhydrazine and acetoxime provided the corresponding *bis*-arylcarbamides (**66**), *bis*-phenylsemicarbazides (**67**) and *bis*-acetoximecarbamates (**68**) shown in Fig. 2.10.2.

2.11 ALKYLPHOSPHONIC DIISOTHIOCYANATES RP(O)(NCS)$_2$

These compounds are prepared by treating alkylphosphonic dichlorides with a slight excess of potassium thiocyanate in acetone (Fig. 2.11.1) *(131,146)*. They are colourless or slightly yellow liquids that distil without decomposition. They turn yellow upon storage and are slowly hydrolysed by moist air.



Alkylphosphonic diisothiocyanates

R	Yield (%)	Bp (°C/mmHg)
Me	nm	99–102/0.05
$ClCH_2CH_2$	56	112–113/0.02
$EtOCH{=}CH_2$	57	111–113/0.03

nm = not measured.

Figure 2.11.1

Under ordinary conditions, and unlike the ease with which the corresponding diisocyanates add nucleophiles, the alkylphosphonic diisothiocyanates do not add alcohols or acetoxime. However, ethoxyvinylphosphonic diisothiocyanate (**69**) does add aniline easily to give the *bis*-phenylthiocarbamide (**70**) in moderate yield (Fig. 2.11.2) *(146)*.

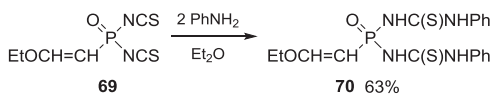


Figure 2.11.2

▶ *2-Chloroethylphosphonic diisothiocyanate* $ClCH_2CH_2P(O)(NCS)_2$ *(146)*. 2-Chloroethylphosphonic dichloride (36.3 g, 0.20 mol) was added dropwise to a stirred suspension of potassium thiocyanate (21.3 g, 0.22 mol) in anhydrous acetone (40 ml) with ice–water cooling, at such a rate that the temperature of the mixture did not exceed 20–30 °C. After 12 h, the mixture was diluted with anhydrous benzene (500 ml). The potassium chloride was filtered off, the benzene was evaporated and the residue was distilled under vacuum to yield the product (25.4 g, 56%). Bp 112–113 °C/0.02 mmHg.

▶ *Ethoxyvinylphosphonic diisothiocyanate* $EtOCH{=}CHP(O)(NCS)_2$ (**69**) *(146)*. An analogous preparation gave the title compound (57%). Bp 111–113 °C/0.03 mmHg.

▶ *Ethoxyvinylphosphonic bis-phenylthiocarbamide* $EtOCH{=}CHP(O)(NHCSNHPh)_2$ (**70**) *(146)*. A solution of aniline (20 mmol) in anhydrous ether (20 ml) was added to a stirred solution of ethoxyvinylphosphonic diisothiocyanate (10 mmol) in anhydrous ether (20 ml). After 24 h, the reaction product was filtered off, washed with ether and petroleum ether and dried (63%). Mp 102–104 °C.

2.12 ALKYLPHOSPHONIC ACIDS $RP(O)(OH)_2$

Modern advances in methods for the introduction of a phosphonic acid group *(36)* and surface modification using phosphonic acids and esters *(37)* have been reviewed. Alkylphosphonic dichlorides react with water to provide ultimately the alkylphosphonic acids *(147)*. The hydrolysis takes place in two stages that have been detected by electrical conductivity measurements, with rate constants that differ by about two orders of magnitude (Fig. 2.12.1) *(148)*. The reactivity of the alkylphosphonic dichlorides depends on the structure of the hydrocarbon group attached to the phosphorus atom. Thus, the hydrolysis rate decreases sharply on passing from $MeP(O)Cl_2$ to $EtP(O)Cl_2$ to *i*-$PrP(O)Cl_2$ and differs little for alkylphosphonic dichlorides having the same number of hydrogen atoms in the α-position; $EtP(O)Cl_2$ and *n*-$PrP(O)Cl_2$ hydrolyse at similar rates, as do *i*-$PrP(O)Cl_2$ and *s*-$BuP(O)Cl_2$. It is clear therefore that the rate of nucleophilic substitution by water depends on the degree of positive charge on the phosphorus atom (electronic effect) and its accessibility (steric effect). These two factors govern all the reactions of phosphonyl (and phosphoryl) halides with nucleophiles *(149–151)*.

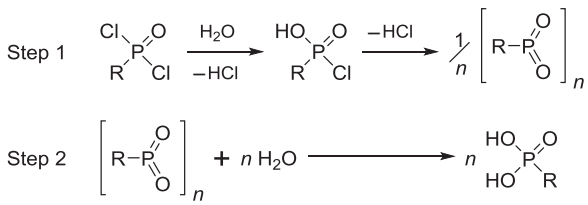


Figure 2.12.1

Alkylphosphonic acids are conveniently prepared by the hydrolysis of alkylphosphonic dichlorides (e.g **22**→**56**) or *P,P*-dialkyl pyrophosphonic acids (e.g. **26**→**56**) (Fig. 2.12.2) *(152)*. The hydrolysis of

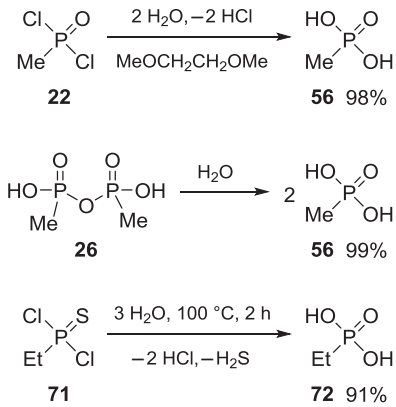


Figure 2.12.2

alkylphosphonothioic dichlorides by boiling water also yields alkylphosphonic acids (e.g. **71**→**72**) with evolution of hydrogen sulfide (*39*).

Warming the alkylphosphonic dichloride (**29**) with an excess of water provides the corresponding acid (**73**) (Fig. 2.12.3) (*117*). An alternative method of preparation of alkylphosphonic acids involves the hydrolysis of dialkyl alkylphosphonates under harshly acidic conditions. This preparation is made possible by the strong P—C bond of the alkyl group that resists cleavage (Chapter 1, Section 1.4). The 'double' dialkyl alkylphosphonate (**28**) when boiled with concentrated hydrochloric acid provides the diacid (**30**) in quantitative yield (*117*).

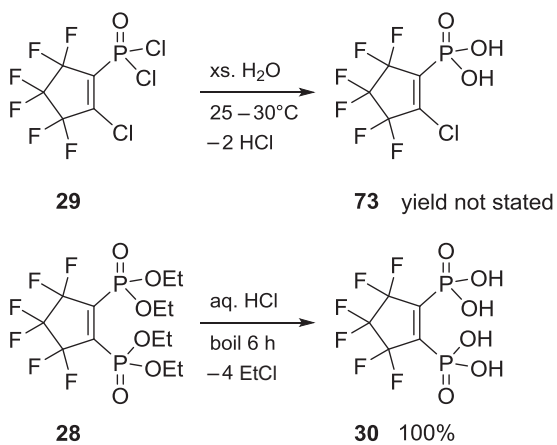
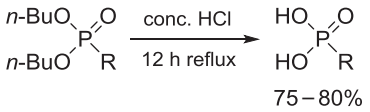


Figure 2.12.3

Di-*n*-butyl *n*-alkylphosphonates prepared by the Michaelis—Becker reaction are convenient starting materials for the synthesis of alkylphosphonic acids (*153*). Conversion of the phosphonates to the phosphonic acids proceeds readily when the esters are refluxed with concentrated hydrochloric acid for several hours (Fig. 2.12.4). Generally, essentially quantitative yields of crude alkylphosphonic acids are obtained, from which pure materials could be isolated in 75—85% yields. Melting points of the acids do not vary in a regular 'sawtooth' pattern, but instead group around 100 °C. Boron tribromide also cleanly and quantitatively converts dimethyl-, diethyl-, diisopropyl- and di-*tert*-butyl alkylphosphonates $(R'O)_2P(O)R$ into the corresponding alkylphosphonic acids $(HO)_2P(O)R$ (*154*).

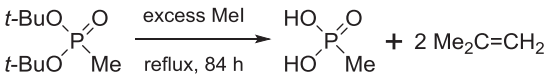


n-Alkylphosphonic acids

R	Mp (°C)	R	Mp (°C)
CH_3	104–105	C_8H_{17}	100–101
C_2H_5	61–62	C_9H_{19}	99–100
C_3H_7	73–75	$C_{10}H_{21}$	102–103
C_4H_9	103–104	$C_{12}H_{25}$	101–102
C_5H_{11}	121–122	$C_{14}H_{29}$	97–98
C_6H_{13}	105–106	$C_{16}H_{33}$	95–96
C_7H_{15}	103–104	$C_{18}H_{37}$	99

Figure 2.12.4

The much greater stability and ease of formation of the *tert*-butyl carbenium ion from di-*tert*-butyl methylphosphonate means that acid-catalysed dealkylation is not essential in this case, and methylphosphonic acid (**56**) can be obtained slowly and in high yield by simply heating a solution of the methylphosphonate in iodomethane for 84 h (Fig. 2.12.5) (*155*). The reaction proceeds autocatalytically once a small amount of the acid product is formed.



56 93%

Figure 2.12.5

Alkylphosphonic acids (e.g. **74**–**75**) can be obtained in excellent yield from palladium-catalysed coupling of hypophosphorous acid $H_2P(O)OH$ with aliphatic alkenes, and unsaturated alcohols, followed by aerial oxidation of the RP(O)(OH)H intermediates (Fig. 2.12.6) (*156*). The use of aromatic halides – usually bromides or iodides – gives arylphosphonic acids (e.g. **76**).

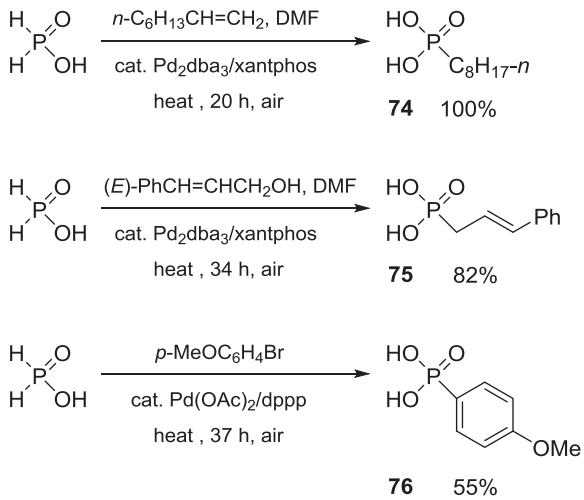


Figure 2.12.6

Vinylphosphonic dichloride (**34**) hydrolyses readily when treated with water to provide via the intermediate (**77**) the vinylphosphonic acid (**78**) (Fig. 2.12.7) (*106*). Styrene (**79**) adds to two molecules of phosphorus pentachloride to yield product (**80**) whose reaction with water gives 2-styrylphosphonic acid (**81**) (*106*). Unsaturated phosphonic acids are useful monomers for the manufacture of various synthetic polymers.

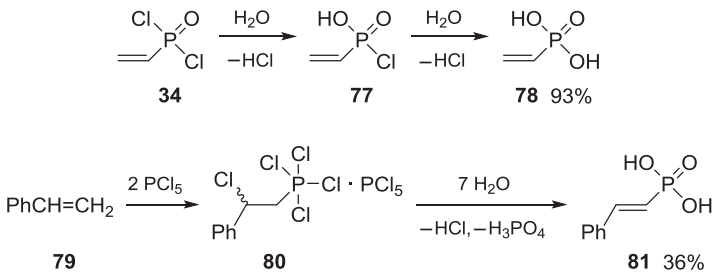
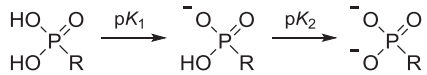


Figure 2.12.7

Alkylphosphonic acids are moderately strong acids (*33*). They are weaker acids than phosphoric acid (H_3PO_4). The acid dissociation constants (p*K*) for the first and second ionisation in aqueous solution are given in Fig. 2.12.8. The p*K* values increase with an increase in the number of carbon atoms in the alkyl group and with the degree of branching of the carbon chain. This effect is due to the electron-donating character of the saturated carbon atom. The median difference between the first and second p*K* values of the alkylphosphonic acids is 5.62 units.



Acid dissociation constants (p*K*) for alkylphosphonic acids (from ref. 33)

R	pK_1	pK_2
OH	1.97	6.82
Me	2.38	7.74
Et	2.43	8.05
n-Pr	2.49	8.18
i-Pr	2.66	8.44
n-Bu	2.59	8.19
i-Bu	2.70	8.43
s-Bu	2.74	8.48
t-Bu	2.79	8.88

Figure 2.12.8

▶ *Methylphosphonic acid MeP(O)(OH)$_2$* (**56**) *(from hydrolysis of methylphosphonic dichloride)* (*152*). Methylphosphonic dichloride (1.33 g, 10 mmol) was dissolved in 1,2-dimethoxyethane (2 ml) and hydrolysed by stirring with water, and the solution evaporated. The acid was dissolved in water, treated with charcoal, filtered and the filtrate concentrated. Drying under vacuum gave the title compound as a crystalline solid (0.94 g, 98%). Mp 104–106 °C. Recrystallisation from methyl ethyl ketone gave a pure specimen with mp 106 °C.

▶ *Methylphosphonic acid MeP(O)(OH)$_2$* (**56**) *(from dealkylation of di-tert-butyl methylphosphonate)* (*155*). Di-*tert*-butyl methylphosphonate (2.08 g, 10 mmol) and iodomethane (20 ml) were heated under reflux for 84 h. Iodomethane was distilled off to leave the title compound (0.89 g, 93%). Mp and mixed mp 104–105 °C.

▶ *Methylphosphonic acid MeP(O)(OH)$_2$* (**56**) *(from hydrolysis of P,P′-dimethyl pyrophosphonic acid)* (*152*). *P,P′*-dimethyl pyrophosphonic acid (0.35 g, 2 mmol) was hydrolysed by warming with water and the extent of reaction monitored by ^{31}P-NMR spectroscopy. The water was removed under reduced pressure, the residue dissolved in acetone and the solution evaporated; this cycle was repeated twice to remove all the water. The acetone solution was concentrated, filtered and just enough petroleum ether

added to cause cloudiness. Upon cooling with ice, pure methylphosphonic acid separated as colourless crystals in nearly quantitative yield (99%). Two recrystallisations from methyl ethyl ketone gave pure material of mp 106 °C.

▶ *Ethylphosphonic acid EtP(O)(OH)$_2$* (**72**) *(from hydrolysis of ethylphosphonothioic dichloride)* (*39*). Ethylphosphonothioic dichloride (16.3 g, 12 ml, 0.1 mol) was boiled with water (40 ml) under reflux for 2 h, whereupon the dichloride dissolved slowly and hydrogen sulfide was evolved. At the end of this time, when all the dichloride had entered into solution, the volatile material was removed at 100 °C under reduced pressure. On cooling, the residue (10.0 g, 91%) solidified. It was purified by solution in warm ethyl acetate and cooling in an ice box. The title compound separated in large shiny, somewhat hygroscopic, prisms (mp 57–58 °C). Its melting point was unchanged on admixture with an authentic specimen of ethylphosphonic acid obtained from hydrolysis of ethylphosphonic dichloride.

▶ *n-Alkylphosphonic acids RP(O)(OH)$_2$ (hydrolysis of di-n-butyl n-alkylphosphonates)* (*153*). A mixture of dibutyl *n*-alkylphosphonate (40 mmol) and conc. hydrochloric acid (50–75 ml) was heated under reflux for 12 h, after which the reflux condenser was arranged for downward distillation. The mixture was distilled with the aid of an oil bath, which removed the *n*-butyl chloride and approximately one-half the volume of hydrochloric acid. On cooling, the alkylphosphonic acids higher than *n*-decyl crystallised rapidly into a crust that was separated. The lower acids, owing to their greater solubility in aqueous media, generally did not give a solid crust; these mixtures were evaporated to dryness. The crude alkylphosphonic acid so obtained was then recrystallised repeatedly from hexane or heptane to a constant melting point, followed by drying under vacuum over solid potassium hydroxide. Ethylphosphonic acid was recrystallised from water due to its poor solubility in petroleum solvents. All acids so obtained crystallised readily, frequently forming crystals 1–2 cm long, generally in clusters of flat fragile needles. Melting points are given in Fig. 2.12.4. Similarly, hydrolysis of di-*n*-butyl α-thienylmethylphosphonate gave α-thienylmethylphosphonic acid 2-ThCH$_2$P(O)(OH)$_2$ as yellowish plates (mp 108–109 °C, from water) (*157*). Likewise, hydrolysis of diethyl ethyl-, diethyl *n*-butyl-, diethyl isopropyl-, diethyl cyclohexyl- and diethyl 3-chloropropyl-phosphonate with concentrated hydrochloric acid yielded these acids: EtP(O)(OH)$_2$ (mp 58–60 °C, from carbon disulfide), *n*-BuP(O)(OH)$_2$ (mp 106–107 °C, from hexane), *i*-PrP(O)(OH)$_2$ (mp 72–74 °C, from carbon disulfide), *c*-C$_6$H$_{11}$P(O)(OH)$_2$ (mp 165–166 °C, from water) (*158*) and ClCH$_2$CH$_2$CH$_2$P(O)(OH)$_2$ (mp 104–105 °C, from chloroform; 76% yield) (*159*).

▶ *3,3,4,4,5,5-Hexafluoro-1-cyclopenten-1,2-ylenediphosphonic acid* (**30**) (*117*). Tetraethyl 3,3,4,4,5,5-hexafluoro-1-cyclopenten-1,2-ylenediphosphonate (448 g, 1.0 mol) was added over 6 h to boiling 19% hydrochloric acid (4000 ml) contained in a 12-litre flask equipped with a mechanical stirrer, a dropping funnel and a reflux condenser. The progress of the reaction was followed by observing the evolution of ethyl chloride through a bubbler attached to the top of the condenser. After addition was complete, the heating was continued until the gas evolution subsided (8 h). The solution was evaporated to dryness and dried to constant weight in a vacuum dessicator over phosphorus pentoxide to leave the acid as an extremely hygroscopic crystalline solid (334 g, 100%). Mp 194–195 °C dec. The acid was soluble in polar solvents (water, acetone, ethanol, ether) and insoluble in hydrocarbon

solvents (benzene, hexane) or chlorinated hydrocarbon solvents (dichloromethane, chloroform, or carbon tetrachloride). The apparent acid dissociation constants (pK') were 4.24 and 11.98.

▶ *2-Chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-ylphosphonic acid* (**73**) (*117*). 2-Chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-ylphosphonic dichloride (32.8 g, 0.1 mol) was added dropwise to water (200 ml) over 25 min at 25–30 °C with external cooling, heated to boiling for 15 min and then evaporated to dryness under vacuum. The residue (30.3 g) was recrystallised thrice from carbon tetrachloride to provide the title compound as a hygroscopic crystalline solid (mp 107–109 °C) that was soluble in water, ethanol and acetone, and insoluble in benzene, hexane and chloroform. The pK' was 5.10 (the other was not determined).

▶ *n-Octylphosphonic acid n-$C_8H_{17}P(O)(OH)_2$* (**74**) (*156*). 1-Octene (0.32 ml, 2 mmol), followed by Pd_2dba_3 (0.0184 g, 0.020 mmol, 2 mol% Pd) and xantphos (0.0254 g, 0.044 mmol, 2 mol%), were added to a stirred solution of aqueous H_3PO_2 (0.528 g, 4 mmol) and DMF (4 ml) at room temperature. The mixture was heated at 110 °C under air for 20 h or until complete oxidation of the intermediate octyl-*H*-phosphinic acid (according to ^{31}P-NMR monitoring of a sample of the reaction mixture). The reaction was considered complete after total disappearance of a signal at 31.8 ppm (doublet) and appearance of a new peak at 29.7 ppm (singlet) corresponding to *n*-octylphosphonic acid. The mixture was then concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with 2 M aqueous HCl (1×). The aqueous phase was extracted with ethyl acetate (2×) and the combined organic fractions were washed with brine. Concentration and drying afforded the pure product as a light yellow solid (0.338 g, 100%). Mp 70–72 °C. δ_P (121.5 MHz, $CDCl_3$) 37.8 ppm.

▶ *Trans-cinnamylphosphonic acid $PhCH{=}CHCH_2P(O)(OH)_2$* (**75**) (*156*). *Trans*-cinnamyl alcohol (0.26 ml, 2 mmol) followed by Pd_2dba_3 (0.0184 g, 0.020 mmol, 2 mol% Pd) and xantphos (0.0254 g, 0.044 mmol, 2 mol%) were added to a stirred solution of concentrated H_3PO_2 (0.264 g, 4 mmol) and DMF (4 ml) at room temperature. The mixture was heated at 85 °C under nitrogen for 20 h. After that time, ^{31}P-NMR analysis of the mixture revealed the formation of cinnamyl-*H*-phosphinic acid at 26 ppm (doublet). The mixture was then opened to air and heated at 110 °C for 22 h, until complete disappearance of the peak at 26 ppm and appearance of a new peak at 22 ppm (singlet). The mixture was concentrated under reduced pressure and the residue was diluted with ethyl acetate and washed with 2 M aqueous HCl (1×). The aqueous phase was extracted with ethyl acetate (2×) and the combined organic fractions were washed with brine. Concentration and drying afforded a white solid (0.325 g, 82%). Mp 162–164 °C. δ_P (121.5 MHz, DMSO-d_6) 24.6 ppm.

▶ *4-Methoxyphenylphosphonic acid 4-$MeOC_6H_4P(O)(OH)_2$* (**76**) (*156*). 4-Bromoanisole (0.25 ml, 2 mmol) and triethylamine (0.84 ml, 6 mmol) followed by $Pd(OAc)_2$ (0.009 g, 0.040 mmol) and dppp (0.0182 g, 0.044 mmol) were added to a stirred solution of 0.5 M concentrated H_3PO_2 (0.264 g, 4 mmol) and DMF (4 ml) at room temperature. The mixture was heated at 85 °C under nitrogen for 15 h, and then opened to air and heated at 110 °C for 22 h. By then the intermediate *H*-phosphinate salt had oxidised completely to the corresponding triethylammonium phosphonate salt. The mixture was concentrated under vacuum and the residue was diluted with ethyl acetate and washed with 2 M

aqueous HCl (1×). The aqueous layer was extracted with ethyl acetate (2×) and the combined organic layers were washed with brine. After drying ($MgSO_4$), concentration, and recrystallisation from dichloromethane–hexane, the product was obtained as a white solid (0.207 g, 55%). Mp 177–178 °C. δ_P (121.5 MHz, DMSO-d_6) 15.1 ppm.

▶ *Vinylphosphonic acid* $CH_2{=}CHP(O)(OH)_2$ (**78**) (*106*). Vinylphosphonic dichloride (4.35 g, 30 mmol) was added gradually to water (9 ml) cooled to 0–5 °C. Water and hydrochloric acid were evaporated from the resulting solution and the residue was dried to constant weight to leave vinylphosphonic acid as a syrupy liquid (3.00 g, 93%). Its distillation under high vacuum gave the anhydride $[CH_2{=}CHP(O)(OH)O]_2$. Bp 235–240 °C/6 × 10^{-4} mmHg.

▶ *2-Styrylphosphonic acid* $PhCH{=}CHP(O)(OH)_2$ (**81**) (*106*). A solution of styrene (52.1 g, 0.5 mol) in dry benzene (500 ml) was treated with phosphorus trichloride (68.7 g, 0.5 mol). This mixture was stirred and cooled in ice and dry chlorine was passed into it. After 5 h the solution had coloured yellow through the presence of free chlorine, and a suspension (reminiscent of cream) of the phosphorus pentachloride addition product of styrene had formed. The reaction product was then hydrolysed with ice (200 g). Evaporation of the benzene layer gave 2-styrylphosphonic acid (32.9 g, 36%). Mp 140–144 °C.

2.12.1 Biography

This biography pays respect to one of the foremost organophosphorus chemists of the last century, who pioneered, among other achievements, the systematic study of alkylphosphonic acids (*153*,*157*) and their derivatives. Unfortunately a photograph was not available at the time of writing.

Gennady Michael Kosolapoff (1909–1976). Professor Gennady Michael Kosolapoff, B.S. in Chemical Engineering (Cooper Union, 1932), M.S. in Biochemistry (University of Michigan, 1933), D.Sc. Chem (University of Michigan, 1936), was born on 2 September 1909 in Viatka in Russia (*160*). Shortly after the Russian Revolution he fled with his family to eastern Asia and lived there for several years before immigrating to the United States in 1924. After receiving his doctorate he worked as a Research Chemist for the Libby-Owens-Ford Glass Company (1936–1938) and then for the Monsanto Chemical Company (1938–1948). In 1948 he accepted the post of Associate Professor of Chemistry at Alabama Polytechnic Institute (renamed the Alabama Polytechnic Institute in 1960) and rose through the ranks to Research Professor of Chemistry (1953–1976). There he wrote the first ever book in English, called *Organophosphorus Compounds* published in 1950, that reviewed comprehensively the chemistry of organic phosphorus compounds. All the information on known phosphorus compounds available up to January 1949 was incorporated into the text and the literature up to January 1950 in an appendix. The material in each chapter was arranged according to the compound class with all known compounds, and physical properties and literature references at the end of each chapter. The scattered nature of the information on organophosphorus compounds at the time made the textbook an important and necessary addition to most chemical libraries; it still remains useful. Among several appointments as a research consultant, Kosolapoff served in 1964 as the Director of Research for the F.J. Seiler Research Laboratory, in the Office of Aerospace Research in Colorado, as consultant to the

Atomic Energy Commission, and as special lecturer of phosphorus (1949–1954). Throughout his life Kosolapoff was dedicated to teaching chemistry (*161*). He was a member of the American Chemical Society (ACS) and Chairman of the Auburn Section from 1957 to 1958. He was also a member of the Chemical Society of London. Over many years he translated Russian abstracts for the Chemical Abstracts Service. One of his hobbies was writing letters to the 'Editor,' mostly to his local paper *The Birmingham News*, on a wide variety of topics. During part of his university tenure he drove a Cord Automobile, manufactured by the Auburn Automobile Company, which many people consider one of the most revolutionary cars ever built.

Kosolapoff died on 1 January 1976 in Alabama and was buried in Garden Hill Cemetery in Auburn, Alabama (*162*). Each year, since 1986, in memory of this fine scientist, a G.M. Kosolapoff Lecture is sponsored by the Auburn Section of the ACS and the Auburn University Department of Chemistry and Biochemistry. The annual award is presented to a scientist in recognition of his or her outstanding technical contribution and includes among its recipients several winners of the Nobel Prize for Chemistry.

2.13 DIALKYL ALKYLPHOSPHONATES $RP(O)(OR)_2$

The dialkyl alkylphosphonates comprise an important group of compounds that may be used in the laboratory synthesis of alkylphosphonic dichlorides $RP(O)Cl_2$ and alkyl alkylphosphonochloridates $RO(R')P(O)Cl$. They are isomeric with the corresponding phosphite triesters but as a general rule have a higher density, boiling point and refractive index than the latter. They are also more resistant to hydrolysis by water. The lower members are miscible in, and hardly hydrolysed by, cold water but the solubility rapidly decreases with increasing molecular weight. Whereas diisopropyl methylphosphonate is miscible with both hot and cold water, diisopropyl ethylphosphonate is miscible with cold water but separates almost quantitatively on heating to 90 °C, redissolving on cooling. The dialkyl alkylphosphonates can be distinguished from the isomeric trialkyl phosphites by the fact that the latter decolourise iodine in the presence of sodium bicarbonate. This reaction is quantitative and was used for the quantitative estimation of trivalent phosphorus compounds occasionally present as impurities prior to the advent of modern analytical techniques.

This section covers the synthesis of dialkyl alkylphosphonates starting from a total of 12 trivalent and pentavalent precursors (Fig. 2.13.1). Methods include the aerial oxidation of dialkyl alkylphosphonites (**A**), the alkylation–oxidation of dialkyl phosphorochloridites (**B**), the Arbuzov reaction of alkyl halides with trialkyl phosphites (**C**), the diesterification of alkylphosphonic dichlorides (**D**) and dibromides (**E**), the Michaelis–Becker reaction of an alkyl halide with a Group(I) metal salt of dialkyl *H*-phosphonates (**F**), the alkylation of trialkyl phosphates (**G**), the transesterification of dialkyl alkylphosphonates (**H**), the reductive deoxygenation of dialkyl acylphosphonates (**I**), the alkylation of dialkyl phosphorochloridates (**J**), the diesterification of *N*,*N*,*N*′,*N*′-tetraalkyl phosphonodiamidates (**K**) and nucleophilic addition to dialkyl vinylphosphonates (**L**). The two most intensively studied and versatile methods of preparation are the Arbuzov and Michaelis–Becker reactions and these are

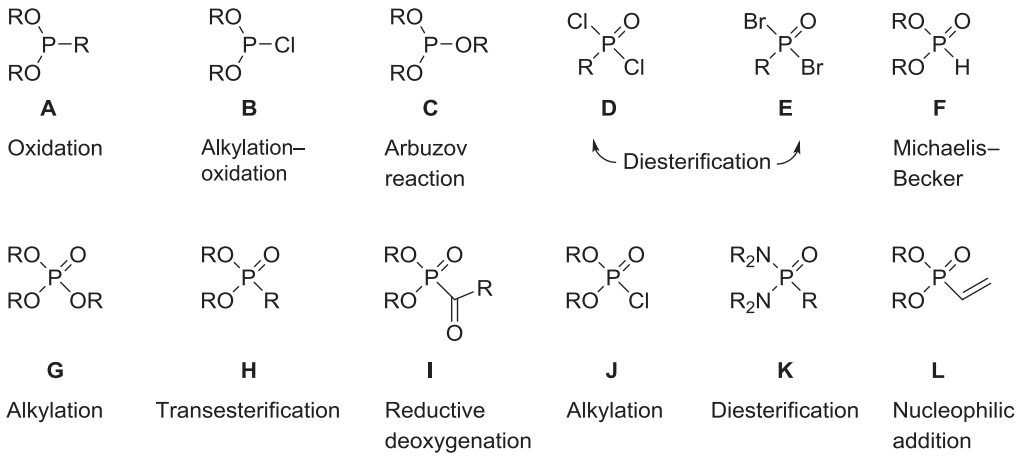


Figure 2.13.1 Precursors to dialkyl alkylphosphonates and the required transformations.

covered next in the greatest depth. Also covered at the end of this section are the syntheses of unsymmetrical dialkyl alkylphosphonates (Section 2.13.13) and the ring-closing metathesis reactions of appropriately substituted dialkyl alkylphosphonates to yield cyclic dialkyl alkylphosphonates (Section 2.13.14).

2.13.1 Aerial oxidation of dialkyl alkylphosphonites

Dialkyl alkylphosphonites resemble in chemical reactivity trialkyl phosphites but are considerably more reactive. They are rapidly oxidised in air to give the corresponding phosphonate. Much heat is liberated, and although the phosphonite does not inflame, the temperature of the oxidation reaches about 160 °C (*39*). Controlled oxidation, by passing a slow current of air through the substance, gives the alkylphosphonate in good yield (Fig. 2.13.1.1).

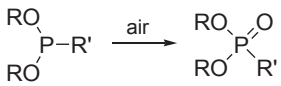


Figure 2.13.1.1

2.13.2 Alkylation–oxidation of dialkyl phosphorochloridites

γ-Butyro- and δ-valerolactone enolates, prepared from the lactones and lithium *N,N*-diisopropylamide (LDA) at −78 °C, react with diethyl phosphorochloridite to give trivalent intermediates (**82a–b**) whose aerial oxidation provides the phosphonolactones (**83a–b**) in acceptable yield (Fig. 2.13.2.1) (*163*). Another approach is to start from the dialkyl phosphorochloridate (refer to Section 2.13.10). Diisopropyl phosphorochloridate reacts with γ-butyro- and δ-valerolactone enolates in hexamethylphosphoramide (HMPA) to give diisopropyl vinyl phosphates (**84a–b**) which rearrange

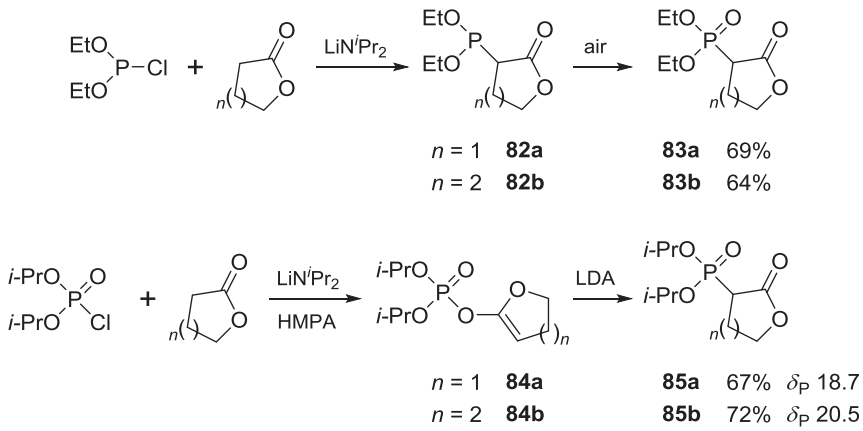


Figure 2.13.2.1

to the phosphonates (**85a**—**b**) when treated with LDA. HMPA acts as a co-solvent and should be handled carefully because of its suspected carcinogenicity.

▷ *α-(Diethoxyphosphinyl)-γ-butyrolactone* (**83a**) (*163*). γ-Butyrolactone (0.192 ml, 2.5 mmol) was added dropwise by syringe to a stirred solution of LDA (2.75 mmol, prepared *in situ* from *n*-butyllithium (1.90 ml, 1.6 M in hexane) and diisopropylamine (0.38 ml) in diethyl ether (6 ml) at −78 °C). After 30 min, diethyl phosphorochloridite (0.39 ml, 2.75 mmol) was added dropwise to the resulting lactone enolate, and the ensuing mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by slow addition of acetic acid in ether (1 M, 3 ml) and the mixture was filtered through a Florisil pad (60—120 mesh). After concentration under vacuum, the resulting liquid was stirred magnetically in a vessel open to the air for 12 h. Purification of the residue by column chromatography on silica gel, eluting with ethyl acetate, gave the phosphonolactone (383 mg, 69%).

▷ *α-(Diethoxyphosphinyl)-δ-valerolactone* (**83b**) (*163*). The previous procedure was followed with a few differences. δ-Valerolactone (250 mg, 2.5 mmol) was treated with LDA (1.1 mol equiv.) in ether. After addition of HMPA (0.48 ml, 2.75 mmol) to the resulting enolate, diethyl phosphorochloridite (0.39 ml, 2.75 mmol) was added. The standard workup, followed by aerial oxidation and chromatography, eluting with 4:1 ethyl acetate—hexane, afforded the phosphonolactone (377 mg, 64%).

▷ *α-(Diisopropoxyphosphinyl)-γ-butyrolactone* (**85a**) (*163*). γ-Butyrolactone (0.38 ml, 5 mmol) was added dropwise by syringe to a stirred solution of LDA (5.5 mmol) in THF (15 ml) at −78 °C. After 30 min, a solution of diisopropyl phosphorochloridate (1.00 ml, 5.5 mmol) in HMPA (0.99 ml, 5.7 mmol) was added to the lactone enolate, and the resulting mixture was allowed to warm to room temperature over 30 min. The mixture was then cooled to −78 °C and a solution of LDA (2.2 mol equiv. in 15 ml THF) was added by syringe, and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by slow addition of acetic acid in ether (1 M, 4.4 mol equiv.) and the resulting mixture was filtered through a Florisil pad. Purification by column chromatography on silica gel, eluting with 1:1 ethyl acetate—hexane, and then 1:1 acetonitrile—ethyl acetate, afforded the phosphonolactone (832 mg, 67%). δ_P ($CDCl_3$) 18.7 ppm.

▷ *α-(Diisopropoxyphosphinyl)-δ-valerolactone* (**85b**) (*163*). The previous procedure was followed with a few differences. δ-Valerolactone (500 mg, 5.0 mmol) was treated with LDA (1.1 mol equiv.), HMPA

(0.99 ml, 5.7 mmol) and diisopropyl phosphorochloridate (1.00 ml, 5.5 mmol). The resulting vinyl phosphate was treated with LDA (2.2 mol equiv.) and quenched by acidic workup. Column chromatography on silica gel gave the phosphonolactone (951 mg, 72%). δ_P ($CDCl_3$) 20.5 ppm.

2.13.3 Arbuzov reaction of trialkyl phosphites and alkyl halides

The Arbuzov reaction, named after the Russian chemist A.Ye. Arbuzov, provides a valuable method of progressing from trivalent phosphorus derivatives to those of pentavalent phosphorus, and also serves to establish the phosphorus–carbon bond that is a feature of a considerable number of compounds. In its simplest form, the reaction consists of heating a trialkyl phosphite with the corresponding alkyl iodide (*164*). Various surveys of the reaction have been written (*165–167*). Reviews of phosphorohalidites in the Arbuzov reaction with halogen-containing compounds (*168*) and the Arbuzov reaction of halogenoacetylenes as a method of synthesis of alkynylphosphonates and other organophosphorus compounds (*169*) are available.

2.13.3.1 Biography

Alexander Yermingel'dovich Arbuzov (1877–1967). Alexander Yermingel'dovich Arbuzov was born on 12 September 1877 in the Arbuzov Baran family of the former Spassk district of the Kazan government. He began his education at a village school and very early, when only a boy of 10, he was transferred to Kazan where he graduated at the 1st Kazan Gymnasium. In 1896 he enrolled in the natural science division of the mathematics-physics faculty of Kazan University. The university was founded in 1804 as the easternmost outpost of Russian higher education during the nineteenth century. At school Arbuzov had been attracted to the natural sciences, especially physics and chemistry, and at university this attraction found favourable conditions for development. The superb work of Alexander Mikhailovich Butlerov (1828–1886) on the synthesis of tertiary alcohols, the object of which was to confirm the theory of the chemical structure of compounds, resolved triumphantly (*170,171*). It was unsurprising therefore that the synthesis of alcohols in the hands of many of Butlerov's pupils was extended and improved. A.Ye. Arbuzov was fortunate in participating in these researches and in 1900 he completed, under the direction of Alexander Mikhailovich Zaitsev (1841–1910) (*172,173*), Professor of the Kazan University, his first scientific work, on

arylmethylphenylcarbinol (*174*). In this work the Grignard reaction was used for the first time in Russian chemistry for the synthesis of tertiary alcohols. Even at this stage the outstanding aptitude and exceptional talent for experiment of the young A.Ye. Arbuzov was evident.

Arbuzov graduated from the university in 1900 with a first class diploma and the title of Candidate of Natural Sciences. On the recommendation of Professor Flavian Mikhailovich Flavitsky, he was appointed to the post of assistant in the department of organic chemistry and agricultural chemical analysis in the New Alexander Institute of Agriculture and Forestry in the Lyublinskii Province (formerly Novaya Aleksandrija, Poland). Arbuzov chose the direction of his scientific researches himself. At this period the structure of phosphorous acid occupied his attention (*175*). Then it was believed that compounds from organisms, including phosphoric acid derivatives, were composed of metabolic waste that had no significant role in life. The theory of chemical structure was then gaining recognition and had proved useful in studying carbon compounds, while it had not yet had any success in inorganic chemistry. Arbuzov therefore directed his energy to the structure of phosphorous acid for which two forms were thought to be possible, although 'only one phosphorous acid was actually known, whatever the method of preparation' (*176*). The structure of phosphorous acid and its organic derivatives had not been established at that time. A few scientists considered that the acid had a symmetrical structure and related it to the derivatives of trivalent phosphorus, i.e. $(HO)_3P$. On the basis of their researches others thought that this acid was constructed asymmetrically and should be classed with the derivatives of pentavalent phosphorus, i.e. $(HO)_2P(O)H$.

Arbuzov first synthesised several 'saturated' esters of phosphorous acid (trialkyl phosphites) from sodium alkoxides and phosphorus trichloride. He used an original method in the synthesis: drying the sodium alkoxides under vacuum and making it possible to obtain them free of solvent. This method ensured the success of the work. Arbuzov was the first to obtain in the pure state trialkyl phosphites and he showed that his predecessors had been studying mixtures of these and the 'intermediate' acid esters (dialkyl *H*-phosphonates). He carried out his experimental work with exceptional care and was extremely exacting as regards the results obtained. After preparing samples of the pure 'intermediate' acid esters, it was necessary to decide whether they should be classed as tri- or pentavalent phosphorus derivatives. The solution to the problem 'consisted in finding a reagent for tri- or pentavalent phosphorus, i.e. a substance which would give a characteristic compound with one or the other type of phosphorus compound' (*176*).

Thinking about the problem of how to elucidate the structure, Arbuzov recalled: 'The happy thought came to me somewhat late in the evening of trying to find a reliable method by means of which it would be possible to distinguish with certainty between the derivatives of so-called trivalent and those of pentavalent phosphorus. Then, I thought the complex picture obtained in the case of organophosphorus compounds could be resolved quite easily. Inspired with this thought I went into the laboratory at 1 o'clock in the morning and began to look for compounds capable of giving characteristic crystalline derivatives of trivalent phosphorus. For more than two hours I tried to find inorganic salts which according to my ideas could give crystalline compounds with the (tri)phenyl phosphite which I had prepared. All my attempts were, however, unsuccessful. The substances expected were either not obtained at all or were formed as thick, non-crystallising syrups…The following morning the same chaotic picture met my eyes. On careful examination however, I observed

two small crystals bright like faceted diamonds at the bottom of the test tubes…' These crystals were of the complex of copper(I) chloride with triphenyl phosphite, $(PhO)_3P \cdot CuCl$, which was the first representative found of the class of such compounds characteristic of trivalent phosphorus (*177*). The complex picture of the structure of the derivatives of phosphorous acid and their classification became clearer. The characteristic reagents found for derivatives of trivalent phosphorus enabled Arbuzov to conclude that 'all undoubted derivatives of triatomic phosphorus in combining with metal monohalides thereby form characteristic compounds; undoubted derivatives of pentavalent phosphorus give no compounds with monohalides' (*178*).

Phosphorous acid and its acid esters do not combine with copper(I) halides either at room temperature or on heating and therefore can be classed as derivatives of pentavalent phosphorus and have the following structures: $(HO)_2P(O)H$ and $(RO)_2P(O)H$. The problem of converting trivalent phosphorus compounds to pentavalent phosphorus compounds remained. Arbuzov was the first chemist to discover (now over a century ago) the isomerisation of phosphite triesters to alkylphosphonate diesters occurring under the action of alkyl halides. This notable reaction, subsequently named the Arbuzov reaction, became the most important method of constructing P—C bonds in the synthetic organophosphorus chemistry repertoire. Its discovery was of fundamental importance to the further development of the whole of organophosphorus chemistry. The synthetic possibilities offered by the Arbuzov reaction were explored extensively by chemists at Kazan University. The accumulated published data permitted a more detailed examination of the questions associated with the mechanism of this reaction. At the present time it is estimated that over a thousand cases of the Arbuzov reaction have been reported. With every justification this method can be called classical. As possibilities for synthesis are, however, far from exhausted, each year brings new, partly unexpected and interesting results.

In 1905 Arbuzov defended his dissertation for the degree of master of chemistry at Kazan University on 'The structure of phosphorous acid and its derivatives.' In 1911, after the death of his mentor A.M. Zaitsev, he was elected in the All-Russian competition to the chair of organic chemistry at the university, where he continued to perform leading studies in organophosphorus chemistry. His interest in this branch of chemistry may have been boosted by collaboration with German chemists in the 1920s and the 1930s when they worked throughout the Soviet Union, including at the University of Kazan, on chemical-warfare-related projects. It has been rumoured that A.Ye. Arbuzov may have been the first person in the Soviet Union, in late 1943, to prepare the nerve agent sarin (structure given in Chapter 1.5). The Soviets became aware of the existence of the German codename for sarin in 1941 when Soviet forces captured documents belonging to the 52nd Chemical Mine Regiment, but they did not know what the codename described until the end of the war (*179*).

Arbuzov stated that 'no scientific work can be completed, it can only be interrupted' and even at 70 years of age often returned home from the laboratory at midnight with his son Boris Aleksandrovich Arbuzov (B.A. Arbuzov also became a distinguished phosphorus chemist) (*180*). Such dedication inspired young people to continue the school of chemistry he founded; he infected his pupils with the 'science bug' for their entire lives. For services to the Soviet Union and Communist Party, A.Ye. Arbuzov was awarded four times the highest Soviet honour, the Order of Lenin and Order of Labour Red Banner (*180*). He was also a skilled painter and violinist; his favourite composers included

Rakhmaninov, Glazunov, Haydn and Borodin (*181*). He had a dacha containing carved decorations and a charming garden, and was an able glassblower. His inexhaustible interest in and love of chemical science, his very wide scientific outlook and the combination in one person of a highly erudite theoretical thinker, outstanding teaching, brilliant experimental skills and talent for organisation enabled the founding of a school of organic chemists that after his death in 1967 continued to make important chemical discoveries. (Photograph reproduced courtesy of Dstl.)

2.13.3.2 Scope of Arbuzov reaction

The Arbuzov reaction in its simplest form consists of heating a trialkyl phosphite with the corresponding alkyl iodide. On distillation, the alkyl iodide is recovered unchanged but the trialkyl phosphite is transformed into the isomeric dialkyl alkylphosphonate (Fig. 2.13.3.2.1) (*182*). This specific case, where the alkyl group of the iodide is the same as all three alkyl groups of the phosphite, resulting in isomerisation, is sometimes referred to as the Arbuzov rearrangement (the alkyl halide here acts catalytically).

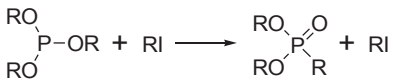


Figure 2.13.3.2.1

The reaction is capable of much wider application. The first variant that can be introduced is made by allowing a trialkyl phosphite to react with a different alkyl halide. Except under special conditions that will be described later, secondary halides do not react, the reaction being confined to primary halides. When triethyl phosphite (**86**) and methyl iodide are allowed to react, the main products are diethyl methylphosphonate (**87**) and ethyl iodide (Fig. 2.13.3.2.2) (*182*). At the same time, the liberated ethyl iodide competes with the methyl iodide for the unreacted triethyl phosphite leading to the formation of some diethyl ethylphosphonate (**88**). Nevertheless, the balance is strongly in favour of attaching the *smaller* alkyl group to the phosphorus atom.

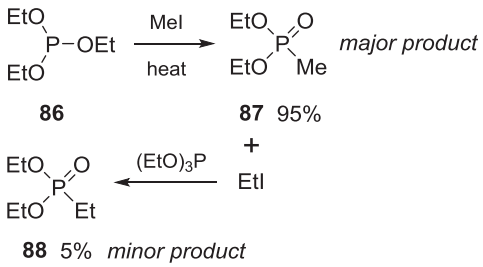


Figure 2.13.3.2.2

When dimethyl ethyl phosphite (**89**) and methyl iodide react, no ethyl iodide forms and the product is ethyl methyl methylphosphonate (**90**) (Fig. 2.13.3.2.3) (*183*). It has been mentioned that, except under special circumstances, secondary alkyl halides do not enter into an Arbuzov reaction.

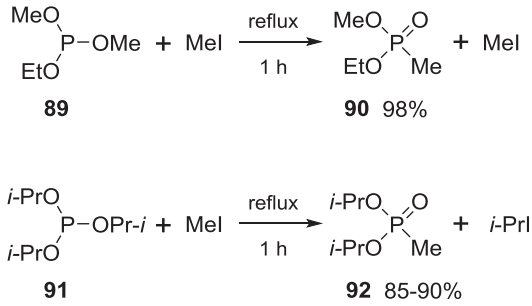


Figure 2.13.3.2.3

When a tri-*sec*-alkyl phosphite, e.g. triisopropyl phosphite (**91**), is treated with methyl iodide, there can be no competing reaction between the latter and the isopropyl iodide formed for any unreacted phosphite. The reaction in this case is vigorous and leads only to diisopropyl methylphosphonate (**92**) and isopropyl iodide (*184*). The reaction between secondary alkyl phosphites and methyl iodide is considerably more energetic than with higher iodides. Sterically hindered and sensitive trialkyl phosphites do not enter easily into the Arbuzov reaction. Tri-*tert*-butyl phosphite does not react with alkyl halides at temperatures below 80—90 °C and above these temperatures decomposes with evolution of isobutylene (*185*).

Alkyl bromides can participate as well as iodides but in this case the reaction is much less vigorous and does not appear to progress at a temperature much below 160 °C. If the appropriate amount of a relatively low-boiling bromide, such as *n*-butyl bromide, is added to, say, triethyl phosphite, the boiling point of the mixed liquids is too low for the reaction to take place at all rapidly. So, not only is the yield of the diethyl *n*-butylphosphonate low, but it is also further reduced by the competing action of the liberated ethyl bromide. With higher boiling bromides such as *n*-hexyl bromide and 1,2-dibromoethane, the method gives excellent results (*182*). It is convenient to let the volatile ethyl bromide formed distil out of the reaction mixture as fast as it is produced. By this precaution, the reaction temperature does not fall and the formation of diethyl ethylphosphonate is minimised. When carrying out reactions of this type, it is desirable that the trialkyl phosphite should be free from any dialkyl *H*-phosphonate impurity. Purification of old samples of trialkyl phosphites can be carried out by distillation under reduced pressure from a small amount of sodium wire.

When α,ω-dibromoalkanes are used, one or both bromine atoms can enter into the reaction according to the experimental conditions (*182*). With an excess of 1,2-dibromoethane, diethyl 2-bromoethylphosphonate (**93**) is the main product; with an excess of phosphite, tetraethyl ethylene-1,2-diphosphonate (**94**) predominates (Fig. 2.13.3.2.4). Compound (**93**) readily loses hydrogen bromide on treatment with triethylamine to generate diethyl vinylphosphonate (**32**). The Arbuzov reaction can therefore be used indirectly for the preparation of dialkyl 1-alkenylphosphonates.

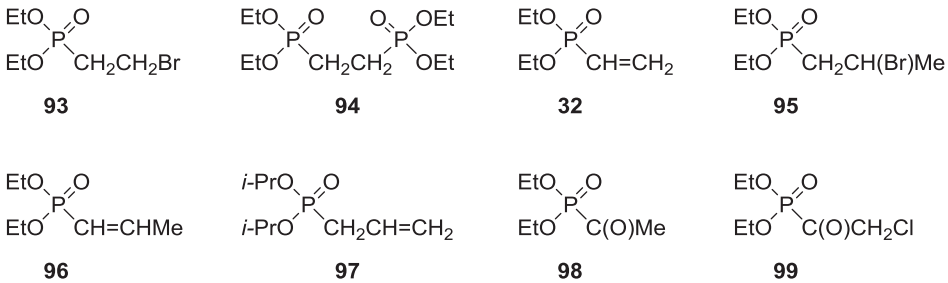


Figure 2.13.3.2.4

It was remarked earlier that, except under special conditions, secondary halides do not undergo this reaction. It is a general rule that, even under these special conditions, the reaction only takes place if the phosphorus ester is also secondary. No reaction under any conditions occurs between trimethyl phosphite and isopropyl iodide (*39*). When catalytic amounts of isopropyl iodide are gradually added to triisopropyl phosphite heated to 160 °C, fair yields of diisopropyl isopropylphosphonate, $(i\text{-PrO})_2P(O)Pr\text{-}i$, are obtained. It has been observed, however, that when a compound such as 1,2-dibromopropane is made to react with triethyl phosphite, formation of diethyl 2-bromopropylphosphonate (**95**) occurs with much greater reluctance than that of diethyl 2-bromoethylphosphonate (**93**) from 1,2-dibromoethane (*39*). The considerably longer period of heating necessary to complete the reaction leads to the formation of a small amount of the tetraethyl alkylenediphosphonate, the carbon atom attached to the β-bromine atom reacting, in addition to that bonded to the α-bromine atom, to a very limited extent. This furnishes an example of a secondary halide undergoing the reaction with a primary alkyl phosphite. However, the harsh conditions result in dehydrobromination of the 2-bromopropylphosphonate (**95**) to give, after repeated fractionation, only diethyl 1-propenylphosphonate (**96**).

β,γ-Unsaturated alkylene halides such as allyl iodide react in the same way as alkyl iodides. For example, triisopropyl phosphite and allyl iodide give diisopropyl allylphosphonate (**97**) in good yield (Fig. 2.13.3.2.4) (*39*). The Arbuzov reaction of trialkyl phosphites and acyl chlorides and derivatives of chloromethyl- and 1-chloromethyl alkyl ethers occurs with great ease, considerable heat being liberated in the process. Thus, triethyl phosphite and acetyl chloride give diethyl acetylphosphonate (**98**). When acetyl chloride is replaced with methylsulfonic chloride, reaction occurs with explosive violence. With chloroacetyl, dichloroacetyl, trichloroacetyl and fluoroacetyl chloride, the course of the reaction is obscure. Chloroacetyl chloride gives a small yield of diethyl chloroacetylphosphonate (**99**), whereas di- and trichloroacetyl chlorides give no "recognisable product" (*39*). Triethyl phosphite and fluoroacetyl chloride, amid much unidentifiable material, gives, unexpectedly, diethyl phosphorofluoridate, $(EtO)_2P(O)F$ (*toxic!*).

As a general rule, the ease with which the Arbuzov reaction occurs with alkyl halides decreases in the order I > Br > Cl. But if the chlorine is sufficiently reactive, compounds containing this halide may be used. Thus triisopropyl phosphite and chloromethyl methyl ether give a good yield of diisopropyl methoxymethylphosphonate $(i\text{-PrO})_2P(O)CH_2OMe$, together with some diisopropyl isopropylphosphonate $(i\text{-PrO})_2P(O)Pr\text{-}i$, which presumably originates from the isopropyl chloride liberated during the reaction (*39*). Similarly, triethyl phosphite and chloromethyl-trisubstituted silanes undergo an Arbuzov reaction when heated (Fig. 2.13.3.2.5) (*186*).

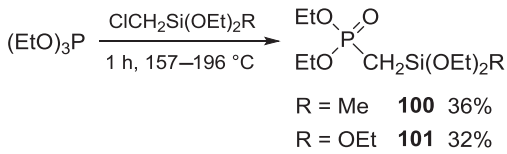


Figure 2.13.3.2.5

The mechanism of the Arbuzov rearrangement has been studied much. A.Ye. Arbuzov suggested that an unstable phosphonium salt is formed, which breaks down to the alkylphosphonate and alkyl iodide (Fig. 2.13.3.2.6). Much experimental evidence has been amassed that supports this suggestion. The necessity for the phosphite species being sufficiently nucleophilic for a successful reaction is illustrated by the finding that methyl phosphorodichloridite $MeOPCl_2$ fails to react with methyl iodide, the starting materials being recovered unchanged (*39*). Knowledge of the decomposition pathway of the intermediates formed from trialkyl phosphites and alkyl halides is critical to helping predict the outcome of any planned Arbuzov reaction. The reactivity of the iodide ion to dealkylation of the phosphonium intermediates decreases in the substituent order OMe > OPr-*n* > OPr-*i* (*14*). The OMe group dealkylates in preference to *n*-, *i*- or *s*-BuO; *t*-BuCH(Me)O; cyclopentoxy; or cyclohexyloxy groups, permitting the synthesis of unsymmetrical dialkyl alkylphosphonates RO(MeO)P(O)Me from alkyl dimethyl phosphites $ROP(OMe)_2$ and methyl iodide (*14*).

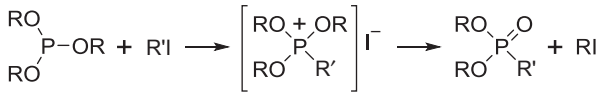
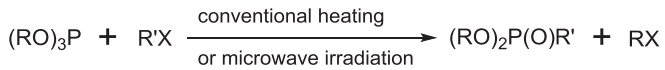


Figure 2.13.3.2.6

If complex formation occurs, the effect of the alkyl iodide should be catalytic. This has been found to be the case experimentally, with only a very small amount of methyl iodide being necessary to convert trimethyl phosphite into dimethyl methylphosphonate. Other alkylating agents besides alkyl halides can be employed. Dimethyl sulfate is even more effective in bringing about the Arbuzov reaction than is methyl iodide. In fact, if more than 0.01 molar equivalents of the former are used, the reaction becomes almost uncontrollable. Alkyl *p*-toluenesulfonates (tosylates) also enter effectively into reaction. By analogy to the well-characterised reaction with alkyl halides, the mechanism probably involves the intermediate formation of the quaternary phosphonium tosylate which then eliminates a molecule of the alkyl tosylate to yield the phosphonate ester: $(RO)_3P + R'OTs \rightarrow [(RO)_3PR']^+[OTs]^- \rightarrow (RO)_2P(O)R' + ROTs$ (*158*). When R and R′ are identical, the overall reaction constitutes a simple isomerisation of the trialkyl phosphite; since it is regenerated, only a catalytic quantity of the alkyl tosylate is needed. Thus on warming in the presence of a small amount of ethyl tosylate, triethyl phosphite is converted into diethyl ethylphosphonate in practically quantitative yield. When R and R′ in the starting materials $(RO)_3P$ and R′OTs are dissimilar the reaction is more complicated and less useful.

Dialkyl alkylphosphonates, especially isomeric variations, are useful for infrared spectroscopic or mass spectrometric studies (*187*). A selection of dialkyl alkylphosphonates accessible by the Arbuzov reaction by conventional heating or microwave irradiation appears in Fig. 2.13.3.2.7.



Dialkyl alkylphosphonates

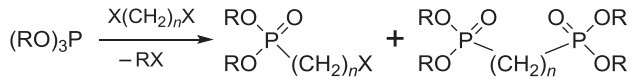
R	R′	X	Yield (%)	Bp (°C/mmHg)	δ_P ($CDCl_3$)	Ref.
Me	Me	I	95	67/10	32.1	(*219*)
Me	Et	I	95	nr	34.8	(*219*)
Et	Me	I	95	51/1	29.4	(*184*)
Et	Et	I	99	56/1	33.9	(*184*)
Et	*n*-Pr	I	93	89/9	31.2	(*219*)
Et	*n*-Bu	Br	nr	74/1	31.6	(*182*)
Et	*n*-C_5H_{11}	Br	nr	86/2	nr	(*182*)
Et	*i*-Pr$(CH_2)_2$	Br	nr	75/1	nr	(*182*)
Et	*n*-C_6H_{13}	Br	nr	103/2	nr	(*182*)
Et	*n*-C_7H_{15}	Br	nr	113/2	nr	(*182*)
Et	*n*-C_8H_{17}	Br	nr	119/1	nr	(*182*)
Et	*n*-$C_{12}H_{25}$	Br	63	160/1	nr	(*182*)
Et	$NCCH_2$	Br	95	nr	13.6	(*219*)
Et	$NC(CH_2)_3$	Br	75	nr	29.2	(*207*)
Et	$PhCH_2$	Br	95	nr	25.5	(*207*)
Et	$Ph(CH_2)_3$	Br	90	nr	30.6	(*207*)
Et	$CH_2{=}CHCH_2$	Br	89	nr	26.7	(*207*)
Et	$PhCH{=}CHCH_2$	Br	95	nr	27.4 (*E*)	(*219*)
Et	$H_2NC(O)CH_2$	Br	94	nr	21.9	(*219*)
Et	$EtOC(O)CH_2$	Br	98	nr	20.5	(*219*)
Et	EtOC(O)CHF	Br	94	nr	8.6	(*219*)
i-Pr	CD_3	I	90	86/15	27.5	(*121*)
i-Pr	Me	I	90	51/1	nr	(*184*)
i-Pr	Et	I	91	61/1	nr	(*184*)
i-Pr	*n*-Pr	I	98	75/3	30.9	(*39,219*)
i-Pr	*n*-Bu	I	96	87/4	30.6	(*39,219*)
i-Pr	CH_2Ph	Br	93	nr	24.5	(*219*)
Me_3Si	Me	I	64	nr	17.9	(*219*)
Me_3Si	CH_2CN	Br	82	nr	–4.7	(*219*)
Me_3Si	CH_2Ph	Br	84	nr	10.1	(*219*)
Bn	CH_2Ph	Cl	88	chrom	28.1	(*193*)

nr = not reported, chrom = purified by careful column chromatography on silica gel.

Figure 2.13.3.2.7

The microwave-assisted reaction can also be performed on a solid support (*188*). Ionic liquid solvents are also able to benefit the Arbuzov reaction (*189,190*).

Dialkyl haloalkylphosphonates (**102**) are prepared most conveniently by the use of an excess of the α,ω-dihaloalkane and the appropriate trialkyl phosphite (Fig. 2.13.3.2.8). The tetraalkyl mono- or polymethylenediphosphonates (**103**) resemble the dialkyl alkylphosphonates but, as may be expected, they boil at much higher temperatures. They are obtained by the action of an excess of the trialkyl phosphite on the α,ω-diiodoalkane or α,ω-dibromoalkane. Tetraisopropyl ethyl-1,2-diphosphonate (mp 52–53 °C) is crystalline at ordinary temperatures (*191*).



102 Monophosphonates **103** Diphosphonates

R	X	*n*	Yield (%)	Bp (°C/mmHg)	Yield (%)	Bp (°C/mmHg)	Ref.
Me	Br	2	nr	nr	nr	144/5	(*195*)
Et	I [a]	1	90	101/1	91	152/2	(*39,219*)
Et	Br	1	nr	nr	60	126/0.5	(*128*)
Et	Br	2	40	101/1	49	157/1	(*39,196*)
Et	Br	3	91	nr	75	171/2	(*207,197*)
Et	Br	4	90	nr	62	169/0.7	(*207,191*)
Et	Br	5	94	nr	63	178/0.6	(*207,191*)
Et	Br	6	nr	nr	nr	nr	not found
Et	Br	7	nr	nr	53	188/0.7	(*115*)
Et	Br	8	nr	nr	70	186/0.2	(*115*)
Et	Br	9	91	nr	63	203/0.7	(*207,115*)
Et	Br	10	88	nr	65	200/0.3	(*207,115*)
i-Pr	Br	2	nr	nr	nr	115/0.01	(*39,191*)

nr = not reported. *a.* When X = Br very little $(EtO)_2P(O)CH_2Br$ forms.

Figure 2.13.3.2.8

Variants of the Arbuzov reaction for the synthesis of dimethyl methylphosphonate are depicted in Fig. 2.13.3.2.9. They include heating the complex formed between trimethyl phosphite and copper(I) chloride to 200 °C in diphenyl ether (*192,194*), the reaction of trimethyl phosphite with methanol catalyst in a sealed tube heated to over 200 °C for 5 h (*198*) and the reaction of trimethyl phosphite with dimethyl hydrogen phosphate in a sealed tube at room temperature for 24 h (*199*) or with phenyl methyl sulfoxide in a sealed tube heated to 110 °C for 5–6 days (*200*).

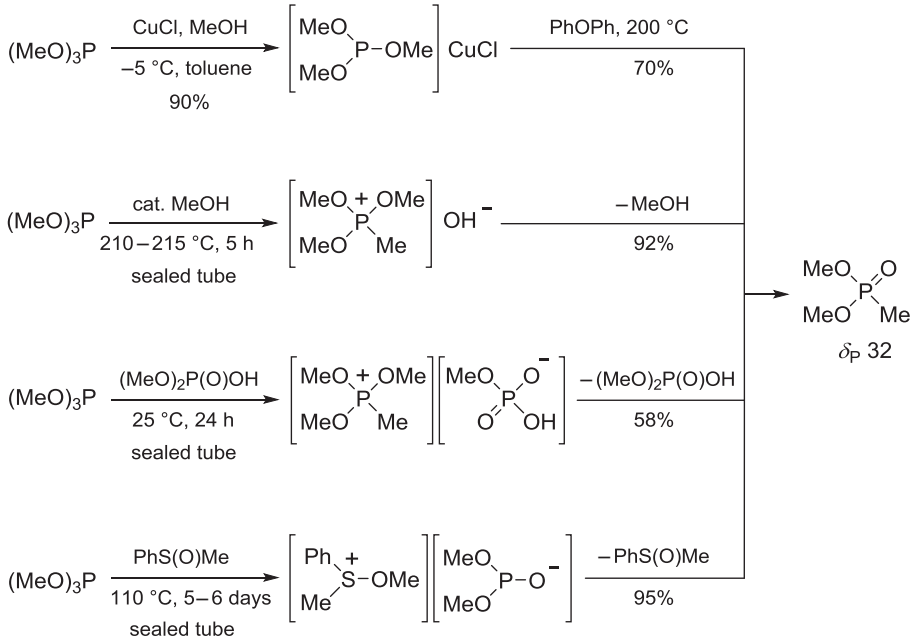


Figure 2.13.3.2.9

Trisubstituted phosphites bearing electronegative substituents (e.g. phenyl) are able to react with methyl trifluoromethanesulfonate (*201*) or methyl iodide (*183*) to give phosphonium salts (e.g. **104** and **105**) which decompose readily to provide diphenyl methylphosphonate (**106**) (Fig. 2.13.3.2.10). The phenyl substituents of triphenyl phosphite can be replaced by alkyl substituents upon strong heating with alcohols, such as methanol and *n*-butanol (*183*), and treatment of the formed alkyl diphenyl phosphites with a catalytic amount of methyl iodide can also produce diphenyl

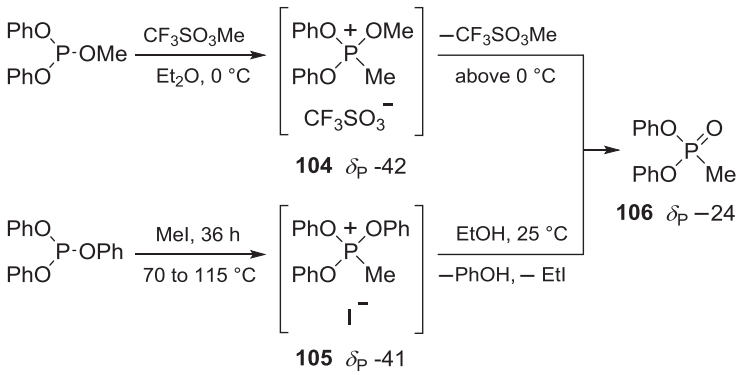


Figure 2.13.3.2.10

methylphosphonate (**106**) (Fig. 2.13.3.2.11). Similarly, benzyl alcohol can be employed to provide diphenyl benzylphosphonate (**107**) (*202*). The phosphonium salt intermediates (**108**) from treatment of triphenyl phosphite and alkyl iodides at 100–155 °C for 11–1000 h (the time required depends on the reactivity of the alkyl iodide) can be observed by NMR spectroscopy. The ^{31}P NMR spectroscopic shifts are shown in Fig. 2.13.3.2.12 (*254*)). Alkaline hydrolysis of these salts provides the corresponding diphenyl alkylphosphonates.

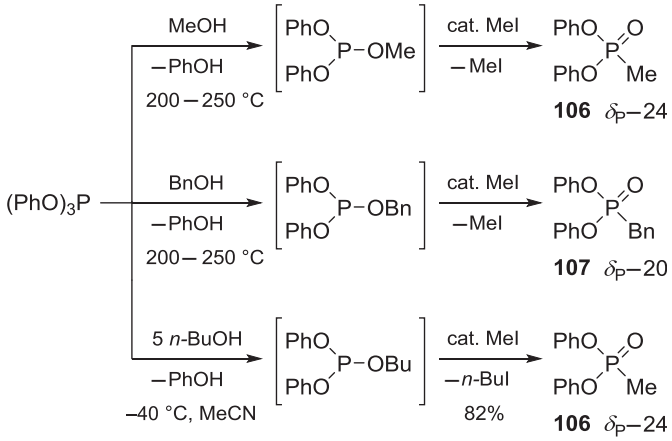
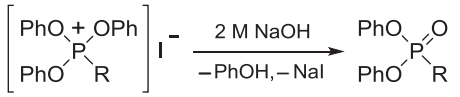


Figure 2.13.3.2.11



108 **109**

R	δ_P ($CDCl_3$)	δ_P ($CDCl_3$)
Me	–41	–24
Et	–40	–27
n-Pr	–38	–27
i-Pr	–38	–26
n-Bu	–38	–27
i-Bu	–38	–26

Figure 2.13.3.2.12

Unsymmetrical trialkyl phosphites can be used to advantage to generate unsymmetrical dialkyl alkylphosphonates (Fig. 2.13.3.2.13). Dimethyl isopropyl phosphite (**110**) is accessible by transesterification of trimethyl phosphite with sodium isopropoxide (*14*) or methanolysis of isopropyl phosphorodichloridite (**111**) (*203*). Heating dimethyl isopropyl phosphite with methyl iodide

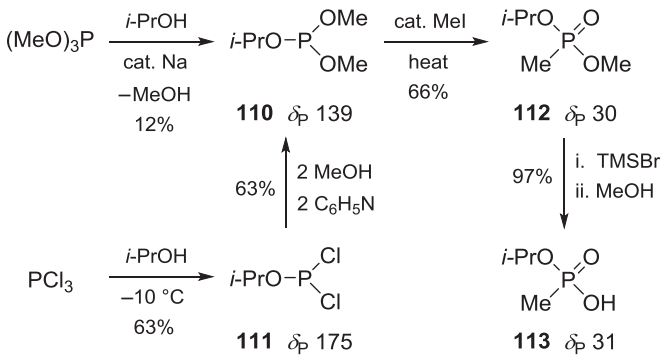
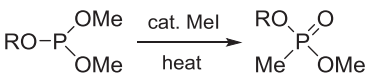


Figure 2.13.3.2.13

provides isopropyl methyl methylphosphonate (**112**) (*14*,*203*). Treatment of this with TMSBr and methanolysis of the formed isopropyl trimethylsilyl methylphosphonate gives isopropyl methylphosphonic acid (**113**). This is an important analyte in investigations of allegations of the use of sarin-filled chemical weapons (*4*,*5*).

The Arbuzov rearrangement of alkyl dimethyl phosphites by heating with methyl iodide provides alkyl methyl methylphosphonates in good yield (Fig. 2.13.3.2.14) (*14*). These can also be converted into the corresponding alkyl methylphosphonic acids by the TMSBr methanolysis two-step process mentioned already.



Alkyl methyl methylphosphonates

R	Yield (%)	Bp (°C/mmHg)	δ_P ($CDCl_3$)
i-Pr	66	21/0.2	29.7
n-Bu	94	55/1	31.1
i-Bu	88	45/0.04	31.6
s-Bu	86	50/0.03	29.5 / 29.8 [a]
Pin	95	65/0.03	29.5 / 30.3 [a]
c-C_5H_9	87	60/1	29.7
c-C_6H_{11}	84	45/0.2	29.6

Pin = pinacolyl *t*-BuCH(Me)-. *a*. Pair of diastereoisomers.

Figure 2.13.3.2.14

Although phenyl substituents in trisubstituted phosphites reduce the nucleophilicity of the phosphorus atom present, such compounds are able to combine with methyl iodide when heated in a sealed tube. Di-*n*-butyl phenyl phosphite (**114**) reacts to provide *n*-butyl phenyl methylphosphonate

(**115**) in acceptable yield (Fig. 2.13.3.2.15) (*204*). The phenyl group of the starting material is retained in the product: the phenoxy group of the phosphonium intermediate, unlike the alkoxy groups, cannot be removed through nucleophilic attack of the iodide ion.

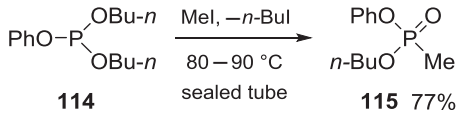
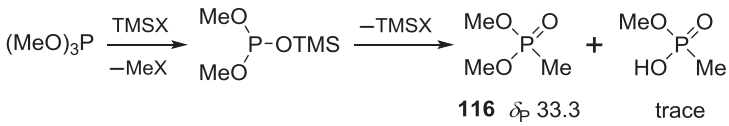


Figure 2.13.3.2.15

A variation of the Arbuzov reaction involves heating trialkyl phosphites with a trimethylsilyl halide catalyst in a sealed tube (*205*). High catalyst purity is vital for high yields of the dialkyl alkylphosphonates. The use of TMSBr is preferred over that of trimethylsilyl iodide (TMSI) despite the longer reaction times required, because of the variable quality of commercial TMSI, which causes irreproducible results. The best isolated yield (91%) of dimethyl methylphosphonate (**116**) was obtained by treating trimethyl phosphite with 5% mol TMSBr at 100 °C for 3 h (Fig. 2.13.3.2.16). Heating diethyl benzyl phosphite (**117**) to 80 °C in the presence of 5% mol TMSBr gave diethyl benzylphosphonate (**118**) in good yield (Fig. 2.13.3.2.17) together with benzyl ethyl ethylphosphonate BnO(EtO)P(O)Et (7% yield) and a trace of diethyl *H*-phosphonate (not shown).



Yield of dimethyl methylphosphonate

X	RT 24 h	50 °C 6 h	100 °C 3 h
Br	5%	62%	91%
I	52%	95%	89%

RT = room temperature.

Figure 2.13.3.2.16

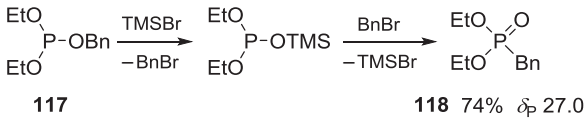


Figure 2.13.3.2.17

Dialkyl trichloromethylphosphonates can be accessed in good yield by Arbuzov reaction of trialkyl phosphites with carbon tetrachloride through conventional heating (*206*) or microwave irradiation (*207*). Under radical conditions in the presence of dibenzoyl peroxide the yields decline (*208*,*209*). Diethyl trichloromethylphosphonate (**119**) is convenient for the preparation of its chloro- and dichloromethylphosphonate derivatives (**120**) and (**121**) by lithiation and silylation followed by hydrolysis (*210*) or treatment with diethyl *H*-phosphonate and triethylamine in ethanol (*211*), respectively (Fig. 2.13.3.2.18). Methods for the synthesis of dialkyl α-halogenated methylphosphonates have been reviewed (*30*).

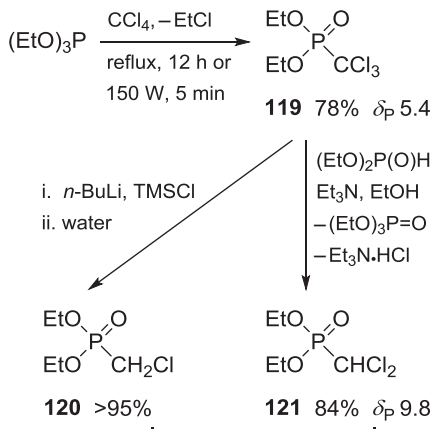


Figure 2.13.3.2.18

Several methods are available for the synthesis of cyclic alkylphosphonates (*202*). Two popular ones include transesterification of diaryl alkylphosphonates with a suitable diol (e.g. **106** → **122**) and the Arbuzov reaction of a cyclic alkyl phosphite with an alkyl bromide or iodide (e.g. **123** → **124**) (Fig. 2.13.3.2.19).

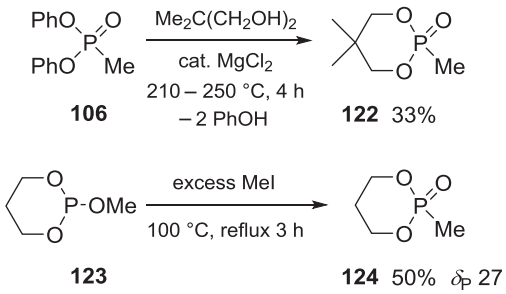


Figure 2.13.3.2.19

The reaction of triethyl phosphite with 1,2-dichloro-3,3,4,4,5,5-hexafluorocyclopentene (**125**) regardless of the ratio of starting materials always leads to formation of the diphosphonate, suggesting that the monophosphonate intermediate is highly reactive towards the starting phosphite (*212*). The use of 2 molar equivalents of triethyl phosphite furnishes the diphosphonate (**28**) and a small amount of diethyl ethylphosphonate (**88**) (Fig. 2.13.3.2.20). Similarly, diethylphosphonyl derivatives of other fluorinated five-membered rings can be prepared through the Arbuzov reaction (*213*,*214*). Heterocycles with reactive C-Cl bonds undergo the Arbuzov reaction with trialkyl phosphites to yield phosphonyl species, such as compounds **126** and **127** (*215*), **128** (*216*) and **129** (*217*) (Fig. 2.13.3.2.21).

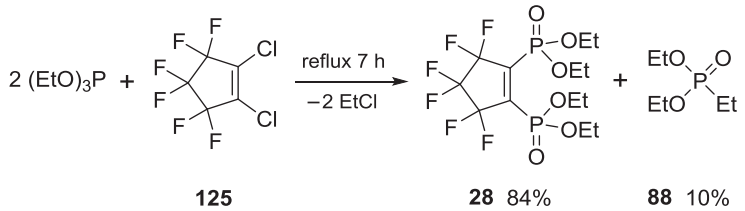


Figure 2.13.3.2.20

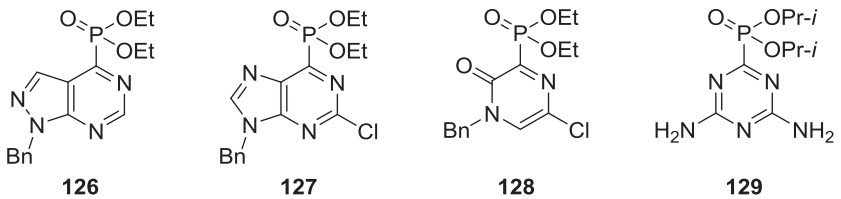
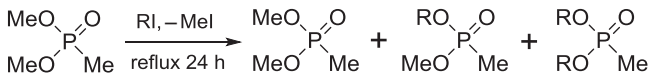


Figure 2.13.3.2.21

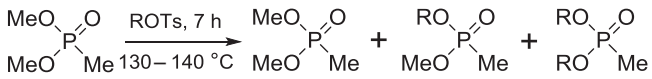
Possible transalkylation of dialkyl alkylphosphonates formed during the Arbuzov reaction under extreme conditions of heat and pressure is worth bearing in mind when planning syntheses of dialkyl alkylphosphonates. Sometimes transalkylation can be harnessed to prepare target compounds. For example, the Arbuzov reaction of trimethyl phosphite with *n*-propyl iodide is not a useful method of preparation of dimethyl *n*-propylphosphonate. Even when the phosphite is added slowly to a large excess of boiling *n*-propyl iodide in a distilling apparatus arranged to permit rapid removal of methyl iodide, to minimise formation of dimethyl methylphosphonate, an intractable mixture of the latter and the target compound, as well as transalkylated products are obtained (*218*). These transalkylated impurities included methyl *n*-propyl methylphosphonate MeO(*n*-PrO)P(O)Me, di-*n*-propyl methylphosphonate $(n\text{-PrO})_2$P(O)Me, methyl *n*-propyl *n*-propylphosphonate MeO(*n*-PrO)P(O)Pr-*n* and di-*n*-propyl *n*-propylphosphonate $(n\text{-PrO})_2$P(O)Pr-*n*. Transalkylation occurs through nucleophilic attack of the phosphonyl oxygen atom of the starting dialkyl alkylphosphonate $(RO)_2P(O)Me$ on the alkyl iodide R′I, which produces intermediates of type $[(RO)_2P(OR')Me]^+I^-$. Such reactions often require high temperatures and long reaction times and have a limited scope.

Heating various dimethyl *H*-phosphonate and alkyl iodide mixtures for 24 h showed that for transalkylation to occur at a useful rate the temperature must be raised sufficiently (Fig. 2.13.3.2.22) (*218*). The large reactivity difference as a function of alkylating agent seems almost entirely due to the temperature (owing to the large excess of alkyl iodide used in these experiments, the temperature of the boiling mixture was quite close to that of the pure iodide). Even the temperature of refluxing ethyl iodide (bp 70 °C) was sufficient for noticeable reaction. It seems that transalkylation at 70–100 °C proceeds too slowly for convenient synthetic application, but fast enough to be troublesome when performing certain Arbuzov reactions. Despite the drawbacks of this process, it is possible to isolate di-*n*-propyl methylphosphonate in 78% yield and >99% purity from dimethyl methylphosphonate heated twice to 130 °C, each time with a 6-fold molar excess of *n*-propyl iodide, for 96 h then 48 h, respectively, in a sealed tube. The similar behaviour of alkyl tosylates to alkyl iodides in such reactions, and their higher boiling points also favours transalkylation, although synthetic applications are scarce.



R	bp of RI (°C)	Yields of the three products (%) [a]		
Et [b]	70	94	6	trace
n-Pr [c]	100	70	25	5
n-Bu [c]	130	12	42	46

a. Yields normalised to 100% (material balance > 90%)
b. Phosphonate-alkyl iodide molar ratio used was 1:20
c. Phosphonate-alkyl iodide molar ratio used was 1:10



R	bp of RI (°C)	Yields of the three products (%) [a]		
Et [b]	300 [c]	2	23	75
n-Pr [b]	> 300	4	29	67

a. Yields normalised to 100% (material balance > 90%)
b. Phosphonate-tosylate molar ratio was 1:20
c. Estimated via pressure-temperature nomograph, bp 160 °C/10 mmHg

Figure 2.13.3.2.22

▶ *Dimethyl methylphosphonate* $(MeO)_2P(O)Me$ *(cuprous chloride method)* (*192*). Phosphorus trichloride (136 g, 1 mol) was added dropwise to a stirred mixture of copper(I) chloride (100 g, 1 mol) and methanol (96 g, 3 mol) in toluene (500 ml) at −5 °C. There was no marked temperature rise. The

solution was green at first but slowly deposited a white solid as the phosphorus trichloride was added. After addition, the white precipitate of $(MeO)_3P \cdot CuCl$ (201 g, 90%) was collected by filtration, washed with anhydrous petrol (200 ml) and dried. A portion of the white solid was suspended in diphenyl ether and heated with stirring to 200 °C. This resulted in its decomposition and dimethyl methylphosphonate was distilled from the diphenyl ether under vacuum (12 mmHg). The yield was approximately 70%.

▷ *Dimethyl methylphosphonate $(MeO)_2P(O)Me$ (TMSBr method)* (205). TMSBr (0.3 g, 2 mmol) was added to trimethyl phosphite (5.0 g, 40 mmol) in a flame-dried nitrogen-flushed pressure-resistant vessel. This was made airtight with a Teflon stopper and after stirring at 100 °C for 3 h the reaction mixture was cooled to room temperature and distilled under reduced pressure to yield dimethyl methylphosphonate (4.5 g, 91%). δ_P (121.5 MHz, $CDCl_3$) 33.3 ppm. In a similar fashion, upon heating at 80 °C for 3 h, benzyl diethyl phosphite gave diethyl benzylphosphonate (74%). δ_P (121.5 MHz, $CDCl_3$) 27.0 ppm.

▷ *Dimethyl methylphosphonate $(MeO)_2P(O)Me$ (methanol in sealed tube method)* (198). A mixture of freshly distilled trimethyl phosphite (5.0 g, 40 mmol) and anhydrous methanol (0.10 g, 3 mmol) was heated in a sealed tube at 210–215 °C for 5 h. Distillation of the reaction product yielded two drops of methanol and dimethyl methylphosphonate (4.6 g, 92%). Bp 88 °C/28 mmHg.

▷ *Dimethyl methylphosphonate $(MeO)_2P(O)Me$ (phenyl methyl sulfoxide method)* (200). Trimethyl phosphite (2 g, 16 mmol) and phenyl methyl sulfoxide (2 g, 14 mmol) were mixed and heated to 110 °C for 5–6 days in a sealed tube. Distillation gave dimethyl methylphosphonate (1.9 g, 96%).

▷ *Dimethyl methylphosphonate $(MeO)_2P(O)Me$ (dimethyl hydrogen phosphate method)* (199). Trimethyl phosphite (3.6 g, 29 mmol) and dimethyl hydrogen phosphate (3.6 g, 29 mmol) were kept in a sealed ampoule for 1 day at room temperature. Distillation from sodium under reduced pressure gave dimethyl methylphosphonate (2.1 g, 58%). Bp 182 °C.

▷ *Methyl isopropyl methylphosphonate MeO(i-PrO)P(O)Me (from mixed phosphite)* (203). Dimethyl isopropyl phosphite (114 g, 0.75 mol) was added dropwise to methyl iodide (109.5 g, 0.77 mol). Once 15 ml had been added, the stirred mixture was heated until an exothermic reaction began. The remaining phosphite was introduced at such a rate that the mixture kept boiling briskly. After addition the mixture was heated at 60 °C for 1 h and distilled through a Vigreux column to give the title compound (90 g, 79%). Bp 84–85 °C/16 mmHg. δ_P (101 MHz, $CDCl_3$) 31.3 ppm.

▷ *Diethyl methylphosphonate $(EtO)_2P(O)Me$ (usual Arbuzov reaction)* (182,184). A mixture of triethyl phosphite (55 g, 0.33 mol) and methyl iodide (50 g, 0.35 mol) were heated under gentle reflux for 2 h. Distillation at ordinary pressure gave ethyl iodide (50 g). Fractionation of the residue under vacuum gave diethyl methylphosphonate (47.6 g, 95%). Separation of the product from the small amount of diethyl ethylphosphonate formed from the interaction of the phosphite with the ethyl iodide liberated in the reaction is difficult. The pure substance boils at 51 °C/1 mmHg and 64–65 °C/2 mmHg.

▷ *Diethyl methylphosphonate $(EtO)_2P(O)Me$ (microwave method)* (207). A mixture of triethyl phosphite (4.15 g, 25 mmol) and methyl iodide (3.55 g, 25 mmol) in a quartz tube was irradiated for

3 min at 150 W in a microwave oven. Distillation of the product gave pure diethyl methylphosphonate (3.76 g, 99%). δ_P ($CDCl_3$) 30.2 ppm. Other microwave methods for the synthesis of dialkyl alkylphosphonates are available (188,219).

▶ *Diethyl ethylphosphonate $(EtO)_2P(O)Et$ (tosylate method)* (158). Triethyl phosphite (16.6 g, 0.10 mol) and ethyl *p*-toluenesulfonate (5.0 g, 0.025 mol) were stirred and heated to 150 °C for 2 h and then overnight at 120 °C. Distillation under reduced pressure gave the title compound (15.8 g, 95%). Bp 52–54 °C/1.5 mmHg.

▶ *Diethyl ethylphosphonate $(EtO)_2P(O)Et$ (from triethyl phosphite and ethyl iodide)* (184). This may be obtained by refluxing triethyl phosphite (348 ml, 332 g, 2 mol) and ethyl iodide (250 g, 1.6 mol) for 3 h. After distillation of ethyl iodide (231 g, 92%), the residue was fractionated under reduced pressure to provide the product (329 g, 99%). Bp 56 °C/1 mmHg.

▶ *Diethyl ethylphosphonate $(EtO)_2P(O)Et$ (from triethyl phosphite and ethyl bromide)* (39). Triethyl phosphite (9.8 g, 10 ml, 59 mmol) and ethyl bromide (7.2 g, 5 ml, 66 mmol) were heated to 100 °C for 4 h in a sealed tube by immersion in a boiling water bath. At the end of this time, the tube was cooled and opened and the contents fractionated. Unchanged triethyl phosphite (7.0 g) was recovered together with diethyl ethylphosphonate (1.5 g, 15%). Bp 57 °C/2 mmHg.

▶ *Diethyl n-dodecylphosphonate $(EtO)_2P(O)C_{12}H_{25}$* (182). Triethyl phosphite (62.5 g, 0.38 mol) and *n*-bromododecane (94.0 g, 0.38 mmol) were heated under a column attached to a condenser set for distillation. At about 160 °C, ethyl bromide started to distil. After about 1.5 h, ethyl bromide (31.5 g) stopped distilling and the residue was fractionated under reduced pressure to give diethyl ethylphosphonate (7.0 g bp 60–70 °C/3 mmHg), *n*-bromododecane (8.0 g, bp 124 °C/1 mmHg) and diethyl *n*-dodecylphosphonate (73.0 g, 63%). Bp 160 °C/1 mmHg. The following esters were prepared similarly: diethyl *n*-butyl- (bp 74 °C/1 mmHg), diethyl *n*-pentyl- (bp 86 °C/1.5 mmHg), diethyl *n*-hexyl- (bp 103 °C/2 mmHg), diethyl *n*-heptyl- (bp 113 °C/1.9 mmHg) and diethyl *n*-octyl-phosphonate (bp 119 °C/1.2 mmHg), and diethyl 3-methyl-1-butylphosphonate (bp 75 °C/0.8 mmHg).

▶ *Di-n-propyl methylphosphonate $(n\text{-}PrO)_2P(O)Me$ (transalkylation of dimethyl methylphosphonate)* (218). A mixture of dimethyl methylphosphonate (6.2 g, 0.05 mol) and *n*-propyl iodide (51 g, 0.30 mol) was heated in a heavy-walled tube at 130 °C for 96 h. The tube was opened, the contents placed in a distillation apparatus and the methyl iodide distilled off. The residue was then returned to the tube and additional *n*-propyl iodide (another 51 g, 0.30 mol) was added. After 48 h at 130 °C, the tube was reopened and the contents distilled to provide di-*n*-propyl methylphosphonate (7.0 g, 78%). Bp 86–87 °C/6 mmHg.

▶ *Diisopropyl methylphosphonate $(i\text{-}PrO)_2P(O)Me$* (183). A dropping funnel fitted to 2-litre round-bottomed flask was filled with triisopropyl phosphite (453 ml, 416 g, 2 mol). The flask was charged with methyl iodide (113 ml, 284 g, 2 mol) and fitted with an efficient water-cooled condenser. The methyl iodide was stirred magnetically and about 50 ml of the phosphite was added. The mixture was heated until an exothermic reaction occurred and the remainder of the phosphite was introduced at such a rate that the mixture boiled briskly. After the addition was complete, the mixture was heated under reflux for 1 h. The condenser was exchanged for a 50–75 cm Vigreux

column attached to a condenser set for distillation. The bulk of the isopropyl iodide was removed at 85–95 °C at atmospheric pressure. The remainder of the isopropyl iodide was distilled at water pump pressure (~12 mmHg), a dry ice trap being interposed between the receiver and the pump to effect complete condensation. A total of 310 g (91%) of isopropyl iodide was recovered. The residue was then fractionated. Except for a small forerun and residue, the title compound was collected as a colourless liquid (308–325 g, 85–95%). Bp 51 °C/1 mmHg or 66 °C/3 mmHg (*182*).

▷ *Diisopropyl d_3-methylphosphonate $(i\text{-}PrO)_2P(O)CD_3$* (*121*). Iodomethane-d_3 (12.47 g, 86 mmol) was added in one portion to a stirred solution of triisopropyl phosphite (17.9 g, 86 mmol) in dichloromethane (20 ml). The reaction mixture warmed up and eventually boiled. The mixture was allowed to cool. Volatile material was removed by rotary evaporation. Fractionation of the residue under reduced pressure gave a colourless liquid (14.27 g, 90%). Bp 86 °C/15 mmHg. δ_P ($CDCl_3$) 27.5 ppm.

▷ *Diisopropyl ethylphosphonate $(i\text{-}PrO)_2P(O)Et$* (*184*). This can be obtained by a similar procedure to diisopropyl methylphosphonate, using the appropriate amount of ethyl iodide instead of methyl iodide. Ethyl iodide is less reactive, and it is necessary to apply heat during the addition of the phosphite, and to permit the mixture to reflux for 7 h after the addition. On a 2-mol scale the recovery of isopropyl iodide was 317 g (93%) and that of the product was 354 g (91%). Bp 61 °C/0.7 mmHg.

▷ *Diisopropyl n-propylphosphonate $(i\text{-}PrO)_2P(O)n\text{-}Pr$* (*39*). Triisopropyl phosphite (102 g, 0.49 mol) and *n*-propyl iodide (85 g, 0.49 mol) were heated to boiling in a flask provided with an efficient reflux condenser. When the reaction had moderated, refluxing was continued for 2 h, and the isopropyl iodide formed distilled from the mixture. Fractionation of the residue under reduced pressure gave the title compound as a colourless liquid (50 g, 49%). Bp 75 °C/3 mmHg. The higher esters can be prepared similarly: diisopropyl *n*-butylphosphonate (bp 87 °C/4 mmHg), diisopropyl *n*-pentylphosphonate (bp 87 °C/2 mmHg) and diisopropyl *n*-hexylphosphonate (bp 113 °C/4 mmHg).

▷ *Di-n-butyl methylphosphonate $(n\text{-}BuO)_2P(O)Me$* (*204*). A mixture of tri-*n*-butyl phosphite (13.3 g, 53.2 mmol) and methyl iodide (15.0 g, 105.6 mmol) was sealed in a tube and heated to 80–90 °C until there was no further change in volume. Fractionation gave the title compound (10.0 g, 90%). Bp 120–122 °C/8 mmHg.

▷ *Diethyl (triethoxysilyl)methylphosphonate $(EtO)_2P(O)CH_2Si(OEt)_3$* (*186*). A mixture of triethyl phosphite (10.7 g, 0.06 mol) and (chloromethyl)triethoxysilane (27.0 g, 0.13 mol) was heated for 1 h at 157–196 °C. Vacuum distillation gave the product (6 g, 32%). Bp 120–122 °C/4 mmHg. NMR ($CDCl_3$) δ_P 30.5 and δ_{Si} −54.9 ppm.

▷ *Dimethyl allylphosphonate $(MeO)_2P(O)CH_2CH{=}CH_2$* (*106*) (*method 1*). Trimethyl phosphite (35 g, 0.28 mol) and allyl bromide (68 g, 0.56 mol) were heated together in a sealed tube for 3 h at 60–65 °C. Distillation of the product gave unchanged allyl bromide (about 40 g), dimethyl methylphosphonate (about 5 g), an intermediate fraction and pure dimethyl allylphosphonate (10 g, 24%). (*Method 2*). Trimethyl phosphite (35 g, 0.28 mol) and allyl bromide (100 g, 0.83 mol) were heated

together in a flask fitted with reflux condenser equipped with a trap cooled in ice salt for the methyl bromide evolved. The mixture was heated for 5 h at 76–78 °C (thermometer in the liquid) and methyl bromide (21 g, about theoretical) was collected. The reaction mixture was then distilled to yield allyl bromide (55 g) and then, under reduced pressure, the product dimethyl allylphosphonate (32 g, 76%). Bp 90–92 °C/13 mmHg.

▶ *Diethyl allylphosphonate* $(EtO)_2P(O)CH_2CH{=}CH_2$ (*39*). This was prepared similarly from triethyl phosphite (83 g, 0.5 mol) and allyl iodide (85 g, 0.5 mol) but repeated fractionations were required to separate accompanying diethyl ethylphosphonate from the product (46 g, 52%). Bp 75 °C/6 mmHg.

▶ *Diisopropyl allylphosphonate* $(i\text{-}PrO)_2P(O)CH_2CH{=}CH_2$ (*39*). An Arbuzov reaction was carried out with triisopropyl phosphite (104 g, 0.5 mol) and allyl iodide (85 g, 0.5 mol) and the product purified by two distillations (60 g, 58%). Bp 67 °C/2 mmHg.

▶ *Diallyl allylphosphonate* $(CH_2{=}CHCH_2O)_2P(O)CH_2CH{=}CH_2$ (*106*). A mixture of triallyl phosphite (9.8 g, 48.5 mmol) and allyl iodide (4.6 g, 27.4 mmol) was placed inside a thick-walled glass tube which was joined in the middle with a piece of glass capillary tubing. The liquid level was adjusted so that it was in the capillary, and the tube was sealed and allowed to stand at room temperature for 24 h, after which the liquid level in the capillary had dropped. The tube was then immersed in water and heated at 80–90 °C for 3 h. After this time the liquid level had dropped about 4.5–5.0 cm and since further heating did not modify the liquid level further, the reaction was judged complete. When the tube was opened there was no pressure inside. Allyl iodide (95 g) was distilled from the reaction mixture and then the remaining liquid under reduced pressure. Two fractions were obtained: 1.20 g (bp 118–121 °C/8.5 mmHg) and 7.98 g (121–122 °C/8.5–9 mmHg). The latter fraction was redistilled to give pure diallyl allylphosphonate (7.9 g, 81%). Bp 120–121 °C/8.5 mmHg. It is a colourless liquid, very soluble in benzene, chloroform, ethanol, ether, petroleum ether and other organic solvents. It is also soluble in water.

▶ *Diphenyl methylphosphonate* $(PhO)_2P(O)Me$ (**106**) (*202*). A solution of methyl iodide (5 g, 35 mmol) in methanol (160 g, 5 mol) was added slowly over 2 h to triphenyl phosphite (1552 g, 5 mol) heated to reflux under a nitrogen atmosphere in a reactor fitted with an efficient condenser, thermometer, mechanical stirrer and side arm addition funnel. Throughout the addition, the temperature of the reaction mixture was maintained between 200 and 250 °C. A further 1 h at 215 °C allowed the reaction to complete. An aspirator vacuum distillation removed phenol (468 g, 5 mol) containing a small quantity of anisole. High-vacuum distillation of the residue provided diphenyl methylphosphonate (1150 g, 92%). Bp 138 °C/0.15 mmHg. Mp 35–36 °C. δ_P ($CDCl_3$) −24.0 ppm. This recipe works also with other triaryl phosphites and yields the respective diaryl methylphosphonate.

▶ *Diphenyl methylphosphonate* $(PhO)_2P(O)Me$ (**106**) (*183*). Triphenyl phosphite (31 g, 0.10 mol) and methyl iodide (21 g, 0.15 mol) were heated under reflux with the exclusion of moisture for 36 h. The temperature of the refluxing mixture rose from 70 °C to 115 °C during reaction. Treatment of the product with anhydrous ether gave small yellowish-brown needles of the methiodide which were washed repeatedly with anhydrous ether and finally dried under vacuum (42 g, 94%). Large colourless

crystals could be obtained by seeding the mixture after 3 h. To obtain pure triphenyl phosphite methiodide, the crude material was warmed gently with analytical-grade acetone. The saturated solution obtained by decantation was treated rapidly with an equal volume of anhydrous ether. The methiodide separated in beautiful flat needles that were collected by centrifugation, washed several times with anhydrous ether and dried over phosphorus pentoxide in a vacuum dessicator. Recrystallisation twice gave pure triphenyl phosphite methiodide, mp 146 °C. During recrystallisation it was essential to minimise the contact time with acetone and to work swiftly and with rigorous exclusion of moisture. The crude material was used in the next step; it was stored under ether, and dried and weighed under vacuum immediately before use. The methiodide (21 g, 46.5 mmol) was dissolved in absolute ethanol (35 ml) by shaking for a few minutes. Distillation gave ethyl iodide (bp 65–79 °C/760 mmHg), phenol (bp 45–60 °C/0.04 mmHg) and another fraction (bp 138–140 °C/0.04 mmHg). The last of these was washed twice with 2 M aqueous sodium hydroxide and subsequently with water. Cooling in ice caused crystallisation of diphenyl methylphosphonate (10.5 g, 91%). Mp 35–36 °C.

▷ *Diphenyl benzylphosphonate* $(PhO)_2P(O)Bn$ (**107**) (*202*). Benzyl alcohol (54 g, 0.5 mol) and methyl iodide (0.5 g, 3.5 mmol) were added over 90 min to refluxing triphenyl phosphite (155 g, 0.5 mol) and after addition the temperature was maintained at 200–250 °C for a further 3.5 h. Thereafter phenol (43.9 g, 0.47 mol) was removed by distillation, followed by diphenyl benzylphosphonate (113 g, 70%). Bp 186–187 °C/0.06 mmHg. Recrystallisation from ligroin gave white needles. Mp 61–62 °C. δ_P ($CDCl_3$) −19.5 ppm.

▷ *n-Butyl phenyl methylphosphonate n-BuO(PhO)P(O)Me* (**115**) (*204*). A mixture of di-*n*-butyl phenyl phosphite (15.1 g, 56 mmol) and methyl iodide (12.5 g, 88 mmol) was sealed in a tube and heated to 80–90 °C until there was no further change in volume. Fractionation gave the title compound (7.57 g, 77%). Bp 100–103 °C/0.05 mmHg.

▷ *2,5,5-Trimethyl-2-oxo-1,3,2-dioxaphosphorinane (transesterification)* (**122**) (*202*). A stirred mixture of diphenyl methylphosphonate (74.4 g, 0.30 mol), neopentyl glycol (31.2 g, 0.30 mol) and magnesium chloride (0.2 g, 2.10 mmol) was heated to 210–250 °C for 4 h. Subsequent distillation yielded phenol (36 g, 0.38 mol) and a liquid with bp 128–130 °C/3.4 mmHg that solidified. Recrystallisation from benzene–heptane afforded white crystals (16.0 g, 33%). Mp 119–121 °C.

▷ *2-Methyl-2-oxo-1,3,2-dioxaphosphorinane (Arbuzov reaction)* (**124**) (*220*). Methyl iodide (31.5 g, 222 mmol) was added slowly over 30 min to 2-methoxy-1,3,2-dioxaphosphorinane (4.6 g, 34 mmol) and the mixture was heated under reflux for 3 h. The mixture was left to stand overnight and then distilled to yield the title compound (2.3 g, 50%). Bp 73 °C/0.4 mmHg. δ_P ($CDCl_3$) 27.3 ppm.

▷ *Diethyl iodomethylphosphonate* $(EtO)_2P(O)CH_2I$ (*39*). Heating a mixture of triethyl phosphite and diiodomethane gave diethyl iodomethylphosphonate (bp 101 °C/0.7 mmHg) and tetraethyl methanediphosphonate (bp 143 °C/1.5 mmHg). The latter was also obtained in poor yield when the diiodomethane was replaced by dibromomethane and the mixture heated for 6 h; the monosubstituted diethyl bromomethanephosphonate was almost entirely absent. A reliable method available for synthesis of diethyl iodomethylphosphonate is as follows (*129*): triethyl phosphite (83 g, 0.50 mol) was added to diiodomethane (200 g, 0.75 mol) at 185 °C which was refluxing halfway up

a 25-cm column containing glass helices and a condenser set for distillation. The rate of addition was adjusted so that distillation (70–110 °C) occurred steadily and the temperature increased, finally to 220 °C. Heating was continued for a further 10 min. Distillation gave ethyl iodide (74 g, 95%) and recovered diodomethane (68 g, 34%) and diethyl iodomethylphosphonate (126 g, 90%). Bp 96–99 °C/0.5 mmHg.

▶ *Diethyl trichloromethylphosphonate* $(EtO)_2P(O)CCl_3$ (**119**) (*206*). Triethyl phosphite (50 g, 0.3 mol) and anhydrous carbon tetrachloride (250 ml) were heated under reflux for 12 h. The mixture was distilled under reduced pressure to yield the title compound as a colourless mobile liquid (72 g, 94%). Bp 127–128 °C/13 mmHg.

▶ *Diethyl chloromethylphosphonate* $(EtO)_2P(O)CH_2Cl$ (**120**) (*211*). A solution of diethyl trichloromethylphosphonate (12.8 g, 50 mmol) and chlorotrimethylsilane (6.0 g, 55 mol) in THF (25 ml) was added dropwise to a stirred solution of *n*-butyllithium (73 ml of a 1.5 M solution in hexane, 110 mmol) in THF (70 ml) cooled to −78 °C. After addition the mixture was stirred at this temperature for 15 min and then warmed to −50 °C. Water (30 ml) was added and the mixture was stirred for 1 h. The aqueous phase was separated and washed with ether (3 × 50 ml), and the organic layers were combined, dried (Na_2SO_4), filtered and evaporated to leave a residue which on distillation gave a colourless mobile liquid (8.9 g, 95%). Bp 78–79 °C/2.5 mmHg (*131*).

▶ *Diethyl dichloromethylphosphonate* $(EtO)_2P(O)CHCl_2$ (**121**) (*210*). Diethyl *H*-phosphonate (16.5 g, 0.12 mol) was added dropwise to a stirred solution of diethyl trichloromethylphosphonate (25.6 g, 0.1 mol) and triethylamine (12.1 g, 0.12 mol) in ethanol (50 ml). The mixture was kept at room temperature and the progress of reaction was monitored by ^{31}P-NMR spectroscopy. After 6 days, or longer if necessary, the solvent was removed and the residue diluted with chloroform (100 ml). The solution was washed with water (2 × 50 ml), dried (Na_2SO_4) and the solvent removed. Distillation of the residue gave triethyl phosphate (bp 60 °C/0.8 mmHg) and the title compound (18.6 g, 84%). Bp 80–82 °C/0.5 mmHg. δ_P (101 MHz, $CDCl_3$) 9.8 ppm.

▶ *Diethyl 2-bromoethylphosphonate* $(EtO)_2P(O)CH_2CH_2Br$ (*39*). Triethyl phosphite (83 g, 0.5 mol) and 1,2-dibromoethane (141 g, 0.75 mol) were heated together as in the preparation of diethyl *n*-dodecylphosphonate. The reaction was complete within 2 h, ethyl bromide (48 g) having distilled over. Fractionation of the residue using the water pump gave recovered 1,2-dibromoethane (77 g) and next using an oil pump gave diethyl ethylphosphonate (15 g, bp 60–70 °C/3 mmHg), diethyl 2-bromoethylphosphonate (48.5 g, 40%, bp 101 °C/0.8 mmHg) and lastly tetraethyl ethane-1,2-diphosphonate (21.0 g, bp 167 °C/1 mmHg).

▶ *Diethyl 2-bromopropylphosphonate* $(EtO)_2P(O)CH_2CH(CH_3)Br$ (*39*). Triethyl phosphite (160 ml, 165 g, 1.0 mol) and 1,2-dibromopropane (182 g, 0.9 mol) were heated to about 170 °C for 11 h. The mixture was then fractionated. After three distillations, the product was obtained (77 g, 30%). Bp 103–105 °C/3 mmHg. The high-boiling residue was distilled under high vacuum and a fraction collected that boiled at 105–110 °C/0.3 mmHg. Redistillation gave nearly pure tetraethyl 1-methylethyl-1,2-diphosphonate, $(EtO)_2P(O)CH_2CH(CH_3)P(O)(OEt)_2$. Bp 98–100 °C/0.006 mmHg.

▷ *Diisopropyl bromomethylphosphonate (i-PrO)$_2$P(O)CH$_2$Br* (221). Triisopropyl phosphite (52 g, 0.25 mmol) and dibromomethane (111 g, 0.64 mol) were added to a round-bottomed flask equipped with a 60-cm-long reflux condenser topped by a distillation apparatus with a narrow downward cooler ending in a graduated measuring cylinder. The mixture was heated for 47 h with a metallic bath at 145–150 °C with the reflux condenser thermostatted at 62 °C during which isopropyl bromide (20.5 ml, 26.6 g, 0.22 mol) distilled off. Double distillation of the residue returned dibromomethane and yielded the title compound (31.0 g, 48%). Bp 46 °C/0.01 mmHg. A second fraction comprised tetraisopropyl methanebisphosphonate (17.2 g, 40%). Bp 90–92 °C/0.01 mmHg.

▷ *Diisopropyl 2-bromopropylphosphonate (i-PrO)$_2$P(O)CH$_2$CH(CH$_3$)Br* (39). This compound was prepared similarly by heating triisopropyl phosphite (340 g, 1.6 mol) and 1,2-dibromopropane (330 g, 170 ml, 1.6 mol) to about 170 °C for 8 h. On fractionation, considerable quantities of unreacted materials were collected followed by the product (118 g, 26%). Bp after two fractionations was 95 °C/1 mmHg. There was a higher boiling residue that on distillation with the aid of a powerful pump yielded an impure sample of tetraisopropyl 1-methylethyl-1,2-diphosphonate, (*i*-PrO)$_2$P(O)CH$_2$CH(CH$_3$)P(O)(OPr-*i*)$_2$. Bp 99–101 °C/0.025 mmHg.

▷ *Tetraethyl methanediphosphonate (EtO)$_2$P(O)CH$_2$P(O)(OEt)$_2$* (128). This ester is prepared by adding triethyl phosphite (62 g, 0.37 mol) to stirred diethyl bromomethylphosphonate (Note 1) (58 g, 0.24 mol) at 180–210 °C (Note 2) in precisely the manner described in the preparation of tetraethyl 1,5-pentanediphosphonate (see later). After working up similarly, the product (37.5–43.0 g, 52–60%) had bp 125–127 °C/0.5 mmHg. By the same technique, tetra-*n*-butyl methanediphosphonate (~180 g, 45% yield; bp 150–155 °C/5 × 10^{-4} mmHg) was obtained from tri-*n*-butyl phosphite (1000 g, 4 mol) and diiodomethane (268 g, 1 mol); tetra-*n*-butyl ethane-1,2-diphosphonate (~210 g, 51%, bp 175–178 °C/5 × 10^{-4} mmHg) was obtained from tri-*n*-butyl phosphite (750 g, 3 mol) and 1,2-dibromoethane (188 g, 1 mol); and diethyl iodomethylphosphonate (~120 g, 90%, bp 96–99 °C/0.5 mmHg) was obtained from triethyl phosphite (83 g, 0.5 mol) and diiodomethane (200 g, 0.7 mol). Notes: (1) An equivalent quantity of diethyl iodomethylphosphonate may be substituted. (2) When the boiling point of the halide is lower than the temperature necessary for reaction, the temperature must be raised by running in a quantity of the trialkyl phosphite initially. The Claisen head must also be replaced by a suitable fractionating column, or by a reflux condenser through whose jacket steam is passed.

▷ *Tetraethyl ethane-1,2-diphosphonate (EtO)$_2$P(O)CH$_2$CH$_2$P(O)(OEt)$_2$* (39,182). Triethyl phosphite (157 g, 0.95 mol) and 1,2-dibromoethane (100 g, 47 ml, 0.53 mol) were allowed to react as in the preparation of diethyl 2-bromoethylphosphonate and the product worked up similarly, yielding bromoethane (75 g, bp 35–40 °C), diethyl ethylphosphonate (55 g, bp 55–60 °C/1 mmHg), diethyl 2-bromoethylphosphonate (18 g, bp 99–115 °C/1 mmHg) and tetraethyl ethane-1,2-diphosphonate (71 g, 49%; bp 157 °C/1 mmHg).

▷ *Tetraethyl propane-1,3-diphosphonate (EtO)$_2$P(O)(CH$_2$)$_3$P(O)(OEt)$_2$* (39,182). This was obtained similarly by heating triethyl phosphite (100 g, 0.6 mol) and 1,3-dibromopropane (60 g, 0.3 mol). Reaction was complete in about 30 min and gave bromoethane (59 g, bp 45–40 °C), diethyl ethylphosphonate (21 g, bp 55–60 °C/2 mmHg), diethyl 3-bromopropylphosphonate (18 g, bp 106–118 °C/1 mmHg) and tetraethyl propane-1,3-diphosphonate (32 g, 34%; bp 175 °C/0.8 mmHg).

▷ *Tetraethyl pentane-1,5-diphosphonate* $(EtO)_2P(O)(CH_2)_5P(O)(OEt)_2$ (*128*). 1,5-Dibromopentane (115 g, 0.5 mol) was placed in a 500-ml three-necked flask fitted with a stirrer, a dropping funnel (250 ml) and a Claisen distillation head leading into a condenser and receiver set for distillation. Each neck of the Claisen head contained a thermometer, that at first dipped into the bromide, which was stirred and heated to 180–200 °C (Note 1), while triethyl phosphite (210 g, 1.3 mol) was added dropwise over 75 min, and crude ethyl bromide distilled out. After addition (Note 2), the reaction mixture was heated at 200–210 °C for a further 30 min, allowed to cool to 100 °C, and then degassed at the water pump. The residue on distillation gave after a large low-boiling range forerun, a fraction of almost pure tetraethyl 1,5-pentanediphosphonate (86–112 g, 50–65% yield). Bp l60–180 °C/0.05 mmHg. Redistillation gave analytically pure material. Bp 178 °C/0.6 mmHg. Notes: (1) The success of the reaction depends upon striking a balance between the rate of addition of the phosphite, the temperature of the reaction mixture, and the rate of removal of the ethyl bromide. The temperature of the reaction mixture should not be allowed to fall below 180 °C, otherwise more of the phosphite isomerises than reacts fruitfully. At the same time the temperature should not be allowed to rise too much or some phosphite may distil out with the ethyl bromide. The best procedure is to regulate the temperature indicated by the thermometer in the second neck of the Claisen head below 120 °C, by moderating the rate of heating of the reaction mixture. The temperature of the latter can be controlled at 180–200 °C by adjusting the rate of addition of the phosphite. (2) The formation of ethyl bromide appears to lag behind the addition of the phosphite. Once the latter has been added, the bromide (total volume 70–75 ml) continues to distil during the final period of heating, almost ceasing towards the end, when the odour of the phosphite disappears.

▷ *Tetraethyl 3,3,4,4,5,5-hexafluoro-1-cyclopenten-1,2-ylenediphosphonate* (**28**) (*212*). Triethyl phosphite (664 g, 4 mol) was added to 1,2-dichloro-3,3,4,4,5,5-hexafluorocyclopentene (490 g, 2 mol) heated to gentle reflux at a rate sufficient to maintain a steady evolution of ethyl chloride. The addition was completed after 4.5 h but the evolution of gas continued for a further 2.5 h. Vacuum fractionation gave crude diethyl ethylphosphonate (60.2 g, 10%, bp 57–62 °C/0.5 mmHg) and the title compound (730 g, 84%). Bp 111–113 °C/0.1 mmHg.

2.13.4 Diesterification of alkylphosphonic dichlorides

Two of the oldest and most reliable methods of synthesis of dialkyl alkylphosphonates rely on diesterification of an alkylphosphonic dichloride (1 mol) with a sodium alkoxide (2 mol) (*155,222,223*) or an alcohol (2 mol) and a base, such as triethylamine, pyridine or *N,N*-diethylaniline (2 mol) (*224–226*). Providing the alkylphosphonic dichloride contains a small unhindered alkyl group, the alkoxide method works with lower alcohols, e.g. as in the synthesis of di-*n*-butyl methylphosphonate (**130**), di-*t*-butyl methylphosphonate (**131**), dimethyl *t*-butylphosphonate (**132**) and diisopropyl *t*-butylphosphonate (**133**) (Fig. 2.13.4.1). With higher alcohols dissolution of sodium in the alcohol requires several hours and necessitates a large excess of alcohol and heating to 120–150 °C (*227*). Addition of the sodium alkoxide solution to the alkylphosphonic dichloride dissolved in benzene or toluene provides the diester and precipitated sodium chloride, which is easily separated by filtration. The use of an alcohol and triethylamine is a milder method for the synthesis of dialkyl

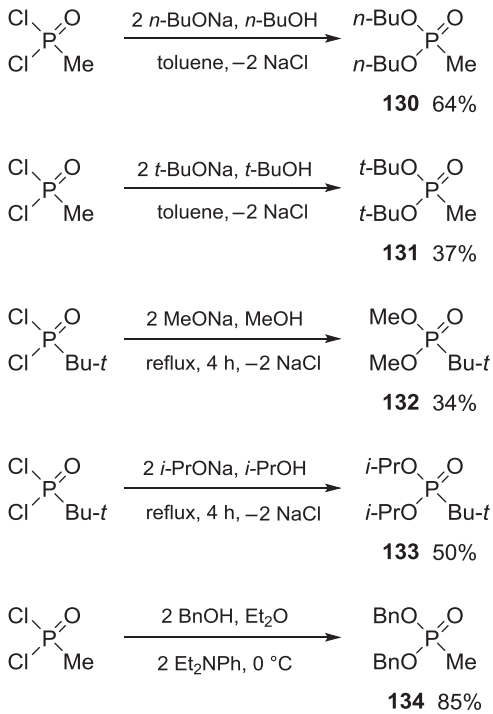
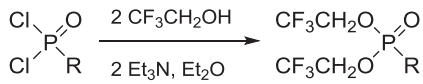


Figure 2.13.4.1

alkylphosphonates. Unlike the alkoxide method it can be used in instances where the alcohol contains substituents potentially unstable to strongly basic conditions. For example, it is compatible with alcohols containing diol protecting groups such as 2,2-dimethyl-1,3-dioxolane-4-methanol (solketal) (*227*). The alkoxide method is preferred over the one using the alcohol and base, e.g. as in the synthesis of dibenzyl methylphosphonate (**134**) (Fig. 2.13.4.1), in cases where the alkylphosphonic dichloride is hindered and therefore relatively unreactive. (The reaction of *tert*-butylphosphonic dichloride and sodium isopropoxide gives the desired diisopropyl *tert*-butylphosphonate (**133**), whereas the alcohol and base method is impractical in this case due to a very slow rate of nucleophilic substitution.)

The mildness of the alcohol and base method can sometimes aid the synthesis of unsymmetrical dialkyl alkylphosphonates. A two-step esterification of methylphosphonic dichloride in the presence of 2 molar equivalents of *N*,*N*-diisopropylethylamine (Hünig's base) and 1-*H*-tetrazole catalyst, first by benzyl alcohol and then by methanol, in benzene provides benzyl methyl methylphosphonate MeO(Me)P(O)OBn in 81% yield (not shown) (*228*). This approach to alkyl benzyl methylphosphonates, which upon hydrogenolysis yield the corresponding alkyl methylphosphonic acids, is of general applicability. Triethylamine is a useful base in cases where disubstitution of alkylphosphonic dichlorides occurs readily, as illustrated in the synthesis of various *bis*(2,2,2-trifluoroethyl)

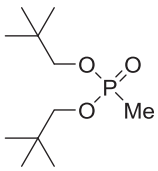


R = Me	**135a**	69%	δ_P 33.5
R = Et	**135b**	67%	δ_P 36.1
R = *n*-Pr	**135c**	66%	δ_P 35.2
R = *i*-Pr	**135d**	69%	δ_P 37.7

Figure 2.13.4.2

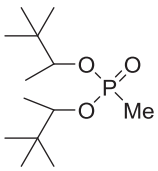
alkylphosphonates (**135a—d**) and their derivatives (Fig. 2.13.4.2) (*229*). Substitution becomes more difficult when the alkyl group in the alkylphosphonic dichloride is branched, e.g. as in iso-propylphosphonic dichloride (*229—231*). Methylphosphonic dichloride reacts with 2 mol each of an alcohol and triethylamine to provide derivatives with acyclic branched ester groups (**136—137**) or cyclic ester groups (**138—139**) (Fig. 2.13.4.3) (*155,227*). After removal of the triethylammonium chloride, the solvent is removed and the liquid products isolated by distillation under reduced pressure. Methylphosphonic dichloride is sufficiently reactive to combine with 2 mol of cholesterol in acetone in the absence of base to give dicholesteryl methylphosphonate (**140**) (Fig. 2.13.4.4) (*232*). In this particular case the cholesteryl ester groups evidently survive the acidic conditions generated upon liberation of 2 mol of hydrogen chloride.

Dialkyl alkylphosphonate formation from alkylphosphonic dichlorides and alcohols can be performed under solvent-free conditions, in the presence of neutral activated alumina (Fig. 2.13.4.5) (*233*). The latter is essential for efficient transformation to product as the yields of phosphonates



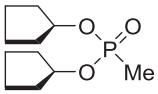
dineopentyl methylphosphonate

136 bp 82 – 84 °C/2 mmHg



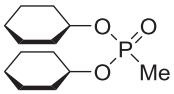
dipinacolyl methylphosphonate

137 bp 70 – 71 °C/0.01 mmHg



dicyclopentyl methylphosphonate

138 bp 94 – 96 °C/1 mmHg



dicyclohexyl methylphosphonate

139 bp 112 – 114 °C/0.3 mmHg

Figure 2.13.4.3

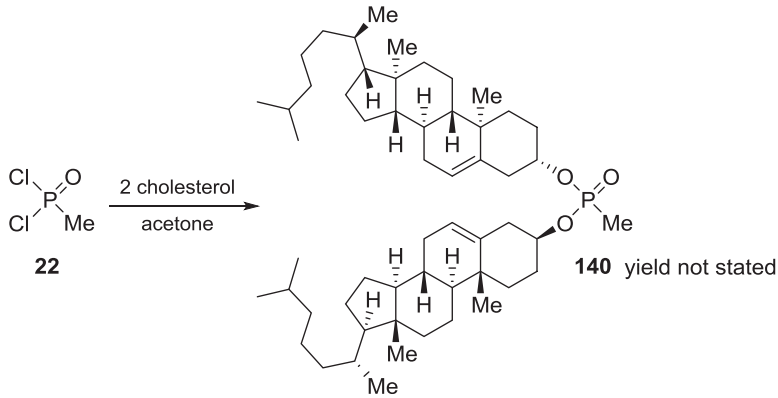
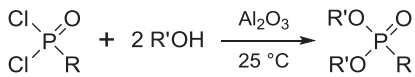


Figure 2.13.4.4



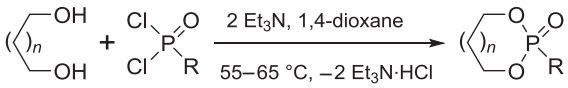
Dialkyl alkylphosphonates

R	R'	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)
Me	Me	95	65/12	33.8
Me	Et	97	67/11	31.1
Me	*n*-Pr	98	83/5	30.8
Me	*i*-Pr	97	70/5	30.9
Me	*n*-Bu	85	73/5	30.1
Me	*i*-Bu	82	72/3	30.0
Me	Ph	54	155/1	24.1
Me	Bn	70	175/0.5	28.2
Me	$CH_2CH{=}CH_2$	75	72/4	29.3
Et	Me	96	75/5	32.9
Et	Et	96	72/4	34.3
Et	Ph	50	155/0.5	24.5
n-Pr	Me	92	85/6	32.1
n-Pr	Et	92	86/4	31.8
n-Pr	Ph	50	158/0.4	24.2
i-Pr	Me	90	70/4	31.9
i-Pr	Et	91	64/2	31.7
i-Pr	Ph	51	155/0.4	24.5

Figure 2.13.4.5

drop from 50–98% to 10–25% when alumina is not added. Reactions with primary aliphatic alcohols complete within 10–20 min with excellent yields. Secondary and aromatic alcohols take 30 min for complete conversion, and tertiary alcohols do not react. The alumina facilitates the reaction by providing a solid support that brings the reactants into close contact and presumably scavenges the liberated hydrogen chloride, which otherwise affects detrimentally the product yield. Attempts to prepare cyclic phosphonates by this method from diols were unsuccessful, probably due to polymerisation on reaction with the bifunctional chloridates (to avoid polymerisation such reactions must be performed under high dilution, which is unachievable on solid support). Properties of 18 of the 52 dialkyl alkylphosphonates prepared by the alumina method appear in Fig. 2.13.4.5 (*233*).

Alcoholysis of alkylphosphonic dichlorides with glycols provides alkylphosphonates bearing a six- or seven-membered ring in the ester portion of the structure (Fig. 2.13.4.6) (*220*,*234*). The reaction is not general for all glycols owing to the formation of linear polymers alongside, or instead of, the desired phosphorus-containing heterocycles. A dilution method based on concurrent addition of the glycol and alkylphosphonic dichloride in the presence of triethylamine in a large excess of 1,4-dioxane at higher temperature affords higher yields of cyclic phosphonates (**141**) (*220*). This modification ensures that the probability of intermolecular esterification is greatly reduced. Many cyclic esters can be prepared in this way. The yield of six-membered cyclic esters is generally higher than that for the seven-membered homologues due to the greater probability of cyclisation in the former synthesis. The ease of cyclisation to give the products depends on the alkyl group of the



141

Cyclic alkylphosphonates

n	R	Yield (%)	Bp (°C/mmHg)	δ_P ($CDCl_3$)
1	Et	61	75/0.4	30.5
1	*n*-Pr	61	80/0.4	29.6
1	*i*-Pr	60	78/0.4	33.0
1	*n*-Bu	75	90/0.4	28.9
1	*i*-Bu	50	81/0.4	29.2
1	*s*-Bu	57	71/0.4	31.4
2	Me	51	78/0.4	33.8
2	*i*-Pr	49	75/0.1	38.5
2	*n*-Bu	47	75/0.1	35.8
2	*i*-Bu	42	85/0.1	34.8
2	*s*-Bu	60	78/0.1	38.1

Figure 2.13.4.6

alkylphosphonic dichloride and a bulky alkyl group can hinder reaction. Thus treatment of glycols with *tert*-butylphosphonic dichloride even in high dilution gives unsatisfactory results. In this case it is necessary to resort to using the disodium glycol salts which provide successfully the cyclic esters (**142a**) and (**142b**) (Fig. 2.13.4.7) (*220*).

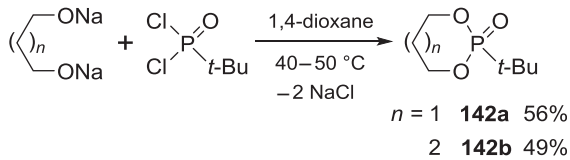


Figure 2.13.4.7

Cyclic fluoroalkenylphosphonic dichlorides can be esterified by alcohols in the presence of triethylamine (e.g. **29**→**143**) or fluoroalcohols without a base (e.g. **31**→**144**) (Fig. 2.13.4.8) (*117*). In contrast to lower alcohols, fluoroalcohols provide esters that are stable to liberated hydrogen chloride, so it is possible here to enforce an efficient synthesis in the absence of base.

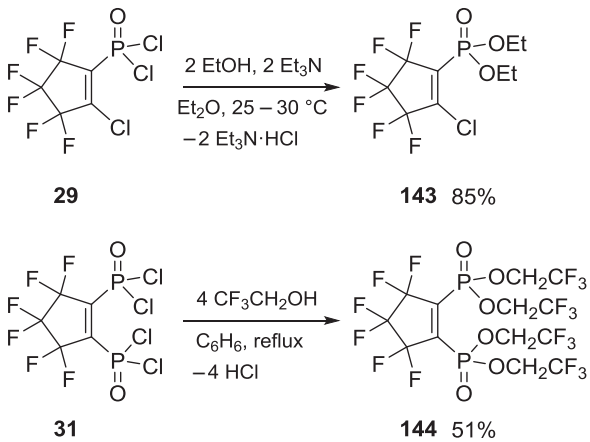


Figure 2.13.4.8

▶ *Bis(2,2,2-trifluoroethyl) methylphosphonate* $(CF_3CH_2O)_2P(O)Me$ (**135a**) (*230*). A 1-litre four-necked round-bottomed flask was equipped with an efficient mechanical stirrer, a thermometer, a reflux condenser with a bubbler, and a 200-ml pressure-equalising dropping funnel with a nitrogen inlet. Under a gentle flow of nitrogen the flask was charged with anhydrous THF (300 ml), 2,2,2-trifluoroethanol (42 g, 0.42 mol) and triethylamine (42.4 g, 0.42 mol). Stirring was started and the flask cooled to ~10 °C using a water bath. A solution of methylphosphonic dichloride (26.6 g,

0.2 mol) in anhydrous THF (100 ml) was added slowly at a constant rate from the dropping funnel over 30 min. The internal temperature rose to 20–30 °C and a white precipitate formed. After addition the water bath was withdrawn and the reaction mixture was stirred at room temperature for 2 h. The precipitate was removed by suction filtration and the filter cake washed with THF (3 × 50 ml). The solvent was removed by rotary evaporation and the residue dissolved in dry ether (100 ml) and filtered to remove insoluble triethylamine hydrochloride, using additional ether (40 ml) to aid filtration/transfer. Removal of the solvent and distillation of the residue under reduced pressure gave the title compound as a colourless liquid (45.3–48.0 g, 89–93%) which crystallised on standing at room temperature or in a freezer. Bp 88–91 °C/14 mmHg. δ_P ($CDCl_3$) 35.0 ppm.

▶ *Di-n-butyl methylphosphonate (n-BuO)$_2$P(O)Me* (**130**) (227). Sodium *n*-butoxide was prepared from sodium metal (11.5 g, 0.50 mol) in *n*-butanol (300 ml) with warming to 120 °C in an oil bath. To this was added a solution of methylphosphonic dichloride (33.2 g, 0.25 mol) in anhydrous toluene (50 ml) with stirring. The resulting mixture was heated under reflux for 4.5 h. Sodium chloride was filtered off and the filtrate concentrated and distilled to yield di-*n*-butyl methylphosphonate (33.2 g, 64%). Bp 108–110 °C/5 mmHg.

▶ *Di-tert-butyl methylphosphonate (t-BuO)$_2$P(O)Me* (**131**) (155). A solution of methylphosphonic dichloride (16.6 g, 0.12 mol) in anhydrous toluene (40 ml) was added to an ice cold stirred solution of sodium (5.8 g, 0.25 mol) and *tert*-butyl alcohol (55.5 g, 0.75 mol) in anhydrous toluene (350 ml) at such a rate that the temperature did not rise above 35 °C. The mixture was stirred at room temperature for 5 days. The sodium chloride was filtered off and the solvent from the filtrate was evaporated at reduced pressure with a bath temperature of less than 35 °C. The mixture was distilled at 0.0001 mmHg in a molecular still with a jacket temperature of 25 °C to give the desired phosphonate (9.5 g, 37%).

▶ *Dipinacolyl methylphosphonate [t-BuCH(Me)O]$_2$P(O)Me* (**137**) (227). Sodium pinacolate was prepared by stirring sodium (6.9 g, 0.30 mol) in pinacolyl alcohol (90 g, 0.90 mol) diluted with anhydrous toluene (200 ml) heated to 130 °C for 5–6 h. To this was added a solution of methylphosphonic dichloride (22.3 g, 0.15 mol) in anhydrous toluene (50 ml). The mixture was refluxed for 5 h. Sodium chloride was removed and the residue distilled to provide dipinacolyl methylphosphonate (12.7 g, 32%). Bp 107–108 °C/3 mmHg.

▶ *Dicyclohexyl methylphosphonate (c-C$_6$H$_{11}$O)$_2$P(O)Me* (**139**) (227). A solution of methylphosphonic dichloride (33.2 g, 0.25 mol) in anhydrous benzene (100 ml) was added dropwise to a stirred solution of cyclohexanol (50 g, 0.5 mol) and triethylamine (55 g, 0.5 mol) in anhydrous benzene (150 ml). The mixture was refluxed for 4.5 h, the triethylamine hydrochloride filtered off and the solvent removed from the filtrate. Distillation of the residue gave the dicyclohexyl methylphosphonate (45.5 g, 70%). Bp 140–141 °C/2 mmHg.

▶ *Dibenzyl methylphosphonate (BnO)$_2$P(O)Me* (**134**) (225). A solution of methylphosphonic dichloride (44.3 g, 0.33 mol) in anhydrous ether (300 ml) was added dropwise to a stirred solution of benzyl alcohol (72.0 g, 0.67 mol) and *N,N*-diethylaniline (100 g, 0.67 mol) in anhydrous ether (200 ml) at 0–5 °C. The mixture was left for 12 h and *N,N*-diethylanilinium hydrochloride (103.0 g, 95%) was filtered off. The filtrate was heated under reflux gently for 24 h, the ether was removed and the liquid was distilled to provide the pure product (78.6 g, 85%). Bp 163–164 °C/0.05 mmHg.

▷ *Dicholesteryl methylphosphonate* (**140**) (*232*). Methylphosphonic dichloride (1.6 g, 12.0 mmol) was added dropwise to a stirred solution of cholesterol (5 g, 12.9 mmol) in anhydrous acetone (20 ml). The next day the crystals were collected by filtration and washed with anhydrous acetone and ether. Recrystallisation from isopropanol containing a small amount of benzene, or glacial acetic acid, gave white leaflets (mp 196–198 °C) that were soluble in benzene or chloroform, and rather insoluble in ether.

▷ *Bis(2,2,2-trifluoroethyl) ethylphosphonate* $(CF_3CH_2O)_2P(O)Et$ (**135b**) (*231*). A flame-dried 2-litre three-necked round-bottomed flask equipped with a Teflon-coated magnetic stirrer bar, thermometer, rubber septum and argon inlet was charged with 2,2,2-trifluoroethanol (24.1 ml, 336 mmol, 2.01 equiv.) and anhydrous THF (500 ml) under an argon atmosphere. The solution was cooled to an internal temperature of 0 °C (ice-sodium chloride bath) and charged dropwise with anhydrous triethylamine (51.3 ml, 369 mmol, 2.20 equiv.) over 10 min, and stirred at 0 °C for 15 min. To this was added dropwise by cannula under argon a solution of ethylphosphonic dichloride (17.9 ml, 167 mmol, 1.00 equiv.) in THF (65 ml) over 15 min while maintaining the internal temperature below 12 °C. The transfer flask was flushed with THF (2 × 10 ml) and the washes added by cannula to the reaction mixture over 5 min. The resultant white slurry was warmed to room temperature over 15 min, stirred at room temperature for 2.25 h, filtered through a sand-covered frit and concentrated by rotary evaporation (35 °C, 20 mmHg) to afford a cloudy liquid (43 g). Fractionation under reduced pressure gave the title compound as a colourless liquid (40.85 g, 89%). Bp 92–95 °C/25 mmHg.

▷ *Dimethyl tert-butylphosphonate* $(MeO)_2P(O)Bu\text{-}t$ (**132**) (*223*). *Tert*-butylphosphonic dichloride (18 g, 0.10 mol) was heated under reflux with sodium methoxide in methanol (from sodium (8 g, 0.35 mol) in methanol (100 ml)). After 4 h benzene (500 ml) was added and the methanol was distilled off. The precipitated sodium chloride was filtered off, and after removal of the benzene, the crude material was distilled to give the title compound (5 g, 34%). Bp 34 °C/0.5 mmHg. Mp 20 °C.

▷ *Diisopropyl tert-butylphosphonate* $(i\text{-}PrO)_2P(O)Bu\text{-}t$ (**133**) (*223*). Sodium (9.2 g, 0.4 mol) was dissolved in absolute isopropanol (50 ml) and *tert*-butylphosphonic dichloride (36 g, 0.2 mol) in isopropanol (100 ml) was added slowly with stirring. The whole was heated under reflux for 4 h, the solution evaporated, a little water added and the mixture extracted twice with ether. The extract was dried ($MgSO_4$), the ether was removed and the crude was distilled to yield the product (23 g, 50%). Bp 62 °C/1 mmHg.

▷ *Diethyl phenylphosphonate* $(EtO)_2P(O)Ph$ (*235*). Phenylphosphonic dichloride (19.5 g, 0.1 mol) in anhydrous ether (50 ml) was added dropwise to sodium ethoxide, from sodium (4.6 g, 0.2 mol) and ethanol (100 ml), and the mixture was boiled under reflux for 2 h. The colloidal precipitate was coagulated by the addition of water (50 ml), dried ($MgSO_4$) and distilled to provide a colourless liquid (13.6 g, 63%). Bp 90–95 °C/0.1 mmHg.

▷ *Dialkyl/aryl alkylphosphonates* $(R'O)_2P(O)R$ *(from alkylphosphonic dichlorides and alumina, general procedure)* (*233*). An alcohol (2.2 mmol) was added to neutral activated alumina (0.306 g, 3.0 mmol) in a single-necked 25-ml round-bottomed flask. This was sealed with a rubber septum and the alkylphosphonic dichloride (1.0 mmol) added by syringe at 0 °C. The resulting suspension was shaken

occasionally at room temperature. Progress of reaction was monitored by thin layer and/or gas chromatography after withdrawing a few milligrams of the mixture and suspending it in diethyl ether (1 ml). After the reaction was complete (which took 10–30 min) the dispersion mixture was extracted with ether (3 × 5 ml) and filtered. The solvent was removed and the residue was distilled under vacuum to furnish the pure dialkyl alkylphosphonate. By this means the products in Fig. 2.13.4.5 were made.

▷ *Cycloalkyl alkylphosphonates* (**141**) *(from glycols and triethylamine)* (*220*). Solutions of the alkylphosphonic dichloride (0.1 mol) in 1,4-dioxane (100 ml) and the glycol (0.1 mol) in 1,4-dioxane (100 ml) were added simultaneously over 3 h from two dropping funnels to a stirred solution of triethylamine (20.2 g, 0.2 mol) in 1,4-dioxane (200 ml) stirred and heated to 55 °C. The rate of addition was adjusted to enable the reaction temperature to remain below 65 °C. Reaction proceeds with the precipitation of triethylammonium hydrochloride. After addition the mixture was refluxed for 1 h. The mixture was cooled, the precipitate was filtered off and the filtrate was concentrated. Vacuum distillation gave the products shown in Fig. 2.13.4.6. The 1,4-dioxane used should be anhydrous to prevent hydrolysis of the starting dichloride.

▷ *Cycloalkyl tert-butylphosphonates* (**142a–b**) *(from disodium glycol salts)* (*220*). A solution of the appropriate glycol (0.1 mol) in 1,4-dioxane (50 ml) was added to a stirred suspension of sodium hydride (7.2 g, 0.3 mol) in 1,4-dioxane (200 ml) under nitrogen. The mixture was heated to 40 °C until the formation of the disodium glycolate completed. The suspension was cooled to room temperature and treated dropwise with a solution of *tert*-butylphosphonic dichloride (17.5 g, 0.1 mol) in 1,4-dioxane (100 ml) and stirred at 40–50 °C for 1 h. The sodium chloride that formed was removed by filtration. The residue remaining after concentration of the filtrate was dissolved in dichloromethane (300 ml) and was washed with water (3 × 80 ml). Removal of solvent gave an oily residue that was crystallised from cyclohexane to provide, for example, the six-membered cyclic dialkyl *tert*-butylphosphonate **142a** (56%). Mp 71–72 °C. δ_P ($CDCl_3$) 35.2 ppm.

▷ *Diethyl 2-chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-ylphosphonate* (**143**) (*117*). 2-Chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-ylphosphonic dichloride (16.4 g, 0.05 mol) was added over 30 min to a stirred solution of anhydrous ethanol (4.6 g, 0.10 mol) and triethylamine (10.1 g, 0.10 mol) in anhydrous ether (100 ml) at 25–30 °C. Additional ether (100 ml) was added to facilitate stirring. After 1 h the mixture was filtered and the filtrate concentrated. Distillation of the residue gave the title compound (14.7 g, 85%). Bp 90–92 °C/1.5 mmHg.

▷ *Tetrakis(2,2,2-trifluoroethyl) 3,3,4,4,5,5-hexafluoro-1-cyclopenten-1,2-ylenediphosphonate* (**144**) (*117*). 2,2,2-Trifluoroethanol (29.1 g, 0.291 mol) was added dropwise over 24 min to a stirred solution of 3,3,4,4,5,5-hexafluoro-1-cyclopenten-1,2-ylenediphosphonic tetrachloride (29.8 g, 0.073 mol) in benzene (100 ml) at room temperature. Hydrogen chloride began to evolve during the addition and subsided after 7 h of stirring. The solvent was removed to leave a residue that was distilled to provide a small forerun (2.2 g) and the title compound (24.6 g, 51%). Bp 84–86 °C/0.1 mmHg.

2.13.5 Diesterification of alkylphosphonic dibromides

Haloalkylphosphonic dihalides undergo under non-extreme conditions selective nucleophilic substitution at the phosphorus atom, the halogen atom in the alkyl group usually being retained. Bromomethylphosphonic dibromide (**45**) reacts readily with 2 mol of sodium ethoxide to give diethyl bromomethylphosphonate (**145**) in good yield (Fig. 2.13.5.1).

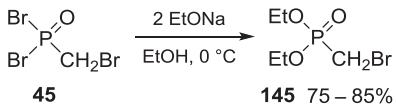


Figure 2.13.5.1

▶ *Diethyl bromomethylphosphonate* $(EtO)_2P(O)CH_2Br$ (**145**) (*128*). Sodium (23 g, 1 mol) was dissolved in excess ethanol (1000 ml) contained in a 2-litre three-necked flask fitted with a dropping funnel (100 ml), a reflux condenser and a mechanical stirrer. The stirred solution was cooled to 0 °C by supporting the flask in an ice salt bath, and bromomethylphosphonic dibromide (150 g, 0.5 mol) was added dropwise from the funnel at such a rate that the temperature did not exceed 15 °C. When the addition was complete, water (10 ml) and filter aid (Celite™, 15 g) were added, and the solution was stirred for 15 min and then filtered. The precipitate was washed with alcohol (100 ml) and from the filtrate and washings the bulk of the alcohol was removed by distillation. The residue after degassing at the water pump was distilled, the fraction of bp 115–125 °C/15 mmHg being collected. Redistillation gave pure diethyl bromomethylphosphonate (87–98 g, 75–85%). Bp 121 °C/15 mmHg, 56 °C/0.25 mmHg.

2.13.6 Alkylation of dialkyl *H*-phosphonates (Michaelis–Becker reaction)

Dialkyl *H*-phosphonates in a neutral diluent (benzene, petrol, etc.) react vigorously with alkali metals, usually sodium, with the evolution of hydrogen to give, for example, dialkyl sodium phosphites. The latter, the higher members of which (di-*n*-butyl and upwards) are soluble in petrol, have the trivalent phosphite structure. They add sulfur energetically to give dialkyl sodium phosphorothioates $(RO)_2P(S)ONa$ and react with alkyl halides to give dialkyl alkylphosphonates $(RO)_2P(O)R'$. The latter probably form by a modification of the Arbuzov reaction, through formation of an unstable phosphonium intermediate (Fig. 2.13.6.1).

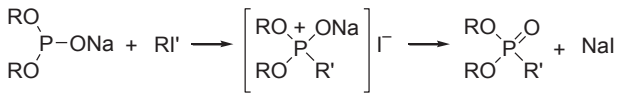


Figure 2.13.6.1

The preparation of alkali metal derivatives has long been a common starting point for the synthesis of phosphonic acid esters by the Michaelis–Becker reaction (*236*) according to the

equation: $(RO)_2P(O)H + Na$ (K, etc.) $\rightarrow (RO)_2PONa + 0.5H_2$. At elevated temperatures, e.g. in hot toluene or xylene with powdered molten sodium or potassium, the process seems to follow the stoichiometry of this equation closely. However, when the reaction is performed at or near to room temperature the amount of alkali metal implied by the equation always proves excessive, indicating deviation from the expected route. This was noted by several early workers in the field, who indicated that 'leftover' metal had to be removed, before proceeding with the rest of the Michaelis–Becker reaction. Performed at relatively low temperatures the reaction produced an odour reminiscent of phosphine.

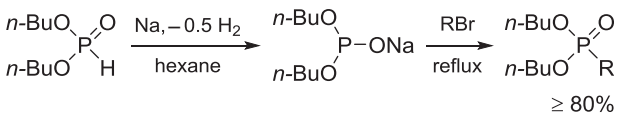
Careful investigation of this phenomenon clarified the exact chemistry occurring (*236*). When the calculated amount of a dialkyl *H*-phosphonate (e.g. diethyl) is added gradually to a hot suspension of finely divided sodium drops in a solvent such as toluene or xylene, the reaction completes swiftly and in accord with the aforementioned equation, without producing a 'phosphine' odour. However, when finely divided sodium (1 g, 0.04 mol) was suspended in toluene ($\sim$100 ml) and frozen using liquid nitrogen, and diethyl *H*-phosphonate (4.14 g, 0.03 mol) was introduced, using a vacuum line evacuated while cold and afterwards warmed to 0 °C, a reaction occurred with gas evolution and formation of the sodium dialkyl phosphite. The reaction stopped only after 24 h when the evolved hydrogen amounted to only 86% of the theoretically expected volume. The volatile products were pumped away and the condensible materials in the vapours collected in a chilled trap. The condensate was found to contain a small quantity of toluene and a substance that did indeed prove to be phosphine.

Evidently, reduction or hydrogenolysis can occur on the alkali metal surface when the reaction proceeds at low or ambient temperature. This accounts for the 'excess' of metal that often remains when the reaction is carried out in a low-boiling solvent (e.g. diethyl ether or hexane), especially when relatively large slices of the metal are used in place of a fine suspension. As toxic phosphine gas is formed in such reactions it is prudent to ensure that Michaelis–Becker chemistry is always performed in an efficient fume cupboard.

The Michaelis–Becker reaction in some cases is a useful alternative to the Arbuzov reaction. For example, the Arbuzov reaction of triethyl phosphite with alkyl halides gives satisfactory yields of the lower members of the dialkyl *n*-alkylphosphonate series, but difficulties are encountered when the higher alkyl halides are used; thus, protracted reaction periods (up to 48 h) are required at a temperature of 150–160 °C to produce modest yields ($\leq$50%) of the phosphonic acid esters (*153*). Also, the necessary distillation of the product from the reaction mixture can lead to troublesome decomposition, even under low pressure. While the reaction time may be reduced by the use of pressure vessels and higher temperatures, these expedients usually cause an increase in the amount of the unwanted byproduct, diethyl ethylphosphonate, and do not counter the decomposition difficulty during fractionation. Hence, although several diethyl alkylphosphonates can be prepared by the Arbuzov method, it is not of sufficient quality in this case to comprise a general synthetic method. Dialkyl sodium phosphites present an alternative method of synthesis. However, diethyl sodium phosphite has some unfavourable characteristics: it has limited solubility in inert solvents, making it almost imperative to use warm anhydrous diethyl ether as the reaction medium, while its hygroscopicity necessitates the use

of equipment carefully designed to exclude moisture. The use of higher dialkyl sodium phosphites overcomes these difficulties. Di-*n*-butyl sodium phosphite is readily soluble in inert organic solvents. Particularly advantageous is its solubility in the lower petroleum fractions (hexanes and heptanes) which have several favourable properties for the Michaelis—Becker reaction: the lack of solubility of the formed sodium halides therein, ease of drying and lower fire hazard compared to diethyl ether. The effect of the solvent on the course of the Michaelis—Becker reaction has been reviewed (*237*).

Solutions of di-*n*-butyl sodium phosphite in hexane are stable at ordinary exposures to atmospheric moisture, making it feasible to use standard laboratory glassware topped by calcium chloride guard tubes. The reactions with the alkyl halides proceed readily at reflux temperature, completing within 3—6 h, thus having a great advantage in terms of speed compared to the Arbuzov method. The di-*n*-butyl *n*-alkylphosphonates obtained are handled more easily than the corresponding diethyl esters. They are more stable to hydrolysis which enables separation of the sodium halide through washing with water (the ethyl esters are more water soluble and more easily hydrolysed, which discourages water washing; instead, the colloidally dispersed sodium halide must often be removed by prolonged centrifugation, and afterwards persistent traces of the sodium halide can cause product decomposition during distillation). Isolation of the dialkyl *n*-alkylphosphonates requires, after washing, only drying and vacuum distillation for pure samples to be obtained in yields of 80% or better (Fig. 2.13.6.2). In view of these points of superiority over the diethyl esters, it is recommended that di-*n*-butyl *n*-alkylphosphonates are synthesised in preference, especially in situations where the ester groups are going to be replaced subsequently, e.g. halogenation to alkylphosphonic dihalides, or hydrolysis to alkylphosphonic acids.

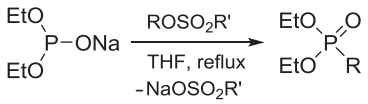


Di-*n*-butyl *n*-alkylphosphonates

R	Bp (°C/mmHg)	R	Bp (°C/mmHg)
CH_3	86–91/1.5	C_8H_{17}	147–148/2
C_2H_5	137–139/17	C_9H_{19}	159–161/2
C_3H_7	133–137/10	$C_{10}H_{21}$	161/1
C_4H_9	160–162/20	$C_{12}H_{25}$	196–199/3
C_5H_{11}	167–169/17	$C_{14}H_{29}$	217–219/3
C_6H_{13}	182–184/20	$C_{16}H_{33}$	226–228/2
C_7H_{15}	188–190/17	$C_{18}H_{37}$	248–250/2

Figure 2.13.6.2

Diethyl sodium phosphite can be prepared by adding a molar equivalent amount of sodium to a solution of diethyl *H*-phosphonate in dry 1,4-dioxane or THF; several hours are required for the sodium to dissolve (*158*). Rather than use an alkyl halide, an alkyl *p*-toluenesulfonate (tosylate) — prepared easily from reaction of an alcohol with an excess of *p*-toluenesulfonyl chloride in pyridine — can be used, and added to the diethyl sodium phosphite in 1,4-dioxane or THF. The sodium salt of *p*-toluenesulfonic acid precipitates and the diethyl alkylphosphonate remains in solution. Because of the high solubility of sodium diethyl phosphite and the insolubility of sodium *p*-toluenesulfonate in 1,4-dioxane or THF, these solvents are excellent for Michaelis—Becker reactions of the diethyl phosphite anion. With esters of primary alcohols, such as ethyl tosylate, the reaction occurs smoothly at room temperature, although gentle heating is recommended to ensure completion. Esters of secondary alcohols, e.g. isopropyl tosylate, react satisfactorily but the yield of phosphonate is modest. Cyclohexyl tosylate reacts slowly even in boiling THF (65 °C) and faster in warm 1,4-dioxane (85 °C), although the yield of diethyl cyclohexylphosphonate is low due to a competing elimination reaction to form cyclohexene. The *n*-butyl esters of *p*-toluenesulfonic acid and methanesulfonic acid react well to give excellent yields of diethyl *n*-butylphosphonate (Fig. 2.13.6.3).



Diethyl alkylphosphonates

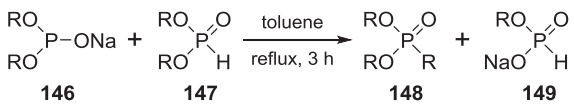
R	R'	Yield (%)	Bp (°C/mmHg)
Et	C_6H_4Me-*p*	54	58–60/2.0
i-Pr	C_6H_4Me-*p*	51	45–47/0.2
c-Hex	C_6H_4Me-*p*	35[a]	50–90/0.1
n-Bu	C_6H_4Me-*p*	82	53–55/0.1
n-Bu	Me	87	61–62/0.4

a. Crude product.

Figure 2.13.6.3

A method for generating diethyl sodium phosphite that avoids treating diethyl *H*-phosphonate with sodium alkoxides or sodium metal, thus avoiding alcohol or phosphine contamination, uses sodium hydride in THF, according to the equation: $(EtO)_2P(O)H + NaH \rightarrow (EtO)_2PONa + H_2$ (*159*). The relative rates of reaction of primary alkyl halides and tosylates with this sodium salt in THF decline in the order RBr > ROTs > RCl (when R was *n*-butyl the relative initial rates at 20 °C were 280:70:1). Advantage can be taken of the differential reactivity of alkyl bromides and chlorides for synthetic purposes. For example, the reaction of diethyl sodium phosphite with 1-bromo-3-chloropropane gives in 54% yield diethyl 3-chloropropylphosphonate $(EtO)_2P(O)CH_2CH_2CH_2Cl$, whose hydrolysis furnishes in 76% yield 3-chloropropylphosphonic acid.

Another side reaction of the Michaelis—Becker reaction is dealkylation by the dialkyl sodium phosphite (**146**) of unreacted dialkyl *H*-phosphonate (**147**) to yield the dialkyl alkylphosphonate (**148**) and sodium alkyl-*H*-phosphonate (**149**) (Fig. 2.13.6.4) (*112*). This secondary reaction occurs at a significant rate above 60 °C and lowers the yield of the dialkyl alkylphosphonates in the usual alkylation reaction with an alkyl halide. It can cause contamination of the alkylation products (dialkyl alkylphosphonates) when the alkyl groups of the alkyl halide and the dialkyl *H*-phosphonate used to prepare the sodium dialkyl phosphite differ. The side reaction between a sodium dialkyl phosphite and a dialkyl *H*-phosphonate can be used for preparative purposes. The two reagents can be heated in equimolar proportions under reflux in toluene for several hours. The dialkyl *H*-phosphonate acts as the alkylating agent in the same way as an alkyl halide or dialkyl sulfate. The ease of dealkylation of the alkyl group of the ester decreases in the order Me ≫ Et > *n*-Pr > *n*-Bu. The sodium alkoxide is preferable to metallic sodium for the preparation of the starting sodium dialkyl phosphites, which are isolated by evaporation of the excess of the respective alcohol. Dimethyl *H*-phosphonate reacts anomalously and while attempting to isolate its sodium salt by evaporation of the methanol in which it had been prepared, an exothermic reaction set in, yielding dimethyl ether and a solid mixture of salts (which could be converted into methylphosphonic dichloride in 50% yield by acidification with methanolic HCl and treatment with PCl_5; see Section 2.3.5). In contrast, other sodium dialkyl phosphites, $(RO)_2PONa$ where R = Et, *n*-Pr and *n*-Bu, were prepared easily and upon treatment with the respective dialkyl *H*-phosphonates, gave good yields of the desired dialkyl alkylphosphonates (Fig. 2.13.6.4), which were easily separated. The Michaelis—Becker reaction is disadvantageous on an industrial scale, as it requires large quantities of sodium metal or sodium alkoxides (prepared from sodium) which pose a fire hazard.



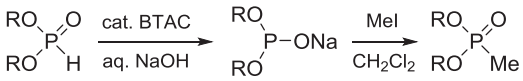
Dialkyl alkylphosphonates

R	Yield (%)	Bp (°C/mmHg)
Me	AR	AR
Et	77	89–97/25
n-Pr	84	113–132/24
n-Bu	87	102–120/2

AR = anomalous reaction : see text.

Figure 2.13.6.4

Another option for the synthesis of dialkyl alkylphosphonates consists of the reaction of dialkyl *H*-phosphonates with alkyl halides in a two-phase system containing aqueous sodium hydroxide—dichloromethane and a suitable phase transfer catalyst (PTC) (*238*). The use of benzyltriethylammonium chloride (BTAC) as the PTC is effective (Fig. 2.13.6.5). Alternatively, an entirely



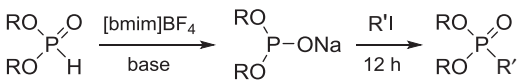
Dialkyl methylphosphonates

R	Yield (%)	δ_P (ppm) [a]
Me	22	34.1
i-Pr	63	29.5
n-Bu	95	30.7
i-Bu	92	31.7

a. Recorded at 100 MHz in $CDCl_3$.

Figure 2.13.6.5

different method involves the treatment of dialkyl *H*-phosphonates with sodium hydroxide or sodium in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 (Fig. 2.13.6.6) (*239*). In this case the yields are greatest when sodium hydroxide is used.



Dialkyl alkylphosphonates

R	R'	Base	Yield (%)	δ_P (ppm)[a]
Me	Me	NaOH	80	34.3
n-Bu	Me	NaOH	91	31.5
n-Bu	Me	Na	60	31.5
n-Bu	Bn	Na	60	32.8

a. 31-P NMR spectra recorded at 162 MHz in $CDCl_3$.

Figure 2.13.6.6

Dialkyl sodium phosphites interact with various $X(CH)_nY$ systems, where X and Y are reactive and nonreactive entities respectively, to give various dialkyl γ-functionalised phosphonates that are not easily accessed by other means (Fig. 2.13.6.7). Preparation of diethyl 2-diethylaminoethylphosphonate from an attempted Arbuzov reaction between triethyl phosphite and 2-diethylaminoethyl chloride, for example, resulted in dimerisation of the halide to 1,1,4,4-tetraethylpiperazinium dichloride, yet under Michaelis–Becker conditions the desired product (**150**) was easily isolated (*240*). Diethyl sodium phosphite adds to levulinic acid in ethanol to give the sodium salt of an acid, which in boiling toluene in the presence of *p*-toluenesulfonic acid, cyclises to give the lactone (**151**) (Fig. 2.13.6.7) (*128*). At the halfway stage of this method, residual ethanol must be removed completely, otherwise the remaining ethanol reacts with the lactone product to form triethyl 4-phosphono-4-hydroxyvalerate, $(EtO)_2P(O)C(Me)(OH)CH_2CH_2CO_2Et$. The reaction of di-*n*-butyl sodium phosphite with allyl bromide yields a high-boiling

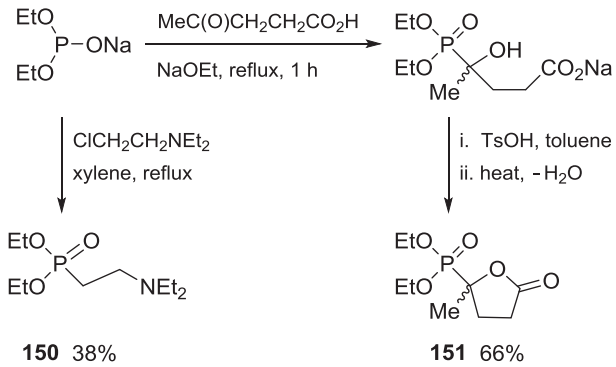
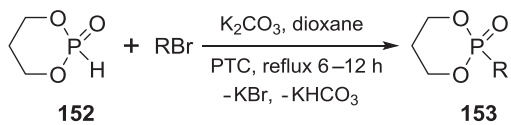


Figure 2.13.6.7

compound that contains two phosphorus atoms per allyl group (*241*). This is probably the disubstituted species $(n\text{-BuO})_2P(O)(CH_2)_3P(O)(OBu\text{-}n)_2$ formed from an initial Michaelis–Becker reaction, followed by a Michael addition of the dialkyl *H*-phosphonate across the double bond of the product.

Classical Michaelis–Becker procedures for alkylation of cyclic dialkyl *H*-phosphonates such as 1,3,2-dioxaphosphorinane-2-oxide (**152**) are often unsuccessful due to ring opening and polymerisation caused by the instability of the cyclic dialkyl sodium phosphite salt. An efficient alternative method involves generation of the potassium salt of the cyclic *H*-phosphonate (**152**) using potassium carbonate and a PTC in 1,4-dioxane, and subsequent alkylation with an alkyl bromide, to give product (**153**) (Fig. 2.13.6.8) (*220*). The effectiveness of the PTC judged by the yield of alkylphosphonate decreases in the following order: 18-crown-6 > tetra-*n*-butylammonium bromide (TBAB) > BTAC. Linear primary alkyl halides such *n*-butyl bromide react better than branched primary alkyl halides such as *i*-butyl bromide (the yields of the respective alkylphosphonates were 86% and 26%). Secondary alkyl halides do not perform well: *s*-butyl bromide failed to give any alkylation product.



Cyclic dialkyl alkylphosphonates

R	Yield (%)	Bp (°C/mmHg)	δ_P ($CDCl_3$)
Et	93	75/0.4	30.5
n-Pr	91	80/0.4	29.6
n-Bu	86	90/0.4	28.9
i-Bu	26	81/0.4	29.2
$CH_2CH{=}CH_2$	95	115/0.7	23.4

Figure 2.13.6.8

Di-*n*-butyl sodium phosphite prepared by the classical Michaelis—Becker method is able to react with a variety of alkyl halides bearing aromatic groups. These include α-chloromethylthiophene to give di-*n*-butyl α-thienylmethylphosphonate (**154**) (*157*) and benzyl chloride to give di-*n*-butyl benzylphosphonate (**155**) (*242*) (Fig. 2.13.6.9). The latter can be transformed into some useful derivatives. Acid hydrolysis provides benzylphosphonic acid (**156**) (*157*) and nitration with a mixture of concentrated sulfuric and nitric acids provides di-*n*-butyl 4-nitrobenzylphosphonate (**157**) (*243*). Reduction of this material to di-*n*-butyl 4-aminobenzylphosphonate (**158**) is accomplished by iron filings in acetic acid (*243*).

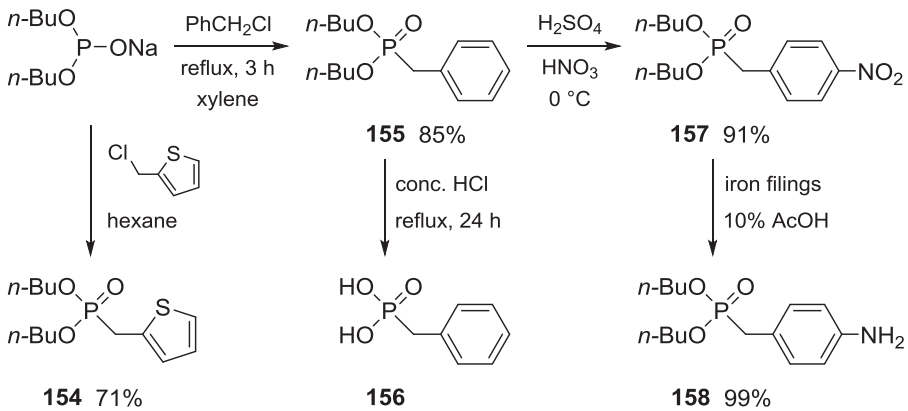
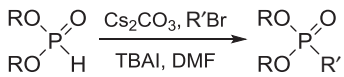


Figure 2.13.6.9

Diethyl sodium phosphite in ethanol reacts with various alkyl iodides to give the expected diethyl alkylphosphonates (*244*). Fascinatingly, the reaction of diethyl sodium phosphite with neopentyl bromide resulted in diethyl *n*-butylphosphonate (!) as the main product (proof by ^{1}H and ^{13}C-NMR spectroscopy and by mass spectrometry); the desired diethyl neopentylphosphonate, $(EtO)_2P(O)CH_2$-*t*-Bu, was only present at <5% and was not isolated. Di-*n*-butyl sodium phosphite reacts with *n*-propyl bromide in benzene to provide di-*n*-butyl *n*-propylphosphonate in 63% yield (*245*). It also reacts with allyl chloride in hexane to give di-*n*-butyl allylphosphonate (*246*). Unsymmetrical dialkyl alkylphosphonates $RO(R^1O)P(O)R^2$ can be prepared similarly (*247*). Mono- and poly-methylenediphosphonic acids and esters can be obtained from the dialkyl sodium salts and α,ω-dihaloalkanes (*248*,*249*). The Michaelis—Becker reaction of diphenyl *H*-phosphonate with 4-nitrobenzyl or trityl bromides in acetonitrile in the presence of the base 1,8-diazabicyclo[5.4.0]undec-7-ene (not shown) comprises a useful approach to diphenyl alkylphosphonates (*250*).

Dialkyl or diaryl *H*-phosphonates react with caesium carbonate and tetra-*n*-butylammonium iodide in DMF to produce anions that can displace halide from haloalkanes (Fig. 2.13.6.10) (*251*). Caesium carbonate is superior to other alkali metal carbonates (Li, Na, K, Rb). Primary and secondary alkyl halides, including cyclohexyl chloride, and allyl bromide react under these conditions, but



Dialkyl/phenyl alkylphosphonates

R	R'	Reaction time (h)	Yield (%)
Me	CH_2Ph [a]	24	97
Et	CH_2Ph	28	82
Et	CH_2CH_2Ph	29	54
n-Pr	CH_2Ph	25	59
i-Pr	CH_2Ph	72	95
n-Bu	CH_2Ph [a]	45	84
CF_3CH_2	CH_2Ph	72	64
Bn	CH_2Ph	29	75
Bn	*n*-Bu	72	95
Bn	CH_2CO_2Et	66	90
Ph	*n*-Pr	49	64
Ph	*n*-Bu	49	52
Ph	*s*-Bu	66	75
Ph	*i*-Bu	48	66
Ph	*n*-pentyl [a]	49	65
Ph	cyclohexyl [a]	70	47
Ph	$CH_2CH{=}CH_2$	40	77

a. alkyl chloride used.

Figure 2.13.6.10

tertiary halides resist alkylation. Alkyl chlorides and alkyl bromides are best employed; with dialkyl *H*-phosphonates, iodide anion liberated from the more reactive alkyl iodides can dealkylate particular dialkyl alkylphosphonates, and reduce the yields. In most examples, the starting *H*-phosphonates were not consumed completely and required separating during purification of the intended product.

A modification of the Michaelis–Becker reaction uses *n*-butyllithium to generate the dialkyl lithium phosphite which can be treated with an alkyl halide. Quenching the dimethyl lithium phosphite formed this way with iodoethane-1,1-d_2 and iodoethane-2,2,2-d_3 gave the isotopomeric dimethyl ethylphosphonates (**159**) and (**160**), albeit in low yield (Fig. 2.13.6.11) (*252*). The products are valuable for mass spectrometry studies (*252–254*).

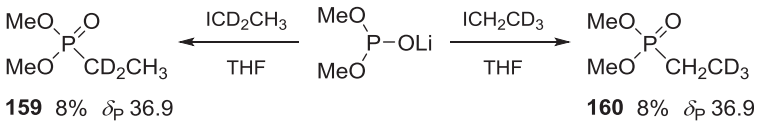


Figure 2.13.6.11

▷ *Dimethyl methylphosphonate $(MeO)_2P(O)Me$ (alkylation of dimethyl sodium phosphite with methyl iodide)* (238). Sodium metal (1.15 g, 50 mmol) was cut into small segments and added to anhydrous chloroform (10 ml) contained in a 100-ml three-necked flask. Dimethyl *H*-phosphonate obtained by treating phosphorus trichloride (4.4 ml, 50 mmol) with methanol (5.5 ml, 0.15 mol) and diluted with anhydrous chloroform (10 ml) was added dropwise to the flask at 25 °C. The reaction mixture was cooled and methyl iodide (3.4 ml, 0.055 mol) was added. After 15 h, it was observed that the reaction was incomplete. More sodium (1.15 g) and methyl iodide (3.4 ml) were therefore added and the mixture was stirred for another 10 h. Centrifugation and filtration removed the sodium iodide. Concentration of the filtrate and drying of the liquid under vacuum gave 80% pure dimethyl methylphosphonate (5.2 g, 84%).

▷ *Dialkyl methylphosphonates $(RO)_2P(O)Me$ (phase-transfer-catalysed method)* (238). A solution of the respective dialkyl *H*-phosphonate (0.1 mol) in CH_2Cl_2 (25 ml) was added dropwise over 20 min to a stirred mixture of methyl iodide (12.4 ml, 0.2 mol), BTAC (0.23 g), aqueous 50% sodium hydroxide (25 g in 25 ml water) and CH_2Cl_2 (25 ml) that was contained in a 200-ml three-necked flask, equipped with a stirring device and inert gas fittings, that was cooled to 0–5 °C. After addition the organic layer was separated, centrifuged and the solvent removed to leave either dimethyl methylphosphonate (22%), diisopropyl methylphosphonate (63%), di-*n*-butyl methylphosphonate (95%) or diisobutyl methylphosphonate (92%).

▷ *Di-n-butyl methylphosphonate $(n\text{-}BuO)_2P(O)Me$ (ionic liquid method)* (239). A 25-ml flask was charged with $[bmim]BF_4$ (~5 ml), powdered sodium hydroxide (0.0512 g, 1.28 mmol) and a magnetic stirrer bar. The flask was heated in an oil bath until the NaOH dissolved and was then removed from the oil bath. Di-*n*-butyl *H*-phosphonate (0.25 ml, 1.3 mmol) was added using a syringe. The resulting mixture was stirred for 15 min and methyl iodide (0.08 ml, 1 mmol) was added in one portion and the mixture stirred for 12 h. The ionic liquid was extracted with ether (~3 ml) and the ether layer was removed with the aid of an oil pump. Chromatography of the residue on silica gel, eluting with 9:1 hexane-ethyl acetate, gave di-*n*-butyl methylphosphonate (0.189 g, 91%).

▷ *Diethyl ethylphosphonate $(EtO)_2P(O)Et$ (alkylation of diethyl sodium phosphite with ethyl p-toluenesulfonate)* (158). Diethyl sodium phosphite in THF (1.5 M, 82 ml, 0.12 mol) was added to a stirred solution of ethyl *p*-toluenesulfonate (24 g, 0.12 mol) in dry THF (50 ml) at room temperature. After addition the mixture was left for 24 h. Sodium *p*-toluenesulfonate was filtered off and the filtrate evaporated. Distillation of the residue gave unchanged ethyl tosylate (24%) and diethyl ethylphosphonate (11 g, 54%). Bp 58–60 °C/2 mmHg.

▷ *Diethyl ethylphosphonate $(EtO)_2P(O)Et$ (alkylation of diethyl sodium phosphite with diethyl H-phosphonate)* (112). A solution of sodium (23 g, 1 mol) in ethanol (500 ml) was cooled to 0–5 °C and diethyl *H*-phosphonate (138 g, 1 mol) was added slowly with stirring. The excess of ethanol was removed at 20 mmHg; the sodium salt remained as colourless crystals (160 g). It was suspended in toluene (100 ml) and heated under reflux. To this boiling suspension was added diethyl *H*-phosphonate (138 g, 1 mol) with stirring. Heating was continued for a further 3 h; then the toluene (from which a white precipitate had separated) was decanted and replaced by ether. The

insoluble sodium ethyl-*H*-phosphonate (125 g, 94%; mp 182 °C from ethanol—acetone) was removed by filtration. Removal of solvent from the filtrate and distillation gave a colourless liquid (127 g, 77%). Bp 89—97 °C/25 mmHg.

▶ *Diethyl isopropylphosphonate $(EtO)_2P(O)Pr$-i (alkylation of diethyl sodium phosphite with isopropyl p-toluenesulfonate)* (158). Isopropyl *p*-toluenesulfonate (21.4 g, 0.1 mol) in THF (40 ml) was added to a stirred solution of diethyl sodium phosphite (24.8 g, 0.1 mol) in THF (55 ml). A solid soon began to precipitate. Stirring was continued at room temperature for 24 h and then at reflux temperature for 17 h. Pentane (95 ml) was added to the mixture and the sodium tosylate was removed by filtration. Concentration of the filtrate and distillation gave diethyl isopropylphosphonate (9.3 g, 51%). Bp 45—47 °C/0.2 mmHg. The starting isopropyl tosylate (mp 18—20 °C from hexane-ether) was prepared in 76% yield by reaction of isopropanol with *p*-toluenesulfonyl chloride (10% molar excess) in pyridine solution (2 h reaction time at room temperature).

▶ *Diethyl n-butylphosphonate $(EtO)_2P(O)Bu$-n (alkylation of diethyl sodium phosphite with n-butyl p-toluenesulfonate)* (158). Diethyl sodium phosphite in THF (1.5 M, 82 ml, 0.12 mol) was added to a stirred solution of *n*-butyl *p*-toluenesulfonate (24.7 g, 0.11 mol) in dry THF (50 ml) at room temperature. After addition the mixture was stirred for 6 h and then heated for several hours longer. Sodium *p*-toluenesulfonate (20 g, 0.10 mol) was filtered off and the filtrate evaporated. Distillation of the residue gave diethyl *n*-butylphosphonate (17.3 g, 82%). Bp 53—55 °C/0.1 mmHg.

▶ *Diethyl n-butylphosphonate $(EtO)_2P(O)Bu$-n (alkylation of diethyl sodium phosphite with n-butyl methanesulfonate)* (158). Diethyl sodium phosphite (1.5 M, 41 ml, 0.06 mol) was treated with *n*-butyl methanesulfonate (7.6 g, 0.05 mol) in dry THF (50 ml) as described in the previous recipe. Precipitation of sodium methanesulfonate did not occur within 20 h at room temperature but took place a few minutes after the mixture was heated to reflux. After refluxing for 6 h the mixture was cooled and hexane (50 ml) and acetic acid (1 ml) were added; the precipitate was removed by centrifugation and washed with 1:1 hexane—THF. The supernatant and washings were combined and concentrated. Distillation of the residual liquid gave the title compound (8.4 g, 87%). Bp 61—62 °C/0.35 mmHg.

▶ *Diethyl sodium phosphite $(EtO)_2PONa$ (from sodium hydride in THF)* (159). The reaction of diethyl *H*-phosphonate with sodium hydride was carried out conveniently in a dry 300-ml two- or three-necked flask fitted with a pressure-equalising dropping funnel and an outlet protected by a drying tube. At the bottom of the flask was a medium porosity fritted glass disc through which the final solution could be filtered via a glass adaptor into a 250-ml volumetric flask. A stream of dry inert gas (e.g. nitrogen) was introduced continuously through this frit to both flush the system and stir the contents of the flask. Anhydrous THF (100 ml) was added to the flask and a bottle of sodium hydride containing 10% molar excess over the diethyl *H*-phosphonate to be used was opened and emptied rapidly into the THF. The mixture was cooled to −12 °C with a dry ice—chloroform—carbon tetrachloride bath and the diethyl *H*-phosphonate was added from the dropping funnel at sufficient rate so that the evolution of hydrogen did not become too vigorous. After addition the mixture was allowed to stand at room temperature until the evolution of hydrogen from the sodium hydride particles had practically ceased. The current of inert gas, now at about 20 mmHg pressure, was

transferred to the original outlet tube to force the reaction mixture through the fritted glass disc into the volumetric flask. The residual sodium hydride was washed with two portions of anhydrous THF which were filtered into the volumetric flask. The latter was detached and its contents made up to the volume with anhydrous THF. The resulting stock solution of diethyl sodium phosphite was colourless, free of the odour of phosphine and apparently stable for several days when stored in a refrigerator.

▷ *Diethyl 3-chloropropylphosphonate* $(EtO)_2P(O)CH_2CH_2CH_2Cl$ (*159*). 1-Bromo-3-chloropropane (63.0 g, 0.40 mol) was added to a stirred solution of diethyl sodium phosphite prepared by the action of excess sodium on diethyl *H*-phosphonate (27.6 g, 0.20 mol) in THF (400 ml). A white solid began to separate after 15 min. The mixture was stirred at room temperature for 4 h, filtered and the filtrate concentrated. Distillation of the residue returned the excess 1-bromo-3-chloropropane followed by a fraction boiling at 85–100 °C at 0.32 mmHg. Redistillation of this gave the title compound (23.2 g, 54%). Bp 97–99 °C/0.25 mmHg.

▷ *Diisopropyl methylphosphonate* $(i\text{-}PrO)_2P(O)Me$ (*238*). Diisopropyl *H*-phosphonate from esterification of phosphorus trichloride (4.4 ml, 50 mmol) with isopropanol (11.5 ml, 0.15 mol) was diluted with heptane (25 ml) and added dropwise to a stirred mixture of small pieces of sodium (1.15 g, 50 mmol) in heptane (25 ml). The mixture was heated under reflux for 30 h. Methyl iodide (6.2 ml, 0.1 mol) was added and the reaction was continued for another 10 h. Centrifugation and filtration removed the sodium iodide. Concentration of the filtrate and drying of the liquid under vacuum gave 95% pure diisopropyl methylphosphonate (3.0 g, 33%).

▷ *Di-n-butyl n-propylphosphonate* $(n\text{-}BuO)_2P(O)Pr\text{-}n$ (*245*). *n*-Propyl bromide (13.5 g, 0.10 mol) was added dropwise to a stirred solution of di-*n*-butyl sodium phosphite prepared from sodium (4.6 g, 0.20 mol) and di-*n*-butyl *H*-phosphonate (42.7 g, 0.22 mol) in anhydrous benzene (250 ml). The mixture was stirred at room temperature for 2 h and then under reflux for 5 h. It was cooled, water was added to dissolve the sodium chloride and the organic layer was separated and washed with water, with 5% aqueous sodium hydroxide and again with water. It was dried ($MgSO_4$) and the benzene was removed. Distillation of the residue gave the title compound as a colourless liquid (29.7 g, 63%). Bp 133–137 °C/10 mmHg.

▷ *Di-n-butyl alkylphosphonates* $(n\text{-}BuO)_2P(O)R$ (*153*). Metallic sodium (1.15 g, 0.05 mol) was placed into a three-necked round-bottomed flask equipped with a dropping funnel, a sealed stirrer and a reflux condenser closed with a calcium chloride tube. Anhydrous hexane or heptane (150 ml) was added to the flask and, while the liquid was being refluxed gently with stirring, di-*n*-butyl *H*-phosphonate (9.7 g, 0.05 mol) was added dropwise over 20–30 min, after which refluxing and stirring were continued until the sodium had completely dissolved (this usually took 3–5 h). The alkyl bromide (0.05 mol) was added over 30–45 min and the mixture was stirred under gentle reflux for 5–6 h. Separation of sodium bromide generally commenced after 15–20 min and completed in 2–3 h. After cooling, the mixture was washed with water, and the organic layer separated and dried by rotary evaporation. Vacuum distillation of the residue gave the pure di-*n*-butyl alkylphosphonate in yields generally 80% or better. Boiling points are given in Fig. 2.13.6.2.

▶ *Di-n-butyl allylphosphonate* $(n\text{-BuO})_2P(O)CH_2CH{=}CH_2$ (*246*). Di-*n*-butyl *H*-phosphonate (98.0 g, 0.5 mol) was allowed to react with sodium (11.5 g, 0.5 mol) in hexane (500 ml). Once hydrogen evolution ceased, the resulting solution was treated over 30 min with allyl chloride (39 g, 0.5 mol). The mixture was refluxed gently for 30 min and was then treated with ice water (100 ml), with external cooling. The upper layer was combined with a hexane extract of the lower part of the mixture and the combined hexane solution was washed with ice water (3 × 50 ml). Distillation gave the crude product (16.5 g, bp 151 °C/15 mmHg). The experiment was repeated, with a 6 h reflux period and a fivefold increase in the amount of water used to wash the mixture (500 ml), and produced additional crude product (15 g). In both cases the bulk of the distillation residue was the high-boiling diphosphonate $(n\text{-BuO})_2P(O)(CH_2)_3P(O)(OBu\text{-}n)_2$ reported elsewhere (*241*). Fractionation of the combined products gave the title compound as a colourless liquid (17 g, 15%, bp 110 °C/0.4 mmHg). Note: the reaction with allyl bromide gave similar results. Addition of allyl bromide (61 g, 0.5 mol) to a refluxing solution of di-*n*-butyl *H*-phosphonate (99 g, 0.5 mol) and sodium (11.5 g, 0.5 mol) in xylene (400 ml) over 3 h, followed by cooling and washing, gave di-*n*-butyl allylphosphonate (39 g, 33%, bp 111 °C/0.5 mmHg). The bulk of the residue that remained was the aforementioned diphosphonate.

▶ *Di-n-butyl 3-oxobutylphosphonate* $(n\text{-BuO})_2P(O)CH_2CH_2C(O)Me$ (*245*). A solution of sodium *n*-butoxide in *n*-butanol was added to a stirred mixture of di-*n*-butyl *H*-phosphonate (43 g, 0.22 mol) and 3-buten-2-one (14 g, 0.20 mol) until the spontaneous liberation of heat stopped, after which the mixture was vacuum distilled to give the title compound (12.5 g, 22%).

▶ *Diethyl 2-diethylaminoethylphosphonate* (**150**) (*240*). Sodium (4.6 g, 0.2 mol) was added to diethyl *H*-phosphonate (27.6 g, 0.2 mol) in xylene (dried over sodium; 400 ml) and the mixture was heated under reflux until salt formation was complete. 2-Diethylaminoethyl chloride (27.0 g, 0.2 mol) was added and boiling was continued for a total of 90 min. Filtration, removal of xylene and distillation gave a liquid (bp 168 °C/40 mmHg) whose fractionation gave the title compound (18 g, 38%). Bp 125–130 °C/12 mmHg.

▶ *Diethyl γ-phosphonovalero-γ-lactone* (**151**) (*128*). Sodium (7.9 g, 0.34 mol) was dissolved in ethanol (180 ml) contained in a 1-litre three-necked flask fitted with a reflux condenser, a dropping funnel and a mechanical stirrer. To the cooled solution (0–5 °C), diethyl *H*-phosphonate (45.2 g, 0.32 mol) was added, followed by levulinic acid (38 g, 0.32 mol) in ethanol (50 ml). The mixture was heated under reflux for 1 h, the bulk of the ethanol was distilled (180 ml) and the residue was sucked dry for several hours at the water pump. Toluene (250 ml) was then added to the dry product which was dispersed by means of the stirrer and the mixture was heated and toluene (~75 ml) was distilled until the boiling point indicated the absence of ethanol (Note). At this stage, *p*-toluenesulfonic acid (59 g, 0.34 mol) in toluene (500 ml) was added using a dropping funnel. The distillation of toluene was continued, while the suspension was stirred to prevent serious bumping, until the boiling point indicated the complete removal of water. The mixture was allowed to cool, was then filtered, and the filtrate was distilled, first at atmospheric pressure to remove toluene and then at low pressure, the fraction of bp 90–140 °C/0.1–0.2 mmHg being collected. Redistillation gave almost pure lactone (50 g, 66%). Bp 100–104 °C/0.2 mmHg. Note: It is imperative to remove the ethanol completely; otherwise the amount that remains reacts with the lactone to give triethyl 4-phosphono-4-hydroxyvalerate.

▷ *2-Alkyl-1,3,2-dioxaphosphorinane-2-oxides* (**153**) (*220*). A stirred mixture of 1,3,2-dioxaphosphorinane-2-oxide (1.9 g, 15 mmol), alkyl bromide (30–50 mmol), anhydrous potassium carbonate (4.0 g, 30 mmol), 18-crown-6, TBAB or BTAC (0.75 mmol) and 1,4-dioxane (20 ml) was heated under reflux for 6–12 h. The progress of reaction was monitored by thin layer chromatography (TLC) on silica gel. The mixture was diluted with 1,4-dioxane and filtered to remove the inorganic salt. Concentration of the filtrate gave an oily liquid that was dissolved in CH_2Cl_2 or $CHCl_3$ (200 ml), washed successively with 5% aq. HCl (30 ml) and saturated brine and dried (Na_2SO_4). The residue remaining after the solvent was removed was purified by fractional distillation or recrystallisation. Physical properties of products appear in Fig. 2.13.6.8.

▷ *Di-n-butyl α-thienylmethylphosphonate* $(n\text{-}BuO)_2P(O)CH_2Th\text{-}2$ (**154**) (*157*). Di-*n*-butyl sodium phosphite (from 45 g of di-*n*-butyl *H*-phosphonate, 0.23 mol) was treated in hexane with α-chloromethylthiophene (31 g, 0.23 mol) under reflux for 3 h to give di-*n*-butyl α-thienylmethylphosphonate (47 g, 71%). Bp 147–150 °C/3 mmHg.

▷ *Di-n-butyl benzylphosphonate* $(n\text{-}BuO)_2P(O)CH_2Ph$ (**155**) (*242*). Benzyl chloride (63.3 g, 0.5 mol) was treated with di-*n*-butyl sodium phosphite (prepared from di-*n*-butyl *H*-phosphonate; 97 g, 0.5 mol (*153*)) in xylene (300 ml). The mixture was refluxed for 3 h, cooled washed thoroughly with water to remove sodium chloride, and distilled under reduced pressure to yield a colourless liquid (121 g, 85%). Bp 140–143 °C/4 mmHg.

▷ *Di-n-butyl p-nitrobenzylphosphonate* $(n\text{-}BuO)_2P(O)CH_2C_6H_4NO_2\text{-}p$ (**157**) (*243*). Di-*n*-butyl benzylphosphonate (28.4 g, 0.1 mol) was added over 30 min to a stirred mixture of concentrated sulfuric acid (25 ml) and concentrated nitric acid (25 ml) at 0–2 °C. The mixture was stirred at this temperature for 1 h and was poured into ice water (1000 ml). Extraction with benzene (300 ml), washing with cold water and aqueous sodium carbonate, and distillation gave a pale yellow liquid (30.0 g, 91%). Bp 210–211 °C/3 mmHg.

▷ *Di-n-butyl p-aminobenzylphosphonate* $(n\text{-}BuO)_2P(O)CH_2C_6H_4NH_2\text{-}p$ (**158**) (*243*). Di-*n*-butyl *p*-nitrobenzylphosphonate (10 g, 30 mmol) was added over 30 min to a mixture of iron filings (20 g, 357 mmol) and 10% acetic acid (60 ml) at 75–80 °C. After addition the mixture was stirred for another 30 min, cooled, mixed with benzene (200 ml), neutralised with aqueous sodium carbonate and filtered. The benzene extract was washed with water, dried and concentrated under vacuum. The residual di-*n*-butyl *p*-aminobenzylphosphonate was a deep yellow undistillable liquid (9 g, 99%) that could not be induced to crystallise.

▷ *Dimethyl benzylphosphonate* $(MeO)_2P(O)CH_2Ph$ (*251*). Caesium carbonate (4.44 g, 13.6 mmol) and $n\text{-}Bu_4NI$ (5.03 g, 13.6 mmol) were added to a solution of dimethyl *H*-phosphonate (0.50 g, 4.54 mmol) in anhydrous DMF (23 ml) under nitrogen and the mixture stirred for 1 h. Benzyl chloride (1.73 g, 13.6 mmol) was added and the mixture stirred for 24 h. The resulting milky-white suspension was poured into water (30 ml) and extracted with ethyl acetate (3 × 30 ml). The combined organic layers were washed with water (2 × 30 ml) and brine (30 ml) and dried (Na_2SO_4). The filtrate was concentrated. Flash chromatography of the residue on silica gel, eluting with 9:1 ethyl acetate-hexane, afforded the product as a yellow liquid (0.88 g, 97%).

2.13.7 From trialkyl phosphates

Triethyl phosphate (**161**) reacts with *n*-butyllithium to give the alkylation–metallation product (**162**) which adds to ethyl formate to provide diethyl 1-propyl-2-oxoethylphosphonate (**163**) (Fig. 2.13.7.1) (*255*). This general method is applicable to the synthesis of many dialkyl 1-formylalkylphosphonates, which are useful intermediates in the Wittig–Horner synthesis of α,β-unsaturated aldehydes and in the synthesis of dialkyl alkylaminophosphonates by reductive amination.

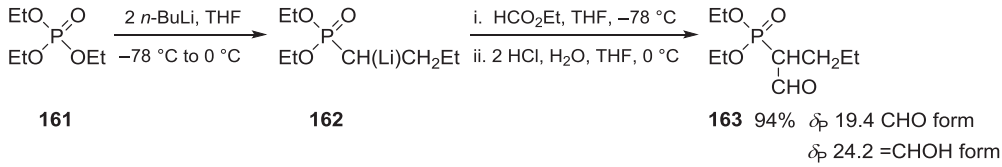


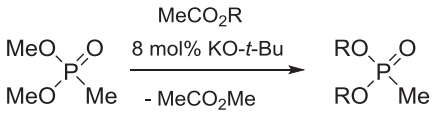
Figure 2.13.7.1

▷ *Diethyl 1-propyl-2-oxoethylphosphonate* $(EtO)_2P(O)CH(CHO)CH_2Et$ (**163**) (*255*). A four-necked 500-ml round-bottomed flask was flame dried and equipped with an efficient mechanical stirrer, a thermometer, a reflux condenser with a bubbler and a 200 ml pressure-equalising dropping funnel with a gas inlet through which was introduced an inert gas (argon or nitrogen). Anhydrous THF (100 ml; from distillation of sodium and benzophenone) was added to the flask. The dropping funnel was filled with *n*-butyllithium (1.5 M solution in hexane, 0.210 mol) (Note 1). The flask was cooled to −20 °C with a dry ice–acetone bath (Note 2), stirring was started and *n*-butyllithium was added to the THF over a few minutes. The resulting yellow solution was cooled to −78 °C. The cooling bath was then maintained just below the bottom of the flask, while a solution of triethyl phosphate (18.2 g, 0.1 mol) in THF (50 ml) was added dropwise from the dropping funnel over 15 min at a rate sufficient to cause the temperature of the reaction mixture to rise slowly to 0 °C (Note 3). The resulting solution was stirred for an extra 15 min at 0 °C. By this time, the yellow colour had almost disappeared completely and the solution was clear. The reaction mixture was cooled to −78 °C and a solution of ethyl formate (7.9 g, 0.107 mol) in THF (20 ml) was added dropwise at this temperature (Note 4). The reaction mixture was stirred for 30 min and then allowed to warm slowly to 0 °C, and quenched by the dropwise introduction of 3 M hydrochloric acid (80 ml). The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 × 50 ml). The extracts were combined with the original layer and dried ($MgSO_4$). The drying agent was filtered off and the filtrate was concentrated on a rotary evaporator. The yellow residue was distilled through an 8-cm fractionating column to provide the pure title compound as a pale yellow liquid (210.0 g, 94%). Bp 110–115 °C/0.05 mmHg. δ_P ($CDCl_3$) 19.4 (CHO form) and 24.2 (=CHOH form) ppm. Notes: (1) The *n*-butyllithium in hexane available commercially can be standardised before use by titration against a solution of benzyl alcohol in toluene and cuproine (2,2′-biquinoline) or with diphenylacetic acid in THF. (2) A Dewar partially filled with liquid nitrogen can be used instead of a dry ice–acetone bath for cooling. (3) The reaction mixture should be only slightly cooled by

placing it just above the cooling bath, so that the reaction proceeds smoothly. (4) *N,N*-dimethylformamide (DMF) can be used instead of ethyl formate with the same operating conditions.

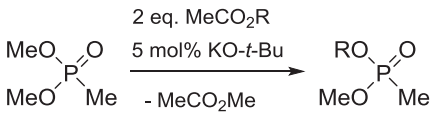
2.13.8 Transesterification of dialkyl alkylphosphonates

Ester interchange between dimethyl methylphosphonate and carboxylic acid esters catalysed by potassium *tert*-butoxide in THF is a convenient route to symmetrical and unsymmetrical dialkyl methylphosphonates (Fig. 2.13.8.1) (*256*). The reactions are sensitive to steric effects with rates paralleling the size of the incoming alkoxy group (*n*- > *i*- > *t*-alkyl). The second substitution occurs at a rate lower than the first.



Symmetrical dialkyl methylphosphonates

R	Yield (%)	δ_P ($CDCl_3$)
Bn	94	31.8
i-Pr	89	28.3



Unsymmetrical dialkyl methylphosphonates

R	Yield (%)	δ_P ($CDCl_3$)[b]
Bn[a]	78	32.5
i-Pr	78	30.9
t-Bu	48	27.5

a. 2 mol% catalyst used *b.* measured at 121.5 MHz

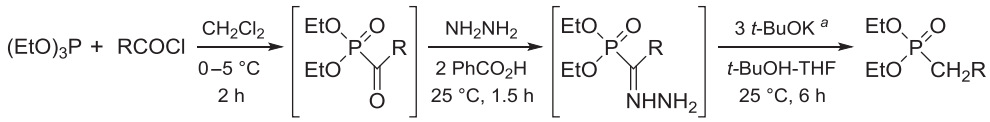
Figure 2.13.8.1

▶ *Benzyl methyl methylphosphonate BnO(MeO)P(O)Me* (*256*). Dimethyl methylphosphonate (13.5 ml, 125 mmol), benzyl acetate (3.62 ml, 25 mmol) and THF (125 ml) were combined in a Schlenk flask. The reaction was initiated by transferring by syringe a solution of potassium *tert*-butoxide (2.5 mmol) in THF (10 ml) to the vessel. After 45 s, the reaction was quenched with saturated brine (2 ml). Under these conditions, 94% of the benzyl acetate was consumed to yield benzyl methyl methylphosphonate and dibenzyl methylphosphonate (94:6 ratio). The solvent was

removed and the phosphonate mixture was filtered from the salts. The excess dimethyl methylphosphonate and unreacted benzyl acetate were removed by distillation under vacuum (35 °C at 0.2 mmHg). Column chromatography of the residue on silica gel, eluting with 63:37 hexane—acetone, gave the title compound as a pale yellow liquid (3.92 g, 78% yield relative to benzyl acetate). δ_P (121.5 MHz, $CDCl_3$) 32.5 ppm.

2.13.9 Reductive deoxygenation of dialkyl acylphosphonates

A mild synthesis of dialkyl alkylphosphonates requiring no heating is a Wolff—Kishner three-step one-pot sequence from a trialkyl phosphite and an acyl chloride (Fig. 2.13.9.1) (*257*). Dichloromethane used as the solvent for the acylphosphonate formation is replaced subsequently by benzene, to which hydrazine and benzoic acid are added. Hydrazone formation is reversible and the equilibrium is pushed towards the hydrazone by removing the released water by freeze-drying. The solid frozen matrix of the hydrazone and benzoic acid is treated with potassium *tert*-butoxide in *tert*-butanol and THF to provide the dialkyl alkylphosphonate.



R	isolated yield (%)
Me	58
Et	74
i-Pr	35 [b]
t-Bu	< 5
Ph	21
CH_2Ph	85
CH_2CH_2Ph	74

a. Potassium benzoate precipitates immediately, reaction mixture turns yellow and N_2 evolved

b. the yield can be raised to 45% if 4 equivalents of $PhCO_2H$ are used for hydrazone formation

Figure 2.13.9.1

Linear acyl chlorides produce the dialkyl alkylphosphonates in high yield: 58% from acetyl chloride (nearly 90% per step). Yields fall significantly for α-branched substrates. Nuclear magnetic resonance analysis of the reaction of isobutyryl chloride showed that the acylphosphonate formed in high yield (35%), but decomposed mostly to diethyl *H*-phosphonate and isobutyryl hydrazide in the second step; an improved yield (45%) resulted using 4 molar equivalents of benzoic acid. Hydrazone formation is affected by steric and electronic factors: trimethylacetyl chloride reacted poorly, while benzoyl chloride was less reactive in the second step. In cases where a $PhCH_2CH_2COCl$ starting material was unavailable, the corresponding carboxylic acid could be used in a four-step, one-pot sequence that employed oxalyl chloride in the first step ($RCO_2H \rightarrow RCOCl$). This four-step method gave $(EtO)_2P(O)CH_2CH_2CH_2C_6H_4R$-4 where R was H (69%), MeO (65%), CN (58%), OAc or NHAc

(<5% yield). The low yield of the last two products, attributed to reaction of the additional carbonyl group with hydrazine, limits this method, despite its favourable comparison to the Arbuzov reaction in many cases.

▶ *Diethyl ethylphosphonate $(EtO)_2P(O)Et$ (from the acyl chloride)* (*257*). Triethyl phosphite (171 μl, 1 mmol) was added dropwise to a stirred solution of acetyl chloride (72 μl, 1 mmol) in CH_2Cl_2 (8 ml) in a 25-ml round-bottomed flask cooled in an ice bath. After 2 h, the solvent was removed, and benzoic acid (245 mg, 2 mmol) was added to the residue, followed by benzene (10 ml). The mixture was stirred to cause complete dissolution. Hydrazine (1.05 ml, 1.0 M in THF, 1.05 mmol) was added dropwise with rapid stirring. After 90 min, the reaction mixture was flash frozen and freeze dried. A mixture of *tert*-butanol (5 ml) and THF (5 ml) was added to the flask and stirred to dissolve the solid. Potassium *tert*-butoxide (5 ml, 0.6 M in 1:1 v/v *tert*-butanol—THF, 3 mmol) was then added to the stirring solution in one portion. After 6 h of stirring at room temperature, the reaction mixture was diluted with EtOAc (50 ml), quenched with 1 M hydrochloric acid (20 ml), washed with saturated $NaHCO_3$ (2 × 15 ml) and then with brine (15 ml), dried (Na_2SO_4), concentrated and purified by flash chromatography on silica, eluting with 85:15 dichloromethane—acetone, to give the product as a colourless liquid (97 mg, 58%). δ_P (121 MHz, $CDCl_3$) 33.6 ppm.

▶ *Diethyl 3-phenylpropyl-1-phosphonate $(EtO)_2P(O)(CH_2)_3Ph$ (from the carboxylic acid)* (*257*). 3-Phenylproprionic acid (150 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (10 ml) in a 25-ml round-bottomed flask cooled in an ice bath. Oxalyl chloride (100 μl, 1.2 mmol) was added in one portion with stirring and the mixture was allowed to warm to room temperature. After 12 h the solvent was removed and the residue was redissolved in dichloromethane (8 ml) and cooled using an ice bath. Triethyl phosphite (171 μl, 1 mmol) was then added dropwise to this chilled solution with stirring and the mixture was allowed to warm to room temperature. After 2 h stirring, the solvent was removed and benzoic acid (245 mg, 2 mmol), and then benzene (10 ml), was added to the residue. Hydrazone formation and reduction were carried out exactly as described in the previous recipe. Flash chromatography on silica gel, eluting with ethyl acetate, gave the product as a faint yellow liquid (177 mg, 69%). δ_P (121 MHz, $CDCl_3$) 32.0 ppm.

2.13.10 Reaction of dialkyl phosphorochloridates with Grignard reagents

The synthesis of disubstituted phosphonates from reactions of disubstituted phosphonochloridates and Grignard or organolithium reagents has been reviewed (*31*) and discussed in Section 2.13.2. An example is the reaction of diphenyl phosphorochloridate (**164**) with allylmagnesium bromide in ether to provide diphenyl allylphosphonate (**165**) in modest yield (Fig. 2.13.10.1) (*39*). Carbanions are not particularly good nucleophiles towards disubstituted phosphorochloridates and such reactions are only usually partially successful.

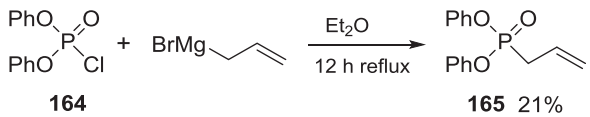
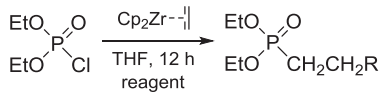


Figure 2.13.10.1

▶ *Diphenyl allylphosphonate* $(PhO)_2P(O)CH_2CH{=}CH_2$ (**165**) (*39*). Magnesium (2.4 g, 100 mmol) was placed in a dry three-necked flask equipped with a condenser and a dropping funnel. Anhydrous ether (75 ml) followed by a solution of allyl bromide (8.65 ml, 100 mmol) in ether (50 ml) was added. The mixture was heated for 1 h. A solution of diphenyl phosphorochloridate (26.9 g, 100 mmol) in ether (50 ml) was then introduced. The mixture was heated under reflux for 12 h. It was cooled and water (50 ml) was added. The organic layer was dried (Na_2SO_4), the ether was removed and the residue was distilled to give the product (5.75 g, 21%).

Diethyl phosphorochloridate can be converted into diethyl ethylphosphonate or diethyl 2-iodoethylphosphonate by treatment with the zirconocene—ethene complex generated from dicyclopentadienyl zirconium dichloride (Cp_2ZrCl_2) and two molar equivalents of ethylmagnesium bromide. The formed diethyl 2-zirconoethylphosphonate $(EtO)_2P(O)CH_2CH_2Zr(Cp)_2Cl$ is then quenched with hydrochloric acid or iodine (Fig. 2.13.10.2) (*258*).

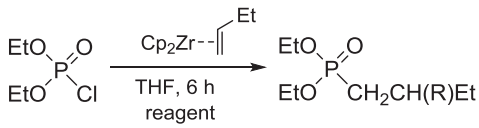


Dialkyl alkylphosphonates

Reagent	R	Yield (%)
HCl	H	63
I_2	I	60

Figure 2.13.10.2

The anion derived from the addition of diethyl phosphorochloridate to the zirconozene—butene complex $Cp_2Zr(CH_2{=}CHEt)$ can be quenched by hydrochloric acid, deuterium oxide, iodine or benzoyl chloride in the presence of copper(I) chloride, to give various diethyl alkylphosphonates (Fig. 2.13.10.3) (*258*). Maintaining the reaction mixture containing diethyl 2-zircono-*n*-butylphosphonate $(EtO)_2P(O)CH_2CH$ $[Zr(Cp)_2Cl]Et$ at room temperature for 24 h resulted in β-hydride



Dialkyl alkylphosphonates

Reagent	R	Yield (%)
3 M HCl	H	58
20% D_2O	D	57
I_2	I	51
PhCOCl, CuCl	COPh	55

Figure 2.13.10.3

abstraction and elimination of Cp_2ZrHCl and diethyl *H*-phosphonate, producing diethyl 2-butenylphosphonate (**166**) as a mixture of diastereomers (Fig. 2.13.10.4).

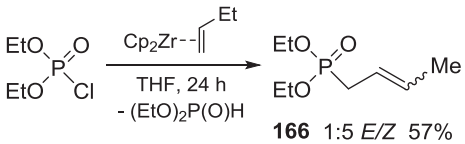


Figure 2.13.10.4

▶ *Diethyl ethylphosphonate $(EtO)_2P(O)Et$ (258)*. Diethyl 2-zirconoethylphosphonate (δ_P 34.7 ppm; 81 MHz, THF) was prepared in 89% yield as follows: diethyl phosphorochloridate (144.6 µl, 1.7 mmol) was added to a solution of $Cp_2Zr(CH_2{=}CH_2)$, generated from Cp_2ZrCl_2 (0.3 g, 1 mmol) and ethylmagnesium bromide (2.4 ml, 1 M in ether, 2.4 mmol), in THF (10 ml). The reaction mixture was kept at room temperature for 12 h and then quenched with 3 M hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated to reveal a light yellow liquid. Chromatography on silica gel, eluting with 2:1 ethyl acetate—petroleum ether, provided diethyl ethylphosphonate (104.6 mg, 63%). δ_P (81 MHz, THF) δ 34.7 ppm.

▶ *Diethyl 2-iodoethylphosphonate $(EtO)_2P(O)CH_2CH_2I$ (258)*. The reaction mixture containing diethyl 2-zirconoethylphosphonate described in the previous recipe was stirred and treated with iodine (305 mg, 1.2 equiv.). After 3 h the mixture was quenched with 3 M hydrochloric acid, stirred at room temperature for 1 h and then extracted with ethyl acetate. The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated to reveal a light brown liquid. Chromatography of this on silica gel, eluting with 2:1 ethyl acetate—petroleum ether, provided the product as a colourless liquid (175.2 mg, 60%). δ_P (81 MHz, THF) 27.0 ppm.

▶ *Diethyl n-butylphosphonate $(EtO)_2P(O)n\text{-}Bu$ (258)*. Diethyl 2-zircono-*n*-butylphosphonate (δ_P 36.8 ppm; 81 MHz, THF) was prepared by addition of diethyl phosphorochloridate (144.6 µl, 1 mmol) to a solution of $Cp_2Zr(CH_2{=}CHEt)$, generated by reaction of Cp_2ZrCl_2 (0.3 g, 1 mmol) with *n*-BuLi (1.5 ml, 1.6 M in hexane, 2.4 mmol), in THF (10 ml) at −78 °C. The reaction mixture was warmed to 0—5 °C, stirred at this temperature for 6 h, treated with 3 M hydrochloric acid, extracted with ethyl acetate and dried ($MgSO_4$). Removal of solvent and purification by chromatography on silica gel, eluting with 3:1 ethyl acetate—petroleum ether, afforded the product as a colourless liquid (113 mg, 58%). δ_P (81 MHz, $CDCl_3$) 33.5 ppm.

▶ *Diethyl 2-benzoyl-n-butylphosphonate $(EtO)_2P(O)CH_2CH(COPh)Et$ (258)*. The reaction mixture containing diethyl 2-zircono-*n*-butylphosphonate, as described in the previous recipe, was treated with CuCl (99 mg, 1.0 mmol) and benzoyl chloride (116 µl, 1.0 mmol) at room temperature. The mixture was stirred at 50 °C for 12 h, treated with 3 M HCl at room temperature, extracted with ethyl acetate and dried ($MgSO_4$). Removal of solvent and purification by chromatography on silica gel, eluting with 3:1 ethyl acetate—petroleum ether, yielded the product as a colourless solid (0.16 g, 55%). δ_P (81 MHz, $CDCl_3$) 31.5 ppm.

▶ *Diethyl 2-butenylphosphonate* $(EtO)_2P(O)CH_2CH{=}CHMe$ (**166**) (*258*). Diethyl 2-zircono-*n*-butylphosphonate (δ_P 38.6 ppm; 81 MHz, THF) was prepared as follows: diethyl phosphorochloridate (217 µl, 0.26 mmol) was added to a solution of $Cp_2Zr(CH_2{=}CHEt)$, generated by reaction of Cp_2ZrCl_2 (0.3 g, 1 mmol) with *n*-BuLi (1.5 ml, 1.6 M in hexane, 2.4 mmol), in THF (10 ml) at −78 °C. The mixture was warmed to room temperature, left for 12 h, treated with 3 M hydrochloric acid, extracted with ethyl acetate and dried ($MgSO_4$). Removal of solvent and purification by chromatography on silica gel, eluting with 2:1 ethyl acetate−petroleum ether, afforded the product as a colourless liquid (0.11 g, 57%, 1:5 *E*:*Z*). Major isomer δ_P (81 MHz, $CDCl_3$) δ 28.3 ppm.

2.13.11 Reaction of *N*-substituted alkylphosphonamidates with alcohols

Heating *N*,*O*-dialkyl methylphosphonamidates with 5 molar equivalents of an alcohol, or *bis*(*N*- or *N*,*N*-dialkyl)methylphosphonodiamidates with 2 molar equivalents of phenol provides disubstituted methylphosphonates (e.g. **167** → **168**, and **169** or **170** → **106**) (Fig. 2.13.11.1) (*259*). The ease of reaction and yield of product depend on the nature of the incoming alcohol and the outgoing amine.

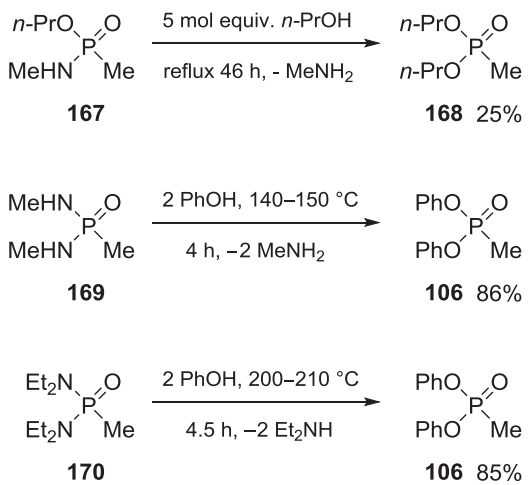


Figure 2.13.11.1

▶ *Di-n-propyl methylphosphonate* $(n\text{-}PrO)_2P(O)Me$ (**168**) (*259*). A mixture of *n*-propyl *N*,*P*-dimethylphosphonamidate (8.0 g, 53 mmol) and *n*-propanol (16.0 g, 267 mmol) was heated under reflux for 46 h. The excess *n*-propanol was removed and the residue was distilled to give a colourless liquid (2.4 g, 25%). Bp 93−96 °C/9 mmHg.

▶ *Diphenyl methylphosphonate* $(PhO)_2P(O)Me$ (**106**) (*259*). A mixture of *bis*(*N*-methyl) methylphosphorodiamidate (2.4 g, 20 mmol) and phenol (3.8 g, 40 mmol) was heated at 140−150 °C for 4 h. Distillation gave the product (4.3 g, 86%). Bp 120−130 °C/0.03 mmHg. Mp 33−35 °C. The

title compound was also prepared in 85% yield by heating *bis*(*N*,*N*-diethyl)methylphosphorodiamidate (1 mol) with phenol (2 mol) at 200–210 °C for 4.5 h.

2.13.12 Nucleophilic addition to dialkyl halovinylphosphonates

Dialkyl haloalkylphosphonates can be prepared by the action of an excess of the α,ω-dihaloalkane on the appropriate trialkyl phosphite (Arbuzov reaction). Esters of 2-haloalkylphosphonic acid lose hydrogen halide rapidly on treatment with triethylamine to give dialkyl α,β-alkenylphosphonates. These esters are somewhat less reactive than the dialkyl alkylphosphonates to certain electrophiles, phosgene having little or no action on them (*40*). Thionyl chloride gives the alkenylphosphonochloridate in poor yield; a considerable amount of pyroester is formed. Diethyl 2-bromoethylphosphonate (**93**) is readily converted into diethyl vinylphosphonate (**32**) upon treatment with triethylamine in benzene (Fig. 2.13.12.1) (*182*) or potassium hydroxide in absolute ethanol (not shown) (*260*). Diethyl 2-aminoethylphosphonates are prepared by nucleophilic substitution of the 2-bromoethylphosphonate by secondary amines (e.g. **150** or **171**) or Michael addition of primary amines to the vinylphosphonate (e.g. to yield **172** and **173**) (*261*). The latter derivatives are produced by heating for 2 h, followed by distillation under vacuum (**172** bp 127–144 °C/0.7 mmHg and **173** bp 105–107 °C/0.03 mmHg).

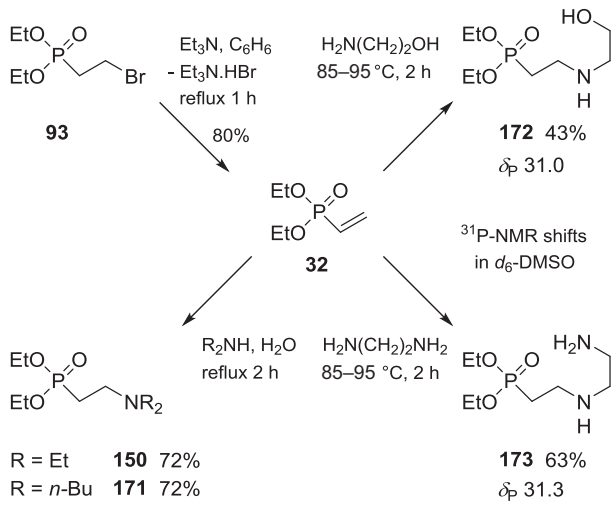


Figure 2.13.12.1

▶ *Diethyl vinylphosphonate* $(EtO)_2P(O)CH{=}CH_2$ (**32**) (*182*). A mixture of diethyl 2-bromoethylphosphonate (48.5 g, 198 mmol), triethylamine (22.0 g, 218 mmol) and benzene (70 ml) was heated under reflux for 1 h. After standing overnight, the triethylamine hydrobromide was filtered off, the benzene was distilled from the filtrate and the residue was fractionated under reduced pressure to give a colourless liquid (26.0 g, 80%). Bp 63 °C/2.5 mmHg.

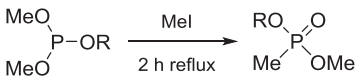
▶ *Diethyl vinylphosphonate* $(EtO)_2P(O)CH{=}CH_2$ (**32**) (*260*). Diethyl 2-bromoethylphosphonate (33.0 g, 0.13 mol) was added over 30 min to a stirred solution of potassium hydroxide (7.5 g, 0.13 mol) in absolute ethanol (250 ml) at 0–5 °C. The mixture was warmed to gentle reflux for 15 min, cooled and filtered. The precipitated potassium bromide was washed with absolute ethanol (50 ml) and the combined fractions were distilled to give a colourless mobile liquid (21.0 g, 95%). Bp 50 °C/1 mmHg. It decolourised permanganate instantly in the cold and was mildly polymerisable.

▶ *Diethyl 2-diethylaminoethylphosphonate* $(EtO)_2P(O)CH_2CH_2NEt_2$ (**150**) (*260*). Diethyl 2-bromoethylphosphonate (24.5 g, 0.1 mol) was added to diethylamine (25.0 g, 0.3 mol) in water (50 ml) and the mixture was refluxed for 2 h. After cooling, 20% *w/w* sodium hydroxide solution (50 ml) was added and the mixture was extracted with benzene (200 ml). Distillation of the organic layer gave a pale yellow liquid (17.0 g, 72%; bp 106–107 °C/3 mmHg) that formed a methiodide (mp 104–106 °C) on treatment with methyl iodide.

▶ *Diethyl 2-di-n-butylaminoethylphosphonate* $(EtO)_2P(O)CH_2CH_2N(n\text{-}Bu)_2$ (**171**) (*260*). Diethyl 2-bromoethylphosphonate (24.5 g, 0.1 mol) was refluxed for 4 h with di-*n*-butylamine (40.0 g, 0.3 mol) and water (50 ml). Isolation, as described in the previous recipe, gave the title compound as a pale yellow liquid (21.0 g, 72%). Bp 140–142 °C/3 mmHg.

2.13.13 Unsymmetrical dialkyl alkylphosphonates

Some examples of unsymmetrical dialkyl alkylphosphonates prepared by the Arbuzov reaction are discussed in Section 2.13.3.2. The Arbuzov reaction of dialkyl methyl phosphites can be used to prepare alkyl methyl methylphosphonates in 66–94% yield (*14*). The reactions employ a molar equivalent of methyl iodide without solvent; less than 1% of dimethyl methylphosphonate by-product is produced. The process works well for $(MeO)_2POR$ where R is *i*-Pr, *n*-Bu, *i*-Bu, *s*-Bu, pinacolyl, cyclopentyl or cyclohexyl, but poorly when it is *t*-Bu, due to decomposition during distillation (not shown) (Fig. 2.13.13.1).



Alkyl methyl methylphosphonates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)
i-Pr	66	21–22/0.2	29.7
n-Bu	94	55/1	31.1
i-Bu	88	45/0.04	31.6
s-Bu	86	50/0.025	29.5/29.8[a]
Pinacolyl	94	65/0.025	29.5/30.3[a]
Cyclopentyl	87	60/1	29.7
Cyclohexyl	84	45/0.2	29.6

NMR data measured in $CDCl_3$. a. Pair of diastereomers

Figure 2.13.13.1

Alternatively, alkyl alkylphosphonochloridates (e.g. **174**) can be treated with a sodium alkoxide to generate the unsymmetrical dialkyl alkylphosphonates (e.g **175** and **176**) (Fig. 2.13.13.2) (*262*). Alkyl alkylphosphonochloridates (e.g. **177**) also react with alcohols in acetone to provide symmetrical (e.g. **87**) or unsymmetrical dialkyl alkylphosphonates (e.g. **90**, **178** and **179**) (*224*). The rate of alcoholysis depends upon the nature of the alkyl alkylphosphonochloridate and the alcohol. The importance of steric hindrance is shown by a rapid decrease in rate of alcoholysis of ethyl methylphosphonochloridate (**177**) in the order MeOH > EtOH > *i*-PrOH > *t*-BuOH. The activation energy also decreases analogously, i.e. with increasing basicity, which is attributed to the increase in bond-forming energy. Note that this reaction is only useful synthetically for preparing acid-tolerant dialkyl alkylphosphonates. The absence of a base and the accumulation of hydrogen chloride as the reaction proceeds slows the nucleophilic substitution and acid-sensitive dialkyl alkylphosphonates can decompose. Thus, the reaction of ethyl methylphosphonochloridate with *tert*-butanol provides *tert*-butyl ethyl methylphosphonate, *t*-BuO(EtO)P(O)Me, which the hydrogen chloride liberated converts to ethyl hydrogen methylphosphonate EtO(HO)P(O)Me, with loss of *tert*-butyl chloride.

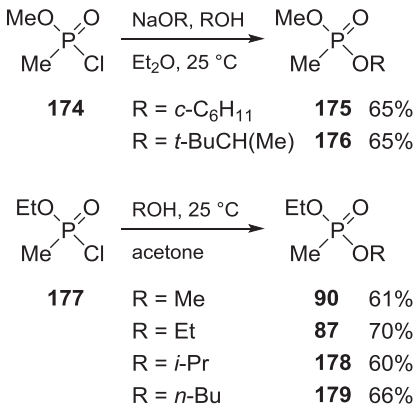


Figure 2.13.13.2

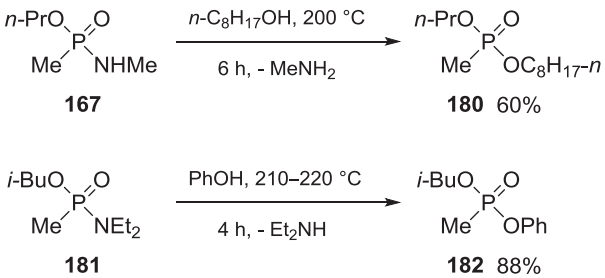


Figure 2.13.13.3

Unsymmetrical dialkyl alkylphosphonates can also be prepared by the alcoholysis of *O*-alkyl *N*-alkyl(or *N*,*N*-dialkyl) alkylphosphonamidates (*259*). Examples are the conversion of *n*-propyl *N*,*P*-dimethylphosphonamidate (**167**) to *n*-octyl *n*-propyl methylphosphonate (**180**) and isobutyl *N*,*N*-diethyl methylphosphonamidate (**181**) to isobutyl phenyl methylphosphonate (**182**) (Fig. 2.13.13.3). Unsymmetrical methylphosphonic diesters are able to react with various nucleophilic reagents (*263*).

▷ *Alkyl ethyl methylphosphonates EtO(RO)P(O)Me* (*224*). Ethyl methylphosphonochloridate (1.2 g, 8.4 mmol) was added to the appropriate alcohol (5 ml) in acetone (100 ml) and stirred for 24 h. Removal of the solvent and distillation of the residual liquid gave ethyl methyl methylphosphonate (**90**) (61%, bp 87–89 °C/20 mmHg), diethyl methylphosphonate (**87**) (70%, bp 92–94 °C/17 mmHg), ethyl isopropyl methylphosphonate (**178**) (60%, bp 90–92 °C/20 mmHg) and *n*-butyl ethyl methylphosphonate (**179**) (66%, bp 100–102 °C/20 mmHg). Ethyl methylphosphonochloridate and *tert*-butanol gave ethyl hydrogen methylphosphonate in 55% yield.

▷ *Cyclohexyl methyl methylphosphonate c-HexO(MeO)P(O)Me* (*262*). A solution of sodium cyclohexoxide (12.20 g, 0.1 mol) in dry ether (100 ml) was added to a stirred solution of methyl methylphosphonochloridate (12.85 g, 0.1 mol) in dry ether (50 ml). After addition the mixture was stirred for 2 h. Sodium chloride was filtered off, the filtrate concentrated and the residue distilled to give the title compound (12.48 g, 65%). Bp 113 °C/10 mmHg. The use of sodium pinacoloxide instead of sodium cyclohexoxide gave methyl pinacolyl methylphosphonate (65%). Bp 100–102 °C/18 mmHg.

▷ *Methyl pinacolyl methylphosphonate t-BuCH(Me)O(MeO)P(O)Me* (**176**) (*14*). The general procedure is illustrated for the synthesis of the title compound. Dimethyl pinacolyl phosphite (9.7 g, 0.05 mol) and methyl iodide (7.1 g, 0.05 mol) were placed into a 50-ml round-bottomed flask equipped with a condenser (fitted with a calcium chloride guard tube) and refluxed for 2 h. A portion of the reaction mixture was analysed by gas chromatography (GC)–mass spectrometry (MS) and shown to contain methyl pinacolyl methylphosphonate and a trace of dimethyl methylphosphonate. The methyl iodide was removed on a rotary evaporator. Bulb-to-bulb distillation of the residue under reduced pressure gave pure title compound as a colourless liquid (9.24 g, 94%). Bp 65 °C/0.025 mmHg. δ_P ($CDCl_3$) 29.5 and 30.3 ppm.

▷ *Isopropyl p-nitrophenyl methylphosphonate i-PrO(p-$O_2NC_6H_4O$)P(O)Me (not shown)* (*39*). Isopropyl methylphosphonochloridate (14 g, 89 mmol) was added to a stirred suspension of powdered anhydrous sodium *p*-nitrophenolate (15 g, 93 mmol) in dry benzene (30 ml). Heat was evolved but was insufficient to cause the benzene to boil. The mixture was stirred and refluxed for 1 h, cooled and filtered. The benzene was removed from the filtrate and the residue distilled at low pressure. After a small amount of forerun, the product was collected (14 g, 61%). Bp 122 °C/0.09 mmHg. There was some high-boiling residue. The title compound was almost insoluble in water. On adding it to a 20% *w*/*v* aqueous sodium hydroxide, no apparent reaction took place but on heating, a sudden spontaneous ebullition set in and it rapidly went into solution; on cooling and acidifying, *p*-nitrophenol was obtained. The d_3-methyl analogue of the title compound has been prepared by an analogous synthetic method in 86% yield (*126*).

▶ *n-Octyl n-propyl methylphosphonate n-PrO(n-C_8H_{17}O)P(O)Me* (**180**) (*259*). A stirred mixture of *n*-propyl *N,P*-dimethylphosphonamidate (4.16 g, 27.5 mmol) and *n*-octanol (3.58 g, 27.5 mmol) was heated at 200 °C for 6 h and then under vacuum at 100 °C for 1 h. Distillation of the residue gave the product (4.10 g, 60%). Bp 158–160 °C/2 mmHg.

▶ *Isobutyl phenyl methylphosphonate i-BuO(PhO)P(O)Me* (**182**) (*259*). A stirred mixture of isobutyl *N,N*-diethyl methylphosphonate (11.32 g, 54.7 mmol) and phenol (5.12 g, 54.5 mmol) was heated at 210–220 °C for 4 h, maintained under vacuum at 15–25 mmHg and then distilled to give a colourless liquid (11.00 g, 88%). Bp 130–140 °C/0.06 mmHg.

2.13.14 Cyclic derivatives from ring-closing metathesis of allyl allylphosphonates

Cyclic phosphonates such as (**183**) can be prepared by ring-closing metathesis of allyl-substituted allylphosphonates (*264*) using a first-generation Grubbs catalyst (*265*) (Fig. 2.13.14.1). Phosphinates are also accessible by this method (*266*).

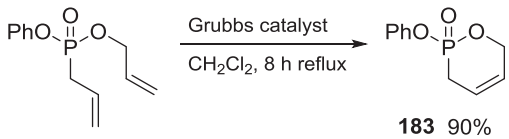


Figure 2.13.14.1

▶ *2-Phenoxy-3,6-dihydro-1,2-oxaphosphinine-2-oxide* (**183**) (*264*). First-generation Grubbs catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$ (45 mg, 3% mol) was added to a stirred solution of allyl phenyl allylphosphonate (300 mg, 1.26 mmol) in anhydrous dichloromethane (80 ml). The mixture was heated under reflux for 8 h, diluted with dichloromethane, flushed with air and stirred at room temperature for 12 h. Removal of solvent and flash chromatography, eluting with 2:1 hexane–ethyl acetate, gave the liquid product (240 mg, 90%).

2.14 DIALKYL ARYLPHOSPHONATES $ArP(O)(OR)_2$

Dialkyl arylphosphonates are important intermediates for bioactive compounds (*33*). General methods for their preparation rely on displacement of halogen from aryl halides (*267*) or an anionic phospho-Fries rearrangement (*35*). Oxidative phosphonylations of C–H bonds promoted by *t*-BuOOH (*268*) or $AgNO_3$ and $Na_2S_2O_8$ (*29*) have been reported. Dialkyl arylphosphonates are readily prepared by alcoholysis of arylphosphonic dichlorides with alcohols in the presence of suitable bases. One example is the reaction of phenylphosphonic dichloride (**20**) with 2 mol each of allyl alcohol and pyridine to provide diallyl phenylphosphonate (**184**) in good yield after distillation (Fig. 2.14.1) (*111*). Diallyl

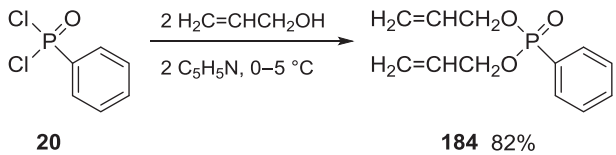


Figure 2.14.1

phenylphosphonate is a useful monomer for plastic production. Upon heating it under a nitrogen atmosphere in the presence of benzoyl peroxide catalyst it gradually becomes viscous and then suddenly changes into a gel. It may be converted by further heating into a strong, hard transparent solid (*269*). This resin is flame resistant and has a high refractive index. Diallyl phenylphosphonate also forms flame-resistant copolymers with vinyl acetate, methyl methacrylate and unsaturated polyesters.

▷ *Diallyl phenylphosphonate* $(CH_2{=}CHCH_2O)_2P(O)Ph$ (**184**) (*111*). Phenylphosphonic dichloride (780 g, 4 mol) was added dropwise over 6 h to a stirred mixture of allyl alcohol (464 g, 8 mol) and pyridine (632 g, 8 mol) contained in a 3-l three-necked flask equipped with a stirrer, a thermometer and a dropping funnel, cooled to 0–5 °C. After addition the mixture was allowed to warm to room temperature. Water (400 ml) was added and the oily layer was separated and distilled under reduced pressure (prolonged standing of the crude wet ester caused some hydrolysis). In effecting the distillation, it was necessary to raise the temperature slowly and during this process to maintain the pressure at ~20 mmHg up to 50 °C, at <10 mmHg from 50 to 100 °C, and at <5 mmHg up to 120 °C. Gaseous products were evolved in heating the crude ester to the distillation point which made it difficult to maintain the necessary low pressure. Heating of the material too rapidly at too high a pressure caused some decomposition and resulted in low product yields; in any event, it was essential to avoid heating the residue to a temperature much beyond 170 °C to avoid rapid decomposition. The distillation of the product was best carried out at 1–2 mmHg in the presence of a little copper resinate inhibitor. This gave the title compound in good yield (777 g, 82%). Bp 128 °C/1 mmHg. Pure diallyl phenylphosphonate is soluble in water to the extent of 2 g/l and in most of the common organic solvents. It readily absorbs carbon dioxide and is stable at room temperature with very little change over a period of more than a year.

The Arbuzov or Michaelis–Arbuzov reactions, which feature nucleophilic attack of a trialkyl phosphite or dialkyl phosphite anion on an alkyl or aryl halide, are probably the most important methods of P–C bond formation. However, since aromatic species are much less susceptible to nucleophilic substitution, this method can only be used in the synthesis of dialkyl arylphosphonates if the aromatic system is activated. The next sections describe the coupling of dialkyl *H*-phosphonates to activated aromatic systems by various methods. Many of these represent newer additions to the synthetic armamentarium.

2.14.1 Aluminium-catalysed coupling

One of the oldest methods of synthesis of disubstituted arylphosphonates involves a modified Friedel–Crafts reaction (*270,271*). Phosphorus trichloride is mixed with the appropriate aromatic hydrocarbon in the presence of aluminium trichloride. Removal of the excess phosphorus trichloride and addition of a polychlorinated hydrocarbon solvent and an alcohol in some cases provides the dialkyl arylphosphonate. However, the yields are usually unsatisfactory. The reaction using bromobenzene yields a mixture of diethyl phenylphosphonate (**185**) and diethyl 4-bromophenylphosphonate (**186**) that are separable by careful distillation (Fig. 2.14.1.1) (*272*). Dialkyl arylphosphonates undergo the usual types of electrophilic substitution reactions on the aromatic group. Nitration of diethyl

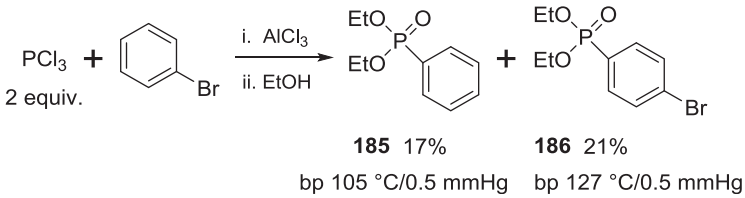
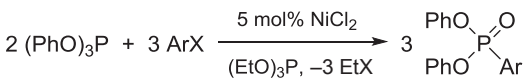


Figure 2.14.1.1

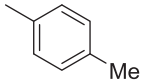
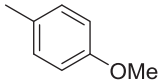
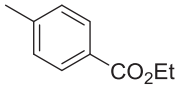
phenylphosphonate results in the formation of appreciable amounts of the 2-nitro isomer, along with the 3-nitro isomer (*273*).

2.14.2 Nickel-catalysed coupling

A convenient method has been developed to prepare diphenyl arylphosphonates from triphenyl phosphite, aromatic halides and triethyl phosphite (Fig. 2.14.2.1) (*274*). It relies on the triethyl phosphite-assisted Ni-catalysed Arbuzov reaction and can be used to synthesise a variety of phosphonates bearing a functionalised aromatic ring. Similarly, heating triethyl phosphite, iodobenzene and tetrakis(triethyl phosphite)nickel(0) catalyst (*275*) provides after distillation diethyl phenylphosphonate (**185**) in excellent yield (Fig. 2.14.2.2) (*276*).

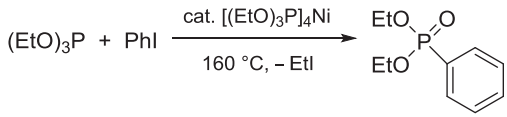


Diphenyl arylphosphonates

Ar	X	Temp. (°C)	Time (h)	Yield (%)[a]
	I	160	4.0	93
	Br	170	6.0	94
	Br	163	2.5	87
	Br	173	6.5	87

a. Isolated yield

Figure 2.14.2.1



185 94%

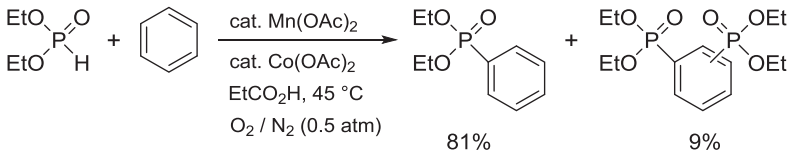
Figure 2.14.2.2

▷ *Tetrakis(triethyl phosphite)nickel(0) [(EtO)$_3$P]$_4$Ni* (*276*). A stirred light yellow mixture of nickel(II) chloride (5 g, 38.5 mmol) suspended in triethyl phosphite (60 ml, 350 mmol) was heated slowly. At 80 °C a heterogeneous black mixture resulted. A clear homogeneous solution was formed at 150 °C. After 1 h at reflux, the solution was cooled and the excess of phosphite was removed to give a white solid. The solid was triturated with acetonitrile, collected and washed with cold methanol to give white crystals (4.6 g, 17%). Mp 106–109 °C. The pure material is insoluble in water, slightly soluble in methanol and very soluble in most nonpolar organic solvents. Tetrakis(triethyl phosphite)nickel(0) is more stable with respect to decomposition than the corresponding trimethyl phosphite complex (*275*).

▷ *Diethyl phenylphosphonate (EtO)$_2$P(O)Ph* (**185**) (*276*). Triethyl phosphite (9.37 g, 56.4 mmol) was added in small portions (~5 drops) to a hot stirred mixture of tetrakis(triethyl phosphite)nickel(0) (10 mg) and iodobenzene (10.00 g, 49.0 mmol) at 160 °C. The solution became deep red upon each addition of a portion of phosphite. The colour faded rapidly to yellow, ethyl iodide was distilled into a cold trap and an exotherm was observed. After complete addition, GC–MS analysis indicated that less than 1% iodobenzene remained. Distillation of the residue provided a colourless liquid (9.88 g, 94%). Bp 97 °C/0.1 mmHg.

2.14.3 Manganese-catalysed coupling

Dialkyl *H*-phosphonates add to arenes under the influence of a Mn(OAc)$_2$/Co(OAc)$_2$/O$_2$ redox couple (Fig. 2.14.3.1) (*277*). The *H*-phosphonate is thought to undergo one-electron oxidation by Mn(III), generated *in situ* from Mn(II) by the action of Co(II) and O$_2$, to form phosponyl radicals that add to the arene. Mixtures of products are produced when the benzene ring is unsubstituted or substituted with one or more atoms or groups (e.g. Me, Cl, CF$_3$). The products are separable by column chromatography on silica gel. Dialkyl *H*-phosphonates and some mono- and disubstituted arenes react in the presence of manganese(III) acetate to afford dialkyl arylphosphonates in good yield (Fig. 2.14.3.2) (*278*). The regioselectivity of addition depends on the arene substituents – MeO, CN and CO$_2$Me are tolerated – and their disposition.



81% 9%

Figure 2.14.3.1

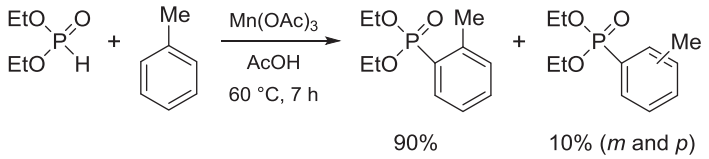


Figure 2.14.3.2

▶ *Diethyl phenylphosphonate (EtO)$_2$P(O)Ph* (277). Diethyl *H*-phosphonate (6 mmol) was added to $Mn(OAc)_2 \cdot 4H_2O$ (0.1 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (0.02 mmol) in benzene (2 mmol) and proprionic acid (1 ml) under nitrogen, in a two-necked flask equipped with a balloon filled with an appropriate concentration of oxygen (overall: O_2 0.5 atm/N_2 0.5 atm). The mixture was stirred at 45 °C for 5 h. Column chromatography (230–400 mesh silica gel), eluting with 1:1 hexane–ethyl acetate, gave the product (81%) and *bis*-substituted material (9%).

▶ *Diethyl o-tolylphosphonate* $(EtO)_2P(O)C_6H_4Me$-2 (278). To a solution of diethyl *H*-phosphonate (0.83 g, 6 mmol) and toluene (0.28 g, 3 mmol) in glacial acetic acid (10 ml) was added $Mn(OAc)_3 \cdot 2H_2O$ (2.41 g, 9 mmol). The mixture was heated at 60 °C for 7 h until the solution changed colour from brown to pale yellow. The mixture was cooled. Water (20 ml) was added and the mixture was extracted with ethyl acetate (3 × 20 ml). The combined organic layer was dried (Na_2SO_4), filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2:1 petroleum ether–acetone, gave the product (0.62 g, 90%).

2.14.4 Copper-catalysed coupling

Dialkyl *H*-phosphonates combine with arenes when heated in toluene in the presence of caesium carbonate and a catalyst formed from copper(I) iodide and either proline or homoproline (pipecolinic acid) (Fig. 2.14.4.1) (279). Iodoarenes react more efficiently than bromoarenes and Me, NO_2, Br or Cl substituents on the ring are tolerated.

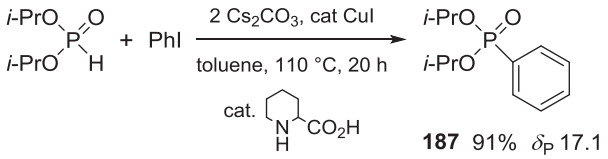
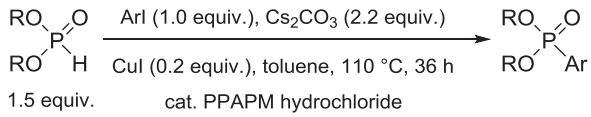
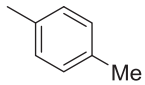
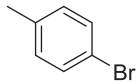
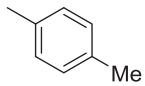
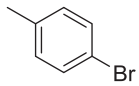


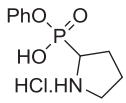
Figure 2.14.4.1

Coupling of dialkyl *H*-phosphonates to aryl iodides is accomplished in good yield using copper(I) iodide, caesium carbonate and pyrrolidine-2-phosphonic acid phenyl monoester (PPAPM) hydrochloride (Fig 2.14.4.2) (280). Addition of the PPAPM ligand increases greatly the reactivity of the copper catalyst but it must be synthesised beforehand (several steps), as to the author's knowledge it is not available commercially. Di-*n*-butyl *H*-phosphonate couples to aryl iodides when heated with a copper(I) iodide-*N*,*N*′-dimethylethylenediamine catalyst and caesium carbonate in toluene (Fig 2.14.4.3) (281).



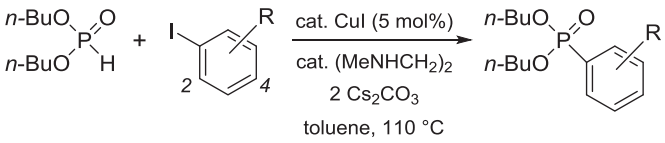
Dialkyl arylphosphonates

R	Ar	Yield (%)[a]	δ_P ($CDCl_3$)[b]
Et		75	16.6
Et		73	16.5
Et		78	16.7
i-Pr		73	17.1
i-Pr		77	16.6
i-Pr		81	17.3

PPAPM hydrochloride = 

a. Isolated yield
b. 121 MHz

Figure 2.14.4.2



R	*Yield (%)*
4-Me	88
2-MeO	85
2-NH_2	86

Figure 2.14.4.3

Primary amino groups on the starting aryl iodide do not need protecting. The yields of product are generally high.

▶ *Diisopropyl phenylphosphonate (i-PrO)$_2$P(O)Ph* (**187**) (279). Diisopropyl *H*-phosphonate (0.18 g, 1.1 mmol), iodobenzene (0.20 g, 1.0 mmol) and pipecolinic acid (0.05 g, 40 mol%) were added to a flask containing Cs_2CO_3 (0.65 g, 2.0 mmol) and toluene (3 ml). The mixture was stirred for 30 min at room temperature under nitrogen. CuI (0.02 g, 10 mol%) was added, the flask immersed in a heated oil bath and the contents stirred at 110 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with ether (10 ml), filtered and the filtrate concentrated. Column chromatography on silica gel, eluting with 4:1 hexane-$CHCl_3$ → 100% $CHCl_3$, gave the product (0.22 g, 91%). δ_P (121 MHz, $CDCl_3$) 17.1 ppm.

▶ *Dialkyl arylphosphonates (RO)$_2$P(O)Ar (general method)* (280). The dialkyl *H*-phosphonate (3 mmol), aryl halide (2 mmol) and PPAPM hydrochloride (104 mg, 0.4 mmol) were added to caesium carbonate (1432 mg, 4.4 mmol) in anhydrous toluene (3 ml). The mixture was stirred under nitrogen for 30 min at room temperature. Copper(I) iodide (76.4 mg, 0.4 mmol) was added. The flask was immersed in an oil bath and the mixture heated to 110 °C for 36 h. The mixture was allowed to cool to room temperature. It was diluted with diethyl ether (10 ml) and filtered. The filtrate was concentrated under vacuum. Purification of the residue by column chromatography on silica gel, eluting with 1:4 chloroform—hexane and then 100% chloroform, afforded the pure products whose structures are shown in Fig. 2.14.4.2.

▶ *Di-n-butyl (2-aminophenyl)phosphonate (n-BuO)$_2$P(O)C$_6$H$_4$NH$_2$-2* (281). An oven-dried Schlenk tube was evacuated and refilled with argon three times and then charged with CuI (10.8 mg, 0.056 mmol, 5 mol%) followed by anhydrous toluene (0.50 ml). *N,N′*-dimethylethylenediamine (35 µl, 0.337 mmol, 30 mol%) and di-*n*-butyl *H*-phosphonate (0.33 g, 1.69 mmol) were added under argon and the resulting light blue solution was stirred for 5—10 min. Then 2-iodoaniline (0.25 g, 1.12 mmol) and Cs_2CO_3 (725.7 mg, 2.24 mmol) were added at once followed by anhydrous toluene (1.75 ml). The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 110 °C for long enough for the halide to be completely consumed (the reaction progress was monitored by GC—MS). The resulting suspension was allowed to reach room temperature and was diluted with water (2 ml) and extracted with diethyl ether (4 × 4 ml). The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue on silica gel eluting with ethyl acetate—hexane provided the product (0.41 g, 86%). δ_P ($CDCl_3$) 22.5 ppm.

2.14.5 Palladium-catalysed coupling

The synthesis of dialkyl arylphosphonates by palladium-catalysed cross-coupling of dialkyl *H*-phosphonates with aromatic halides was first reported in the 1980s (282,283). Since then it has established itself as a mainstream method of P—C bond construction (284). Palladium-catalysed coupling of dialkyl *H*-phosphonates with aromatic bromides or iodides assisted by tetrakis(triphenylphosphine) palladium(0) catalyst and triethylamine was pioneered by Hirao and colleagues (282,283). Satisfactory yields of dialkyl arylphosphonates were obtained without solvent, although the high-cost of the 5 mol % $Pd(PPh_3)_4$ catalyst needed dissuaded against multigram syntheses, and attempts to reduce the

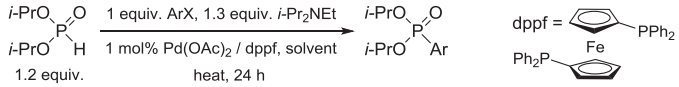
amount of catalyst resulted in lower yields (*285*). The quantity and type of catalyst, and the nature of the dialkyl *H*-phosphonate and tertiary amine, are critical to success. A greater amount of catalyst accelerates coupling, while the combination of the dialkyl *H*-phosphonate and tertiary amine determines the extent of degradation through the side reaction $(RO)_2P(O)R' + \text{Base-H} \rightarrow RO(HO)P(O)R' + \text{Base-R}$, where $R' = H$ (starting material) or Ar (product). The rate of dealkylation depends on the strength of the base and the structure of the R group (and decreases in the order primary > secondary > tertiary). Dialkyl *H*-phosphonates with secondary alkyl substituents, and the use of amines more hindered than triethylamine, are recommended for good yields of dialkyl arylphosphonates. Montchamp optimisation (*285*) of the Hirao method, using fivefold less palladium (1 mol% $Pd(OAc)_2$ complexed to 1,1′-*bis*(diphenylphosphino)ferrocene (dppf)), the base *N,N*-diisopropylethylamine and a solvent (MeCN or DMF), with heating for 24 h under nitrogen, enables an economical coupling of diisopropyl *H*-phosphonate with aromatic species bearing a halide (I, Br, Cl) or triflate (Tf) leaving group (Tables 2.14.5.1 and 2.14.5.2). Many of the mechanistic details of Pd(0)-catalysed phosphorus-carbon bond formation have been resolved (*286–291*). A microwave-assisted method is available (*292*).

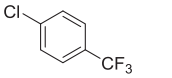
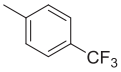
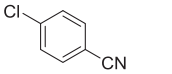
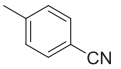
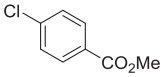
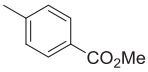
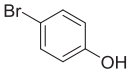
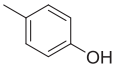
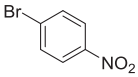
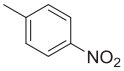
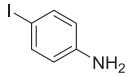
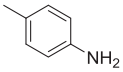
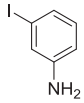
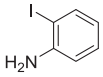
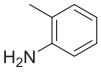
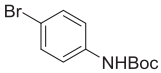
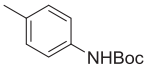
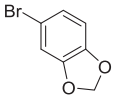
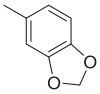
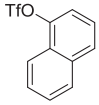
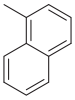
Diisopropyl (hetero)arylphosphonates (Tables 2.14.5.1 and 2.14.5.2) (*285*). Aromatic halide (4 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (0.9 ml, 5.2 mmol, 1.3 equiv.), $Pd(OAc)_2$ (0.01 g, 0.04 mmol, 1 mol%) and dppf (0.02 g, 0.044 mmol, 1.1 mol%) were added to a solution of diisopropyl *H*-phosphonate (0.8 g, 4.8 mmol, 1.2 equiv.) in MeCN or DMF (both previously dried over 4 Å molecular sieves; 15 ml). The solution was heated for 24 h at reflux (MeCN) or at 110 °C (DMF) under nitrogen. After cooling to room temperature the mixture was concentrated under vacuum. The residue was partitioned between deionised water and EtOAc, and the aqueous phase was extracted with EtOAc (3×). Organic fractions were combined and washed with brine (1×). Drying and concentration furnished the crude compound, which was purified by radial or column chromatography, eluting with ethyl acetate–hexane.

An efficient variant of the Pd(0) cross-coupling reaction is available for the synthesis of diethyl arylphosphonates bearing amino groups on the aromatic ring such as **188a–c** (Fig. 2.14.5.1) or alkylamino groups (not shown) (*289*). A microwave-assisted synthesis of dialkyl arylphosphonates from the dialkyl *H*-phosphonate, aryl bromide or iodide, $Pd(PPh_3)_4$ (5 mol%) and Cs_2CO_3 (1.2 equiv.) in THF, heated in a sealed tube to 120 °C for 10 min, has been developed (*292*). It allows rapid access to a broad spectrum of dialkyl arylphosphonates and is completely stereospecific. Diethyl 4-[(α,β,β-trifluorovinyl)oxy]phenylphosphonate (**189**), a monomer useful for preparing fluorinated plastics, can be prepared in modest yield by coupling diethyl *H*-phosphonate with 4-[(α,β,β-trifluorovinyl)oxy]bromobenzene in the presence of commercially-available tetrakis (triphenylphosphine)palladium(0) and triethylamine (Fig. 2.14.5.2) (*293*).

▶ *Diethyl 4-[(α,β,β-trifluorovinyl)oxy]phenylphosphonate* $(EtO)_2P(O)C_6H_4OCF{=}CF_2$-*4* (**189**) (*293*). Diethyl *H*-phosphonate (6.60 g, 48 mmol) and 4-[(α,β,β-trifluorovinyl)oxy]bromobenzene (10.80 g, 43 mmol) in anhydrous toluene (70 ml) were added to a two-necked round-bottomed flask equipped

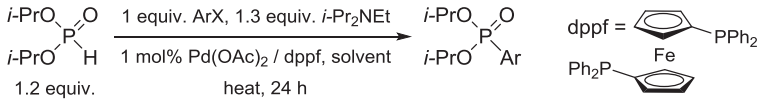
Table 2.14.5.1 Syntheses of some diisopropyl arylphosphonates *(285)*

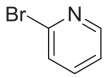
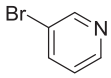
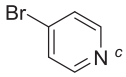
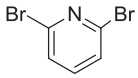
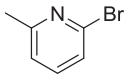
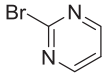
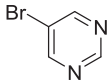
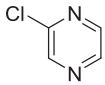
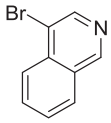
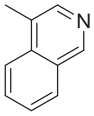


No.	Substrate	Conditions	Ar	Yield (%) [a]	δ_P (ppm) [b]
1		MeCN, reflux		93	17.6
2		DMF, 110 °C		22	16.5
3		DMF, 110 °C		57	14.2
4		DMF, 110 °C		44	14.7
5		DMF, 110 °C		76	19.9
6		DMF, 110 °C		60	13.9
7		MeCN, reflux		70	19.2
8		MeCN, reflux		72	18.5
9		DMF, 110 °C sealed tube		70	20.2
10		MeCN, reflux		82	18.1
11		MeCN, reflux		99	17.8
12		DMF, 110 °C sealed tube		86	17.8

a. Isolated yield of pure compound after chromatography on silica gel. *b*. 121.5 MHz, $CDCl_3$

Table 2.14.5.2 Syntheses of some diisopropyl heteroarylphosphonates (*285*)



No.	Substrate	Conditions	Ar	Yield (%) [a]	δ_P (ppm) [b]
1		MeCN, reflux		85	9.9
2		MeCN, reflux		61	14.6
3	 [c]	DMF, 110 °C		63	13.6
4		DMF, 110 °C		30	7.6
5		MeCN, reflux		67	4.7
6		MeCN, reflux		83	10.9
7		MeCN, reflux		97	7.7
8		DMF, 110 °C		46	19.3

a. Isolated yield after chromatography on silica gel. *b*. 121.5 MHz and $CDCl_3$ solvent
c. Hydrochloride salt used with 3 equiv. Et_3N instead of 1.3 equiv. *i*-Pr_2NEt

with a reflux condenser and a magnetic stirrer and flushed with nitrogen. Triethylamine (15 ml) and tetrakis(triphenylphosphine)palladium(0) (5.01 g, 4 mmol) were added. The reaction mixture was stirred under nitrogen, heated to 110 °C and maintained at this temperature for 72 h. The mixture was cooled to room temperature. Ethyl acetate was added and the solid was filtered off. The solvent was removed from the filtrate and the residue was distilled under vacuum to give a colourless liquid (4.27 g, 32%). Bp 110–115 °C/5 mmHg. δ_P (250 MHz, $CDCl_3$) 17.9 ppm.

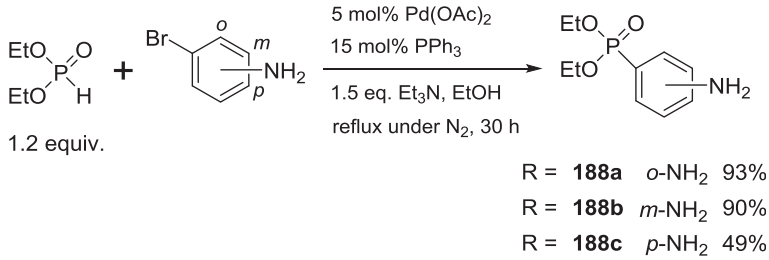


Figure 2.14.5.1

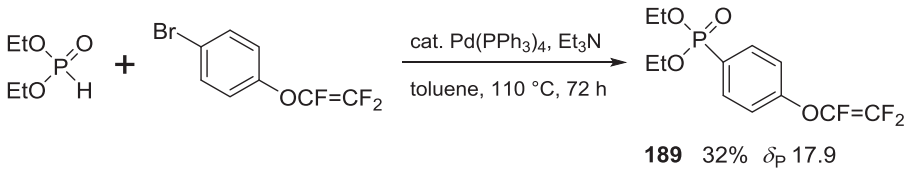


Figure 2.14.5.2

Dialkyl *H*-phosphonates and arylimidazole sulfonates, prepared from *N*,*N*′-sulfonyldiimidazole and phenols (*294*), couple when refluxed in 1,4-dioxane with palladium(II) acetate, 1,3-*bis*(diphenylphosphino)propane (dppp) and *N*,*N*-diisopropylethylamine (*295*) (Fig. 2.14.5.3). Arylimidazole sulfonates bearing alkyl, alkoxy, acetyl, chloro and phenyl substituents are compatible, and naphthylimidazole sulfonates give dialkyl naphthylphosphonates.

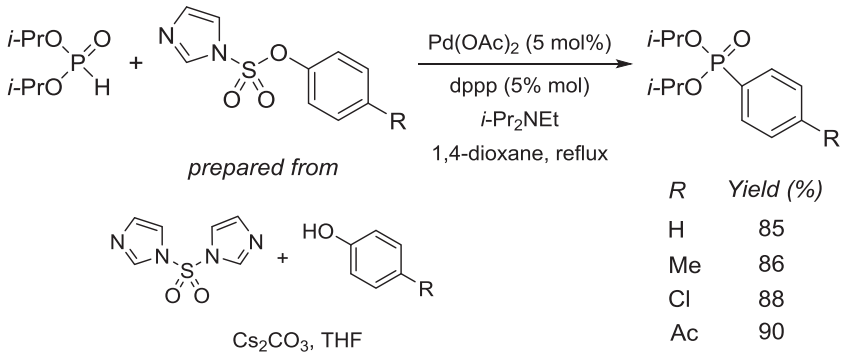


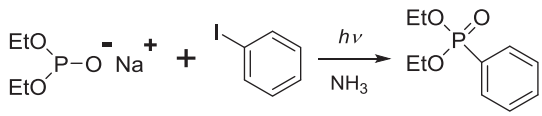
Figure 2.14.5.3

▶ *Diisopropyl 4-methylphenylphosphonate (i-PrO)₂P(O)C₆H₄Me-4* (*295*). A mixture of 4-methylphenol (1.00 g, 9.30 mmol), *N*,*N*′-sulfonyldiimidazole (3.69 g, 18.60 mmol) and caesium

carbonate (1.52 g, 4.65 mmol) in THF (100 ml) were stirred at room temperature for 16 h and sampled. Reaction was judged complete when a liquid chromatography peak area percentage of ≤5% of the starting 4-methylphenol remained. The mixture was concentrated, ethyl actetate was added, the mixture was cooled to 0 °C and saturated aqueous ammonium chloride was added. The layers were separated and the aqueous layer was washed twice with ethyl acetate. The combined organic extracts were washed with water and then brine, dried (Na_2SO_4) and concentrated onto Celite™. Flash chromatography of this on silica gel, eluting with 3:1 hexane—ethyl acetate, gave 4-methylphenylimidazole sulfonate as a colourless liquid (2.01 g, 91%) (*294*). A mixture of this (47.6 mg, 0.20 mmol), diethyl *H*-phosphonate (33.1 mg, 0.24 mmol), $Pd(OAc)_2$ (2.7 mg, 5 mol%), dppp (4.9 mg, 5 mol%), and *N,N*-diisopropylethylamine (51.6 mg, 0.40 mmol) in 1,4-dioxane (2 ml) was stirred and heated under reflux. After completion of the reaction as indicated by TLC, the mixture was diluted with ethyl acetate (10 ml), washed with saturated brine (2 × 10 ml) and dried (Na_2SO_4). Evaporation of the solvent followed by purification on silica gel provided the product (44 mg, 86%) (*295*).

2.14.6 Radical anion arylation

The sodium salt of diethyl *H*-phosphonate reacts with iodobenzene upon ultraviolet irradiation to give diethyl phenylphosphonate (**185**) in high yield (Fig. 2.14.6.1) (*296,297*). A disadvantage of the method is that a photochemical reactor is required, although it is possible to replace this by several conventional kitchen-type fluorescent lamps. The reaction is believed to occur by an S_RN1 mechanism that involves radical and radical ion intermediates (*298,299*).



185 83%

Figure 2.14.6.1

▶ *Diethyl phenylphosphonate (EtO)$_2$P(O)Ph* (**185**) (*300*). A 2-l three-necked round-bottomed flask was fitted with an ammonia condenser (an enlarged cold finger design with the inside of the finger used as a reservoir for dry ice and isopropanol) with an outlet protected with a soda lime drying tube, a dropping funnel, a nitrogen inlet and a magnetic stirrer. A slow stream of nitrogen was passed through the system and the condenser was charged with dry ice and isopropanol. The funnel was removed briefly, liquid ammonia (~1 l) was added from a commercial cylinder and the funnel was replaced. Shiny freshly cut sodium metal (11.8 g, 0.51 mol) was added, which coloured the mixture blue. Diethyl *H*-phosphonate (70.4 g, 0.51 mol) was added dropwise cautiously to the sodium in ammonia in the manner of a titration; the end point was signalled by a change from blue

to colourless (some white foam formed as the diethyl *H*-phosphonate was added. As water in the ammonia consumes some of the sodium, not quite all the diethyl *H*-phosphonate is required to reach the end point; excess diethyl *H*-phosphonate is deleterious). Iodobenzene (52.4 g, 0.26 mol; dried over molecular sieves) was added slowly, giving the solution a slightly yellowish tint. The dropping funnel was replaced by a stopper, the frost was wiped off the outside of the flask with a towel dampened with acetone and the whole system was mounted in a photochemical reactor (Rayonet Model RPR-100 Photochemical Reactor manufactured by the Southern New England Ultraviolet Company, Hamden, Connecticut 06514, equipped with 16 Cat. No. RPR-3500A fluorescent lamps (~24 W each) rated to emit maximally at 350 nm. Equally good yields were obtained with lamps rated to emit maximally at 300 nm. Alternatively, for reactions on a 0.05 mol scale, irradiation for 1 h with two circular kitchen-type fluorescent lamps mounted on either side of the flask to partially encircle it gave excellent yields of the desired product). *Caution! The lamps must be shielded to prevent exposure of the eyes or skin to harmful ultraviolet radiation.* The flask was irradiated for 1 h (the yield was not significantly improved by irradiating for 2 h), but every 20 min the lamps were turned off briefly while the exterior of the flask was freed of frost by spraying it, still mounted in the reactor, with isopropanol from a wash bottle. After irradiation, the flask was removed from the reactor, and solid ammonium nitrate (~50 g, 0.62 mol) was added with stirring to acidify the mixture. Diethyl ether (200 ml) was added, the nitrogen flow was stopped, the condenser was removed and the open flask was placed on a cork ring in the fume cupboard and allowed to stand overnight, to enable the ammonia to evaporate safely. The following day water (300 ml) and ether (300 ml) were added, the ether layer was separated, the water layer was extracted twice with ether and the combined ether extracts were dried (Na_2SO_4) (diethyl phenylphosphonate is appreciably soluble in water, thus excessive amounts of water should be avoided during workup). The solvent was removed and the residue was distilled under reduced pressure using a short Vigreux column to provide after a short forerun pure diethyl phenylphosphonate (46.0 g, 83%). Bp 73–74 °C/0.02 mmHg, 90–92 °C/0.1 mmHg.

2.14.7 Dialkyl pyridinylphosphonates $(RO)_2P(O)C_5H_4N$

The alkali metal salts of dialkyl *H*-phosphonates react with *N*-alkoxypyridinium salts to give, via addition–elimination, dialkyl 2-pyridinylphosphonates (e.g. **190**) in acceptable yield (Fig. 2.14.7.1) (*301*,*302*). They also react with 1-triphenylmethylpyridinium salts that lack α-substituents to generate similarly dialkyl 4-pyridinylphosphonates (**191**–**192**) (*303*,*304*). The synthesis of dialkyl heteroarylphosphonates, including dialkyl pyridinylphosphonates, by palladium-catalysed coupling of dialkyl *H*-phosphonates with heteroaryl bromides or chlorides is discussed in a previous section (Table 2.14.5.2) (*285*). A method for the preparation of diethyl 3-pyridinylphosphonate (**193**) based on such chemistry is provided in this section (*292*). The preparation of dinucleoside 2- and 4-pyridinylphosphonates has also been reported (*305*,*306*). Pyridinylphosphonic acids are also of biological interest (*307*).

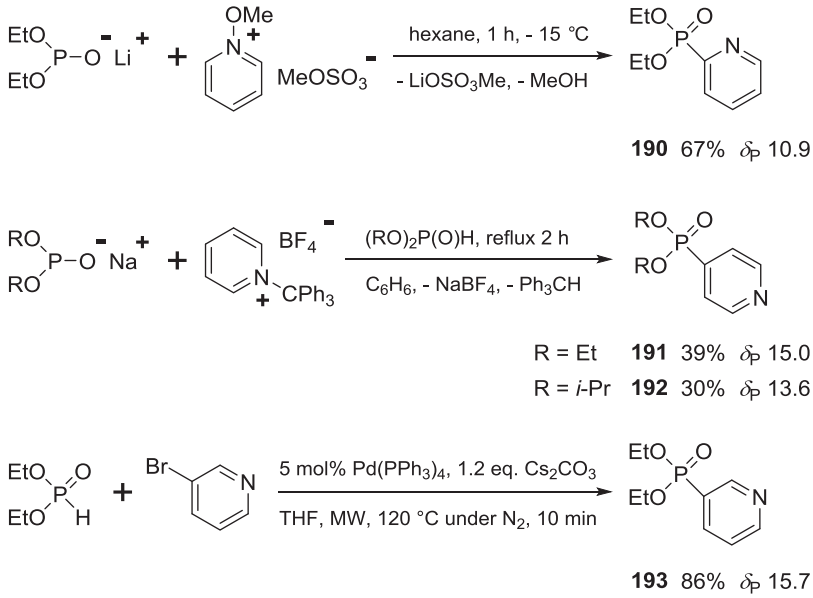


Figure 2.14.7.1

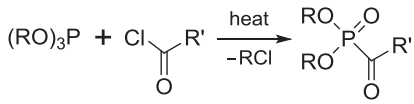
▶ *Diethyl 2-pyridinylphosphonate (EtO)$_2$P(O)C$_5$H$_4$N-2* (**190**) (*301*). *n*-Butyllithium (23% in hexane, 63 ml, 0.15 mol) was added dropwise over 2 h to stirred diethyl *H*-phosphonate (25.0 g, 0.18 mol) cooled to −20 to −30 °C. To the resulting diethyl lithium phosphite was added *N*-methoxypyridinium methyl sulfate [from pyridine *N*-oxide (14.3 g, 0.15 mol) and dimethyl sulfate (18.9 g, 0.15 mol)] in diethyl *H*-phosphonate (40 ml) over 1 h at −15 °C. After addition, the mixture was stirred at room temperature for 12 h and water (100 ml) was added. The mixture was extracted with chloroform (3 × 75 ml) and the organic extract was separated into neutral and basic fractions by extraction (4 M hydrochloric acid), basification and re-extraction with chloroform. The basic portion was distilled to give diethyl 2-pyridinylphosphonate (22.9 g, 67%). Bp 105–112 °C/0.08 mmHg. Redistillation gave an analytically pure sample (bp 96–97 °C/0.03 mmHg).

▶ *Diisopropyl 4-pyridinylphosphonate (i-PrO)$_2$P(O)C$_5$H$_4$N-4* (**192**) (*303*). Pyridine (10 ml) was added to a stirred solution of triphenylcarbenium tetrafluoroborate (19.0 g, 58 mmol) in dichloromethane (250 ml) with cooling. After standing at 5 °C overnight, the resulting crystals of triphenylmethylpyridinium tetrafluoroborate were collected by filtration (13.6 g). To a suspension of these crystals in benzene (130 ml) was added a solution of diisopropyl sodium phosphite (35 mmol) in diisopropyl *H*-phosphonate (14 ml) over 45 min at 5–10 °C. The mixture was heated under reflux for 2 h and allowed to cool. Water (50 ml) was added and the organic phase was separated and extracted with 3 M hydrochloric acid to recover the basic portion. Distillation of the crude base yielded pyridine and diisopropyl 4-pyridinylphosphonate (2.5 g, 30%; bp 104–105 °C/0.4 mmHg) which solidified on standing. Recrystallisation from hexane gave the pure product. Mp 45–46 °C.

▶ *Diethyl 3-pyridinylphosphonate (i-PrO)$_2$P(O)C$_5$H$_4$N-3* (**193**) (*292*). Pd(PPh$_3$)$_4$ (72 mg, 0.06 mmol, 5 mol%), Cs$_2$CO$_3$ (489 mg, 1.50 mmol) and 3-bromopyridine (0.21 g, 1.38 mmol) were placed in a microwave tube. The tube was sealed with a lid and filled with nitrogen gas, by applying three cycles of vacuum, and then nitrogen. THF (5 ml) and diethyl *H*-phosphonate (0.17 g, 1.25 mmol) were added successively through the septum. The tube was heated in the microwave oven (SmithCreator single-mode microwave cavity — Personal Chemistry AB, Uppsala, Sweden — producing a continuous irradiation of 300 W at 2450 MHz) for 10 min at 120 °C. After cooling, the solids were filtered off and washed with dichloromethane. The combined filtrate and washings were evaporated. The residue was purified by column chromatography on silica gel, eluting with 95:5 dichloromethane—methanol, to give the title compound (0.26 g, 86%). δ_P (162 MHz, CDCl$_3$) 15.7 ppm.

2.15 DIALKYL α-KETOPHOSPHONATES (RO)$_2$P(O)C(O)R′

Lower trialkyl phosphites undergo the Arbuzov reaction with acetyl chloride or benzoyl chloride with ease to provide dialkyl α-ketophosphonates (Fig. 2.15.1) (*308*). The reaction appears to follow the classic mechanism: the phosphonium salt intermediate decomposes instantly to the α-ketophosphonate and alkyl halide. When methylsulfonyl chloride is used in place of acetyl chloride, the reaction occurs with explosive violence. The reaction of triethyl phosphite with ethyl chloroformate gives diethyl ethoxycarbonylphosphonate (Fig. 2.15.1, last entry) (*308*).



Dialkyl alpha-ketophosphonates

R	R'	Yield (%)	bp (°C/mmHg)
Et	Me	88	100–103/8
Et	Et	80	99–100/7
Et	Ph	90	127–130/4
i-Pr	Me	72	115–117/20
i-Pr	Et	78	121–124/20
i-Pr	Ph	34	133–135/3
Et	OEt	91	72–74/2

Figure 2.15.1

The lower trialkyl phosphites react with benzoyl chlorides exothermically and the reactions proceed rapidly at room temperature to give homogeneous solutions. The alkyl halides formed usually distil from the reaction flask or can be removed by a nitrogen current (employed to ensure anhydrous conditions).

Distillation under reduced pressure is sometimes only partially successful in providing pure specimens of dialkyl benzoylphosphonates, as some decomposition can occur on heating to leave polymeric tars. Allyl-substituted phosphorus compounds are prone to polymerisation. To prevent this during their synthesis it is advisable to add a small amount of a polymerisation inhibitor such as hydroquinone. The Arbuzov reaction can also be applied to the synthesis of dialkyl α-ketophosphonates bearing unsaturated side chains, such as dimethyl (*E*)-but-2-enoylphosphonate (**194**) or diallyl acetylphosphonate (**195**) (Fig. 2.15.2) (*128*,*309*).

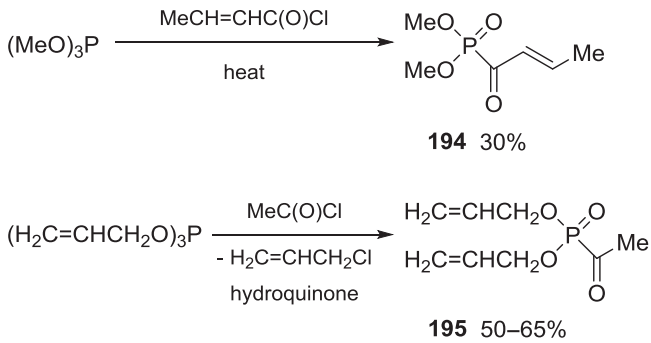


Figure 2.15.2

Oxidation of dialkyl α-hydroxyphosphonates often gives the corresponding dialkyl α-ketophosphonates (e.g. **196**) in acceptable yields (Fig. 2.15.3). Potassium permanganate is a convenient oxidising agent for this purpose (*310*). Manganese dioxide or chromium trioxide also effect the transformation.

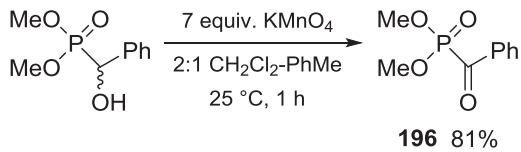


Figure 2.15.3

Dialkyl acetylphosphonates show quite different reactivity to dialkyl benzoylphosphonates. While diethyl acetylphosphonate is water soluble and hydrolyses with great ease to give diethyl hydrogen phosphate and acetaldehyde, diethyl benzoylphosphonate is insoluble in water and hydrolyses relatively slowly, the products being diethyl *H*-phosphonate and benzoic acid (Fig. 2.15.4). Furthermore, on treatment with ammonia, diethyl benzoylphosphonate gives benzamide ($PhCONH_2$) (*39*). The lower dialkyl benzoylphosphonates are pale yellow, high-boiling viscous liquids that are extremely moisture sensitive (*311*).

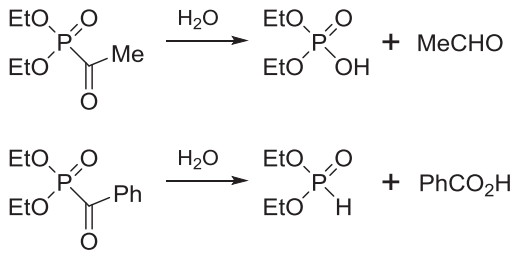


Figure 2.15.4

Dialkyl α-ketophosphonates undergo interesting transformations courtesy of their carbonyl group (Fig. 2.15.5). Dialkyl benzoylphosphonates (**197**) react with caesium fluoride and cyanotrimethylsilane to generate an acyl anion that undergoes phosphonate—phosphate rearrangement prior to addition of ketones, providing high yields of dialkyl alkyl phosphates (**198**) (*312*). They react with *N*-methylindole in the presence of indium triflate to furnish *bis*(indolyl)methylphosphonates (**199**) (*313*), enter into a Darzens reaction with α-haloketones in the presence of caesium carbonate to give epoxyphosphonates (**200**) (*314*) and undergo Wittig-type olefination with ethyl diazoacetate,

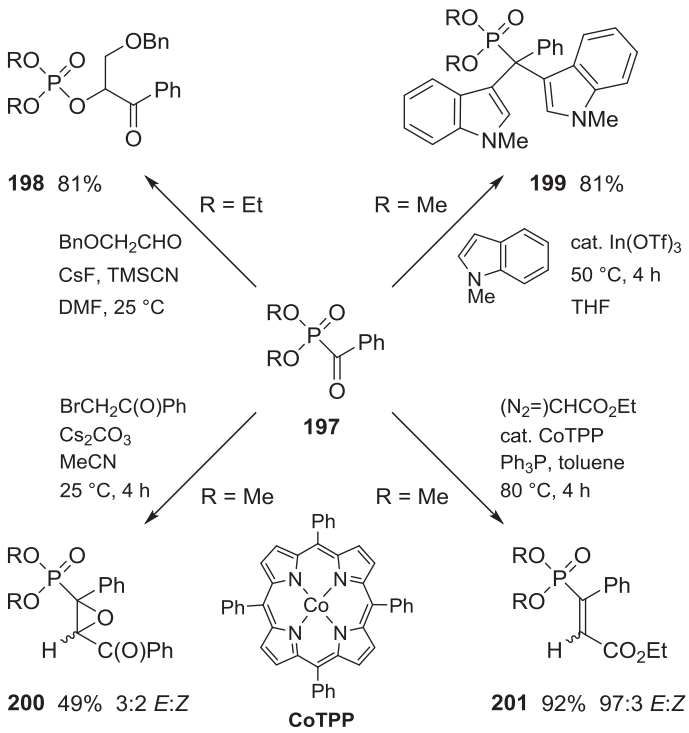


Figure 2.15.5

cobalt(II) tetraphenylporphyrin catalyst (CoTPP) and triphenylphosphine to provide vinylphosphonates (**201**) often with high *E*:*Z* selectivities (*315*).

▶ *Diethyl acetylphosphonate* $(EtO)_2P(O)C(O)Me$ (*39*). Acetyl chloride (22.1 g, 20 ml, 0.28 mol) was added dropwise to triethyl phosphite (46.5 g, 48 ml, 0.28 mol) in a flask fitted with a dropping funnel, sealed stirrer and reflux condenser. Considerable heat was evolved during the reaction, the temperature of the mixture reaching 100 °C. On fractionation, diethyl acetylphosphonate was obtained (28 g, 56%; bp 71 °C/1.2 mmHg). Refractionation gave a pure specimen (bp 69 °C/1 mmHg). A yellowish involatile residue remained. Diethyl acetylphosphonate is rapidly hydrolysed by dilute aqueous alkali, producing acetaldehyde.

▶ *Diisopropyl acetylphosphonate* $(i\text{-}PrO)_2P(O)C(O)Me$ (*309*). Triisopropyl phosphite (208 g, 1.0 mol) was added to acetyl chloride (86 g, 1.1 mol) at −10 °C. The mixture was allowed to reach room temperature and was distilled to yield a liquid (129–150 g, 62–72%). Bp 56 °C/0.1 mmHg.

▶ *Diallyl acetylphosphonate* $(CH_2{=}CHCH_2O)_2P(O)C(O)Me$ (*128*). Triallyl phosphite (103 g, 0.5 mol) containing hydroquinone (1 g, 9 mmol) was added dropwise to acetyl chloride (40 g, 0.5 mol) in a flask cooled at −10 °C in an ice–salt bath, with gentle stirring to ensure mixing. The mixture was allowed to attain room temperature within 30 min – there was no necessity to heat the mixture at this stage, as prolonged heating affects the yield adversely – and volatile matter was removed by rotary evaporation. The residue, after degassing, gave a distillation forerun (2–8 g) followed by a fraction of bp 70–78 °C/0.25 mmHg and considerable residue. Redistillation of the main fraction gave pure diallyl acetylphosphonate (50–67 g, 50–65% yield). Bp 71 °C/0.25 mmHg. This is a typical example of the preparation of a dialkyl α-ketophosphonate by the Arbuzov reaction employing an acyl halide. When phosphites of saturated alcohols are used in the reaction, yields of the ketophosphonate are better (65–80%) and the presence of hydroquinone is unnecessary.

▶ *Dimethyl benzoylphosphonate* $(MeO)_2P(O)C(O)Ph$ (*311*). Trimethyl phosphite (4.96 g, 0.04 mol) was added with stirring to benzoyl chloride (4.22 g, 0.03 mol) under nitrogen at such a rate that the temperature of the reaction mixture did not exceed 35 °C. The mixture was yellow and methyl chloride was rapidly evolved during the exothermic reaction. Distillation gave the title compound (5.2 g, 81%). Bp 146 °C/2.5 mmHg.

▶ *Diethyl benzoylphosphonate* $(EtO)_2P(O)C(O)Ph$ (*39*). Benzoyl chloride (39.4 g, 32.5 ml, 0.28 mol) was added dropwise to triethyl phosphite (46.5 g, 48.0 ml, 0.28 mol) in a flask fitted with a dropping funnel, sealed stirrer and reflux condenser. Considerable heat was evolved during the reaction, the temperature of the mixture rising during addition. Fractionation gave diethyl benzoylphosphonate as a pale, golden somewhat viscous liquid (47.4 g, 70%; bp 129–131 °C/0.7 mmHg), sparingly soluble in water and dilute aqueous alkali. It is slowly hydrolysed on boiling with water and alkali to give benzoic acid. On treatment with ammonia (d 0.880 g/ml), it gives benzamide (mp 127 °C) not altered on admixture with an authentic specimen. A similar protocol (*235*) where triethyl phosphite (16.6 g, 0.1 mol) was added over 45 min to benzoyl chloride (14.1 g, 0.1 mol) at 0 °C,

followed by addition of triethyl phosphite (49.8 g, 0.3 mol) at 0 °C, then heating to 100 °C for 2 h, followed by distillation, gave diethyl benzoylphosphonate (18.6 g, 77%). Bp 105–108 °C/0.1 mmHg.

▶ *Di-n-butyl benzoylphosphonate (n-BuO)$_2$P(O)C(O)Ph* (*309*). Tri-*n*-butyl phosphite (250 g, 1.0 mol) was added to benzoyl chloride (155 g, 1.1 mol) at −10 °C. The mixture was allowed to reach room temperature and was distilled to yield a liquid (194 g, 65%). Bp 160–164 °C/0.1 mmHg.

▶ *3-(Benzyloxy)-1-oxo-1-phenylpropan-2-yl diethyl phosphate* (**198**) (*312*). A mixture of diethyl benzoylphosphonate (242 mg, 1.0 mmol), benzyloxyacetaldehyde (165 mg, 1.1 mmol), caesium fluoride (30 mg, 0.2 mmol), cyanotrimethylsilane (30 mg, 0.3 mmol) and DMF (2 ml) was stirred for 5–10 min at room temperature. The solvent was removed by rotary evaporation. Flash chromatography of the residue on silica gel, eluting with 3:1 ether–petroleum ether, gave a colourless liquid (318 mg, 81%). δ_P (161 MHz, $CDCl_3$) −2.3 ppm.

▶ *Dimethyl bis(1-methyl-1H-indol-3-yl)(phenyl)methylphosphonate* (**199**) (*313*). Dimethyl benzoylphosphonate (214 mg, 1.0 mmol) was added to a solution of indium(III) trifluoromethanesulfonate (56 mg, 0.1 mmol) in THF (5 ml) under argon at room temperature. The mixture was stirred for 5 min and 1-methylindole (288 mg, 2.2 mmol) was added. The resulting mixture was heated at 50 °C for 4 h whereupon the benzoylphosphonate had been consumed, as indicated by TLC. The mixture was cooled to room temperature, diluted with ether (30 ml), washed with saturated aqueous sodium bicarbonate (3 × 10 ml), dried ($MgSO_4$) and the solvent removed. Purification of the residue by flash chromatography on silica gel, eluting with 4:1 ethyl acetate–hexane, gave orange needles (371 mg, 81%). R_f 0.43 (ethyl acetate). Mp 222–223 °C.

▶ *Dimethyl 3-benzoyl-2-phenyloxiran-2-ylphosphonate* (**200**) (*314*). Dimethyl benzoylphosphonate (214 mg, 1.0 mmol) was added to a stirred mixture of α-bromoacetophenone (239 mg, 1.2 mmol) and caesium carbonate (489 mg, 1.5 mmol) in anhydrous acetonitrile (5 ml) under argon at room temperature. The mixture was stirred for 4 h whereupon the benzoylphosphonate had been consumed, as indicated by TLC. Water (5 ml) was added and the mixture extracted by ethyl acetate (3 × 10 ml), the organic layers combined, dried ($MgSO_4$) and the solvent removed. Purification of the residue by flash chromatography on silica gel, eluting with 5:1 ether–petroleum ether, gave the title compound as the (*E*)-isomer (white solid; 100 mg, 30%; mp 125 °C) (δ_P (161 MHz, $CDCl_3$) 16.1 ppm) and (*Z*)-isomer (white solid; 64 mg, 19%; mp 120–122 °C) (δ_P (161 MHz, $CDCl_3$) 16.6 ppm).

▶ *Ethyl (E)-3-(dimethoxyphosphinyl)-3-phenyl-2-propenoate* (**201**) (*315*). The cobalt(II) tetraphenylporphyrin catalyst (CoTPP) was prepared from tetraphenylporphyrin and an excess of anhydrous cobalt(II) chloride in the presence of 2,6-lutidine (2 mol equiv.) in boiling DMF, followed by recrystallisation from acetonitrile–dichloromethane (*316*). Dimethyl benzoylphosphonate (214 mg, 1.0 mmol) followed by ethyl diazoacetate (137 mg, 1.2 mmol) were added in single portions to a stirred mixture of CoTPP (25 mg, 40 μmol) and triphenylphosphine (314 mg, 1.2 mmol) in anhydrous toluene (2 ml) under argon in a Schlenk tube. The mixture was heated to 80 °C for 4 h whereupon the benzoylphosphonate had been consumed, as indicated by TLC. Addition of diethyl ether (15 ml) prompted the precipitation of triphenylphosphine oxide. The liquid phase was

decanted and volatile components removed by rotary evaporation. Column chromatography of the residue on silica gel, eluting with 1:1 dichloromethane—ethyl acetate, gave a pale yellow liquid (260 mg, 92%). R_f 0.47. δ_P (161 MHz, $CDCl_3$) 17.0 ppm. The minor (*Z*)-diastereoisomer had a δ_P value of 15.3 ppm.

2.16 DIALKYL α-HYDROXYPHOSPHONATES $(RO)_2P(O)CH(OH)R'$ (PUDOVIK REACTION)

The Pudovik reaction, celebrating the Russian chemist Arkady Pudovik, was discovered in the 1940s—1950s and describes the addition of dialkyl *H*-phosphonates to C═C, C═N, C═O or other double bonds, usually under basic conditions (*317*) (Fig. 2.16.1). If the two substituents R^3 and R^4 at the reactive end of the double bond differ, then an asymmetric centre next to the phosphorus atom forms. The early development of the reaction took place at the A. E. Arbuzov Institute of Organic and Physical Chemistry in Kazan, the capital city of the Republic of Tatarstan, Russia.

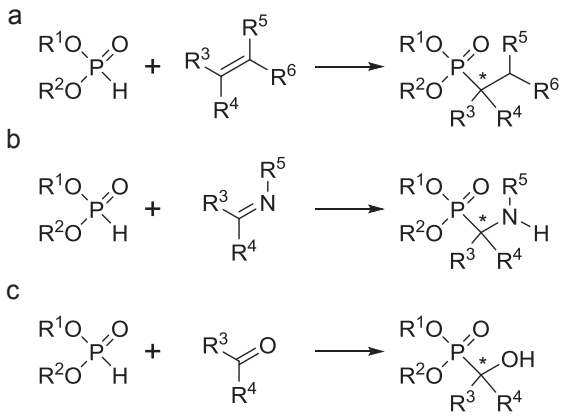


Figure 2.16.1 Dialkyl *H*-phosphonates undergo the Pudovik reaction with alkenes, imines or aldehydes or ketones to give respectively: (a) dialkyl alkylphosphonates, (b) dialkyl α-aminoalkylphosphonates and (c) dialkyl α-hydroxyalkylphosphonates. When R^3 and R^4 are different groups, a chiral centre denoted by an asterisk forms.

The Pudovik reaction is a modified Michaelis—Becker reaction: dialkyl phosphite alkali metal salts were often employed as the phosphorus reagent in the pioneering studies. Now it is common to use a stoichiometric amount of a strong base such as an alkoxide or amine instead. When the alkene, imine, aldehyde or ketone are activated by one or more electron-withdrawing groups, e.g. CF_3 (*318*) or CCl_3 (*319*), the dialkyl *H*-phosphonate often adds across the double bond with great facility, and addition of a base is often unnecessary. These types of reactions are typified by those leading to the CF_3- and CCl_3-containing phosphonates (**202**) and (**203**) (Fig. 2.16.2).

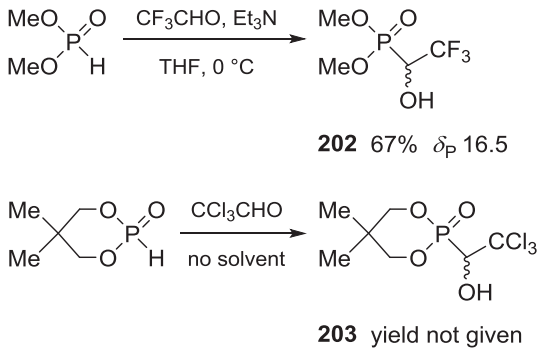


Figure 2.16.2

The choice of solvent is dictated by the choice of base and with liquid dialkyl *H*-phosphonates there is no need to add one. The products of dialkyl *H*-phosphonate addition to amines (α-aminophosphonates) are discussed later in connection with the related Kabachnik—Fields reaction (Section 2.18). The kinetics and mechanism of the Pudovik reaction have been reviewed (*320*). The reaction can be catalysed by ytterbium(III) trifluoromethanesulfonate (*321*) and different activation methods for ionic and radical Pudovik reactions have been compared (*322*).

The Pudovik reaction of diethyl *H*-phosphonate with paraformaldehyde occurs at elevated temperatures to give diethyl hydroxymethylphosphonate (**204**) (*323*) (Fig. 2.16.3). This reagent undergoes many of the transformations expected of a primary alcohol. Especially useful is its conversion to tetrahydropyranyl ester (**205**), a handy reagent for the Wittig—Horner synthesis of enol ethers, which are intermediates in one-carbon homologations of carbonyl compounds (*324*). The hydroxy group of α-hydroxyphosphonates behaves like that of a typical alcohol and can be

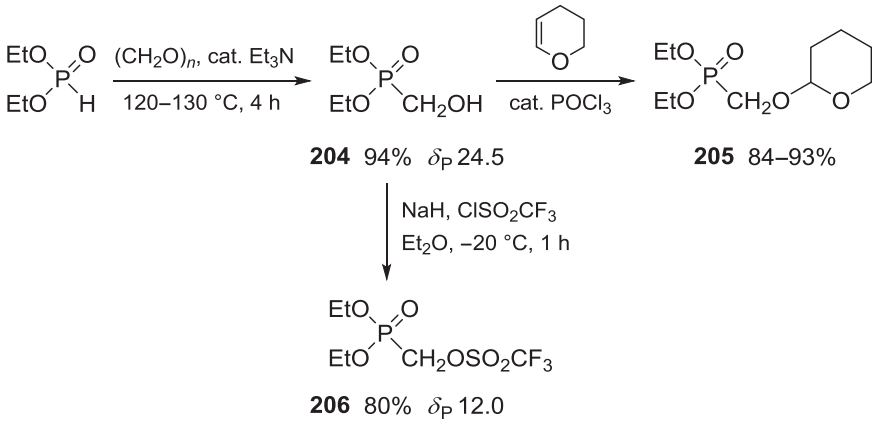


Figure 2.16.3

transformed into other groups, e.g. the azide group through the Mitsunobu reaction (*325*) or a fluorine atom from treatment with diethylaminosulfur trifluoride (*326*). Diethyl hydroxymethylphosphonate (**204**) is readily converted into diethyl phosphonomethyltriflate (**206**) which reacts with a variety of nucleophiles with loss of triflic acid to provide other α-functionalised derivatives (*327*).

Reaction of lower dialkyl *H*-phosphonates with aliphatic or aromatic aldehydes occurs upon mixing and absorption onto alumina (*328*) or upon treatment with sodium ethoxide (*329*). A comparison of the synthesis of dialkyl α-hydroxy-4-nitrobenzylphosphonates (**207**) and (**208**) appears in Fig. 2.16.4. The two methods work well with benzaldehydes having many different types of ring substituents (e.g. alkyl, alkoxy, cyano, halogen).

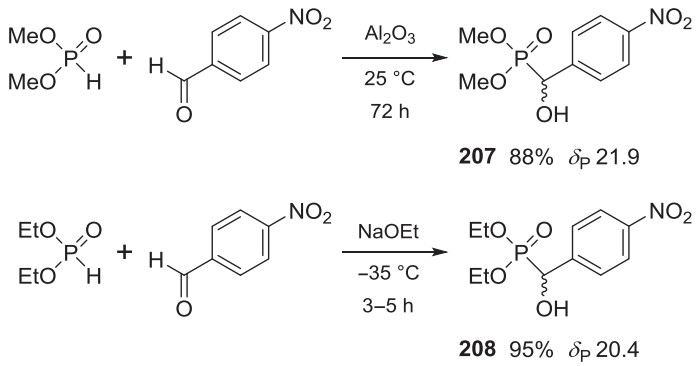


Figure 2.16.4

High yields of the addition products of diethyl *H*-phosphonate and aryl halides have also been realised using MoO_2Cl_2 catalysis (*330*). The stereoselective synthesis of dialkyl α-hydroxyphosphonate enantiomers attracts interest because of the many useful biological properties of such compounds (e.g. as bone resorption inhibitors and anti-hypercalcaemia drugs, Chapter 1, Fig. 1.8.8) and has been reviewed (*331*,*332*). Highly enantioselective hydrophosphonylations of aldehydes catalysed by chiral aluminium(III) complexes (*333*,*334*) or phosphonium salts (*335*) have been reported.

Dialkyl acyl- and aroylphosphonates also add trimethyl-, triethyl- and triethynylaluminium reagents across the carbonyl double bond to give after careful hydrolysis tertiary α-hydroxyalkylphosphonates (e.g. **209**) (*336*) (Fig. 2.16.5). Some dialkyl acyl- and aroylphosphonates can also add organolithium or Grignard reagents across the carbonyl group to give after hydrolysis dialkyl α-alkoxyalkylphosphonates (*308*). Diethyl benzoylphosphonate, for example, reacts with methyl- or phenylmagnesium bromide to give, respectively, diethyl 1-hydroxy-1-phenylethylphosphonate (**210a**) or diethyl 1,1-diphenyl-1-hydroxymethylphosphonate (**210b**) (Fig. 2.16.5). The corresponding organolithium reagents MeLi and PhLi instead of Grignard reagents give none of the required dialkyl α-hydroxyphosphonates in this instance.

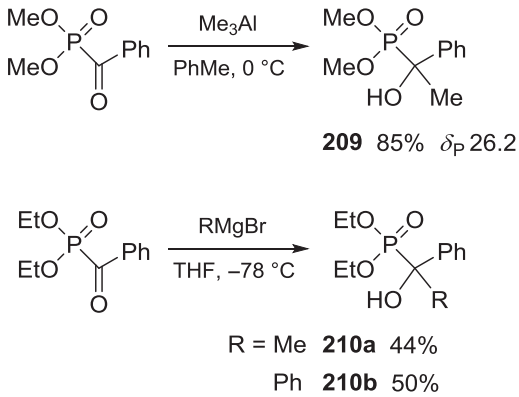
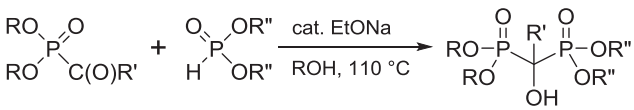


Figure 2.16.5

Dialkyl α-ketophosphonates also add sodium dialkyl phosphites to produce symmetrical 1,1-*bis*(dialkylphosphono)alcohols (Fig. 2.16.6) (*309*). When preparing unsymmetrical products, it is best to employ as solvent a small quantity of alcohol having the same alkyl group as the sodium dialkyl phosphite to reduce the chance of transesterification. Addition of the two phosphorus components is exothermic and the amount of heat generated depends on the nature of the alkyl groups; ethyl esters react more rapidly than the diisopropyl esters, presumably mainly for steric reasons.



R	R'	R"	Yield (%) [a]	Bp (°C/mmHg)
Me	Me	Me	30	126–128/0.07
Et	Me	Et	67	125/0.06
Allyl	Me	Allyl	55	137/0.15
i-Pr	Me	*i*-Pr	63	115/0.06
n-Bu	Me	*n*-Bu	72	159/0.12
Me	Me	Et	35	124–128/0.07
Et	Me	*i*-Pr	40	124–129/0.1
Et	Me	*n*-Bu	35	130/0.05
Me	Ph	Me	-	undistillable
Et	Ph	Et	72	149/0.07

a. Yield before distillation which lowered the isolated yield.

Figure 2.16.6

▶ *Dimethyl 1-hydroxy-2,2,2-trifluoroethylphosphonate* $(MeO)_2P(O)CH(OH)CF_3$ (**202**) (*318*). Trifluoroacetaldehyde hydrate (5.0 g, 43.1 mmol) was added dropwise to a stirred mixture of phosphorus pentoxide (2.2 g, 15.5 mmol) and concentrated sulfuric acid (8 ml) heated to 95 °C. The gaseous trifluoroacetaldehyde formed was bubbled into a stirred mixture of dimethyl *H*-phosphonate (2.2 g, 20 mmol), triethylamine (1.0 g, 10 mmol) and anhydrous THF (20 ml) at 0 °C. After addition the mixture was warmed to 70 °C and stirred for 30 min. Distillation under reduced pressure (~130 °C/2 mmHg) gave the title compound (2.8 g, 67%). Mp 53 °C. δ_P ($CDCl_3$) 16.5 ppm.

▶ *2,2-Dimethyl-1,3-propanediol cyclic 2,2,2-trichloro-1-hydroxyethylphosphonate* (**203**) (*319*). 2,2-Dimethyl-1,3-propanediol cyclic *H*-phosphonate (15.0 g, 0.1 mol) and chloral (14.7 g, 0.1 mol) were mixed with stirring. Although the flask was cooled in an ice bath, the temperature of the reaction mixture rose to 120 °C, and at this temperature the system solidified to a white solid. A small sample of this material was recrystallised from ethanol to obtain the title compound as transparent square platelets (yield not stated, mp 209–210 °C) that were insoluble in benzene, chloroform, cyclohexane and water.

▶ *Diethyl hydroxymethylphosphonate* $(EtO)_2P(O)CH_2OH$ (**204**) (*323*). Diethyl *H*-phosphonate (69.0 g, 64.4 ml, 0.5 mol), paraformaldehyde (15.0 g, 0.5 mol) and triethylamine (5.1 g, 0.05 mol) were added to a 250-ml round-bottomed flask equipped with a magnetic stirrer bar and an efficient reflux condenser. The flask was immersed in an oil bath preheated to 100–120 °C, the temperature was increased to 120–130 °C and the mixture was stirred at this temperature for 4 h. The stirrer bar was retrieved, the flask transferred to a rotary evaporator and triethylamine removed (bath temperature ~80 °C at ~15 mmHg). Bulb-to-bulb distillation of the residue gave the title compound (41.4–54.9 g, 49–65%). Bp 125 °C/0.05 mmHg. Attempted isolation of this compound by the standard vacuum technique resulted in significant decomposition. A Kugelrohr apparatus allowed the isolation to be achieved at a lower temperature, resulting in a higher yield. Experiments on four times the scale and distillation using a molecular still (wall temperature 110–120 °C at 0.1 mmHg) gave 84–94% yields. The product had a retention factor (R_f) of ~0.1 and ~0.3 by TLC on silica plates eluting with ethyl acetate or 19:1 dichloromethane–methanol, respectively (visualisation with 1.5% phosphomolybdic acid spray, then heating).

▶ *Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate* (**205**) (*323*). Phosphorus oxychloride (20 drops) was added with swirling to a mixture of diethyl hydroxymethylphosphonate (33.63 g, 0.2 mol), dihydropyran (21.00 g, 0.25 mol) and diethyl ether (150 ml) in a stoppered flask. The reaction was monitored by TLC after 3 h by adding five drops of the mixture to a mixture of 20 drops of diethyl ether and 1 drop of triethylamine (the product had an R_f of ~0.4 eluting with ethyl acetate). If TLC indicated the presence of diethyl hydroxymethylphosphonate, additional dihydropyran (5 g) and $POCl_3$ (10 drops) was added, and the reaction checked for completeness after a further hour, after which the mixture was worked up. The mixture was diluted with diethyl ether, transferred to a separating funnel and shaken successively with saturated aqueous $NaHCO_3$, water (100 ml) and saturated brine (100 ml). The ether layer was dried ($MgSO_4$), filtered and the solvent removed from the filtrate by rotary evaporation. Bulb-to-bulb distillation of the residue gave the title compound (42.4–46.9 g, 84–93%). Bp 110 °C/0.05 mmHg. Experiments on up to nine times the scale could be conducted with only a small reduction in yield. Distillation using a molecular still (wall temperature at 105–115 °C at 0.1 mmHg) gave 81–83% yields.

▷ *Dialkyl 1-hydroxyalkyl(or aryl)phosphonates* $(RO)_2P(O)CH(OH)R$ (e.g. **207**) *(alumina support method)* (*328*). Basic aluminium oxide (40 g, chromatography grade) was added gradually to a stirred mixture of dialkyl *H*-phosphonate (0.1 mol) and the appropriate carbonyl compound (0.1 mol) at room temperature. The reactants were completely absorbed by the alumina. After 72 h the product was extracted with dichloromethane (2 × 200 ml) and the combined extracts were rotary-evaporated to give the crude product, which was purified by distillation under reduced pressure (0.05 mmHg) or by recrystallisation from cyclohexane. This method is general purpose and works well for dimethyl *H*-phosphonate and a range of different aldehydes, e.g. to give dimethyl α-hydroxy-4-nitrobenzylphosphonate, which was isolated as an off-white crystalline solid (88%). Mp 101 °C. δ_P (101 MHz, $CDCl_3$) 21.9 ppm.

▷ *Diethyl 1-hydroxy-p-nitrobenzylphosphonate* $(EtO)_2P(O)CH(OH)C_6H_4NO_2$*-p* (**208**) *(sodium ethoxide method)* (*329*). Diethyl *H*-phosphonate (1.05 ml, 7.60 mmol) was added by syringe to a stirred solution of sodium ethoxide (0.77 g, 11.25 mmol) in dichloromethane (10 ml) at −35 °C under argon. The mixture was stirred for 30 min and a solution of 4-nitrobenzaldehyde (1.00 g, 6.62 mmol) in dichloromethane (5 ml) was added. The mixture was stirred for 3–5 h and then quenched with 0.1 M HCl and the resulting solution was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and the solvent removed. Flash column chromatography of the residue on silica gel gave a white solid (1.81 g, 95%). Mp 86–88 °C. δ_P (162 MHz, $CDCl_3$) 20.4 ppm (*330*).

▷ *Dimethyl 1-hydroxy-1-phenylethylphosphonate* $(MeO)_2P(O)C(Me)(OH)Ph$ (**209**) *(addition of trimethylaluminium)* (*336*). A 2 M solution of trimethylaluminium in heptane (3 mol equiv.) was added dropwise to a stirred 0.5 M solution of dimethyl benzoylphosphonate in anhydrous toluene (1 M equiv.) at 0 °C under argon. After addition the mixture was stirred for 10 min at 0 °C and then cautiously hydrolysed with water (exothermic and accompanied by gas evolution). The mixture was filtered through Celite™ and washed with ethyl acetate. The solvent was removed. Chromatography of the residue on silica gel, eluting with ethyl acetate, gave a white crystalline solid (85%). Mp 142–143 °C. δ_P (161 MHz, $CDCl_3$) 26.2 ppm.

▷ *Diethyl 1-hydroxy-1-phenylethylphosphonate* $(EtO)_2P(O)C(Me)(OH)Ph$ (**210a**) *(addition of methylmagnesium bromide)* (*308*). A solution of methylmagnesium bromide (0.39 g, 3.3 mmol) in THF (10 ml) was added gradually by syringe to a stirred solution of diethyl benzoylphosphonate (0.73 g, 3.0 mmol) in THF (10 ml) at −78 °C and stirred for 10 min. The reaction was quenched by adding saturated aqueous NH_4Cl (5 ml) and the resulting mixture poured into aqueous NH_4Cl (100 ml) and extracted with dichloromethane (2 × 100 ml). The combined organic layer was washed with brine (100 ml), dried (Na_2SO_4) and concentrated. Chromatography of the residue, eluting with hexane–ethyl acetate, gave after recrystallisation from benzene–hexane the title compound as white crystals (0.34 g, 44%). Mp 74–75 °C. An analogous procedure starting with phenylmagnesium bromide, with recrystallisation from chloroform–hexane, gave diethyl 1,1-diphenyl-1-hydroxymethylphosphonate as white crystals (50%). Mp 115–117 °C.

▷ *1,1-Bis-(dialkylphosphono)ethanols* $[(RO)_2P(O)]_2CR'OH$ (*309*). To a mixture of dialkyl acetylphosphonate (0.25 mol) and dialkyl *H*-phosphonate (0.30 mol) was added sodium (0.01 mol) dissolved in

the minimum quantity of alcohol having the same alkyl group as that of the dialkyl *H*-phosphonate. The temperature of the mixture rose spontaneously by 20–60 °C and was maintained about 50 °C higher than the maximum initially attained for 2–4 h. The exotherm was governed by the nature of the alkyl groups; the diisopropyl esters reacted more sluggishly than the ethyl esters under equivalent conditions. Volatile matter was removed and the residue was separated into two main fractions by distillation at low pressure. Redistillation of the higher boiling fraction afforded the pure tetraester alcohol in adequate yields (Fig. 2.16.6). The method is illustrated by the preparation of 1,1-*bis* (diisopropylphosphono)ethanol (*128*): To a mixture of diisopropyl acetylphosphonate (52 g, 0.25 mol) and diisopropyl *H*-phosphonate (50 g, 0.30 mol) sodium (0.05 g, 2.18 mmol) dissolved in isopropanol (3 ml) was added. The temperature of the mixture rose from 27 to 55 °C during 5 min. The mixture was heated to 100–110 °C for 4 h and allowed to cool, after which volatile matter was removed at the water pump. Distillation of the residue afforded a first fraction (29.3 g; bp 44–100 °C/0.1–0.2 mmHg), a second fraction (63.6 g, 63% crude yield; bp 100–140 °C/0.1–0.2 mmHg (bulk at 124–126 °C/0.15 mmHg) accompanied by slight decomposition) and a residue (10.7 g). Redistillation of the second fraction afforded pure 1,1-*bis*(diisopropylphosphono)ethanol (48.5 g, 52%). Bp 114–116 °C/0.06 mmHg.

2.17 DIALKYL α-SILOXYPHOSPHONATES $(RO)_2P(O)CH(OSiMe_3)R'$ (ABRAMOV REACTION)

The Abramov reaction named after the Russian chemist V. S. Abramov involves the addition of a trialkyl phosphite to an aldehyde, ketone or imine, followed by alkyl group transfer (analogous to the second step of the Arbuzov reaction). The original Abramov reaction involved heating a trialkyl phosphite with an aldehyde to yield a dialkyl α-alkoxyphosphonate. The first step of the mechanism consists of reversible nucleophilic addition of the trialkyl phosphite to the aldehyde carbonyl group to give a tetrahedral intermediate (**211**) (Fig. 2.17.1). Under mild conditions reversion to the starting materials is faster than conversion to the target (**212**). High temperature and pressure forces the conversion. Intramolecular transfer of the R group is a disfavoured 5-*endo*-*tet* process (Baldwin's rules) and when conversion does occur, alkyl transfer is intermolecular. The Abramov reaction is only useful once this problem is addressed;

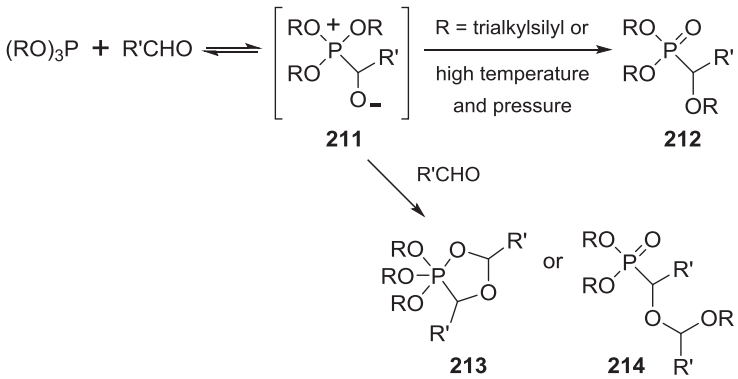


Figure 2.17.1

silyl groups offer the best solution, as transferable esters or trapping reagents, and provide dialkyl α-siloxyphosphonates (**212**), which can be hydrolysed usually under mild conditions to dialkyl α-hydroxyphosphonates (these can also be accessed through the Pudovik reaction). If two molar equivalents of an aldehyde are employed the tetrahedral intermediate can react further to give the cyclic phosphorane (**213**) or linear product (**214**).

The reaction of a trialkyl phosphite, an aldehyde and chlorotrimethylsilane (TMSCl) to prepare dialkyl 1-(trimethylsilyloxy)alkylphosphonates is readily conducted in the absence of a solvent without the need for protection from atmospheric moisture (Fig. 2.17.2) (*337*).

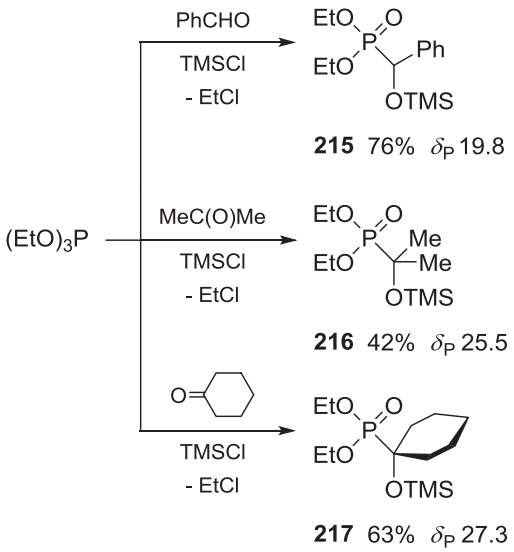
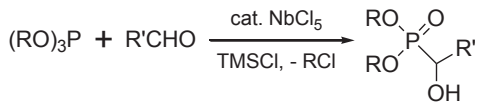


Figure 2.17.2

Formation of the product (e.g. **215**) is accomplished by the production of an alkyl chloride, which is easily removed, and the pure product is obtained after vacuum distillation. The optimum conditions comprise gradual addition of the carbonyl compound to a stirred mixture of the trialkyl phosphite and TMSCl with external cooling. After addition, moderate heating ensures completion. Aldehydes generally react faster than ketones, although methyl ketones and cycloketones react smoothly (e.g. to give **216** and **217**). Benzaldehydes substituted on the ring with alkyl, alkoxy, halogen and nitro groups are among those that give products that are easily isolated. This strategy is more straightforward than the alternative approach that involves the reaction of carbonyl compounds with dialkyl trialkylsilyl phosphites, which are less available than trialkyl phosphites, and much more sensitive to hydrolysis.

The Abramov reaction of a trialkyl phosphite, aldehyde and TMSCl can be catalysed by niobium(V) chloride (*338*) (Fig. 2.17.3). In this case even sterically hindered aldehydes react smoothly. The corresponding reactions with ketones under the same conditions proceed less easily. Triethyl phosphite reacts with methyl ethyl ketone, cyclohexanone and acetophenone to give the



R	R'	Yield (%)
Me	*n*-Pr	88
Me	*i*-Pr	88
Me	*t*-Bu	93
Me	*c*-hexyl	93
Me	Ph	92
Et	Ph	94

Figure 2.17.3

corresponding diethyl α-hydroxyphosphonates in 84%, 59% and 44% yield, respectively (not shown), and benzophenone does not react. In successful experiments, the silylated phosphonate derivatives are presumably hydrolysed on aqueous workup to furnish the α-hydroxyphosphonate products. Enantioselective routes to dialkyl α-hydroxyphosphonates are of interest. Chiral phosphine oxides (Lewis bases) catalyse the silicon-chloride-mediated Abramov reaction (not shown) (*339*). In specific cases moderate enantioselectivities can be achieved.

▶ *Diethyl 1-(trimethylsilyloxy)benzylphosphonate* $(EtO)_2P(O)CH(OTMS)Ph$ (**215**) (*337*). Benzaldehyde (5.3 g, 50 mmol) was added dropwise to a stirred mixture of triethyl phosphite (8.4 g, 50 mmol) and TMSCl (5.4 g, 50 mmol) at 0–5 °C. After addition the mixture was stirred at room temperature for 10 min and then heated to 50 °C for 5 h. Volatile material was removed by rotary evaporation. Distillation of the residue under reduced pressure gave the title compound as a colourless liquid (12.0 g, 76%). Bp 135–138 °C/2 mmHg. δ_P 19.8 ppm.

▶ *Diethyl 1-hydroxy-1-benzylphosphonate* $(EtO)_2P(O)CH(OH)Ph$ *(niobium pentachloride catalysis)* (*338*). Niobium(V) chloride (1 mg, 0.05 mol%) and TMSCl (0.54 g, 5 mmol) were added to a stirred mixture of triethyl phosphite (0.83 g, 5 mmol) and benzaldehyde (0.53 g, 5 mmol). After addition the mixture was stirred for 20 min and dichloromethane (15 ml) was added. The organic layer was washed with water (15 ml), saturated aqueous sodium bicarbonate (15 ml) and then brine (15 ml). The organic layer was dried ($MgSO_4$) and filtered. Removal of the solvent from the filtrate gave a white solid (1.15 g, 94%). Mp 76–78 °C.

2.18 DIALKYL α-AMINOPHOSPHONATES $(RO)_2P(O)CR_2NR_2$ (KABACHNIK–FIELDS REACTION)

Dialkyl α-aminophosphonates are conveniently accessed by various methods (*340*). Condensation of a dialkyl *H*-phosphonate with a carbonyl compound (aldehyde or ketone) and ammonia or an amine (primary or secondary) is one of the most convenient (Fig. 2.18.1). This three-component process, the

Figure 2.18.1

Kabachnik–Fields reaction, is named after the two chemists who discovered it independently in 1952, Martin I. Kabacknik and Ellis K. Fields (*341*).

2.18.1 Biography

Martin Izrailevich Kabachnik (1908–1997). Martin Izrailevich Kabachnik graduated from the Chemical Department of Moscow Higher Technical College, developing as a scientist in the school of the distinguished Russian chemist A. E. Chichibabin. He worked at the N. D. Zelinsky Institute of Organic Chemistry from 1932 to 1954 and at the A. N. Nesmeyanov Institute of Organoelemental Compounds from 1954 to his last days (where he was the Deputy Director). He is remembered mainly for his pioneering work in physical organic chemistry and organophosphorus chemistry (*342*). His works on tautomerism and dual reactivity of organic compounds are well known; he discovered many novel types of tautomerisms (e.g. thiono–thiolic and amido–imidic). He contributed to the chemistry of physiologically active substances and the study of their biological action and metabolism. In doing so, he discovered many new classes of compounds and developed convenient methods for their preparation; the Kabachnik–Fields reaction is an example of one of his better-known discoveries. Synthetic research combined with a deep exploration of fundamental features was a characteristic of his work.

Kabachnik is believed to have contributed to the chemical weapons programme of the Soviet Union (*343*). In September 1944, he prepared the organophosphorus nerve agent sarin while working at the University of Kazan. His synthesis was independent of that of Gerhard Schrader (Chapter 1, Section 1.5.2), which had occurred in Germany in 1939 and was probably unknown to the Soviet Government at the time because of World War II. In 1946, Kabachnik received the Stalin Prize, First Class, in recognition of this achievement. He also received the Lenin Prize, the highest honour of the

former Soviet Union, in 1974 for his role in the development of V-type organophosphorus nerve agents (Chapter 1, Section 1.5.3) in the Soviet Union (*344*).

Kabachnik paid attention to scientific organisation. He had good relationships after the Cold War ended in 1991 with many leading scientists abroad and then lectured widely; he was considered an authority on organophosphorus chemistry, and he often helped organise international conferences on phosphorus chemistry. He was elected a member of the Polish Chemical Society and an honorary citizen of Lodz (Poland). Remembered within Russia as a 'person of rare scale, intellect, activity, and humanism', he is survived by a powerful school of organophosphorus chemists that he helped found and a vast legacy of scientific papers (*342*). The photograph shows three of the heavyweights of Russian phosphorus chemistry, namely, Academicians Aleksander Yermingel'dovich Arbuzov (*left*), Boris Aleksandrovich Arbuzov (*middle*) and Martin Izrailevich Kabachnik (*right*) (photograph reproduced courtesy of Dstl).

2.18.2 The Kabachnik-Fields reaction

In the 1950s, multicomponent processes were 'exotic birds' (*345*) and are now highly desirable for the construction of diverse combinatorial libraries. The first step of the Kabachnik-Fields reaction is the formation of the imine $R^3R^4C{=}NR^5R^6$ with loss of water, followed by the addition of the dialkyl *H*-phosphonate to the C═N bond (Pudovik reaction) (refer to Fig. 2.18.1). The Mannich reaction, in which formaldehyde is condensed with ammonia and a compound with an active hydrogen atom, is a related process. The Kabachnik-Fields reaction is especially satisfactory for reactions with aldehydes. Fewer examples where ketones have been used successfully are available and tend to involve simple ones (mainly acetone, cyclohexanone and acetophenone). Small and electronegative ketones form imines quickly, and the rate of P—H addition to the formed imine depends upon the electronegativity of the C═N carbon atom of the imine. The Kabachnik-Fields reaction offers much scope for the generation of novel compounds.

The reaction of diallyl *H*-phosphonate (**218**) with equimolar quantities of aqueous formaldehyde and diethylamine furnishes after distillation pure diallyl *N*,*N*-diethylaminomethylphosphonate (**219**) (Fig. 2.18.2.1) (*128*). This is a typical example of the preparation of an *N*,*N*-dialkylaminoalkyl phosphorus compound and is applicable to almost any compound having one or more P—H bonds, as well as a large variety of aldehydes and amines.

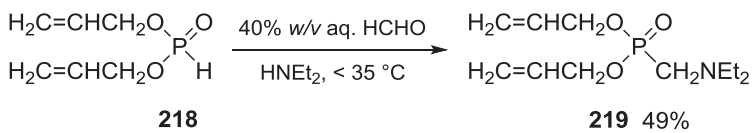
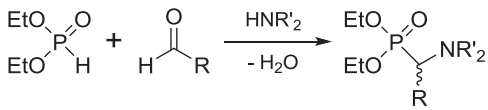


Figure 2.18.2.1

A specific order of addition is required to maximise the chances of success. It is best to add the aldehyde or ketone to a mixture of the dialkyl *H*-phosphonate and amine at a rapid rate. This enables formation of the imine and selective combination of it with the dialkyl *H*-phosphonate, while suppressing the likelihood of a competing Abramov reaction, that is, $(RO)_2P(O)H + RC(O)$

R → $(RO)_2P(O)CR_2OH$. This side reaction is undesirable, as the dialkyl α-hydroxyphosphonate cannot usually react with the amine, even under severe conditions, to provide the dialkyl α-aminophosphonate (*341*). If the order of addition is changed so that the amine is added to a mixture of the dialkyl *H*-phosphonate and carbonyl compound, the latter have time to undergo an Abramov reaction, reducing the yield of dialkyl α-aminophosphonate and increasing the probability of obtaining an intractable mixture of products. By using the correct order of addition, it is possible to obtain various dialkyl α-aminoalkylphosphonates in good yield (Fig. 2.18.2.2) (*341*).



Dialkyl α-dialkylaminoalkylphosphonates

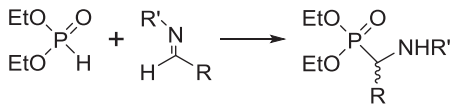
R	R'	Yield (%)	Bp (°C/mmHg)
H	Et	94	96/3
H	*i*-Pr	91	112/2
H	*n*-Bu	94	127/2
H	*c*-Hex	81	149/2
H	*n*-Oct	86	175/2
Me	Et	81	94/1
Et	Et	78	95/1
n-Pr	Et	79	106/1
n-Pr	*n*-Bu	91	147/2
$CH{=}CH_2$	Et	87	116/4

Figure 2.18.2.2

Water is formed during the Kabacknik-Fields reaction. Its formation is unimportant in cases where the dialkyl *H*-phosphonate resists hydrolysis and the reaction to yield the desired product is quick. However, in the case of dialkyl *H*-phosphonates sensitive to moisture or instances when the reaction rate is slow, appreciable hydrolysis of the starting dialkyl *H*-phosphonate can occur. Suppressing hydrolysis and increasing the reaction rate can be accomplished by removing the water (using a dehydrating reagent, e.g. $MgSO_4$ or molecular sieves, or its azeotropic distillation from the reaction mixture) and adding a catalyst (e.g. $AlCl_3$, $InCl_3$, $LiClO_4$ or SmI_2) (*346*). In some cases, microwave irradiation is more beneficial than conventional heating (*347*).

Several adaptations that avoid the formation of water are available. The addition of a dialkyl *H*-phosphonate to a preformed imine proceeds vigorously and is of general application. This approach works well for imines derived from aldehydes and ketones, but not for those derived from formaldehyde (formaldimines usually polymerise too rapidly to be useful). The starting ketimines may be

prepared by stirring a mixture of a primary amine and a ketone with anhydrous potassium carbonate. The reaction between equimolar quantities of a dialkyl *H*-phosphonate and an imine often occurs on mixing after an induction period of several minutes; the mixture heats up and the yields of α-aminophosphonate are often excellent (Fig. 2.18.2.3) (*341*).



Dialkyl α-alkylaminoalkylphosphonates

R	R'	Yield (%)	Bp (°C/mmHg)
Me	Me	94	87/2
Me	Et	91	84/1
n-Pr	Me	93	110/2
n-Pr	*n*-Bu	94	119/2
Et	Et	89	93/2
Ph	Ph	97	mp 92 °C

Figure 2.18.2.3

Another way to avoid water formation in the synthesis of dialkyl α-aminophosphonates is to use *N*,*N*,*N*′,*N*′-tetraalkylmethanediamines or *N*,*N*-dialkylaminomethyl methyl ethers in place of the carbonyl and amine components (*341*). Warming the dialkyl *H*-phosphonates with these substitutes and distillation of dialkylamine and methanol by-products, respectively, from the reaction mixture leaves the target compounds (Fig. 2.18.2.4). Diethyl *H*-phosphonate similarly adds to 1-pyrroline

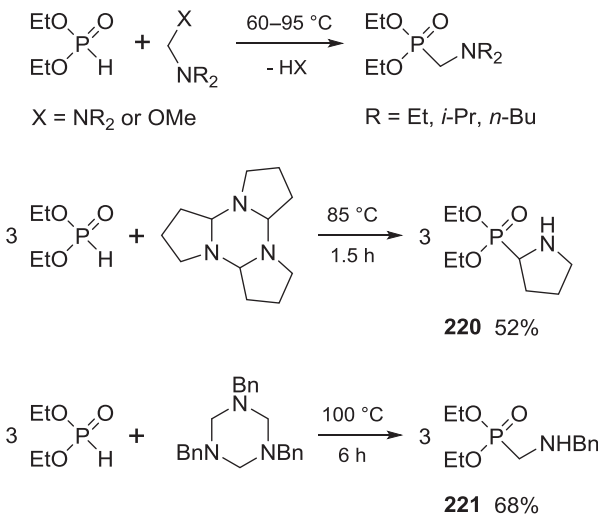


Figure 2.18.2.4

trimer to provide 2-phosphonopyrrolidine (**220**) (*348*). It also reacts analogously with 1,3,5-tribenzylhexahydro-*s*-triazine to afford diethyl *N*-benzylaminomethylphosphonate (**221**) (*349*). This compound can be debenzylated by catalytic hydrogenation.

Appropriate solvents for the Kabachnik—Fields reaction include chloroform, benzene, toluene and isopropanol. Trifluoroethanol is a useful solvent and an acid catalyst for the synthesis of dimethyl α-aminoalkylphosphonates from a combination of trimethyl phosphite, an alkyl or aryl substituted aldehyde, and an aromatic amine in one pot (*350*). A sulfonic acid-functionalised ionic liquid can catalyse product formation even in water at room temperature (*351*). The use of a trialkyl phosphite instead of a dialkyl *H*-phosphonate has also been exploited in the indium trichloride-catalysed addition of triethyl phosphite to *N*-benzyloxycarbonyl (CBz)-protected sulfones (Fig. 2.18.2.5) (*352*). Reagent (**222**) is prepared from the combination of *p*-toluenesulphonic acid (TsOH), benzaldehyde and H_2NCBz in aqueous formic acid, and its use in this case gave species (**223**).

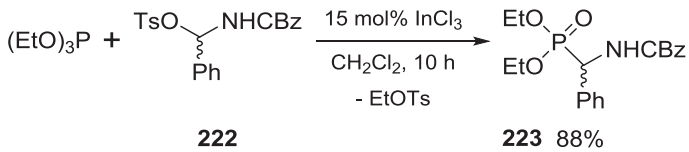


Figure 2.18.2.5

Aminophosphonic acids may be viewed as phosphorus analogues (biosteres) of α-amino acids and have received considerable interest due to their biological activity. Optically active α-aminophosphonates are sought as building blocks for pharmaceutical targets, anti-HIV drugs, enzyme inhibitors and peptides with unusual structures (*353*). Enantioselective reaction of dialkyl *H*-phosphonates with imines comprises a versatile route for their preparation. α-Aminophosphonates can be prepared by Kabachnik—Fields reactions involving enantiomeric amines (*346*). Lithium diethyl phosphite, prepared from *n*-butyllithium and diethyl *H*-phosphonate, is able to add to homochiral imines with high asymmetric induction thought to arise from coordination of the lithium counterion to the ether oxygen atom and imino nitrogen atom (*354*). This generates a five-membered transition state, and addition occurs anti to the phenyl ring leading to the *R*,*R*-diastereoisomer (**224**), whose catalytic hydrogenolysis provides (*R*)-(−)-α-aminophosphonate (**225**) (Fig. 2.18.2.6).

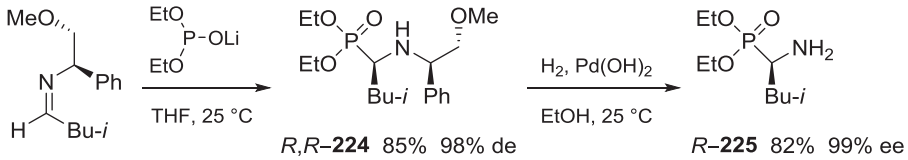
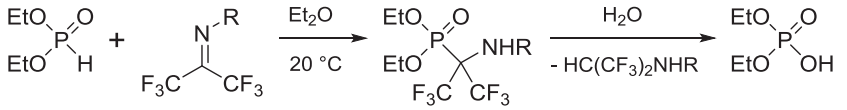


Figure 2.18.2.6

Dialkyl *H*-phosphonates add to imines derived from hexafluoroacetone to give dialkyl alkylphosphonates bearing a $P(O)C(CF_3)_2NHR$ group (e.g. **226** and **227**) (Fig. 2.18.2.7) (*355,356*). The P—C bond in these compounds is unusually weak due to the electronegative groups connected to it and is cleaved relatively easily by oxygen nucleophiles to yield the dialkyl hydrogen phosphate (e.g. **228**). For this reason, compounds such as **226** and **227** inhibit serine hydrolase enzymes and have anticholinesterase activity (*357,358*).

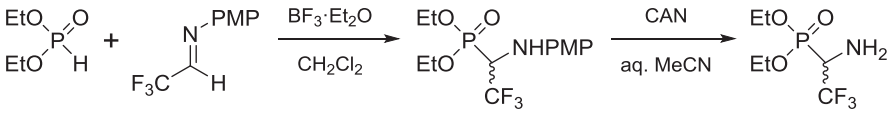


R = COEt **226** 71% δ_P 9.7 **228** δ_P 0.4

R = SO_2Ph **227** 78% δ_P 8.2

Figure 2.18.2.7

The Kabachnik—Fields reaction can be used to provide α-aminophosphonate intermediates for subsequent Ugi-type transformation to more complex derivatives (*359*). This combination of two multicomponent processes in one pot provides a powerful means of quick generation of elaborate dialkyl α-aminophosphonates from simple starting materials. Dialkyl *H*-phosphonates do not add to *N*-substituted fluoroalkylaldimines when mixed but require a molar equivalent of boron trifluoride etherate to effect conversion to the dialkyl α-aminophosphonate (*360*). *Para*-methoxyphenyl-protected compounds (e.g. **229**) made this way can be deprotected at room temperature with cerium ammonium nitrate (CAN) in aqueous acetonitrile to give the dialkyl α-aminophosphonate (e.g. **230**) (Fig. 2.18.2.8).



PMP = *p*-methoxyphenyl **229** 55% δ_P 19.6 **230** 55% δ_P 21.1

Figure 2.18.2.8

The first catalytic enantioselective hydrophosphonylation of ketimines using cinchona alkaloids and a base was reported recently (*361*). Diphenyl *H*-phosphonate reacts with the *N*-(2,4,6-trimethylbenzenesulfonyl) ($MesSO_2$)-substituted imine derived from acetophenone, sodium carbonate and hydroquinine or hydroquinidine to furnish (*R*)-(**231**) or (*S*)-(**232**) in high yield and enantioselectivity (Fig. 2.18.2.9). The sulfonyl group is removed from (*S*)-(**232**) by treatment with methanesulfonic acid and anisole in trifluoroacetic acid to give diphenyl (*S*)-1-amino-1-phenylethylphosphonate (**233**) in a similarly high yield.

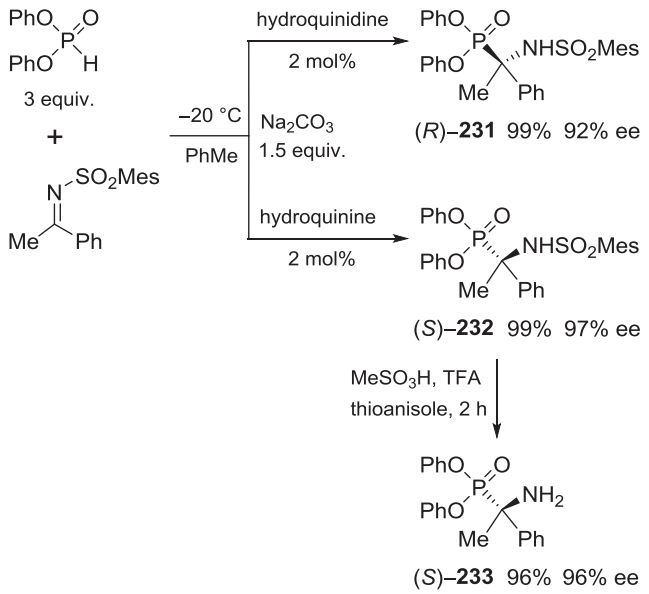


Figure 2.18.2.9

Several α-aminoalkyl bisphosphonates are used to treat bone diseases, and this class of compounds is therefore of medicinal interest (Chapter 1, Section 1.8, Fig. 1.8.8). To make such materials efficiently, a mixture of a dialkyl *H*-phosphonate, triethyl orthoformate and an amine can be microwaved on alumina (*362*) or in the absence of a solid support (*363*) (Fig. 2.18.2.10). A wide variety of amines can be used similarly to access a large number of products of diverse structures. This three-component variant of the Kabachnik—Fields reaction can be catalysed efficiently by ytterbium (III) perfluorooctanoate in 1-butyl-3-methylimidazolium chloride ionic liquid (*364*).

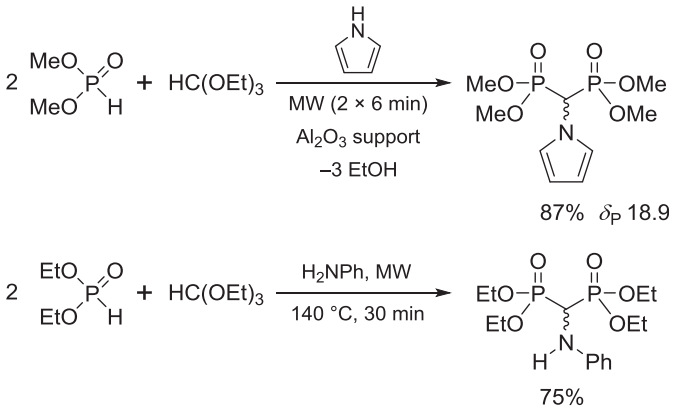
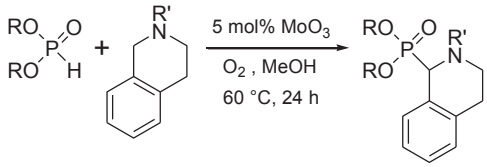


Figure 2.18.2.10

A new method of dialkyl α-aminophosphonate formation involves molybdenum trioxide-catalysed oxidative cross-dehydrogenative coupling of dialkyl *H*-phosphonates with *N*-aryl tetrahydroisoquinolines under aerobic conditions (*365*). A benzylic sp^3 C—H bond is α-phosphonylated (Fig. 2.18.2.11).



Dialkyl α-aminophosphonates

R	R'	Yield (%)
Me	Ph	87
Et	Ph	94
i-Pr	Ph	92
Bn	Ph	88
Me	PMP	93
Et	PMP	90
i-Pr	PMP	93
Bn	PMP	91

PMP = *p*-methoxyphenyl

Figure 2.18.2.11

Substituted dialkyl α-aminophosphonates of a low molecular weight are pale yellow or colourless mobile liquids that can be distilled under vacuum. The lower members are very soluble in water. Diethyl *N,N*-diethylaminomethylphosphonate $(EtO)_2P(O)CH_2NEt_2$ resembles its carbon analogue, ethyl *N,N*-diethylglycinate $EtOC(O)CH_2NEt_2$, in that it dissolves in cold water but separates when the solution is heated (*341*). The compounds are soluble in common organic solvents and are extremely stable to acids and bases, especially the compounds derived from secondary amines; diethyl *N,N*-diethylaminomethylphosphonate refluxed for 48 h with concentrated hydrochloric acid or 10% aqueous sodium hydroxide does not change appreciably. Concentrated alcoholic potassium hydroxide or 48% hydrobromic acid does hydrolyse the ester after heating for 1—5 h, yielding the potassium salt or acid, respectively.

▶ *Diallyl N,N-diethylaminomethylphosphonate* $(H_2C{=}CHCH_2O)_2P(O)CH_2NEt_2$ (**219**) (*128*). Aqueous formaldehyde (40% w/v, 15 ml) was added to a stirred mixture of diallyl *H*-phosphonate (32.4 g, 0.2 mol) and diethylamine (15.0 g, 0.2 mol) in a 100-ml round-bottomed flask. The temperature was kept below 35 °C by immersing the flask in a cold water bath. After 1 h, the mixture was fractionated to give the product (24.5 g, 49%). Bp 104—105 °C/0.07 mmHg.

▷ *Dialkyl α-aminoalkylphosphonates* (*from dialkyl H-phosphonate, carbonyl reagent and amine*) (*341*). The aldehyde or ketone was added rapidly to a stirred mixture of equimolar quantities of secondary amine and dialkyl *H*-phosphonate while maintaining the temperature below 85 °C. Fifteen minutes after the addition, the mixture was cooled, dried (Na_2SO_4), filtered and the filtrate was distilled under reduced pressure. Altering the order of addition, for example, by adding the amine to a mixture of the dialkyl *H*-phosphonate and the aldehyde, produced several products, and these, in general, were not easily separated.

▷ *Dialkyl α-aminoalkylphosphonates* (*from dialkyl H-phosphonate and N,N,N′,N′-tetraalkylmethanediamine or N,N-dialkylaminomethyl methyl ether*) (*341*). An equimolar mixture of a dialkyl *H*-phosphonate and an *N,N,N′,N′*-tetraalkylmethanediamine or *N,N*-dialkylaminomethyl methyl ether was heated to 60–65 °C in a flask connected to a take-off condenser. A vigorous reaction usually occurred, which caused the secondary amine or alcohol, respectively, to distil. The reaction vessel was heated to complete the distillation of the liberated amine or alcohol. Distillation of the residue under vacuum gave the dialkyl α-aminoalkylphosphonate.

▷ *Dialkyl α-aminoalkylphosphonates* (*from dialkyl H-phosphonate and an imine*) (*341*). The imines were prepared by treating the aldehyde or ketone with the primary amine in the presence of anhydrous K_2CO_3, separating the imine from the aqueous layer, and drying over solid KOH or K_2CO_3. For example, the imine from acetone and ethylamine was prepared as follows: acetone (58.0 g, 1.00 mol), ethylamine (47.3 g, 1.05 mol) and anhydrous K_2CO_3 (10.0 g, 72.46 mmol) were heated under reflux for 30 min. The cooled organic layer was separated, dried (K_2CO_3) and filtered. The imine was isolated in 80% yield and used in the next step (the imines of lower molecular weight were distilled before use, as they tended to polymerise, especially when incompletely dried). Next, an equimolar mixture of a dialkyl *H*-phosphonate and the imine was allowed to stand until no more heat was evolved, and was then distilled under reduced pressure. Cooling was required when lower molecular weight imines were reacting.

2.19 DIALKYL ALKENYLPHOSPHONATES $(RO)_2P(O)C{=}CR_2$

Dialkyl alkenylphosphonates find use in medicinal chemistry (*366*), physical chemistry (spectroscopic studies) (*367*) and synthesis (*368–371*). The literature on the chemistry of vinylphosphonates in organic synthesis up to 1992 (*372*) and 2002 (*34*) has been reviewed. The generation of alkenylphosphonates from substrates having a PCH_2CH_2Cl group (*119*) by treatment with a base has already been discussed (refer to Figs 2.3.6.5 (*106*) and 2.13.3.2.4). They can also be prepared from substrates with the group PCH_2CH_2X where X is a suitable leaving group, such as Br (refer to Fig. 2.13.12.1) (*182,260,373*) or a dialkyl phosphate group, e.g. $OP(O)(OEt)_2$ (*374*). The reaction between dialkyl 2-bromopropylphosphonates and triethylamine is more sluggish than that of the corresponding dialkyl 2-bromoethylphosphonates (*39*). The synthesis of a vinylphosphonate from dialkyl benzoylphosphonates has already been noted (Fig. 2.15.5) (*315*).

▷ *Diisopropyl 1-propenylphosphonate* $(i\text{-}PrO)_2P(O)CH{=}CHCH_3$ (*39*). Diisopropyl 2-bromo-2-methylethylphosphonate (118 g, 0.4 mol), triethylamine (75 ml) and benzene (200 ml) were refluxed for 9 h. Triethylamine hydrobromide was removed by filtration, the solvent was evaporated

and the residue was fractionated. After two distillations, the product was obtained pure (52 g, 63%). Bp 70 °C/2 mmHg.

Addition of alkenes to phosphorus pentachloride generates phosphorane intermediates that can be oxidised to alkenylphosphonic derivatives (*375*,*376*) by a variety of routes, including hydrolysis (refer to Fig. 2.12.7) (*106*). Styrene (**79**) adds to 2 mol of phosphorus pentachloride suspended in benzene to give phosphorane (**80**) whose oxidation with sulfur dioxide proceeds smoothly to yield styrylphosphonic dichloride (**234**) (Fig. 2.19.1) (*377*).

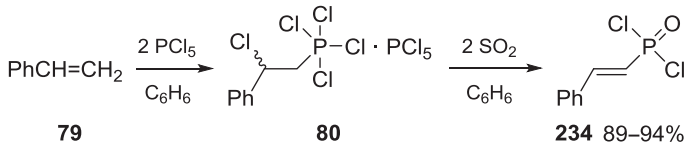


Figure 2.19.1

▶ *Styrylphosphonic dichloride PhCH═CHP(O)Cl*$_2$ (**234**) (*377*). A solution of styrene (26 g, 0.25 mol) in anhydrous benzene (50 ml) was added dropwise through a dropping funnel over 30 min to a three-necked flask, equipped with a sealed mechanical stirrer and a reflux condenser carrying a drying tube, containing phosphorus pentachloride (104 g, 0.50 mol) suspended in anhydrous benzene (150 ml) at 0–5 °C (care must be taken not to freeze the benzene before the styrene is added). A dense crystalline solid began to form immediately. After addition, the mixture was stirred for 30 min at room temperature. The dropping funnel was replaced by a gas inlet tube that was connected to a cylinder of sulfur dioxide through a wash bottle containing concentrated sulfuric acid. Sulfur dioxide was bubbled through the mixture until all the precipitate dissolved. The mildly exothermic reaction was controlled by occasional cooling of the reactants with an ice bath. The solvent was removed from the clear solution under reduced pressure. The residue was distilled from a Claisen flask with Vigreux indentations to give the title compound (49–52 g, 89–94%). Bp 107–110 °C/0.2 mmHg. The distillate solidified during or after distillation. Mp 71–72 °C.

Treatment of diethyl *H*-phosphonate with chlorotrimethylsilane and triethylamine generates diethyl trimethylsilyl phosphite (**235**), which adds through its nucleophilic phosphorus atom to *α*-chloroacrylonitrile to generate diethyl (*E*)-(2-cyanovinyl)phosphonate (**236**) (Fig. 2.19.2) (*378*).

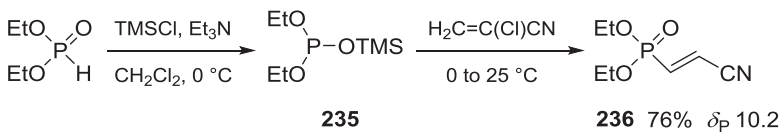


Figure 2.19.2

▶ *Diethyl (E)-(2-cyanovinyl)phosphonate* $(EtO)_2P(O)CH{=}CHCN$ (**236**) (*378*). Chlorotrimethylsilane (0.35 ml, 0.30 g, 2.76 mmol) was added dropwise to a stirred solution of diethyl *H*-phosphonate (0.35 g, 2.53 mmol) and triethylamine (0.39 ml, 0.28 g, 2.80 mmol) in dichloromethane (50 ml) maintained at 0 °C under argon. α-Chloroacrylonitrile (0.22 g, 2.53 mmol) was added after 15 min, and the solution was allowed to warm to room temperature. After 6 h, the reaction mixture was poured into water (50 ml), and the organic products were extracted with dichloromethane (2 × 75 ml). The organic extracts were dried ($MgSO_4$) and concentrated. Kugelruhr distillation of the residue gave a colourless liquid (0.4 g, 76%). Bp 130 °C/0.5 mmHg. δ_P (36 MHz, $CDCl_3$) 10.2 ppm. ν_{max} 2230 (C≡N), 1603 (C=C), 1258 (P=O)/cm.

The Arbuzov reaction of dialkyl *H*-phosphonates or trialkyl phosphites with 5 mol% nickel(II) bromide catalyst under argon yields dialkyl alkenylphosphonates generally in acceptable yield (not shown) (*379*). The catalyst prepared from nickel *bis*(acetylacetonate) [$Ni(acac)_2$] and 1,2-*bis*(diphenylphosphino)ethane (dppe) performs excellently in the hydrophosphorylation of alkynes (Fig. 2.19.3) (*380*). Regioselective addition to terminal alkenes occurs (e.g. to give **237**) and 1,2-disubstituted alkynes also participate successfully (e.g. to give **238**).

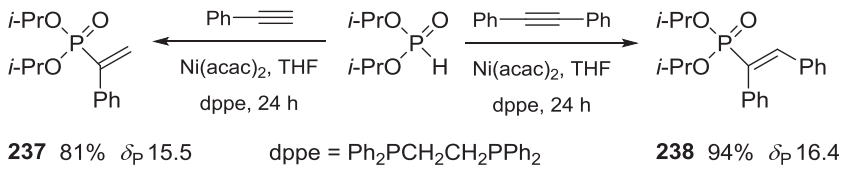


Figure 2.19.3

▶ *Diisopropyl (1-phenylvinyl)phosphonate* $(i\text{-}PrO)_2P(O)C(Ph){=}CH_2$ (**237**) (*380*). The catalyst $Ni(acac)_2$ (23.1 mg, 9.0×10^{-5} mol), dppe (71.7 mg, 18.0×10^{-5} mol) and tetrahydrofuran (THF; 1 ml) were added to a reaction vessel and stirred at room temperature for 5 min until a heterogeneous dark brown solution was formed (formation of a white precipitate was also observed). Diisopropyl *H*-phosphonate (0.2 g, 1.0×10^{-3} mol) and ethynylbenzene (0.1 g, 1.0×10^{-3} mol) were added to the obtained solution at 100 °C with stirring. The alkyne was added slowly using a syringe pump, or in small portions manually 6 h after the start of the 24 h heating period. The mixture was cooled to room temperature, and the solvent was removed. Column chromatography on silica gel, eluting with a hexane—ethyl acetate gradient, gave the title compound (0.2 g, 81%). δ_P (202 MHz, $CDCl_3$) 15.5 ppm. Similarly, the use of 1,2-diphenylethyne at 120 °C gave diisopropyl [(*E*)-1,2-diphenylvinyl] phosphonate **238** (94%). δ_P (202 MHz, $CDCl_3$) 16.4 ppm.

Heating trialkyl phosphites with vinyl bromides and copper(I) bromide gives dialkyl alkenylphosphonates (e.g. **239—241**) in excellent yields (Fig. 2.19.4) (*381*). Such reactions can be performed in solvent (e.g. *N,N*-dimethylformamide (DMF) or THF) using bases (e.g. potassium hydride or triethylamine) (*382*). A mild stereoselective preparation of dialkyl 2-arylvinylphosphonates at room

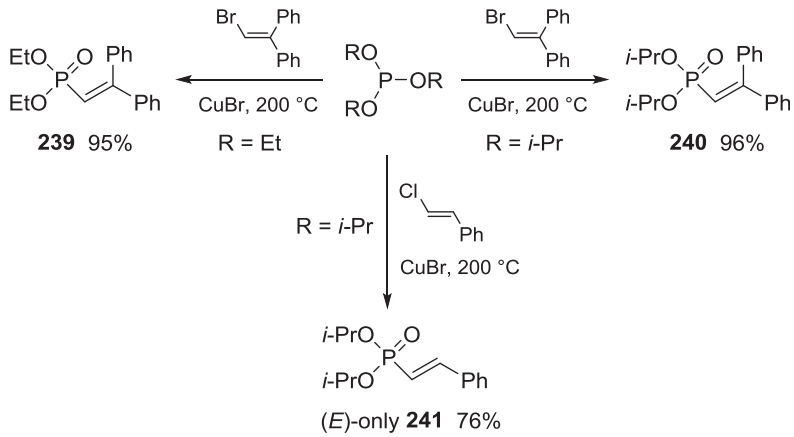


Figure 2.19.4

temperature involves copper iodide-mediated cross-coupling of dialkyl *H*-phosphonates with vinyliodonium tetrafluoroborates (not shown) (*383*).

▶ *General procedure for dialkyl alkenylphosphonates* (*381*). A stirred mixture of the copper(I) halide complex of the trialkyl phosphite (50 mmol) and vinylic halide (35 mmol) was heated to 200 °C for 1 h in a 50-ml round-bottomed flask equipped with a short Vigreux column topped with a Dean—Stark trap, a condenser and a nitrogen inlet. The alkyl halide produced was collected in the Dean—Stark trap. The mixture was cooled to room temperature and was poured into toluene (60 ml). Ethylenediamine (5 ml) was then added dropwise with stirring. The solid material was filtered and washed with toluene. The combined toluene extracts were washed with 10% hydrochloric acid (10 ml) then water (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel, eluting with a gradient of hexane—ethyl acetate, enabled separation of the dialkyl alkenylphosphonate and vinylic halide. The dialkyl alkenylphosphonate was distilled under vacuum to give analytically pure material.

Dimethyl *H*-phosphonate adds to alkynes such as 1-octyne in the presence of *cis*-$PdMe_2(PPh_2Me)_2$ catalyst to efficiently generate dimethyl oct-1-en-2-ylphosphonate (**242**, major product) and dimethyl (*E*)-oct-1-en-1-ylphosphonate (**243**, minor product) in a 91% overall yield (Fig. 2.19.5) (*384*). A variety of palladium species are able to catalyse similar phosphonylations of alkynes (*385*).

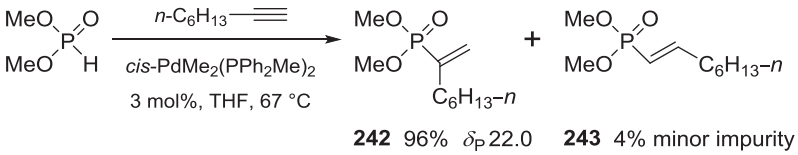


Figure 2.19.5

▶ *Dimethyl oct-1-en-2-ylphosphonate* $(MeO)_2P(O)C(n\text{-}C_6H_{13}){=}CH_2$ (**242**) (*384*). Dimethyl *H*-phosphonate (110 mg, 1 mmol) and 1-octyne (110 mg, 1 mmol) were added to a stirred mixture of *cis*-$PdMe_2(PPh_2Me)_2$ (16 mg, 0.03 mmol) in THF (5 ml) in a Schlenk tube under argon at room temperature. The solution turned yellow. The Schlenk tube was immersed in an oil bath maintained at 67 °C, and the mixture was stirred for 12 h. Evaporation of the solvent yielded a yellow liquid. Kugelrohr distillation of this at 5 mmHg gave a colourless liquid (200 mg, 91%). δ_P (121.5 MHz, C_6D_6) 22.0 ppm.

Palladium-catalysed acetoxylation of dimethyl 2-cyclohexenylphosphonate (**244**) using potassium acetate in acetic acid, in the presence of oxygen, isopentyl nitrite and palladium(II) chloride catalyst, yields dimethyl (3-acetoxycyclohexen-1-yl)phosphonate (**245**) (Fig. 2.19.6) (*386*). The mechanism proposed for the reaction involves a palladium nitro-nitroso redox couple (not shown). Other substitutions of dialkyl 2-alkenylphosphonates by nucleophiles can be enabled by catalysis by palladium complexes (*387*). Palladium-catalysed coupling of diethyl *H*-phosphonate (**246**) with chiral bromoalcohol (**247**), prepared by reduction of 3-bromocyclohexenone with sodium borohydride-$CeCl_3$ in methanol and resolution by lipase Amano AK, gives diethyl (*S*)-(−)-(3-hydroxy-1-cyclohexenyl) phosphonate (**248**) (*388*). Tetrakis(triphenylphosphine)palladium(0) is a good catalyst and enables the coupling of diethyl *H*-phosphonate to a variety of vinyl bromides whose stereochemistry is retained in the products (*389*).

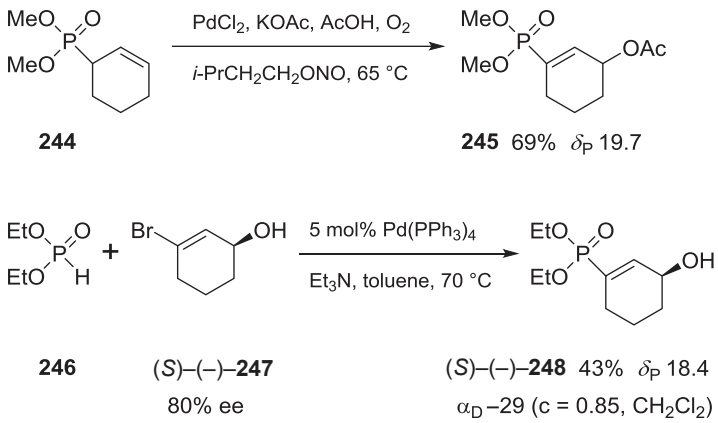


Figure 2.19.6

▶ *Dimethyl* (3-*acetoxycyclohexen*-1-*yl*)*phosphonate* (**245**) (*386*). A mixture of dimethyl 2-cyclohexenylphosphonate (190 mg, 1 mmol), palladium chloride (18 mg, 0.1 mmol), and potassium acetate (196 mg, 2 mmol) in acetic acid (2 ml) was stirred in a two-necked round-bottomed flask fitted with a rubber septum and a condenser that was flushed with oxygen via a gas burette. The system was purged with oxygen by three vacuum/flushing cycles. Isopentyl nitrite (200 µl, 1.5 mmol) was added via a syringe, and the mixture was stirred at 60 °C. The reaction was monitored by gas

chromatography mass spectroscopy (GC—MS) or by measuring the oxygen uptake. Once the reaction was complete, the mixture was cooled, diluted with diethyl ether (2 × 15 ml) and filtered through a short pad of Celite™. The filtrate was washed with 10% sodium bicarbonate, brine and dried ($MgSO_4$). The residue obtained after filtration and solvent removal was chromatographed on silica gel with ethyl acetate to give a colourless liquid (171 g, 69%). δ_P (40.5 MHz, $CDCl_3$) 19.7 ppm.

▶ *Diethyl* (*S*)-(−)-(3-*hydroxy*-1-*cyclohexenyl*)*phosphonate* (**248**) (*388*). A solution of diethyl *H*-phosphonate (0.14 g, 1 mmol), (*S*)-(−)-3-bromocyclohexen-2-ol (158 mg, 0.89 mmol) and triethylamine (0.43 ml, 3 mmol) in anhydrous toluene (1.5 ml) was degassed by bubbling with nitrogen and added to tetrakis(triphenylphosphine)palladium(0) (115.6 mg, 0.1 mmol) in a round-bottomed flask under nitrogen. The mixture was stirred and heated gradually to 70 °C and maintained at this temperature for 1 h, after which a white precipitate appeared. The mixture was cooled to room temperature, ethyl acetate (20 ml) was added and the mixture was filtered. Removal of solvent and purification by chromatography on silica gel, eluting with 9:1 ethyl acetate—methanol, afforded a pale yellow liquid (101 mg, 43%). δ_P (40.5 MHz, $CDCl_3$) 18.4 ppm.

Triethyl phosphite reacts upon heating with alkenylboronate esters in the presence of palladium(II) acetate and oxygen to give diethyl (*E*)- or (*Z*)-2-phenylethenylphosphonate (**249**) or (**250**) in an acceptable yield (Fig. 2.19.7) (*390*). The products are purified by column chromatography on silica gel.

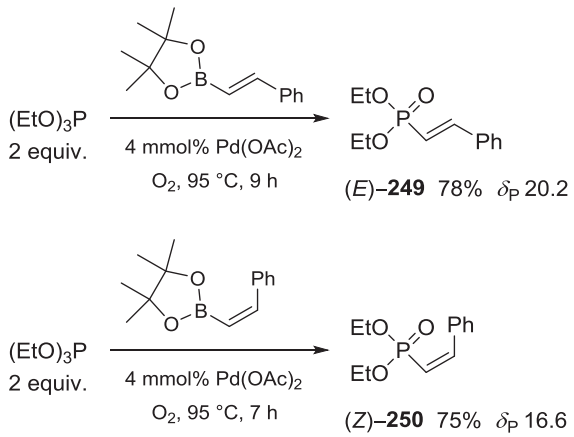


Figure 2.19.7

▶ *Diethyl* (*E*)-2-*phenylethenylphosphonate* $(EtO)_2P(O)CH{=}CHPh$ (**249**) (*390*). A stirred mixture of triethyl phosphite (332 mg, 2.00 mmol), pinacolato (*E*)-2-phenylethenylboronate (230 mg, 1.00 mmol) and palladium(II) acetate (9 mg, 0.04 mmol) was heated to 95 °C in a 10-ml round-bottomed flask under an oxygen atmosphere. The mixture was dissolved in ethyl acetate, washed with water (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel, eluting with 2:3 ethyl acetate—hexane, afforded the title compound (187 mg,

78%). δ_P (400 MHz, $CDCl_3$) 20.2 ppm. The use of pinacolato (*Z*)-2-phenylethenylboronate gave the corresponding (*Z*)-phosphonate **250** (180 mg, 75%). δ_P (400 MHz, $CDCl_3$) 16.6 ppm.

2.20 DIALKYL ALKYNYLPHOSPHONATES $(RO)_2P(O)C{\equiv}CR$

The synthesis of dialkyl alkynylphosphonates has been reviewed (*25,391*) and will not be repeated here in detail. The Arbuzov reaction of trialkyl phosphites with chloroalkynes provides these products in an acceptable yield. The reaction of trialkyl phosphites with dichloroethyne diethyl ether azeotrope (*392,393*) provides monosubstituted products (**251a–b**) or disubstituted products (**252a–c**) depending on the stoichiometry (Fig. 2.20.1) (*394,395*). Such products should be handled with care as certain derivatives are toxic: $(MeO)_2P(O)C{\equiv}CP(O)(OMe)_2$ and $(EtO)_2P(O)C{\equiv}CCO_2Et$ have LD_{50} values of 25 and 10 mg/kg, respectively, to mice by intraperitoneal injection (*396*).

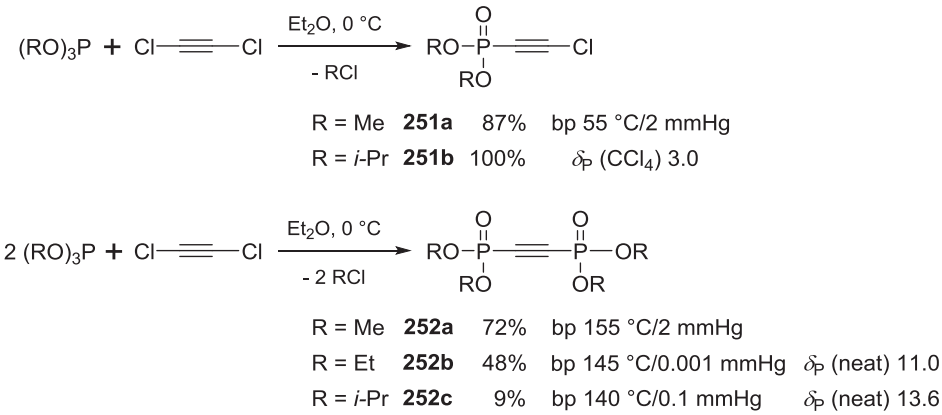


Figure 2.20.1

▶ *Dimethyl chloroethynylphosphonate* $(MeO)_2P(O)C{\equiv}CCl$ (**251a**) (*394*). Dichloroethyne diethyl ether azeotrope was prepared by a literature method (*392*) from 0.5 mol each of trichloroethene and diethyl ether and distilled (bp 32 °C/760 mmHg) into a 250-ml three-necked flask cooled to −78 °C and equipped with a magnetic flea, a gas inlet tube and an exit tube leading to a bubbler. To the flask was added trimethyl phosphite (12.4 g, 0.1 mol) under nitrogen. The reaction mixture was warmed slowly to 0 °C and after 1 h to room temperature. The evolution of gaseous methyl chloride was observed. The reaction mixture was kept at room temperature overnight. The unreacted dichloroethyne and the diethyl ether were evaporated in a stream of nitrogen, with the flask being warmed to 30–35 °C. Distillation of the brown liquid residue (17.2 g) gave a colourless liquid (14.7 g, 87%). Bp 55 °C/2.2 mmHg.

▶ *Diisopropyl chloroethynylphosphonate* $(i\text{-}PrO)_2P(O)C{\equiv}CCl$ (**251b**) (*395*). Triisopropyl phosphite (52 g, 0.25 mol) was added dropwise to a stirred ethereal solution of the dichloroethyne prepared from trichloroethene (132 g, 1 mol), ether (75 ml), potassium hydroxide (200 g) and calcium oxide (100 g) (*392*). After addition, the mixture was heated under reflux for 1 h, and the volatile products were removed under vacuum to give a pale yellow liquid (56 g, 100%). δ_P (CCl_4) 3.0 ppm.

▶ *Tetramethyl ethynyldiphosphonate* $(MeO)_2P(O)C{\equiv}CP(O)(OMe)_2$ (**252a**) (*394*). Dimethyl chloroethynylphosphonate (4.21 g, 25 mmol) and trimethyl phosphite (3.72 g, 30 mmol) were mixed at 0 °C in a 250-ml three-necked flask cooled to −78 °C and equipped with a magnetic flea, a gas inlet tube, and an exit tube leading to a bubbler. The mixture was warmed slowly to 10−15 °C and stirred at this temperature for 15 h. Evolution of gas was observed. Finally, the reaction mixture was heated to 30 °C for 1 h (rapid heating from 0 °C to room temperature can result in an exothermic uncontrollable reaction). The brown liquid mixture was then heated at 1 mmHg while the external oil-bath temperature was raised slowly to 100 °C; trimethyl phosphite (0.55 g) distilled into the cooled trap, leaving a brown liquid (6.1 g). Distillation of the latter gave a colourless liquid (4.35 g, 72%). Bp 155−156 °C/1.5 mmHg. Mp 13−15 °C.

▶ *Tetraethyl ethynyldiphosphonate* $(EtO)_2P(O)C{\equiv}CP(O)(OEt)_2$ (**252b**) (*395*). Triethyl phosphite (16.6 g, 0.1 mol) was added dropwise to a stirred ethereal solution of dichloroethyne (prepared as described in ref. (*392*)) first at −5 °C and then under reflux for 1 h. The ether was removed to provide a residue of $(EtO)_2P(O)C{\equiv}CCl$ (15.9 g, 81%; 81 mmol). To this was added dropwise triethyl phosphite (17 ml, 16.5 g, 99 mmol). A strongly exothermic reaction ensued, and the temperature rose to 90 °C. The mixture was cooled and then left at room temperature for 12 h. Distillation yielded a colourless liquid (11.6 g, 48%). Bp 145 °C/0.001 mmHg. δ_P (neat) 11.0 ppm.

Ethyne diphosphonates are versatile synthons. They readily undergo Diels-Alder reactions, with cyclopentadiene and 1,3-cyclohexadiene to give norbornadienediphosphonate (**253**) and 1,2-diphosphonylbenzene (**254**), and 1,3-dipolar additions with diazomethane to yield 2-pyrazolines (**255**) (Fig. 2.20.2) (*394*). Ethyne diphosphonates react with some nucleophiles with P−C bond cleavage. Excess ethanol and sodium ethoxide catalyst result in a single P−C bond cleavage to give phosphonoacetaldehyde diethyl acetal (**256**), whereas *n*-butanethiol causes two P−C bond cleavages to give phosphorothiolate (**257**) and ethyne (*395*).

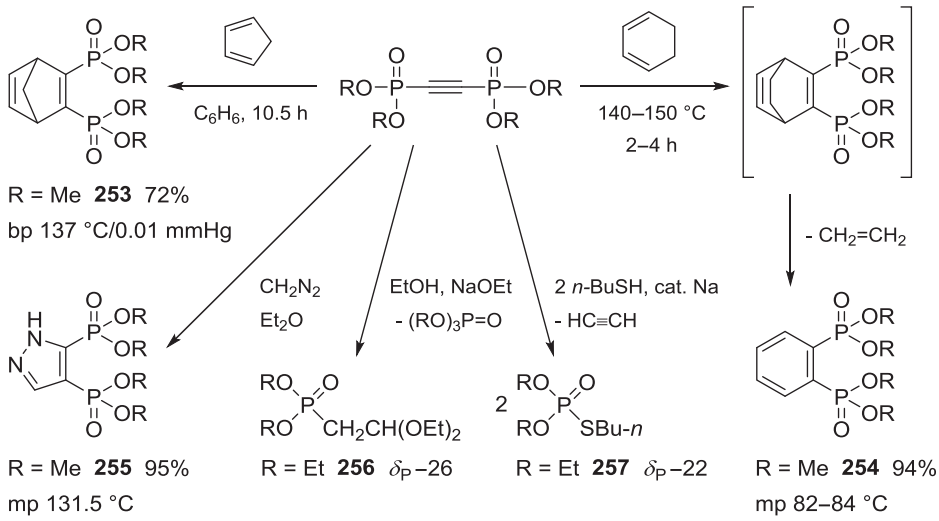


Figure 2.20.2

▶ *Diels–Alder reactions* (*394*). Equimolar amounts of the alkyne and diene were heated together without solvent under nitrogen with stirring using an oil bath heated to 140–150 °C for 2–4 h, or in the case of the tetramethyl ethynyldiphosphonate, were heated in benzene solution for 10.5 h. These methods yielded tetramethyl norbornadiene-2,3-diphosphonate **253** (72% yield; bp 137 °C/0.01 mmHg) and tetramethyl 1,2-phenylenediphosphonate **254** (94%; mp 82–84 °C from benzene–heptane).

▶ *Diazomethane reaction* (*394*). A solution of diazomethane in diethyl ether was added to a stirred solution of the alkyne (10 mmol) in diethyl ether (20 ml) until the yellow colour of the diazomethane was no longer discharged. A white crystalline solid precipitated immediately upon the addition of the first drops of the diazomethane solution. The solid was filtered off and recrystallised from chloroform–hexane to give 2-pyrazoline **255** as white needles (95%). Mp 131.5 °C.

Dialkyl ethynylphosphonates can also be prepared from commercial precursors in three steps. Diphenyl disulfide reacts with phenylacetylene in dimethyl sulfoxide (DMSO) in the presence of copper(I) iodide to provide phenylalkynyl phenyl sulfide (**258**) in high yield (Fig. 2.20.3) (*397*). Its oxidation by *meta*-chloroperbenzoic acid (MCPBA) gives sulfone (**259**) (*398*) whose Arbuzov reaction with trialkyl phosphites occurs cleanly upon heating (*399*). The pure dialkyl alkynylphosphonates (**260a–c**) are isolated by chromatography on silica gel.

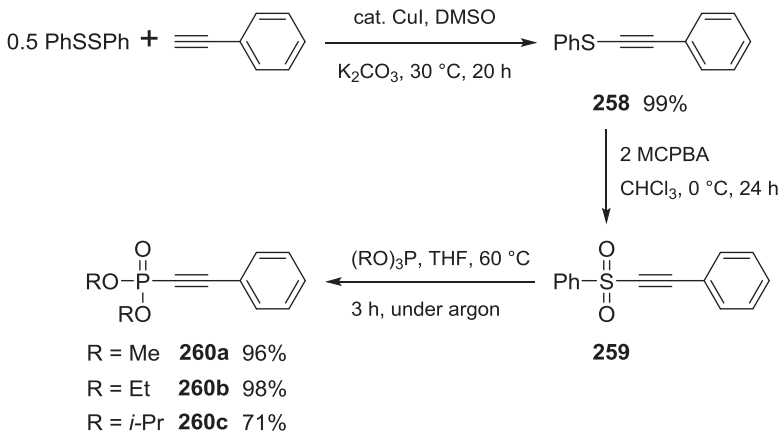


Figure 2.20.3

▶ *Dialkyl 1-phenylethynylphosphonates* $(RO)_2P(O)C{\equiv}CPh$ (**260a–c**) (*399*). A solution of the sulfone (2 mmol) and trialkyl phosphite (2 mmol) in THF (4 ml) was heated at 60 °C for 3 h under argon. After cooling, the mixture was concentrated, and the residue was chromatographed on silica gel, eluting with 2:1 hexane–ethyl acetate, to give the target compound. The sulfone $PhSO_2C{\equiv}CCH_2CH_2Ph$ and trimethyl phosphite gave the phosphonate $(MeO)_2P(O)C{\equiv}CCH_2CH_2Ph$ (93% yield; δ_P −2.7 ppm).

Another route to dialkyl alkynylphosphonates involves palladium-catalysed coupling of dialkyl *H*-phosphonates to 1,1-dibromo-1-alkenes (Fig. 2.20.4) (*400*). A good system for this transformation is palladium(II) acetate, 1,1′-*bis*(diphenylphosphino)ferrocene (dppf), propylene oxide and DMF at

80 °C. The reaction tolerates a range of functional groups in the dialkyl *H*-phosphonate and 1,1-dibromo-1-alkene coupling partners, allowing, for example, the isolation of dialkyl alkynylphosphonates (**260a**) and (**261a–c**).

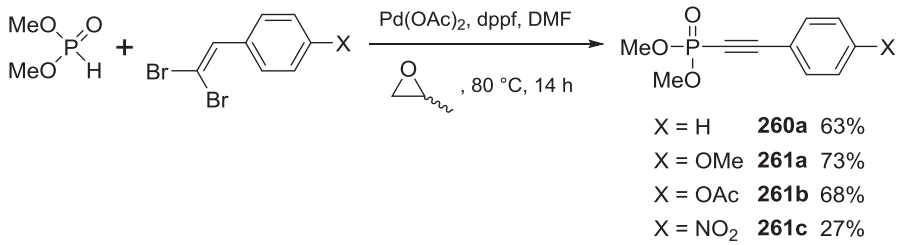


Figure 2.20.4

▷ *Dimethyl 1-arylethynylphosphonates* $(RO)_2P(O)C{\equiv}CAr$ (**260a**) and (**261a–c**) (*400*). A solution of the 1,1-dibromo-1-alkene (0.165 mmol) in DMF (1.5 ml), propylene oxide (35 µl, 0.50 mmol) and dimethyl *H*-phosphonate (30 µl, 0.33 mmol) was added to a stirred mixture of palladium(II) acetate (7 mg, 0.033 mmol) and dppf (36 mg, 0.066 mmol) in DMF (1 ml) that had been flushed with dry nitrogen and stirred at room temperature for 20 min beforehand. After addition, the reaction mixture was heated to 80 °C (bath temperature) for 14 h and then cooled to room temperature. Rotary evaporation of the solvent left a residue that was chromatographed on silica gel, eluting with 3:1 ethyl acetate–pentane, to afford the product.

Dialkyl 1-phenylethynylphosphonates (**260b–d**) can be prepared by copper (I) iodide-catalysed aerobic oxidative coupling of dialkyl *H*-phosphonates with terminal alkynes (Fig. 2.20.5) (*401*). This procedure works with a diverse range of dialkyl *H*-phosphonates and alkynes and allows the easy construction of dialkyl alkynylphosphonates.

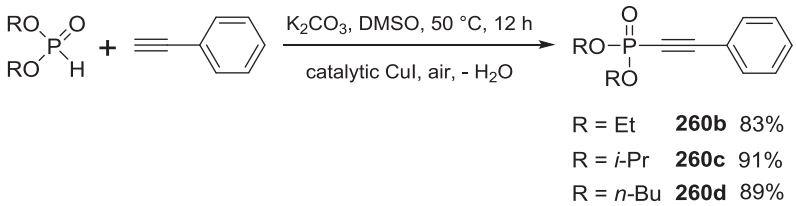


Figure 2.20.5

▷ *Diisopropyl 1-phenylethynylphosphonate* (**260c**) (*401*). Under dry air, diisopropyl *H*-phosphonate (83 mg, 0.5 mmol) and phenylacetylene (61 mg, 0.6 mmol) were added to a stirred mixture of copper(I) iodide (10 mg, 0.05 mmol) and potassium carbonate (7 mg, 0.05 mmol) in DMSO (1 ml) to generate a yellow suspension. The mixture was heated to 50 °C for 12 h. All of the insoluble material dissolved to produce a clear yellow solution, in which a 91% yield of the title compound had formed, as indicated by ^{31}P NMR spectroscopy. The pure product was isolated by column chromatography on silica gel.

Other strategies for constructing dialkyl alkynylphosphonates start from dialkyl alkylphosphonates, such as $(EtO)_2P(O)CCl_3$ (*402*) or $(EtO)_2P(O)CH_2C(O)R$ (*403*), and seem less versatile than some of the methods already noted. A convenient P(V) approach involves treating a lithium acetylenide, prepared from lithium diisopropylamide (LDA) and the alkyne, with a dialkyl phosphorochloridate. This allows the formation of *ortho*-substituted dialkyl phenylethynylphosphonates such as (**262**) in high yield (Fig. 2.20.6) (*404*).

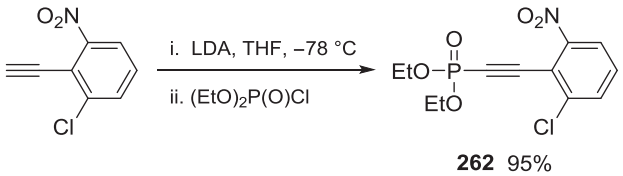


Figure 2.20.6

▶ *Diethyl 2-(2-chloro-6-nitrophenyl)ethynylphosphonate* (**262**) (*404*). A solution of 2-chloro-6-nitrophenylethyne (46.3 mg, 0.254 mmol) in THF (0.5 ml) was added via a cannula to a stirred solution of LDA prepared from diisopropylamine (25.7 mg, 36.0 µl, 0.254 mmol) and *n*-BuLi (1.6 M in hexanes, 0.16 ml, 0.254 mmol) in THF (0.3 ml) at −78 °C. After 30 min, the dark brown mixture was added via a cannula to a solution of diethyl phosphorochloridate (35.8 mg, 28.9 µl, 0.203 mmol) in THF (0.5 ml). After 30 min, the solution was allowed to warm to room temperature, then quenched with saturated aqueous ammonium chloride (10 ml), diluted with dichloromethane (15 ml) and washed with water (10 ml) and saturated brine (10 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel, eluting with 0—2% methanol—dichloromethane, to give a yellow liquid (62.0 mg, 95%).

2.21 ALKYL ALKYLPHOSPHONOCHLORIDATES R(R′O)P(O)Cl

The preparation of alkyl alkylphosphonochloridates usually starts from the alkylphosphonic dichloride, dialkyl alkylphosphonate or dialkyl alkylphosphonothionate. Alkylphosphonic dichlorides can be treated with one equivalent of the appropriate alcohol and one of a base (e.g. *N,N*-diethylaniline, pyridine or triethylamine). Another method consists of treating a dialkyl alkylphosphonate or dialkyl alkylphosphonothionate with a chlorinating agent, such as phosphorus oxychloride, phosgene, oxalyl chloride or thionyl chloride. The effectiveness of these transformations is discussed in this section. The literature on the phosphonate—phosphonochloridate conversion up to the year 2000 has been reviewed (*405*).

The chlorine atom of alkyl alkylphosphonochloridates is as a rule very reactive, though certain modifications to the structure of these compounds alter this reactivity markedly. The reactivity to nucleophilic substitution depends upon the nature and the size of the hydrocarbon group attached to the phosphorus atom; a lengthening or branching of this group markedly reduces reactivity. Little data on the toxicity of alkyl alkylphosphonochloridates are available. These compounds are far less toxic than their fluoridate counterparts. The LD_{50} values in rats (route not stated, but presumably injection) for EtO(Me)P(O)Cl and *i*-PrO(Me)P(O)Cl are 14.0 mg/kg and 4.5 mg/kg (*406*).

2.21.1 From alkylphosphonic dichlorides and alcohols

Methylphosphonic dichloride (**22**) reacts with a molar equivalent of an alcohol in diethyl ether in the presence of a base, such as pyridine, with cooling to provide after distillation the pure alkyl methylphosphonochloridate. The synthesis of methyl methylphosphonochloridate (**174**) and cyclohexyl methylphosphonochloridate (**263**) is accomplished in this way (Fig. 2.21.1.1) (*262*). Triethylamine is a popular base for achieving such transformations and has proved to be successful in the synthesis of many alkyl alkylphosphonochloridates (Fig. 2.21.1.2).

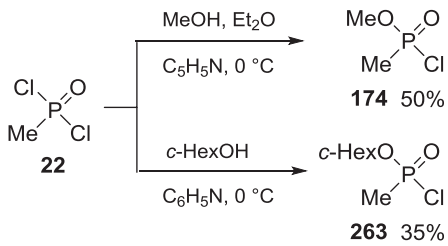
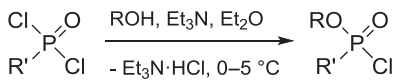


Figure 2.21.1.1



Alkyl alkylphosphonochloridates

R	R'	Bp (°C/mmHg)	Yield (%)	Ref.
Me	Me	54/4	55	(*408,409*)
Et	Me	44/2.5	55	(*408,409*)
n-Pr	Me	52/2	nr	(*409*)
i-Pr	Me	44/0.6	56	(*409,411*)
t-BuCH$_2$	Me	68/1	nr	(*409*)
t-BuCH(Me)	Me	52/0.01	71[a], 49[b]	(*409,411*)
Ph	Me	80/0.5	67	(*408*)
Me	Et	39/0.2	74	(*408*)
Et	Et	52/2	72	(*408*)
n-Pr	*n*-Pr	65/2	nr	(*39,410*)
i-Pr	*n*-Pr	78–79/6	nr	(*39,410*)
n-Bu	*n*-Pr	87/2.5	nr	(*39,410*)
i-Bu	*n*-Pr	86–87/4	nr	(*39,410*)
n-Pr	*i*-Pr	60/3	nr	(*39,410*)
i-Pr	*i*-Pr	72–73/6	nr	(*39,410*)
Et	*i*-Pr	89/23	nr	(*409*)
Et	*t*-Bu	32/0.5	nr	(*409*)
Et	ClCH$_2$	64/1.2	30	(*147*)
Et	Ph	98/0.05	88	(*408,409*)

a. Benzene, 2.5 h reflux. *b.* 4 h reflux (bp 52–54 °C/0.02 mmHg) (*155*)
nr = not reported in the reference cited

Figure 2.21.1.2

Catalytic mono-esterification of methylphosphonic dichloride (**22**) with secondary fluoroalcohols such as racemic *n*-BuCH(CF_3)OH can be achieved by heating a mixture of these reagents to 160 °C for 1–3 h in the presence of 1–5 mol% lithium chloride or magnesium chloride. The fluoroalkyl methylphosphonochloridate (**264**) forms as an equimolar mixture of diastereomers (Fig. 2.21.1.3) (*407*). This method is only applicable to the synthesis of chloridates whose *P*-alkoxy group is resistant to dealkylation by the liberated hydrogen chloride; acid-sensitive chloridates cannot be accessed in this way.

Figure 2.21.1.3

▷ *Alkyl alkylphosphonochloridates RO(R′)P(O)Cl (from alcoholysis of alkylphosphonic dichlorides)* (*409*). A solution of the appropriate alcohol (1 mol) and triethylamine (1 mol) was added dropwise to a stirred solution of methylphosphonic dichloride (1 mol) in ether at 0–5 °C. After addition, the mixture was left to stand for 12 h. The precipitate of triethylamine hydrochloride was filtered off, and the filtrate was concentrated. Fractionation of the residue under reduced pressure gave the title compounds as colourless liquids (Fig. 2.21.1.2).

▷ *Methyl methylphosphonochloridate MeO(Me)P(O)Cl* (**174**) (*262*). A solution of anhydrous methanol (16.0 g, 0.5 mol) and anhydrous pyridine (39.5 g, 0.5 mol) in anhydrous ether (50 ml) was added dropwise to a stirred solution of methylphosphonic dichloride (66.5 g, 0.5 mol) in anhydrous ether (300 ml) at 0–5 °C. After addition, the mixture was stirred at this temperature for 15 min and then at room temperature for 3 h. Pyridine hydrochloride was filtered off, the filtrate concentrated and the residue distilled to give the title compound (32.1 g, 50%). Bp 72 °C/20 mmHg. The use of cyclohexanol instead of methanol on a 0.3 mol scale gave cyclohexyl methylphosphonochloridate **263** (35%). Bp 110 °C/5 mmHg.

▷ *Isopropyl methylphosphonochloridate i-PrO(Me)P(O)Cl* (**57**) (*411*). A solution of isopropanol (2.9 ml, 37.6 mmol) and triethylamine (5.6 ml, 40.2 mmol) in anhydrous ether (20 ml) was added dropwise to a stirred solution of methylphosphonic dichloride (5.0 g, 37.6 mmol) in anhydrous ether (50 ml) at 0–5 °C. After addition, the reaction mixture was stirred under argon at room temperature. A white precipitate formed immediately. After 3.5 h, the precipitate was removed by filtration through Celite™, and the filtrate was concentrated. Fractionation of the residue under reduced pressure gave a colourless liquid (3.3 g, 56%). Bp 92 °C/60 mmHg. δ_P (121.4 MHz, $CDCl_3$) 39.7 ppm.

▷ *Cyclohexyl methylphosphonochloridate c-HexO(Me)P(O)Cl* (**263**) (*411*). A solution of cyclohexanol (4.5 g, 45.1 mmol) and triethylamine (6.7 ml, 48.3 mmol) in anhydrous ether (24 ml) was added dropwise to a stirred solution of methylphosphonic dichloride (6.0 g, 45.1 mmol) in anhydrous ether (60 ml) at 0–5 °C under argon. A white precipitate formed immediately. The mixture was stirred

for 20 h at room temperature and then filtered through Celite™. The filtrate was concentrated under vacuum. Fractionation of the residue under reduced pressure gave a colourless liquid (4.7 g, 53%). δ_P (121.4 MHz, $CDCl_3$) 37.9 ppm.

▶ *Pinacolyl methylphosphonochloridate t-BuCH(Me)O(Me)P(O)Cl (411)*. A solution of pinacolyl alcohol (9.4 ml, 75.2 mmol) and triethylamine (10.7 ml, 76.7 mmol) in benzene (10 ml) was added dropwise to a stirred solution of methylphosphonic dichloride (10.0 g, 75.2 mmol) in benzene (44 ml). After addition, the mixture was stirred under argon at room temperature for 1 h before it was heated under reflux for 2.5 h. The mixture was cooled to room temperature, diluted with anhydrous ether, and filtered through Celite™. The Celite™ pad was washed with ether, and the filtrate and washes were combined and concentrated. Fractionation of the residue provided a colourless liquid comprising two diastereoisomers (10.6 g, 71%). Bp 81–88 °C/5–10 mmHg. δ_P (121.4 MHz, $CDCl_3$) 40.0 and 40.6 ppm.

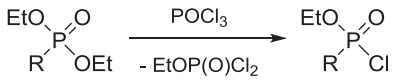
▶ *Isopropyl ethylphosphonochloridate i-PrO(Et)P(O)Cl (39)*. A mixture of isopropanol (30 g, 0.5 mol) and triethylamine (50.5 g, 0.5 mol) in petroleum ether (bp 60–80 °C, 200 ml) was added dropwise to a solution of ethylphosphonic dichloride (73.5 g, 0.5 mol) in the same solvent (300 ml). The experimental details were similar to those of the previous recipe. Distillation under reduced pressure gave the product (55 g, 65%). Bp 62 °C/5 mmHg. Redistillation gave the pure material. Bp 61 °C/45 mmHg.

▶ *Isopropyl n-pentylphosphonochloridate i-PrO(n-Pentyl)P(O)Cl (39)*. A mixture of isopropanol (26.5 g, 0.44 mol), *N,N*-diethylaniline (66 g, 0.44 mol) and petroleum ether (bp 60–80 °C, 200 ml) was heated under reflux in a flask fitted with a sealed stirrer, a dropping funnel and reflux condenser. To this stirred mixture was added a solution of *n*-pentylphosphonic dichloride (84 g, 0.44 mol) in petroleum ether (60 ml). After the addition, which took 30 min, the mixture was heated under reflux for a further 3 h, cooled and filtered. The solvent was evaporated from the filtrate, and the residue was fractionated to give the chloridate (65.5 g, 70%). Bp 84 °C/3 mmHg.

▶ *Ethyl phenylphosphonochloridate EtO(Ph)P(O)Cl (412)*. Absolute ethanol (9.2 g, 0.2 mol) was added dropwise to a stirred solution of phenylphosphonic dichloride (39.0 g, 0.2 mol) in anhydrous chloroform (100 ml) at 0 °C. The mixture was stirred for 4 h, and the solvent was removed. Distillation of the residue gave the title compound (30.7 g, 75%). Bp 120 °C/2 mmHg.

2.21.2 From dialkyl alkylphosphonates and phosphorus oxychloride

Some dialkyl alkylphosphonates can be converted into alkyl alkylphosphonochloridates by heating with a slight molar excess of phosphorus oxychloride for several hours (Fig. 2.21.2.1) (*413*). The mixture is then distilled to separate the product from the alkyl phosphorodichloridate by-product. The yields of the chloridate are satisfactory. This process is often superior to the treatment of dialkyl alkylphosphonates with phosphorus pentachloride in the cold (*414*), which can lead to the desired chloridate forming together with the alkylphosphonic dichloride; the two are very difficult to separate by fractionation (*415*).



Ethyl alkylphosphonochloridates

R	$POCl_3$ [a]	Temp. (°C) [b]	Time (h)	Bp (°C/mmHg)	Yield [c] (%)	δ_P (ppm)
$ClCH_2$	1:1	70	3	48/0.2	85	31.2
ClCH(Me) [d]	1:1	70	3	52/0.2	82	36.0, 35.3
$BrCH_2CH_2$	1:3	70	2	74/0.2	84	37.0
$PhCH_2$	1:1	60	4	117/0.1	78	39.4
$CH_2{=}CHCH_2$	1:1	60	4	53/0.1	79	39.5

a. Molar equivalent with respect to the phosphonate. *b.* Bath temperature. *c.* Distilled product.
d. Mixture of two diastereoisomers.

Figure 2.21.2.1

▶ *Ethyl alkylphosphonochloridates (from diethyl alkylphosphonates and phosphorus oxychloride)* (*413*). A stirred mixture of the diethyl alkylphosphonate (10 mmol) and freshly distilled phosphorus oxychloride (quantity given in Fig. 2.21.2.1) was heated to a precise temperature for a specified time under nitrogen. The bath temperature was checked carefully during the entire reaction period to ensure that no overheating occurred. The crude mixture was distilled under reduced pressure, with the excess of phosphorus oxychloride and ethyl phosphorodichloridate being collected first.

2.21.3 From dialkyl alkylphosphonates and phosgene

Phosgene, with proper temperature control, only removes one alkoxy group from dialkyl alkylphosphonates as the alkyl chloride, often giving a good yield of the alkyl alkylphosphonochloridate (*39*,*416*,*417*), although sometimes pyrophosphonate formation can occur. Two reaction pathways are potentially available: alkylation of the phosphoryl oxygen atom (P═O) or an ester oxygen atom (RO—P). It is not possible to decide unambiguously between the two mechanisms on present evidence, although the former seems more probable, giving a quasi-phosphonium intermediate that decomposes with the loss of carbon dioxide (Fig. 2.21.3.1). The final stage involves the removal of an alkyl group analogous to the last step of the Arbuzov reaction. Anhydrous phosgene

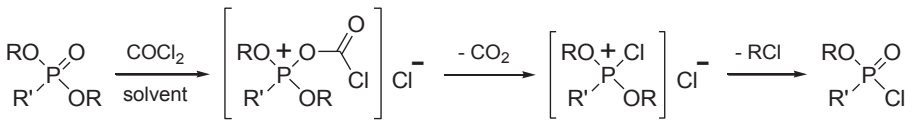
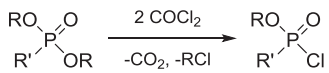


Figure 2.21.3.1

is bubbled through the neat dialkyl alkylphosphonates at a temperature below 25 °C for 10–24 h depending on the structure of the dialkyl alkylphosphonate. Temperature control is important. Above 150 °C, the dialkyl alkylphosphonates are converted by phosgene into polymeric alkyloxophosphine oxides $(RPO_2)_n$, but this may be due to pyrolysis of the alkylphosphonochloridate first formed (*39*). No reaction appears to take place between tetraalkyl polymethylenediphosphonates and phosgene.

The alkyl alkylphosphonochloridates are isolated by distillation under a reduced pressure of not >3–4 mmHg. To isolate the pure chloridate, the dialkyl alkylphosphonate must be converted completely into the target alkylphosphonochloridate; separation by fractional distillation is difficult, because the two species have very similar boiling points. The highest yields are obtained when the R alkyl group has no more than three carbon atoms (Fig. 2.21.3.2). A longer chain or a more hindered alkyl group necessitates longer reaction times (several days) and results in lower yields (*405*). When diisopropyl methylphosphonate is treated with phosgene, a 90% yield of pure isopropyl methylphosphonochloridate can be realised (*132*). Dialkyl alkylene and alkenylphosphonates are more resistant to phosgenation than are corresponding dialkyl alkylphosphonates, and diisopropyl *tert*-butylphosphonate is recovered unchanged even after prolonged treatment with phosgene (*418*).



Alkyl alkylphosphonochloridates

R	R'	Yield (%)	Bp (°C/mmHg)	Ref.
Me	Me	73	164–165	(*419*)
Et	Me	100	37/0.7	(*418*)
Et	Et	100	43/1.0	(*418*)
Et	CH_2=CH	28	75/18.0	(*39*)
n-Pr	*n*-Pr	nr	65/2.0	(*410*)
i-Pr	Me	91–100	40/1.0	(*408*)
i-Pr	Et	100	38/1.0	(*408*)
i-Pr	*n*-Pr	80	62/3.0	(*39*)
i-Pr	*n*-Bu	nr	76/3.0	(*39*)
i-Pr	*n*-Pentyl	nr	84/3.0	(*39*)
i-Pr	*n*-Hexyl	nr	96/2.5	(*39*)
i-Pr	CH_2=$CHCH_2$	nr	72/3.0	(*39*)

nr = not reported in the references

Figure 2.21.3.2

▶ *Methyl methylphosphonochloridate MeO(Me)P(O)Cl* (**174**) (*419*). A stirred solution of dimethyl methylphosphonate (2.0 g, 16 mmol) in benzene (50 ml) was treated with an excess of phosgene at

0–5 °C. The benzene was removed, and the residue distilled to give a colourless liquid (1.5 g, 73%). Bp 164–165 °C.

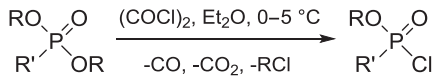
▶ *Isopropyl methylphosphonochloridate i-PrO(Me)P(O)Cl* (**57**) (*132*). Diisopropyl methylphosphonate (40 g, 0.22 mol) was treated with phosgene at 400 ml/min for 9 min. The temperature rose to 60 °C during the passage of the gas. After allowing to stand for 2 h, the mixture was again treated with phosgene at 400 ml/min for 7 min and at 200 ml/min for 12 min, with the temperature rising to 44 °C. After standing overnight, the mixture was transferred to a distillation flask fitted with a fractionating column, heated on an oil bath to 55 ± 5 °C and connected to a water pump until the pressure fell to ≤14 mmHg. The residue was then distilled with the aid of an oil pump. Practically, the entire product distilled at 47 °C/3 mmHg. The yield was 27.5 g (80%). A similar preparation, but keeping the temperature below 45 °C during the passage of the phosgene by surrounding the apparatus with a beaker of cold water, gave very similar results. The yield from 40 g of the starting material was 28.0 g (81%). Alternatively, a stirred solution of diisopropyl methylphosphonate (10.0 g, 56 mmol) in anhydrous benzene (250 ml) was treated similarly with phosgene. Distillation gave isopropyl chloride (4.3 g, bp 37 °C) and isopropyl methylphosphonochloridate (8.0 g, 91%). Bp 38–40 °C/1 mmHg (*419*).

▶ *Isopropyl n-propylphosphonochloridate i-PrO(n-Pr)P(O)Cl* (*39,420*). Diisopropyl *n*-propylphosphonate (29.1 g, 0.14 mol) was treated with phosgene. The reaction was vigorous at first. After degassing, distillation under reduced pressure gave the product (21 g, 80%). Bp 62 °C/3 mmHg. Higher esters can be prepared similarly: isopropyl *n*-butyl (bp 76 °C/3 mmHg), isopropyl *n*-pentyl (bp 84 °C/3 mmHg) and isopropyl *n*-hexylphosphonochloridate (bp 96 °C/2.5 mmHg).

▶ *Isopropyl allylphosphonochloridate i-PrO(CH_2=$CHCH_2$)P(O)Cl* (*39*). Diisopropyl allylphosphonate was phosgenated in the usual manner. The product boiled at 64.5–66.5 °C/1.5 mmHg (71–73 °C/3 mmHg) but could not be obtained pure; some decomposition occurred upon the final distillation. The product was pure enough to be used to make various derivatives. When phosgene was replaced by thionyl chloride, very little phosphonochloridate was obtained; the product in this case was diisopropyl diallylpyrophosphonate (bp 132 °C/2 mmHg) together with a considerable amount of an involatile dark sticky residue.

2.21.4 From dialkyl alkylphosphonates and oxalyl chloride

Oxalyl chloride reacts with some dialkyl alkylphosphonates in diethyl ether to often furnish the desired alkyl alkylphosphonochloridates cleanly and in high yield (Fig. 2.21.4.1) (*125,406*). The by-products are carbon monoxide, carbon dioxide and the corresponding alkyl chloride, whose lower members are low boiling and easily removed. The reaction is therefore usually accompanied by gentle effervescence. In the case of the less reactive dialkyl alkylphosphonates, it is sometimes advisable to add a small amount of DMF to the reaction mixture as a catalyst; its presence generally accelerates the chlorination process. Formation of carbon monoxide necessitates the use of an efficient fume cupboard.



Alkyl alkylphosphonochloridates

R	R'	Yield (%)	Bp (°C/mmHg)	Ref.
Me	Me	85	73/22	(*406*)
Et	Me	88	83/21	(*406*)
n-Pr	Me	87	94/21	(*406*)
i-Pr	Me	61	83/22	(*406*)
n-Bu	Me	93	105/19	(*406*)
i-Pr	CD_3	78	82–84/15–25	(*125*)

Figure 2.21.4.1

Selective monodeprotection of alkylphosphonate benzyl esters using quinuclidine and chlorination of the subsequent salts with oxalyl chloride allows the preparation of some alkyl alkylphosphonochloridates in a convenient one-pot procedure (Fig. 2.21.4.2) (*421*). Chloridates of structure BnO(Me)P(O)Cl, for example, are versatile intermediates, and are not easily obtained pure by the alternative reaction of $MeP(O)Cl_2$ and a molar equivalent each of benzyl alcohol and a base (due to a propensity to undergo double substitution). Their treatment with an alcohol under basic conditions gives species BnO(Me)P(O)OR that can be obtained in excellent purity by chromatography on silica gel. Debenzylation of these species by catalytic hydrogenation gives the alkyl alkylphosphonic acids RO(Me)P(O)OH, which are the first hydrolysis products of organophosphorus nerve agents, and therefore important analytical standards in investigations of alleged chemical warfare (*17*,*18*,*422*–*424*).

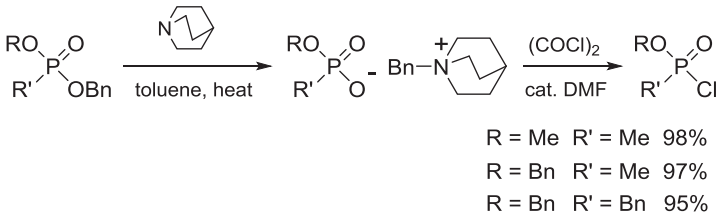


Figure 2.21.4.2

▶ *Alkyl methylphosphonochloridates RO(Me)P(O)Cl (from dialkyl methylphosphonates and oxalyl chloride)* (*406*). A solution of oxalyl chloride (14.6 g, 0.115 mol) in anhydrous ether (10 ml) was added dropwise to a stirred solution of the dialkyl methylphosphonate (0.100 mol) in anhydrous ether (150 ml) at 0–5 °C. The mixture was left to stand at room temperature for 24 h. The solvent and alkyl chloride formed were evaporated, and the residue was distilled under reduced pressure to give the chloridate (Fig. 2.21.4.1).

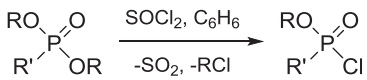
▶ *Ethyl methylphosphonochloridate EtO(Me)P(O)Cl (411)*. A solution of oxalyl chloride (8 ml, 94.5 mmol) in chloroform (20 ml) was added dropwise to a stirred solution of diethyl methylphosphonate (10 g, 65.7 mmol) in chloroform (20 ml) under argon. The mixture was stirred at room temperature for 20 h. The solvent was removed, and the residue was fractionated under reduced pressure to give a colourless liquid (7.2 g, 77%). Bp 70 °C/10–15 mmHg. δ_P (202 MHz, $CDCl_3$) 40.5 ppm.

▶ *Benzyl methylphosphonochloridate BnO(Me)P(O)Cl (421)*. Dibenzyl methylphosphonate (0.78 g, 2.84 mmol) and quinuclidine (316 mg, 2.84 mmol) were stirred in anhydrous refluxing toluene (5 ml) for 2 h under argon. The mixture was cooled to 0 °C and oxalyl chloride (495 µl, 5.68 mmol) and DMF (2 µl) were added. After 30 min, the white precipitate of benzyl quinuclidinium chloride was filtered off. The solvent was removed from the filtrate to provide benzyl methylphosphonochloridate (0.52 g, 97%).

▶ *Isopropyl d_3-methylphosphonochloridate i-PrO(CD_3)P(O)Cl (125)*. Diisopropyl d_3-methylphosphonate (3.41 g, 18.6 mmol) was added to anhydrous ether (20 ml), and the solution was cooled in an ice bath for 10 min. Oxalyl chloride (2.69 g, 21.2 mmol) in anhydrous ether (5 ml) was then added dropwise with stirring under nitrogen. Afterwards, the solution was warmed to room temperature, and stirring was continued for another 36 h. Fractional distillation gave the title compound (2.33 g, 78%). Bp 82–84 °C/15–25 mmHg.

2.21.5 From dialkyl alkylphosphonates and thionyl chloride

Treatment of dialkyl alkylphosphonates with thionyl chloride in boiling benzene, or without solvent with heating, gives results that depend very much on the structure of the phosphorus reactant (*39,406*). In the methylphosphonate series, the dimethyl and diisopropyl esters yield only polymeric products, yet the diethyl, di-*n*-propyl and di-*n*-butyl esters provide the desired alkyl methylphosphonochloridates in >80% yield (Fig. 2.21.5.1) (*406*). Diethyl vinylphosphonate (**32**) reacts with



Alkyl alkylphosphonochloridates

R	R'	Yield (%)	Bp (°C/mmHg)	Ref.
Me	Me	0	–	(*406*)
Et	Me	80	83–84/23	(*406*)
n-Pr	Me	85	63/4	(*406*)
i-Pr	Me	0	–	(*406*)
n-Bu	Me	87	70/3	(*406*)
Et	CH_2=CH	28	75/18	(*39*)

nr = not reported in the references

Figure 2.21.5.1

thionyl chloride to give ethyl vinylphosphonochloridate (**265**), albeit in a much lower yield, plus a minor quantity of vinylphosphonic dichloride (**34**) (Fig. 2.21.5.2). In general, this method has only limited utility for the synthesis of alkyl alkylphosphonochloridates.

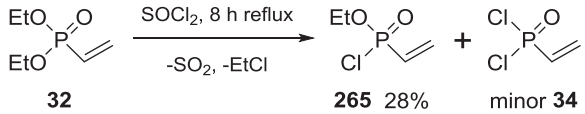


Figure 2.21.5.2

▶ *Alkyl methylphosphonochloridates* (*from dialkyl methylphosphonates and thionyl chloride*) (*406*). A stirred mixture of the dialkyl methylphosphonate (1 mol), in an equivalent volume of anhydrous benzene, with thionyl chloride (2.5 mol) was heated under reflux for 3 h, and then distilled under reduced pressure, to give the products listed in Fig. 2.21.5.1.

▶ *Ethyl vinylphosphonochloridate* $EtO(CH_2{=}CH)P(O)Cl$ (*39*). Diethyl vinylphosphonate (50 g, 0.3 mol) and thionyl chloride (50 ml, 0.7 mol) were refluxed for 8 h, whereafter evolution of ethyl chloride and sulfur dioxide had almost ceased. After removing the excess of thionyl chloride, distillation under reduced pressure gave a small forerun of vinylphosphonic dichloride (bp 65 °C/18 mmHg), followed by the title compound (13 g, 28%). Bp 75 °C/18 mmHg. It could not be obtained entirely free from the dichloride. The high-boiling residue comprised mainly diethyl divinylpyrophosphonate.

2.21.6 From dialkyl alkylphosphonothionates and phosgene

At room temperature, certain dialkyl alkylphosphonothionates react with phosgene with loss of sulfur as carbonyl sulfide, providing another route to alkyl alkylphosphonochloridates (e.g. **177** and **266**) (Fig. 2.21.6.1) (*420*). Phosgenation of (±)- or (−)-*O*-ethyl hydrogen ethylphosphonothioate gives (±)-ethyl ethylphosphonochloridate (**267**) (*425*). When the sodium salt of the (−)-acid is used, the (+)-chloridate is obtained. The (+)- and (−)-isopropyl methylphosphonochloridates are prepared similarly. The stereochemical course of this reaction, which could not be varied whether run in hexane—phosgene, acetone—phosgene, or dioxane—phosgene, proceeds with inversion of configuration.

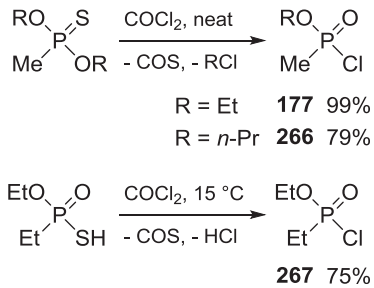


Figure 2.21.6.1

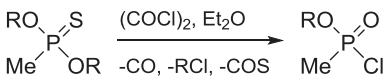
▶ *Ethyl methylphosphonochloridate EtO(Me)P(O)Cl* (**177**) (*420*). Diethyl methylphosphonothionate (4.75 g, 28.3 mmol) was treated with phosgene for 5 h at room temperature during which time the volume of the mixture doubled. The product, after being degassed the next day by passage of dry air, gave the title compound (4.0 g, 99%).

▶ *n-Propyl methylphosphonochloridate n-PrO(Me)P(O)Cl* (**266**) (*420*). Di-*n*-propyl methylphosphonothionate (4.75 g, 24.2 mmol) was treated similarly but was kept for 3 days before the excess of phosgene was removed. Fractionation gave the title compound (3.0 g, 79%). Bp not stated.

▶ *Ethyl ethylphosphonochloridate EtO(Et)P(O)Cl* (**267**) (*425*). Phosgene was bubbled through *O*-ethyl hydrogen ethylphosphonothioate (5.0 g, 32 mmol) for 5 h under anhydrous conditions at 10–20 °C. The mixture was allowed to stand at room temperature for 24 h and was then degassed at 200 mmHg. The residue was distilled under reduced pressure to give the product (3.8 g, 75%). Bp 49–50 °C/3 mmHg.

2.21.7 From dialkyl alkylphosphonothionates and oxalyl chloride

Dialkyl methylphosphonothionates react with oxalyl chloride in diethyl ether to provide alkyl methylphosphonochloridates in a high yield (Fig. 2.21.7.1) (*406*). The by-products are carbon monoxide, alkyl halide and presumably carbonyl sulfide.



Alkyl methylphosphonochloridates

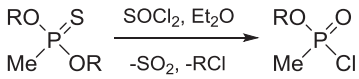
R	Yield (%)	Bp (°C/mmHg)
Me	85	73/22
Et	87	83/21
n-Pr	95	94/21
i-Pr	75	83/22
n-Bu	91	105/19

Figure 2.21.7.1

▶ *Alkyl methylphosphonochloridates RO(Me)P(O)Cl (from dialkyl methylphosphonothionates and oxalyl chloride)* (*406*). Oxalyl chloride (1.5 mol for the methyl ester, 1.75 mol for the ethyl and isopropyl esters, 2 mol for the *n*-propyl and *n*-butyl esters) in ether (200 ml) was added to a stirred solution of the dialkyl methylphosphonothionate (1 mol) in ether (200 ml). After 24 h, the volatile material was distilled off, and the product was fractionated under vacuum.

2.21.8 From dialkyl alkylphosphonothionates and thionyl chloride

Dialkyl methylphosphonothionates react with thionyl chloride in diethyl ether to provide alkyl methylphosphonochloridates in high yield (Fig. 2.21.8.1) (*406*). The by-products are sulfur dioxide and the alkyl halide.



Alkyl alkylphosphonochloridates

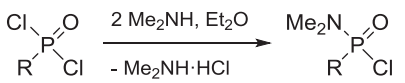
R	Yield (%)	Bp (°C/mmHg)
Me	50	73/22
Et	72	83/21
n-Pr	80	94/21
i-Pr	62	83/22
n-Bu	82	105/19

Figure 2.21.8.1

▶ *Alkyl methylphosphonochloridates RO(Me)P(O)Cl (from dialkyl methylphosphonothionates and thionyl chloride)* (*406*). The diester (1 mol) was added dropwise to a stirred solution of thionyl chloride (2.5 mol). The spontaneous reaction, which was accompanied by precipitation of sulfur, was completed by heating the mixture under reflux for 2 h. The sulfur was filtered off, and the alkyl methylphosphonochloridate was fractionated.

2.22 *N,N*-DIALKYL ALKYLPHOSPHONAMIDOCHLORIDATES $R(R'_2N)P(O)Cl$

Treatment of alkylphosphonic dichlorides with 2 molar equivalents of dimethylamine in ether provides *N,N*-dimethyl alkylphosphonamidochloridates (**268**) and (**269**) in a good yield (Fig. 2.22.1) (*426*). These compounds are purified by distillation under reduced pressure.



R = *i*-Pr **268** 84%
R = $ClCH_2$ **269** 82%

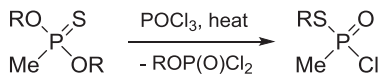
Figure 2.22.1

▶ *N,N-Dimethyl isopropylphosphonamidochloridate* $Me_2N(i\text{-}Pr)P(O)Cl$ (**268**) (*426*). A solution of dimethylamine (4.5 g, 100 mmol) in ether (50 ml) was added dropwise to a stirred solution of isopropylphosphonic dichloride (8.05 g, 50 mmol) in ether (100 ml) at 0–5 °C. After addition, the mixture was warmed to room temperature and allowed to stand for 12 h. The precipitate of dimethylamine hydrochloride was filtered off. Concentration of the filtrate and distillation of the residue gave a colourless liquid (7.1 g, 84%). Bp 63 °C/0.1 mmHg.

▶ *N,N-Dimethyl chloromethylphosphonamidochloridate* $Me_2N(ClCH_2)P(O)Cl$ (**269**) (*426*). A similar protocol using dimethylamine (4.5 g, 100 mmol) and chloromethylphosphonic dichloride (8.4 g, 50 mmol) gave a colourless liquid (7.2 g, 82%). Bp 77–79 °C/0.1 mmHg. Likewise, diethylamine (7.3 g, 100 mmol) gave *N,N*-diethyl chloromethylphosphonamidochloridate $Et_2N(ClCH_2)P(O)Cl$ (8.7 g, 85%). Bp 115–120 °C/0.1 mmHg.

2.23 *S*-ALKYL ALKYLPHOSPHONOCHLORIDOTHIOLATES R(R′S)P(O)Cl

An efficient method of synthesis of these compounds consists of heating dialkyl alkylphosphonothionates with phosphorus oxychloride (Fig. 2.23.1) (*427*). Isomerisation of the P═S to the P–S bond occurs during chlorination. A temperature of 80–100 °C is required for complete reaction. Increasing the chain length or steric bulk of the two alkoxy groups in the starting thionate results in slower chlorination, and higher temperatures and longer reaction times are required for efficient conversion to the product. When the R group is isopropyl or *tert*-butyl, the desired chloridothiolate forms with difficulty. Purification of the product is achieved by distillation, with the alkyl phosphorodichloridate by-product being collected first. The main advantage of this synthetic method is that the dialkyl alkylphosphonothionates, obtained from alkylphosphonothioic dichlorides and cheap low-molecular-weight alcohols, are used as starting materials; this avoids the use of expensive alkyl bromides or malodorous thiols, especially methanethiol (bp 6 °C), which is difficult to deliver to any reaction mixture in precise amounts.



S-Alkyl alkylphosphonochloridothiolates

R	T (°C)	Time (h)	Bp (°C/mmHg)	Yield (%)
Me	80	1.5	72–74/8	74
Et	100	13	73–75/6	75
n-Pr	100	5	91–93/8	77
n-Bu	100	7	90–92/1	71

Figure 2.23.1

Dialkyl alkylphosphonothionates also react with phosgene in the absence of a solvent (Fig. 2.23.2) (*420*). Again isomerisation of the P═S to the P–S bond occurs during chlorination. The starting material is saturated with phosgene and then degassed to remove the volatile by-products. Distillation provides the target compound (e.g. **270**). *O,S*-Dialkyl alkylphosphonothiolates also react with phosgene to provide the chloridothionate (e.g. **271**). The mechanism of these reactions is not

understood fully but is postulated to involve the initial nucleophilic attack of the doubly bonded sulfur or oxygen atom of the starting material on the phosgene carbonyl group. Although the method is mild, it does involve the prolonged passage of toxic phosgene, and this necessitates careful working in a well-ventilated fume cupboard.

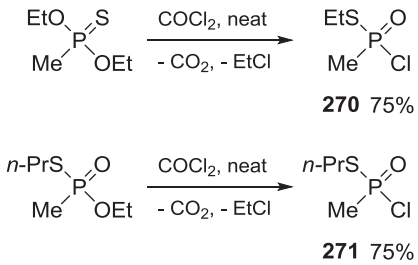


Figure 2.23.2

The selective mono-thiolation of alkylphosphonic dichlorides with aliphatic thiols in the presence of organic bases is generally a poor method for the synthesis of chloridothiolates (e.g. **270–272**) (Fig. 2.23.3) (*428*). Alkylphosphonic dichlorides are quite unreactive towards thiol nucleophiles, and often for reaction to occur readily heat has to be employed. The reaction is rarely selective. Usually, a mixture of unreacted dichloride, mono- and *bis*-substituted products, is obtained, which can be difficult to separate. Even if they can be isolated individually, the yields of the mono- and di-thiolo compounds are often low due to their ready dealkylation during synthesis by the thiolate anion, for example, $RSH + Et_3N + R'S(Me)P(O)Cl \rightarrow RSR' + Et_3N{\cdot}HCl + MeP(=S)=O$ (presumed). This type of degradation is particularly prevalent when the starting thiol is a primary one with a short alkyl chain, as the phosphorus-substituted products dealkylate easily. However, the use of secondary, hindered thiols can be advantageous and provide chloridothiolates that are otherwise unobtainable by other methods (*39*).

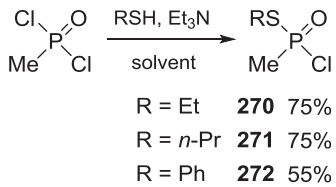


Figure 2.23.3

Low-molecular-weight *S*-alkyl alkylphosphonochloridothiolates are colourless liquids that have an obnoxious odour. They hydrolyse easily, especially under alkaline conditions, to the corresponding acids $R(R'S)P(O)OH$, and then more slowly to the alkylphosphonic acids $RP(O)(OH)_2$. In the

presence of tertiary bases such as triethylamine, *S*-alkyl alkylphosphonochloridothiolates react with various nucleophiles (NuH), for example, alcohols, phenols, thiols and amines, to yield derivatives of general formula R(R′S)P(O)Nu with loss of hydrogen chloride.

▶ *S-Ethyl methylphosphonochloridothiolate EtS(Me)P(O)Cl* (**270**) (*phosphorus oxychloride method*) (*427*). A stirred mixture of diethyl methylphosphonothionate (3.95 g, 24 mmol) and phosphorus oxychloride (3.70 g, 24 mmol) was heated to 95–100 °C for ≥3 h until the thionate had been consumed (monitoring by thin layer chromatography (TLC), eluting with 5:1 petroleum ether (bp 60–80 °C)–ethyl acetate). The ethyl phosphorodichloridate by-product was then removed by distillation by applying a vacuum of 10 mmHg and heating to 70 °C with an oil bath. The residue was distilled under reduced pressure to give a colourless liquid (2.85 g, 75%). Bp 73–75 °C/8 mmHg. This is a general method for converting dialkyl alkylphosphonothionates to *S*-alkyl alkylphosphonochloridothiolates (refer to Fig. 2.23.1).

▶ *S-Ethyl methylphosphonochloridothiolate EtS(Me)P(O)Cl* (**270**) (*thionate and phosgene method*) (*420*). Phosgene was bubbled through stirred diethyl methylphosphonothionate for 12 h at room temperature in an apparatus protected by drying tubes (full of anhydrous silica gel). The mixture was degassed by passing an inert gas through it. Distillation of the liquid gave the title compound (75%). Bp 46 °C/0.1 mmHg.

▶ *S-Ethyl methylphosphonochloridothiolate EtS(Me)P(O)Cl* (**270**) (*dichloride and thiol method*) (*429*). A solution of ethanethiol (31.0 g, 0.5 mol) and triethylamine (50.5 g, 0.5 mol) in anhydrous ether (100 ml) was added dropwise to a stirred solution of methylphosphonic dichloride (66.5 g, 0.5 mol) in anhydrous ether (250 ml). The mixture was left for 12 h and was then heated to 40 °C for 1.5 h. The precipitate was filtered off, and the filtrate was concentrated. Distillation of the residue three times yielded the title compound (25.2 g, 32%). Bp 93–95 °C/10 mmHg. δ_P (rel. to H_3PO_4) −60 ppm. The same method, but using benzenethiol, gave *S*-phenyl methylphosphonochloridothiolate (55%). Bp 116–118 °C/0.04 mmHg. δ_P (rel. to H_3PO_4) −52 ppm.

▶ *S-n-Propyl methylphosphonochloridothiolate n-PrS(Me)P(O)Cl* (**271**) (*420*). Phosgene was bubbled through stirred *O*-ethyl *S*-*n*-propyl methylphosphonothiolate for 9 h and left overnight before being degassed. Production of the title compound was confirmed by conversion of the crude product to *S*-(*n*-propyl) *N*-phenyl methylphosphonamidothiolate, which was recrystallised from benzene–light petroleum (bp 60–80 °C) to yield pure *n*-PrS(Me)P(O)NHPh (75%). Mp 98–100 °C.

▶ *S-Isopropyl methylphosphonochloridothiolate i-PrS(Me)P(O)Cl* (*39*). 2-Propanethiol (38.0 g, 0.5 mol) and triethylamine (50.5 g, 0.5 mol) in petroleum ether (bp 60–80 °C, 150 ml) were added dropwise over 15 min to a stirred solution of methylphosphonic dichloride (66.5 g, 0.5 mol) in the same solvent (150 ml). The reaction was carried out in a flask fitted with a sealed stirrer, dropping funnel and reflux condenser. The dropping funnel and condenser were equipped with calcium chloride guard tubes to confine, as far as possible, the odour of the thiol. After refluxing for 2 h, the mixture was cooled, and the triethylamine hydrochloride was filtered off. The solvent was removed

from the filtrate, and the residue was distilled to yield three fractions: (1) unchanged methylphosphonic dichloride (14 g, bp 40–41 °C/3 mmHg, solidified on cooling); (2) (32 g, bp 74–78 °C/2.5 mmHg) and (3) bp 105–112 °C/2 mmHg. Redistillation of Fractions 2 and 3 gave the title compound (bp 76 °C/2 mmHg) and *S,S′*-diisopropyl methylphosphonodithiolate (*i*-PrS)$_2$P(O)Me (bp 104 °C/2.5 mmHg). Similarly, *i*-PrS(Et)P(O)Cl (bp 82 °C/1.8 mmHg) and (*i*-PrS)$_2$P(O)Et (bp 108 °C/2 mmHg) were prepared starting from ethylphosphonic dichloride.

2.24 ALKYL ALKYLPHOSPHONOFLUORIDATES R(R′O)P(O)F

These compounds are highly toxic and exposure to milligram quantities can cause paralysis or death (Chapter 1) (*430,431*). The most toxic are covered by the legal framework of the Chemical Weapons Convention (*13*). Their preparation can only be accomplished safely by trained experts, working in accordance with national and international laws, and using specialist safety practices. Any deviation from this may result in legal prosecution and/or severe accident. It is inappropriate to cite the best synthetic methods for making these fluoridates. The most publicised routes, on which information is openly available, are noted for completion; fluorine-containing phosphorus compounds have been reviewed (*432,433*). Alkyl alkylphosphonofluoridates with a biotin side chain have been in vogue as reagents for profiling serine hydrolases and other macromolecules of biological interest (Chapter 1, Section 1.12) (*434–436*).

Cycloalkyl alkylphosphonofluoridates are good inhibitors of serine esterases and *O*-cyclohexyl benzyl- and phenethylphosphonofluoridates are potent inhibitors of chymotrypsin (*437*). They are prepared in acceptable yields by the reaction of the respective alkyl alkylphosphonochloridates with potassium fluoride (not shown). The dependence of the reactivity of alkyl alkylphosphonochloridates on the nature and size of the ester group is particularly marked in their reactions with sodium fluoride (*39*). Isopropyl methylphosphonochloridate can be fluorinated in boiling dichloromethane (~42 °C), the ethylphosphonochloridate requires boiling benzene (~80 °C) and the next three higher members boiling toluene (~110 °C). Isopropyl *n*-hexylphosphonochloridate cannot be fluorinated by this means. It is recovered unchanged after the reagents are mixed in boiling toluene; with higher boiling solvents, e.g. chlorobenzene, pyrolysis of the phosphonochloridate takes place before fluorination can occur.

Alkylphosphonic difluorides react with alcohols in the presence of an amine to provide alkyl alkylphosphonofluoridates and the amine hydrochloride (Fig. 2.24.1) (*438–440*). The rate depends on the choice of alcohol and amine.

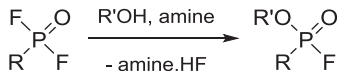


Figure 2.24.1

A well-known classical method of synthesis of isopropyl methylphosphonofluoridate (sarin) involves reaction of isopropanol with an equimolar mixture of methylphosphonic dichloride and methylphosphonic difluoride (di—di mixture) (*441*,*442*) in the overall reaction depicted in Fig. 2.24.2 (*132*). The relative esterification rates of methylphosphonic halides in isopropanol solution, obtained from heat evolution measurements, decline in the order: $MeP(O)ClF > MeP(O)Cl_2 >$ equimolar $MeP(O)Cl_2$-$MeP(O)F_2$ mixture > *i*-PrO(Me)P(O)Cl > $MeP(O)F_2$ (*443*). The esterification of methylphosphonic difluoride is catalysed by acids, whereas that of isopropyl methylphosphonochloridate is not.

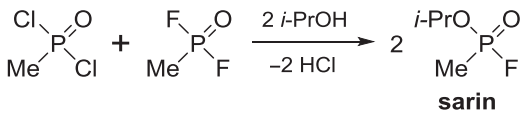


Figure 2.24.2

Studies of the mechanism of the 'di—di' reaction were made in Germany after the initial preparation of sarin by Gerhard Schrader (Chapter 1, Section 1.5.2) and also in England and the United States of America after World War 2. Based on observations of the ease of reaction and the nature and relative quantities of products formed in reactions of derivatives of methylphosphonic acid, B. J. Perry working at Porton Down UK postulated the sequence of the reactions shown in Fig. 2.24.3 (*39*).

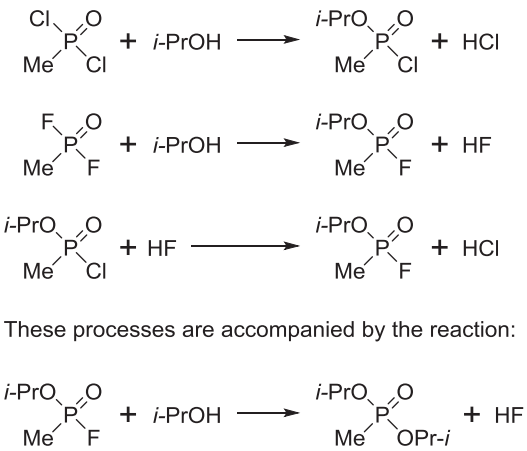


Figure 2.24.3

Evidence in support of Perry's hypothesis was his observation that production of small amounts of diisopropyl methylphosphonate was accompanied by the recovery of equivalent amounts of methylphosphonic difluoride. Another proposal was that the methylphosphonic dichloride and methylphosphonic difluoride equilibrated to form the more reactive methylphosphonic chlorofluoride (Fig. 2.24.4) and that this reacted with the isopropanol present. When a mole of isopropanol was added to the mixture containing a mole each of MeP(O)ClF, $MeP(O)Cl_2$ and $MeP(O)F_2$, a mole of sarin was produced, and the original quantities (within 5%) of the dichloride and difluoride were recovered by distillation (*443*).

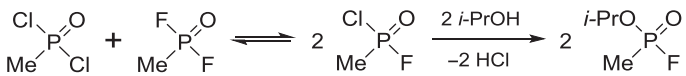


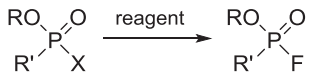
Figure 2.24.4

In considering the mechanism of esterification of the 'di—di' mixture, it is expected that any chlorofluoride present would react first. The only remaining question concerning the participation of the chlorofluoride is whether attainment of equilibrium is sufficiently rapid to replenish the supply of chlorofluoride reacting. The esterification of the 'di—di' mixture is essentially complete within 30 min at 25 °C. The metathesis of an equivalent mixture of methylphosphonic dichloride and methylphosphonic difluoride was studied by ^{1}H and ^{31}P NMR spectroscopy; at 100 °C, the amount of methylphosphonic chlorofluoride formed at equilibrium was found to be 25 mol% (*444*). Therefore, although the 'di—di' reaction seems to be adequately explained by Perry's mechanism, the possibility exists that at room temperature, the equilibrium formation of the chlorofluoride may constitute a contributory pathway to sarin.

Nearly all alkylphosphonic dichlorides can be used to yield a 'di—di' mixture, and since any of these mixtures will react with a great variety of alcohols, a large number of alkyl alkylphosphonofluoridates can be prepared by this method. The 'di—di' mixture containing alkylphosphonic dihalides with longer hydrocarbon groups reacts rather more sluggishly, as do certain hindered alcohols such as $i\text{-}Pr_2CHOH$. Two instances of failure may be recorded. A mixture of *tert*-butylphosphonic dichloride and *tert*-butylphosphonic difluoride does not give alkyl *tert*-butylphosphonofluoridates on treatment with alcohols since both the dihalides are abnormally unreactive. Also, when 4-nitrobenzyl alcohol is treated with an equimolar mixture of methylphosphonic dichloride and methylphosphonic difluoride, the product is not the expected 4-nitrobenzyl methylphosphonofluoridate but 4-nitrobenzyl chloride.

O,S-Dialkyl alkylphosphonothiolates contain an *S*-alkyl leaving group and react with fluoride under certain conditions to provide alkyl alkylphosphonofluoridates. Fluoride sources include tetra-*n*-butylammonium fluoride (*445,446*), silver(I) fluoride (*447*) and monohydroxyfluoboric acid (*448*). Various organophosphorus species can be converted into alkyl alkylphosphonofluoridates by

treatment with different reagents, as outlined in Fig. 2.24.5. Note that alkyl alkylphosphonofluoridates, for example, sarin, undergo basic hydrolysis (*449*) and react facilely with 1,2-dihydroxyphenols (*450*).



Alkyl alkylphosphonofluoridates

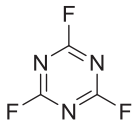
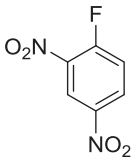
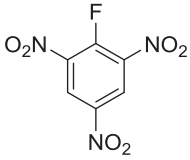
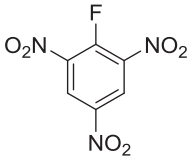
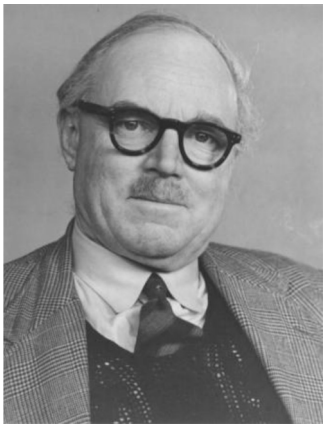
X	Reagent	Conditions	Ref.
OH		$ClCH_2CH_2Cl$	(*451*) (*452*)
OH	KF, 18-crown-6	$SOCl_2$	(*453*)
SR		Et_3N, C_6H_6	(*522*)
SNa		NaOH, acetone	(*455*)
CH_2CO_2Et		NaH, THF	(*456*)

Figure 2.24.5

▶ *Methyl methylphosphonofluoridate MeO(Me)P(O)F (di—di reaction)* (*441*). A solution of methanol (0.64 g, 20 mmol) in dichloromethane (10 ml) was added to a mixture of methylphosphonic dichloride (1.33 g, 10 mmol) and methylphosphonic difluoride (1.00 g, 10 mmol) in dichloromethane (50 ml) at 0 °C. After the solution had stood at room temperature for 24 h, the solvent was removed under vacuum (100 mmHg) and the product was distilled to give the fluoridate (1.10 g, 98%). Bp 80—82 °C/100 mmHg. δ_P (C_6D_6, from external H_3PO_4) 32.4 ppm (dqq, $^1J_{PF}$ 1045 Hz, $^2J_{PH}$ 18.6 Hz, $^3J_{PH}$ 11.4 Hz).

2.24.1 Biography



Arthur Henry Ford–Moore (1896-1958). Arthur Henry Ford–Moore was a brilliant experimentalist, whose working life was spent at the bench or at the laboratory table writing up the results of his own research (*454*). He had an infectious enthusiasm for his work, and a willingness and an outstanding ability to explain to others his experiments, their objects, results and implications. His written papers were a model of lucid reporting (*39*). His vivid use of words brought enlightenment and pleasure to the many audiences he faced during his career. His output was prodigious, and there is no doubt that, were it not for the secrecy surrounding his work, he would have been recognised as one of the leading chemists of his day. His outstanding ability for research was recognised in 1952 by special promotion – a mark of high distinction – to the UK government grade of Senior Principal Scientific Officer.

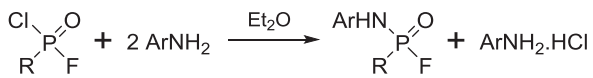
Ford–Moore was born at Ealing, Middlesex, in England, on October 11, 1896, and died suddenly at his home in Salisbury on May 29, 1958. After service as a Captain with the London Regiment in Palestine from 1915 to 1919, he graduated in 1921 with a BSc degree from Trinity College, Cambridge, and that year joined the Chemical Defence Experimental Station, Porton Down (United Kingdom). He was employed there until his death, except between 1942 and 1944 when he collaborated with the British pharmacologist Harry Raymond Ing FRS (1899–1974) (*457*) at the Dyson-Perrins Laboratory, Oxford (United Kingdom). Although security considerations restricted publication of much of his work, Ford–Moore was accepted internationally as an authority on chemical defence problems, particularly on the chemistry of organic compounds containing phosphorus and sulfur (*182*,*184*,*458*,*459*), and anticholinesterases (*460*). He was particularly saddened by the death of a colleague, Lawrence John Lermit (1916–1953), whose obituary he wrote (*461*). At the time of his own death in 1958, Ford–Moore was preparing a series of papers describing his latest results (*132*).

In his early researches, Ford—Moore gained recognition for his work on the toxicity of 1,4-dioxane (*462,463*), synthesis of nitroacetophenones (*464*) and chemistry of mustard gas, $S(CH_2CH_2Cl)_2$, and related compounds (*465—468*). He devoted his later years to the chemistry of organophosphorus compounds, and it is for work in this field, where his superb laboratory technique found ample scope, that he will be primarily remembered. He carried out a comprehensive examination of the chemistry of insecticidal and toxic organophosphorus compounds. This included the elucidation of chemical reactions of importance in the preparation of these compounds, the establishment of synthetic routes for producing them in high purity and the effect of variations in molecular structure on activity.

Ford—Moore also made lesser but valuable contributions to other branches of synthetic chemistry. Particularly noteworthy is the result of his collaboration with H. R. Ing. Together they prepared some 40 alkamine esters, mostly of the benzylic acids (*469*). Their testing as mydriatics (drugs that cause dilation of the pupil of the eye) was carried out in 1947. An outcome of this work was the manufacture and use in medicine of the mydriatic drug lachesine, $Ph_2C(OH)CO_2CH_2CH_2N^+Me_2Et\ Br^-$ (photograph reproduced courtesy of Dstl).

2.25 *N*-ALKYL OR *N,N*-DIALKYL ALKYLPHOSPHONAMIDOFLUORIDATES R(R′XN)P(O)F (X = H or R′)

Alkylphosphonic chlorofluorides (or alkylphosphonic difluorides) react with aromatic amines to give *N*-aryl alkylphosphonamidofluoridates (Fig. 2.25.1) (*142*). These colourless crystalline substances are readily soluble in the usual organic solvents, but poorly soluble in petroleum ether. A sample of 2-methyl-1-propenylphosphonic difluoride (**273**) containing 22% of 2-chloroisobutylphosphonic difluoride (**274**) reacted with morpholinotrimethylsilane on warming to provide a mixture of morpholides (**275**) and (**276**) (Fig. 2.25.2) (*470*).



N-Aryl alkylphosphonamidofluoridates

R	Ar	Yield (%)	Mp (°C)
Me	*p*-MeC_6H_4	79	81–83
Me	*p*-ClC_6H_4	62	128–131
Et	*p*-ClC_6H_4	51	67–73
$ClCH_2$	*p*-ClC_6H_4	49	122–124
Cl_2CH	*p*-ClC_6H_4	52	167–171
$ClCH_2CH_2$	*p*-ClC_6H_4	71	84–88

Figure 2.25.1

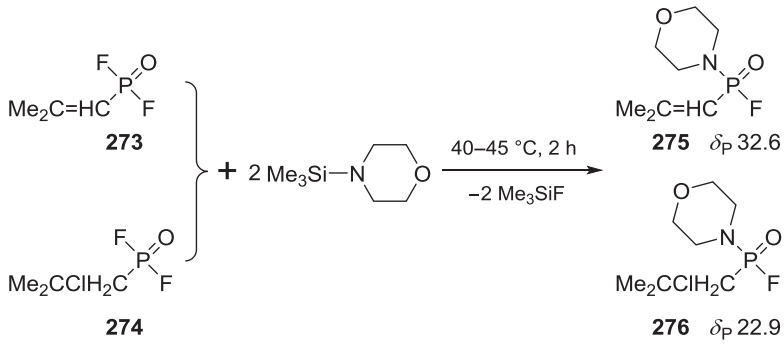


Figure 2.25.2

▶ *N-Aryl alkylphosphonamidofluoridates ArNH(R)P(O)F (142)*. A solution of the appropriate amine (40 mmol) in anhydrous ether (40 ml) was added to a stirred solution of an alkylphosphonic chlorofluoride (20 mmol) in anhydrous ether (40 ml). The amine hydrochloride was filtered off, the ether was evaporated, and the title compounds were crystallised from carbon tetrachloride, petroleum ether or a mixture of benzene and petroleum ether.

▶ *N,N-Dimethyl methylphosphonamidofluoridate $Me_2N(Me)P(O)F$ (39)*. A cold (−10 °C) solution of anhydrous dimethylamine (198 g, 4.4 mol) in light petrol (bp 40−60 °C, 200 ml) and benzene (100 ml) was added slowly to methylphosphonic difluoride (200 g, 2.0 mol) with continuous stirring; the temperature was held at −5 to 0 °C during the addition. The mixture was then filtered, and the base-hydrofluoride was washed with cold petrol. After removal of the diluents, the product was distilled under reduced pressure and collected at 45 °C/1 mmHg. It contained a small amount of methylphosphonic difluoride, which was removed by redistillation using a 40-cm column packed with glass helices, to give the pure product (187.5 g, 75%). Bp 45 °C/10 mmHg.

▶ *N,N-Dimethyl isopropylphosphonamidofluoridate $Me_2N(i\text{-}Pr)P(O)F$ (39,426)*. A solution of dimethylamine (4.5 g, 100 mmol) in ether (50 ml) was added dropwise to a stirred solution of isopropylphosphonic difluoride (made by heating the corresponding dichloride with antimony trifluoride at 60−70 °C in the absence of solvent; 6.4 g, 50 mmol) in ether (100 ml) at 0−5 °C. After addition, the mixture was warmed to room temperature and left for 12 h. The reaction mixture was washed with ice-cold water (2 × 25 ml), the ether layer separated, dried ($MgSO_4$) and the drying agent filtered off. Concentration of the filtrate and distillation of the residue gave the title compound as a colourless liquid (5.7 g, 75%). Bp 36 °C/0.1 mmHg. A similar protocol starting with chloromethylphosphonic difluoride gave $Me_2N(ClCH_2)P(O)F$ as a colourless liquid (73%). Bp 48−49 °C/0.05 mmHg.

▶ *2-Methyl-1-propenylphosphonomorpholinofluoridate* (**275**) *and 2-chloroisobutylphosphonomorpholinofluoridate* (**276**) *(470)*. Morpholinotrimethylsilane (23.8 g, 0.15 mol) was added dropwise to the mixture of difluorides **273** and **274** (21 g) at room temperature. The stirred mixture was heated at 40−45 °C for 1−2 h until no further fluorotrimethylsilane was liberated. Fractionation gave a mixture

comprising 78% **275** and 22% **276** (9.7 g, bp 114 °C/1 mmHg) with corresponding δ_P values of 32.6 ppm ($^1J_{PF}$ 1050 Hz) and 22.9 ppm ($^1J_{PF}$ 1004 Hz).

2.26 *S*-ALKYL ALKYLPHOSPHONOFLUORIDOTHIOLATES R(R′S)P(O)F

S-Isopropyl methylphosphonofluoridothiolate cannot be prepared by the interaction of isopropyl thiol and an equimolar mixture of methylphosphonic dichloride and methylphosphonic difluoride ('di—di' mixture) either alone or in the presence of a base (*39*). Although *S*-isopropyl methylphosphonochloridothiolate (**277**) reacts with water with the evolution of heat, it is very resistant to fluorination, treatment with dry sodium fluoride or potassium fluoride in boiling toluene for 7 h giving practically no fluoro compound, the product being the unattacked chloro body. Rather a poor yield of phosphonofluoridate (**278**) (24%) is obtained if the alkali fluoride is slightly damp (Fig. 2.26.1) (*39*). It seems probable that the moisture in the alkali fluoride partly hydrolyses the chloridothiolate, liberating hydrogen chloride, which in turn gives rise to hydrogen fluoride, the latter bringing about the fluorination. A small amount of the fluoro compound is obtained when the chloridothiolate is treated with antimony trifluoride in benzene, and antimony pentachloride is added as a catalyst (not shown). However, a considerable quantity of viscous undistillable material forms simultaneously.

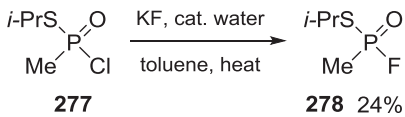


Figure 2.26.1

▶ *S-Isopropyl methylphosphonofluoridothiolate i-PrS(Me)P(O)F* (**278**) (*39*). *S*-Isopropyl methylphosphonochloridothiolate (25.9 g, 0.15 mol), undried potassium fluoride (12.8 g, 0.22 mol) and toluene (35 ml) were stirred and heated under reflux for 2 h. The mixture was cooled and filtered, and the toluene was distilled from the filtrate under slightly reduced pressure. Fractionation of the residue gave the title compound (5.6 g, 24%). Bp 55 °C/2 mmHg. During fluorination, considerable fuming was noted, and after distillation, much high-boiling viscous residue remained. No fluorination occurred if the potassium fluoride was dried prior to use.

2.27 ALKYL ALKYLPHOSPHONOCYANIDATES R(R′O)P(O)CN

Alkyl methylphosphonocyanidates (**279—281**) can be prepared by warming methylphosphonic dichloride (*Method A*) or methylphosphonic difluoride (*Method B*) with alkoxydimethylcyanosilanes (Fig. 2.27.1) (*471*). Isopropyl methylphosphonocyanidate (**281**) can also be obtained by treating isopropyl methylphosphonochloridate with hydrogen cyanide and triethylamine at low temperature (*Method* C). The P—CN bond of the cyanidate products is labile, and the cyanide group can be substituted by nucleophiles under mild conditions. In the presence of water, hydrolysis is rapid and provides the corresponding alkyl methylphosphonic acid.

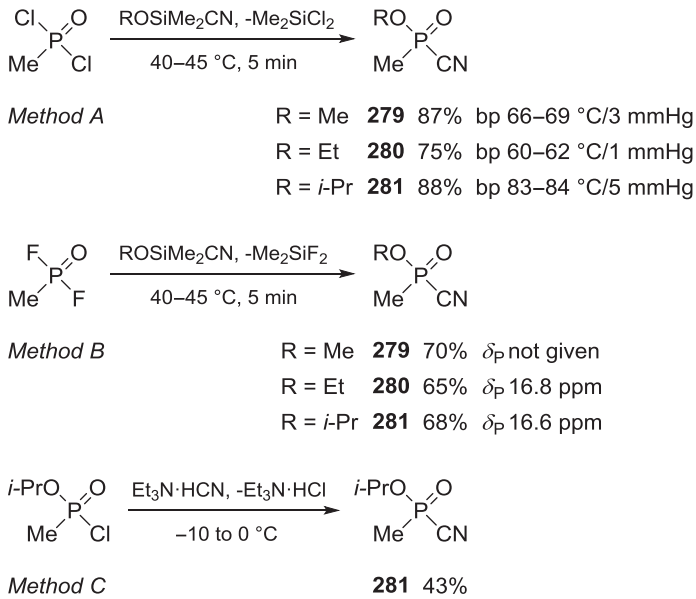


Figure 2.27.1

▶ *Alkyl methylphosphonocyanidates RO(Me)P(O)CN (general methods) (471).*

Method A. Methoxydimethylcyanosilane (11.5 g, 0.1 mol) was added dropwise to methylphosphonic dichloride (13.3 g, 0.1 mol). This stirred mixture was heated to 40–45 °C and maintained at this temperature for 5 min. Fractional distillation gave dimethyldichlorosilane (12.5 g, 97%; bp 69–70 °C/749 mmHg) and methyl methylphosphonocyanidate (10.4 g, 87%). Bp 66–69 °C/3 mmHg.

Method B. Methoxydimethylcyanosilane (11.5 g, 0.1 mol) was added dropwise to methylphosphonic difluoride (10.0 g, 0.1 mol). The mixture was heated to 45–50 °C and maintained at this temperature for 3–5 min. Fractionation gave methyl methylphosphonocyanidate (8.3 g, 70%). Bp 89–92 °C/13 mmHg.

Method C. Anhydrous hydrocyanic acid (2.7 g, 0.1 mol) was added to a stirred solution of isopropyl methylphosphonochloridate (15.7 g, 0.1 mol) in anhydrous ether (200 ml) at −10 °C. Anhydrous triethylamine (10.1 g, 0.1 mol) was added at the same temperature. The mixture was stirred at −10 °C for 1 h, at 0 °C for 1 h, and at 20 °C for 6 h. The precipitated triethylamine hydrochloride was removed by filtration and washed with anhydrous ether (2 × 30 ml), the ether extracts were combined, the solvent was removed and the residue was fractionated to yield isopropyl methylphosphonocyanidate (6.3 g, 43%). Bp 83–84 °C/5 mmHg.

2.28 ALKYL ALKYLPHOSPHONIC ACIDS R(R′O)P(O)OH

Alkyl alkyl- and arylphosphonic acids are strong acids whose acid dissociation constants (pK_a) are in the region 3–4 (Fig. 2.28.1) (*262*), lower than those of carboxylic acids (RCO_2H), which are

Acid dissociation constants for alkyl alkyl/arylphosphonic acids

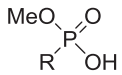
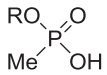
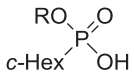
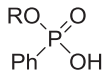
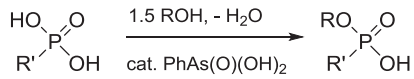
Structure	R	pK_a (20 °C)	Solvent system
	Me	3.11	1:1 H_2O-dioxane
	c-Hex	3.78	
	Ph	2.97	
	*i*-Pr	3.86	2:3 H_2O-dioxane
	c-Hex	4.16	
	Pin	4.30	
	*i*-Pr	4.44	2:3 H_2O-dioxane
	Bn	3.96	
	*i*-Pr	3.66	2:3 H_2O-dioxane
	Bn	3.27	

Figure 2.28.1

generally 4—5 (*472*). The phosphonic acids are therefore stronger acids. The acid strength depends on the electronic character of the substituents, with electronegative substituents (e.g. Ph) stabilising the anion and increasing the acidity (and electron-donating substituents doing the opposite). Thus, when measured in aqueous 1,4-dioxane, the acidity of *O*-methyl-substituted phosphonic acids decrease in the order of inductive effect of the substituent R bonded to the phosphorus atom, that is, Ph > Me > cyclohexyl (*262*). As expected from consideration of inductive effects, *P*-aryl phosphonic acids are more acidic than their *P*-alkyl counterparts, having pK_a values lower than those of formic acid (HCO_2H, pK_a 3.77 (*472*)). Some alkyl methylphosphonic acids are the hydrolysis products of organophosphorus nerve agents and are important in biomedical (*473*) and environmental (*19,474,475*) sample analyses. Consequently, several improved methods for their synthesis have emerged, especially since the Chemical Weapons Convention entered into force in 1997.

Fischer-type mono-esterification of alkyl- or arylphosphonic acids can be accomplished by an alcohol in the presence of phenylarsonic acid (*476*). The water formed during the reaction is removed azeotropically. A selection of phosphonic monoesters that can be prepared is given in Fig. 2.28.2. The reaction with lower primary alcohols, such as ethanol does not work well, and limits the method.

Condensation of alkylphosphonic acids with alcohols mediated by *N,N′*-dicyclohexylcarbodiimide (DCC) absorbed onto Celite™ offers a simple and efficient method for the synthesis



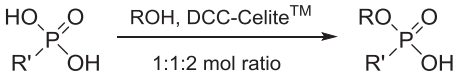
Alkyl alkylphosphonic acids

R	R'	Time [a] (h)	Yield (%)	δ_P ($CDCl_3$)
n-Bu	Me	28	90	34.0
c-Hex	Me	28	39 [b]	33.2
n-Bu	Ph	28	98	21.8
n-Hex	Ph	28	98	21.1
$EtSCH_2CH_2$	Ph	19	76 [c]	20.6
$MeOCH_2CH_2$	Bn	28	74 [b]	30.2

a. Heating time. *b.* 1.2 mol equiv. ROH. *c.* 1.3 mol equiv. ROH

Figure 2.28.2

of lower and higher alkyl alkylphosphonic acids (Fig. 2.28.3) (*477*). Mono-esterification with primary alcohols takes 30–45 min, secondary alcohols take longer (45–60 min) and tertiary alcohols do not react. Esterification proceeds well with 2-methoxyethanol to give acids of structure $MeOCH_2CH_2O(R)P(O)OH$ where R = Me, Et, *n*- or *i*-Pr (δ_P 31.8, 33.6, 34.2 and 34.9 ppm,



Alkyl alkylphosphonic acids

R	R'	RT [a] (h)	Yield (%)	Bp (°C/mmHg)	δ_P (CD_3OD) [b]
Et	Me	30	80	108–110/0.1	31.2
n-Pr	Me	40	82	112–116/0.1	31.6
i-Pr	Me	35	85	102–104/0.1	31.5
n-C_5H_{11}	Me [c]	45	90	110–111/0.1	31.0
t-BuCH(Me)	Me [c]	60	92	114–116/0.1	31.5
i-Pr	Et	40	80	90–100/0.1	33.6
$MeOCH_2CH_2$	Et	45	86	oil	33.1
n-C_6H_{13}	Et [c]	50	91	mp 52–54	32.9
t-BuCH(Me)	Et [c]	80	89	105–106/1	32.8
Et	*n*-Pr	40	83	122–124/0.2	34.1
n-Bu	*n*-Pr	60	84	oil	33.8
i-$PrCH_2$	*n*-Pr	70	84	oil	33.4
n-Pr	*i*-Pr	55	81	122–124/0.1	38.2
n-Bu	*i*-Pr	60	87	oil	39.8
n-C_5H_{11}	*i*-Pr [c]	70	88	oil	41.7

a. RT = reaction time. *b.* Measured at 162 MHz. *c.* Reaction performed at 50–60 °C

Figure 2.28.3

respectively, measured at 162 MHz in $CDCl_3$) (*478*). The advantages of DCC—Celite™ are that it is prepared from commercial materials, and the by-product *N,N′*-dicyclohexylurea is removed by filtration after treatment of the reaction mixture with diethyl ether.

Condensation of alkylphosphonic acids (**282**) with alcohols in the presence of DCC in the absence of solvent on TLC plates can be promoted by microwave or conventional heating (*479*). Low boiling alcohols are unsuitable as they tend to evaporate before they have time to react, but with less volatile alcohols, such as *n*-pentanol and higher homologues, reaction occurs to give alkyl alkylphosphonic acids (**283**) or dialkyl alkylphosphonates (**284**) depending on the starting stoichiometry of reagents (Fig. 2.28.4). A 1:2:2 molar ratio of alkylphosphonic acid, alcohol and DCC is optimal for simultaneous production of alkyl alkylphosphonic acids and dialkyl alkylphosphonates, a mixture that is useful for verification analysis of samples suspected of once containing alkyl methylphosphonofluoridate nerve agents. Silica chloride is also effective as a heterogeneous catalyst for the rapid esterification of alkylphosphonic acids to the corresponding dialkyl alkylphosphonates (*480*).

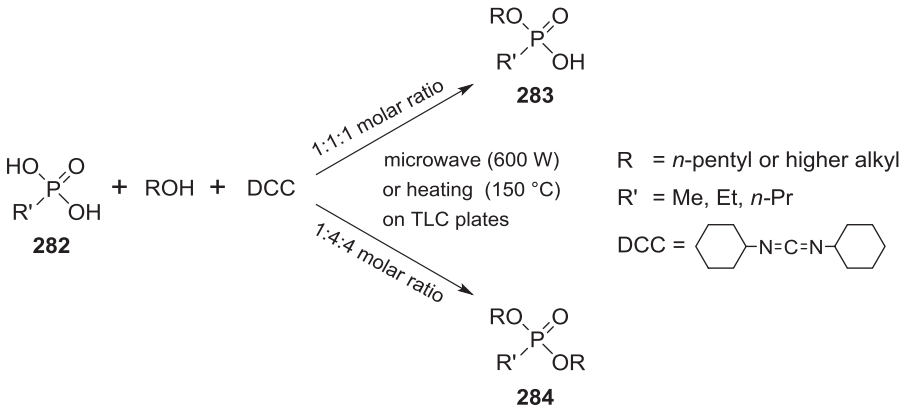
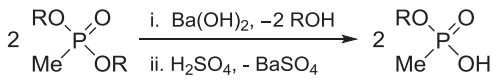


Figure 2.28.4

Basic hydrolysis of dialkyl alkylphosphonates, followed by neutralisation of the salts formed by acid, is a classical method for synthesising alkyl alkylphosphonic acids. The rate of hydrolysis is strongly influenced by the nature of the organic moiety R in the ester group, and is very sensitive to steric effects (*481*). The relationship between the size of the R group and the velocity of hydrolysis is particularly evident in the case of barium hydroxide-treated dialkyl alkylphosphonates (Fig. 2.28.5) (*482*). The OMe group is much more rapidly hydrolysed (18 h) under these conditions than, for instance, the OEt group (48 h). For this reason, unsymmetrical dialkyl alkylphosphonates having a P—OMe group are useful substrates for targeted alkaline hydrolysis to the desired acids (Fig. 2.28.6) (*262*). Dilute aqueous sodium hydroxide can be used to effect this transformation (*409*).

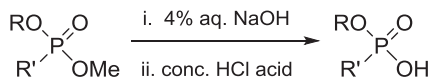


Alkyl alkylphosphonic acids

R	Yield (%)	Bp (°C/mmHg)	Time (h) [a]
Me	75	103–104/0.1	18
Et	79	106–107/0.1	48
n-Pr	72	104–105/0.05	3 days
i-Pr	41	97–98/0.08	30 days
n-Bu	70	120–121/0.1	21 days
n-Pentyl	40	143–144/0.1	40 days
i-Pentyl	33	126–127/0.1	42 days

a. Duration of alkaline hydrolysis for efficient conversion to acid

Figure 2.28.5



Alkyl alkylphosphonic acids

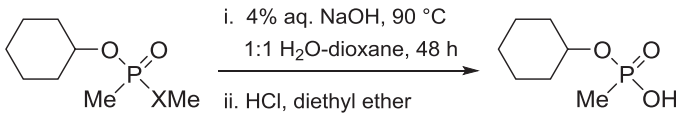
R	R'	Yield (%)	Bp (°C/mmHg)
Me	Me	94	112/0.5
i-Pr	Me	60	115/0.5
n-Bu	Me	76	132/0.5
c-Hex	Me	56	165/0.015
Bn	*c*-Hex	74	mp 82–83 [a]
Bn	Ph	90	mp 60 [b]

a. Recrystallised from petroleum ether

b. Recrystallised from petrol-ether

Figure 2.28.6

Upon prolonged heating in aqueous 1,4-dioxane, cyclohexyl methylphosphonate (**175**) yields cyclohexyl methylphosphonic acid (**286**) in good yield (Fig. 2.28.7) (*262*). Hydrolysis of *O*-cyclohexyl *S*-methyl methylphosphonothiolate (**285**) gives the same product (**286**), but in a greater yield. This may reflect the fact that SR groups bonded to a phosphorus atom are usually more easily displaced in S_N2 processes than are comparable OR groups bonded to a phosphorus atom (the P—SR bond is weaker than a comparable P—OR bond and therefore more easily broken).

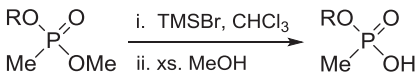


X = O **175**
X = S **285**

286 85%
286 94%

Figure 2.28.7

Rather than having to use aqueous alkali to remove an OMe group in unsymmetrical dialkyl alkylphosphonates, where the water is difficult to remove later, it is possible to convert the OMe group to a trimethylsilyl (TMS) group using bromotrimethylsilane (Fig. 2.28.8) (*14*). Treatment of this silyl ester with methanol gives the alkyl alkylphosphonic acid. Water can be used instead of methanol (Fig. 2.28.9) (*483*) but is more troublesome to remove from the resulting acid.

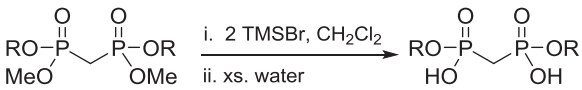


Alkyl methylphosphonic acids

R	Yield (%)	Bp (°C/mmHg)	δ_P ($CDCl_3$)
i-Pr	97	80/0.04	31.4
n-Bu	82	75/0.01	31.6
i-Bu	88	75/0.01	32.1
s-Bu	89	80/0.04	31.4 [a]
Pin	90	90/0.02	31.5
c-C_5H_9	64	95/0.04	30.2
c-C_6H_{11}	60	105/0.02	31.0

Pin = pinacolyl group, viz *t*-BuCH(Me)- , *a*. 90% pure.

Figure 2.28.8



P,*P'*-Dialkyl methylenediphosphonic acids

R	Yield (%)	Mp (°C)	δ_P ($CDCl_3$)
n-Bu	96	colourless oil	19.4
Ph	85	181–183	15.4 [a]

a. Measured in CD_3OD

Figure 2.28.9

Benzyl phosphonates such as **287** and **134** can be mono-debenzylated selectively using stoichiometric amounts of 1,4-diazabicyclo[2.2.2]octane in refluxing toluene (Fig. 2.28.10) (*484*). The yields of the target acids **24** and **288** approach quantitative and pure compounds are obtained without the need for extensive purification.

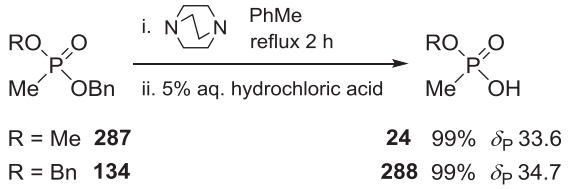


Figure 2.28.10

Dialkyl dialkylpyrophosphonates can be used to access alkyl alkylphosphonic acids, but suffer the drawback that they are toxic, and therefore best avoided. Diisopropyl dimethylpyrophosphonate (**59**) is hydrolysed by boiling water to give isopropyl methylphosphonic acid (**113**) in a nearly quantitative yield (Fig. 2.28.11) (*39*).

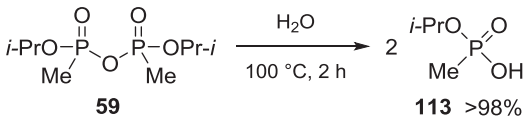


Figure 2.28.11

One-pot methods for the synthesis of alkyl alkylphosphonic acids starting from alkylphosphonic dichlorides are known, and their success depends upon the reactivity and size of the alcohol added to the dichloride — larger ones suppress the possibility of double substitution — prior to hydrolysis of the formed alkyl alkylphosphonochloridate. Stoichiometric addition of isopropanol or cyclohexanol to methylphosphonic dichloride (**22**) in toluene and subsequent addition of water provides a mixture of products from which acids **113** or **286** can be isolated by solvent extraction (Fig. 2.28.12) (*485*). A more selective reaction is possible using bulky alcohols. Thus, methylphosphonic dichloride reacts with a molar equivalent each of cholesterol and pyridine to produce cholesteryl methylphosphonochloridate, which can be hydrolysed *in situ* by dilute aqueous potassium hydroxide

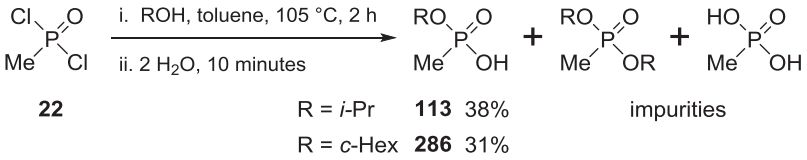
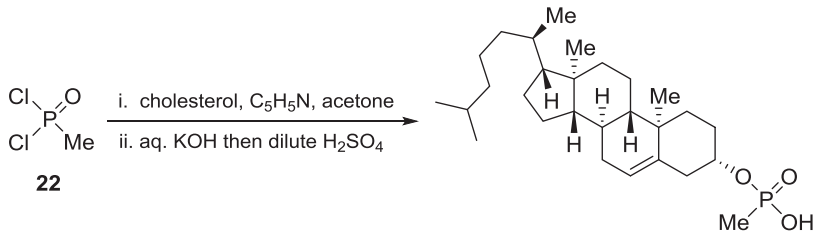


Figure 2.28.12

(Fig. 2.28.13) (*232*). The desired acid (**289**) precipitates from the aqueous solution upon acidification.



289 yield not stated

Figure 2.28.13

The chlorine atom of alkyl alkylphosphonochloridates is generally very reactive, and such compounds are obvious precursors to the corresponding acids. Several methods are available for the synthesis of the acids. Ethyl methylphosphonochloridate upon treatment with formic acid (*224*) or *tert*-butanol (*39*) provides ethyl methylphosphonic acid in 76% and 55% yield, respectively (Fig. 2.28.14).

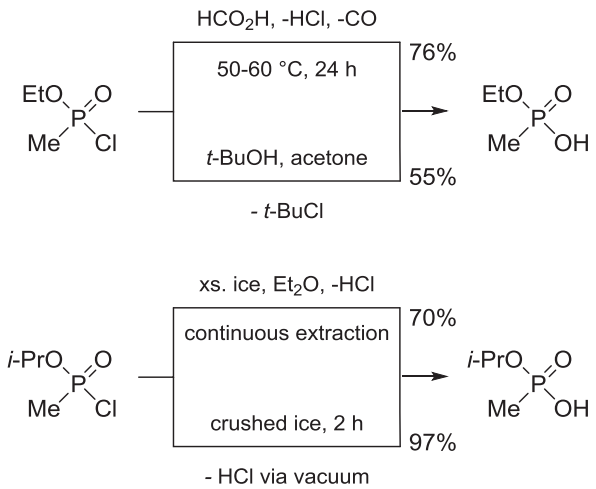
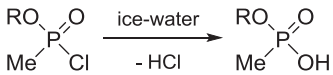


Figure 2.28.14

The reaction of alkyl alkylphosphonochloridates with water gives the corresponding acids and hydrogen chloride. The reaction is strongly exothermic and to obtain good yields, it is necessary to add the chloridate gradually to ice. Dealkylation of the product by the hydrogen chloride formed is avoided by continuous extraction into ether or the removal of all volatile material under vacuum at a temperature below 30 °C. The alkyl alkylphosphonic acid is isolated pure by distillation under reduced pressure (Fig. 2.28.15) (*409*).



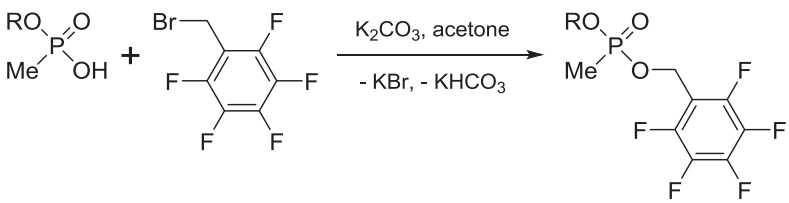
Alkyl methylphosphonic acids

R	Bp (°C/mmHg)
Me	92/0.10
Et	110/0.05
n-Pr	106/0.05
i-Pr	88/0.02
t-BuCH$_2$	110/0.02
t-BuCH(Me)	98/0.05

Figure 2.28.15

Isopropyl methylphosphonofluoridate (sarin) reacts with water to produce isopropyl methylphosphonic acid and hydrogen fluoride (*486*), but this reaction is best avoided on safety grounds. This specific transformation has been studied since the 1940s in the search for improved decontaminating agents. The hydrolysis rate is accelerated by catechols (*450*), hypochlorite (*487*), peroxide (*488*), hydroxamic acids (*489*) and oximes (*490—492*).

Alkyl alkylphosphonic acids are high-boiling, syrupy, strongly acidic liquids (or low melting solids) that can be distilled under reduced pressure without disproportionation. They are miscible with water in all proportions and in most organic solvents with the exception of petroleum ether and have very low toxicity. They form highly stable crystalline silver salts that are soluble in water and to some extent organic solvents (details of their preparation appear in Section 2.30). Alkyl alkylphosphonic acids can be benzylated using phenyldiazomethane derived from polymer-supported *N*-benzyl-*N*-nitroso-4-toluenesulfonamide (*493*). This method provides isopropyl benzyl methylphosphonate (δ_P 30.5 ppm in $CDCl_3$) and pinacolyl benzyl methylphosphonate as a mixture of two diastereoisomers (δ_P 30.1 and 30.4 ppm in $CDCl_3$). Alkyl alkylphosphonic acids can be converted into pentafluorobenzyl esters (e.g. **290—292**) by treatment with pentafluorobenzyl bromide and potassium carbonate in acetone (Fig. 2.28.16) (*494*). These esters are useful for GC—MS studies.



R = Et **290** 67%
R = *i*-Pr **291** 81%
R = Pin **292** 89%

Figure 2.28.16

▷ *Alkyl alkylphosphonic acids RO(R)P(O)OH* (*synthesis on TLC plates*) (*479*). Aluminium-backed TLC plates were cut into 3 × 6 cm strips. Solutions of alkylphosphonic acids (2 mmol), alcohols (4 mmol) and DCC (4 mmol) were prepared in anhydrous acetonitrile. Aliquots of each solution (50 μl) were withdrawn and mixed in an auto-sampler vial (1 ml). A sample of this mixture (2 μl) was spotted onto the TLC plate. The plate was irradiated in a microwave reactor at 600 W for 10 min or heated in an oven at 155 °C for 45 min. Some of the mixture (2 μl) was spotted separately for the control run. The spots on the plate were eluted with 4:1 *v*/*v* benzene—acetone, and after evaporation of the solvent were visualised in an iodine chamber. For product characterisation, the reaction process was repeated, and silica from the plates corresponding to the retention factor (R_F) of a given ester was scratched off and transferred into a 2-ml test tube. The silica was extracted with acetone (4 × 700 μl), and the extract was analysed by GC—MS and ^{31}P NMR spectroscopy after centrifugation and filtration. To characterise the *O*-alkyl alkylphosphonic acids, the extract was evaporated almost to dryness and derivatised with *N*,*O*-*bis*(trimethylsilyl)trifluoroacetamide at 80 °C for 30 min after reconstitution in acetonitrile (50 μl).

▷ *P,P′-di-n-butyl methylenediphosphonic acid HO(n-BuO)P(O)CH$_2$P(O)(OBu-n)OH* (*silyl ester cleavage*) (*483*). Bromotrimethylsilane (1.15 g, 7.5 mmol) was added to a stirred solution of methylenebis(*n*-butyl methylphosphonate) monohydrate (1.00 g, 3.0 mmol) in anhydrous dichloromethane (5 ml). The mixture was stirred at room temperature for 30 min. Volatile material was removed by rotary evaporation, and the residue was treated with water (5 ml). Removal of the water at 60 °C under reduced pressure using a rotary evaporator equipped with a water aspirator gave the title compound (0.50 g, 96%). δ_P ($CDCl_3$) 19.4 ppm. This method is a general one and similarly can be used to make other acids in this class, such as *P,P′*-diphenyl methylenediphosphonic acid (85%, after recrystallisation from water; mp 181—183 °C). δ_P (CD_3OD) 15.4 ppm.

▷ *Ethyl methylphosphonic acid EtO(Me)P(O)OH* (*from chloridate and formic acid*) (*224*). A stirred mixture of ethyl methylphosphonochloridate (3.0 g, 21.1 mmol) and formic acid (100 ml, ∼0.7% water) was heated to 50—60 °C for 24 h. The formic acid was removed, and the residual liquid was distilled to provide the title compound (2.0 g, 76%). Bp 105—110 °C/0.2 mmHg.

▷ *Ethyl methylphosphonic acid EtO(Me)P(O)OH* (*from chloridate and tert-butanol*) (*224*). Ethyl methylphosphonochloridate (1.20 g, 8.42 mmol) was added to acetone (100 ml) containing *tert*-butanol (5 ml), and the mixture was stirred for 24 h. Removal of the solvent and distillation under reduced pressure gave the title compound (0.57 g, 55%). Bp 120 °C/0.3 mmHg.

▷ *Isopropyl methylphosphonic acid i-PrO(Me)P(O)OH* (*chloridate hydrolysis*, *method* 1) (*39*). Isopropyl methylphosphonochloridate (56.3 g, 0.36 mol) was added in four portions to roughly broken ice cubes (∼150 g) contained in a conical flask with continuous stirring. After addition, the mixture was allowed to stand for about 5 min, by which time all the ice had melted. The contents of the flask were then transferred to a continuous extraction apparatus of about 300-ml capacity. The volume of liquid in the extractor should not exceed 250 ml. After extracting with ether for 4 h, the reflux condenser surmounting the extractor was removed, and the ether remaining in the latter was transferred to the extraction flask by running water carefully down the inner tube of the extractor. The ether and last traces of water were removed by rotary evaporation. Vacuum fractionation of the residue gave the pure

acid (35.0 g, 70%). Bp 80 °C/0.008 mmHg. Notes: (1) Ether is appreciably soluble in the concentrated aqueous solution of the isopropyl methylphosphonic acid. Consequently, at the start of the extraction, the ether—water interface rises in the extractor. If the latter is filled too full, there is a danger of the aqueous phase spilling over into the ether-extraction flask. (2) Other alkyl alkylphosphonic acids may be made by a similar procedure, starting with the appropriate alkyl alkylphosphonochloridate.

▶ *Isopropyl methylphosphonic acid i-PrO(Me)P(O)OH* (*chloridate hydrolysis*, *method* 2) (*39*). Isopropyl methylphosphonochloridate (37.3 g, 0.27 mol) was added slowly to crushed ice (100 g). After standing for 2 h, the water and hydrogen chloride were removed under high vacuum. The residue on fractionation gave isopropyl methylphosphonic acid (36.1 g, 97%). Bp 73 °C/0.05 mmHg. Isopropyl ethylphosphonic acid, *i*-PrO(Et)P(O)OH, was prepared similarly from isopropyl ethylphosphonochloridate in an almost quantitative yield. Bp 83 °C/0.05 mmHg.

▶ *Isopropyl methylphosphonic acid i-PrO(Me)P(O)OH* (*pyrophosphonate hydrolysis*) (*39*). Diisopropyl dimethylpyrophosphonate (7.2 g, 28 mmol; Caution! Toxic) and distilled water (20 ml) were heated at 100 °C for 2 h. The excess water was removed under reduced pressure, and the product was distilled under high vacuum. The yield of isopropyl methylphosphonic acid was nearly quantitative (98%). Bp 78 °C/0.05 mmHg. The following were prepared similarly: isopropyl ethylphosphonic acid *i*-PrO(Et)P(O)OH (bp 87—88 °C/0.07 mmHg) and ethyl methylphosphonic acid EtO(Me)P(O)OH (bp 86 °C/0.05 mmHg). The starting pyrophosphonates are toxic and should be handled with care with appropriate skin protection. Used glassware should be decontaminated with aqueous bleach.

▶ *Isopropyl methylphosphonic acid i-PrO(Me)P(O)OH* (*phosphonate diester hydrolysis*) (*39*). Diisopropyl methylphosphonate (90 g, 0.50 mol) was heated under reflux for 8 h with 10% *w/v* aqueous sodium hydroxide solution (600 ml). The next day, the solution was extracted with ether (2 × 100 ml), filtered and extracted again. The aqueous liquid was acidified at 10 °C with concentrated hydrochloric acid (135 ml, 1.55 mol), saturated with brine and extracted with chloroform (6 × 100 ml). The chloroform solution was dried ($MgSO_4$), filtered, evaporated and the yellow residue (62.5 g) distilled under reduced pressure using a molecular still. The product was collected as a colourless liquid (58 g, 84%). Bp 39—43 °C/0.001 to 0.00001 mmHg.

▶ *Pinacolyl methylphosphonic acid t-BuCH(Me)O(Me)P(O)OH* (*chloridate hydrolysis*) (*155*). Pinacolyl methylphosphonochloridate (3.97 g, 20 mmol) was suspended in distilled water (50 ml), and aqueous sodium hydroxide (50 ml of 5 M solution) was added dropwise. The mixture was warmed to 60 °C for 2 h. The solution was acidified and evaporated to dryness under vacuum. Extraction with ether and distillation of the extract gave the acid (2.50 g, 70%). Bp 116—118 °C/0.1 mmHg.

▶ *Pinacolyl methylphosphonic acid t-BuCH(Me)O(Me)P(O)OH* (*silyl ester cleavage*) (*14*). Methyl pinacolyl methylphosphonate (0.97 g, 5 mmol) was weighed into a 50-ml round-bottomed flask to which anhydrous chloroform (10 ml) and a magnetic flea were added. The flask was stoppered with a rubber septum and purged with argon. The mixture was stirred and bromotrimethylsilane (0.66 ml, 5 mmol) was added by means of a syringe. After 12 h, the solvent was removed to leave a colourless liquid. Methanol (2 ml) was added and then removed by rotary evaporation; this was repeated two more times. The resultant viscous oil was distilled using a Kugelrohr apparatus to give a colourless

liquid (0.81 g, 90%). Bp 90 °C/0.02 mmHg. δ_P (202 MHz, $CDCl_3$) 31.5 ppm. This method is general for the conversion of alkyl methyl methylphosphonates to alkyl methylphosphonic acids (Fig. 2.28.8).

▶ *Cholesteryl methylphosphonic acid* (**289**) (*232*). A solution of cholesterol hydrate (5.6 g, 13.8 mmol) in anhydrous pyridine (28 ml, 346.2 mmol) was added in portions to a stirred solution of methylphosphonic dichloride (5.6 g, 42.1 mmol) in anhydrous acetone (28 ml) with cooling under running water. After addition, the mixture was left to stand for 3 days at room temperature and was then filtered. The residue was washed once with water. The remaining material was dissolved in warm potassium hydroxide solution and precipitated by acidification with dilute sulfuric acid. Drying and recrystallisation from boiling glacial acetic acid gave the title compound as a white solid (yield not stated). Mp 159–161 °C. It is soluble in ether, ethanol or aq. KOH (0.5 M) upon warming, but insoluble in aq. NaOH. When dissolved in ether and stirred into water, the acid formed a stable aqueous solution of pH 4.0–4.5, flocculating only when dilute mineral acid was added.

2.29 ALKYLPHOSPHONOFLUORIDIC ANHYDRIDES R(F)P(O)OP(O)(F)R

When compounds of the type XYP(O)Cl are treated with those of the type HOP(O)YX under suitable conditions, hydrogen chloride is eliminated and anhydride formation occurs (*39*). Theoretically, therefore, alkylphosphonofluoridic anhydrides could be prepared by the interaction of alkylphosphonofluoridic acids R(F)P(O)OH with alkylphosphonic chlorofluorides ClP(O)(F)R. The alkylphosphonic chlorofluorides (Section 2.7) are extremely troublesome to prepare, but they can, however, be obtained *in situ* and will then react with the hydroxyl compound present. Thus, when an alkylphosphonofluoridic acid (e.g. **52** or **293**) is heated with about 0.5 mol of thionyl chloride, then the excess of alkylphosphonofluoridic acid present reacts with the chlorofluoride formed to give a good yield of the target anhydride (e.g. **60** or **294**)(Fig. 2.29.1).

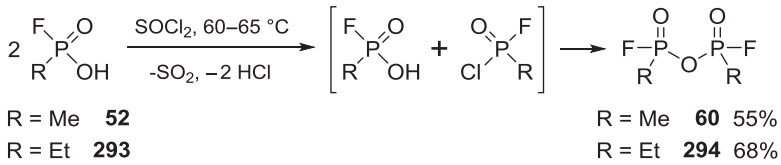


Figure 2.29.1

This method can, of course, only yield symmetrical anhydrides. Should unsymmetrical compounds be required, it would be necessary to undertake the arduous task of first preparing the appropriate chlorofluoride. The methyl and ethyl compounds (**60**) and (**264**) are slightly viscous, colourless liquids that can be distilled without decomposition under high vacuum. Their hydrolysis by water is strongly exothermic, the temperature of a mixture of the alkylphosphonofluoridic anhydride (1 ml) and distilled water (1 ml) rising from 18 to 81 °C in 15 s. The fluorine atom as well as the pyro-oxygen bridge is affected, as the resulting solution gives a very strong positive test for ionic fluorine. This is only to be expected since the anhydrides are readily hydrolysed, especially on warming in acid solution.

▶ *Methylphosphonofluoridic anhydride Me(F)P(O)OP(O)(F)Me* (**60**) (*39*). A mixture of freshly distilled methylphosphonofluoridic acid (23.0 g, 0.23 mol) and thionyl chloride (14.6 g, 0.12 mol) was warmed to 60–65 °C in a flask fitted with a reflux condenser protected by a guard tube filled with anhydrous calcium chloride. After 2.5 h, the reaction appeared to be complete. After degassing completely with the aid of a water pump, the residue was fractionated under vacuum, giving the product (14.0 g). Re-fractionation yielded the pure substance (11.5 g, 55%). Bp 45 °C/0.1 mmHg. Ethylphosphonofluoridic anhydride was prepared similarly in 68% yield. Bp 46 °C/0.08 mmHg.

2.30 DIALKYL DIALKYLPYROPHOSPHONATES R(R′O)P(O)OP(O)(OR′)R

Dialkyl dialkylpyrophosphonates often form as impurities when organophosphorus nerve agents – such as sarin, soman, VX, and their analogues – are prepared or stored. There are several methods for the deliberate synthesis of such species (*495,496*). The simplest analogue, *P,P′*-dimethyl pyrophosphonic acid, can be prepared by mixing methylphosphonic dichloride (**22**) with DMSO or by treating methylphosphonic acid with acetic anhydride (Fig. 2.30.1) (*152*). In the former case, the methylphosphonic acid (**56**) combines with DMSO to provide the salt (**295**), which is postulated to lose hydrogen chloride and chloromethyl methyl sulfide. The resultant methylphosphonochloridic acid (**296**) is thought to react further to provide intermediate (**297**), and then *P,P′*-dimethyl pyrophosphonic acid (**26**). The reaction between methylphosphonic acid (**56**) and acetic anhydride may provide a mixed anhydride (**298**) that disproportionates to symmetrical products: acetic anhydride and *P,P′*-dimethyl pyrophosphonic acid (**26**). It should be noted that these mechanisms, although plausible, have not been confirmed. For synthetic purposes, the second reaction with acetic anhydride, seems the most convenient for accessing a variety of *P,P′*-disubstituted pyrophosphonic acids.

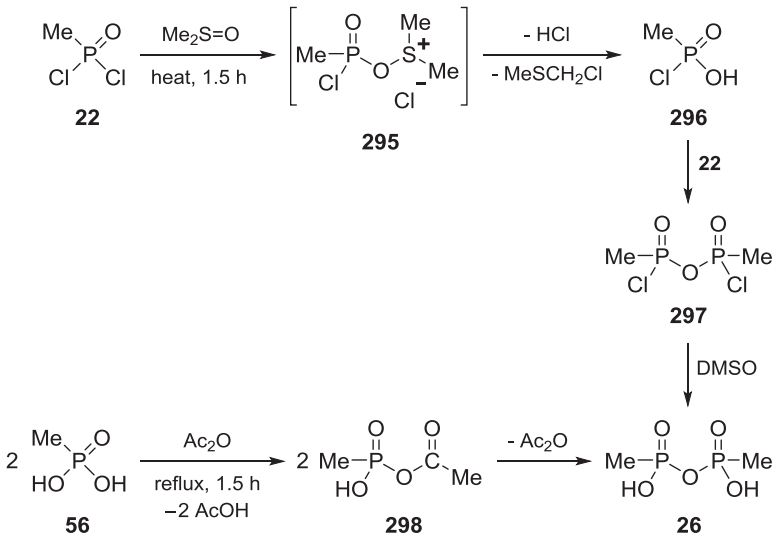


Figure 2.30.1

During the preparation of alkyl alkylphosphorochloridates by treating dialkyl alkylphosphonates with phosgene (*39*), it was noticed that when phosgenation was incomplete and the reaction mixture was overheated, a residue remained after the alkyl alkylphosphonochloridate was distilled. This residue yielded a high-boiling but distillable product, identified as the dialkyl dialkylpyrophosphonate, whose formation may have arisen by the action of heat on the unreacted dialkyl alkylphosphonate and the alkylphosphonochloridate (Fig. 2.30.2) or by the action of moisture on the chloridate (Fig. 2.30.3). The first of these reactions was shown to occur quite readily. When diethyl ethylphosphonate and ethyl ethylphosphonochloridate are heated to about 120 °C, ethyl chloride distils and a good yield of diethyl diethylpyrophosphonate (R and R′ = Et) can be isolated. This reaction is quite general and several such pyro-esters are accessible, including those with 'mixed' or 'unsymmetrical' ester groups.

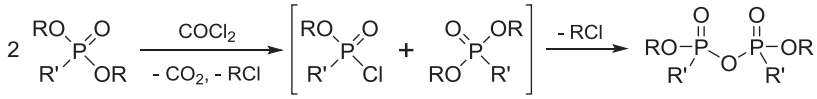


Figure 2.30.2

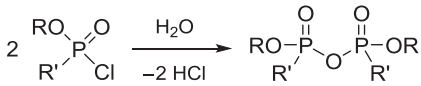


Figure 2.30.3

As this method of preparation of dialkyl dialkylpyrophosphonates is rather brutal, the second route shown in Fig. 2.30.3 was studied, and found to be practicable. When the alkylphosphonochloridate is treated with *N*,*N*-diethylaniline and an appropriate amount of water in benzene solution, the base-hydrochloride separates and a good yield of the pyro-ester results. A slightly more involved but at the same time quite simple method involves treating an alkyl alkylphosphonochloridate with an excess of water, to provide a good yield of the alkyl alkylphosphonic acid. A compound of this type, on treatment with an aqueous suspension of fresh silver(I) oxide, gives a stable highly crystalline silver salt, freely soluble in water, readily in ethanol and sparingly, though definitely soluble in benzene. The dry silver salt is then warmed with an equivalent quantity of an alkyl alkylphosphonochloridate in anhydrous benzene, giving a good yield of highly pure pyro-ester (Fig. 2.30.4) (*39*). Using a different

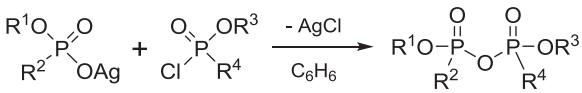
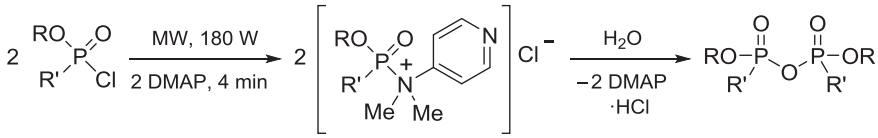


Figure 2.30.4

alkylphosphonochloridate from that used to prepare the silver salt allows the synthesis of unsymmetrical pyro-esters.

A one-pot solvent-free microwave-assisted synthesis of dialkyl dialkylpyrophosphonates from alkyl alkylphosphonochloridates, 4-dimethylaminopyridine (DMAP), and water has been developed (*497*). It provides the pyrophosphonates in high yield after distillation under vacuum (Fig. 2.30.5). The same team also reported the synthesis of unsymmetrical dialkyl dialkylpyrophosphonates by coupling alkyl methylphosphonochloridates and alkyl methylphosphonic acids on alumina as a solid support



Dialkyl dialkylpyrophosphonates [a]

R	R'	Yield (%) [b]	Bp (°C/mmHg)	δ_P (ppm) [c]
Et	Me	86	115/2	22.5, 22.2
n-Pr	Me	91	120/2	26.3, 26.0
n-Bu	Me	92	135/1.5	26.3, 25.9
n-Pentyl	Me	90	145/1.5	26.3, 25.9
Pinacolyl	Me	88	160.1.5	22.6, 21.0
Et	*i*-Pr	89	132/1	28.3, 28.2
n-Pr	*i*-Pr	85	149/1	28.6, 28.5
n-Bu	*i*-Pr	93	158/1	28.6, 28.5
i-Bu	*i*-Pr	88	160/1	28.3, 28.2
n-Pentyl	*i*-Pr	94	165/1	31.7, 31.6

a. All reactions were complete within 5–6 min at 180 W. *b*. Isolated yield. *c*. ^{31}P NMR spectra were measured in $CDCl_3$ at 162 MHz.

Figure 2.30.5

(*498*). Pyrophosphylated products form when sarin and soman are left in solution in phosphate buffer (*499*).

The toxicities of dialkyl dialkylpyrophosphonates to mammals, although not commensurate with sarin, are nevertheless quite high. They produce typical nerve agent symptoms on injection through inhibition of the enzyme acetylcholinesterase (*39*). They are soluble in water, and their rate of hydrolysis in the cold is very slow. Treatment with a small amount of water at 90 °C provides a good yield of the corresponding alkyl alkylphosphonic acid. When mixed with cold 20% *w*/*v* aqueous

sodium hydroxide, hydrolysis occurs rapidly and with the production of heat. The pyrophosphonates are soluble in most organic solvents with the exception of petroleum ether.

▶ *P,P′-Dimethylpyrophosphonic acid Me(HO)P(O)OP(O)(OH)Me* (**26**) (*from methylphosphonic dichloride and DMSO*) (152). DMSO (1.56 g, 20 mmol) was added slowly to a stirred solution of methylphosphonic dichloride (1.33 g, 10 mmol) in DMSO (2 ml) cooled in an ice bath to moderate the exothermic reaction and maintain the temperature at 10–15 °C. After addition, the temperature of the mixture was allowed to rise to 25 °C and further heated at 30–40 °C for 1 h. The solid precipitate was removed by centrifugation and washed with acetonitrile (2 × 0.5 ml) and with acetone (0.5 ml), and the solvent was removed to provide the title compound (0.86 g, 99%). Mp 141–142 °C.

▶ *P,P′-Dimethylpyrophosphonic acid Me(HO)P(O)OP(O)(OH)Me* (**26**) (*from methylphosphonic acid and acetic anhydride*) (152). Acetic anhydride (2 ml, 21 mmol) was added to stirred methylphosphonic acid (1.12 g, 12 mmol), and the mixture was heated under reflux for 90 min to produce a clear yellowish solution from which crystals separated on cooling. The crude solid was washed with acetone (4 × 1 ml) and centrifuged. Each time the solid was crushed, and the last traces of solvent were eliminated by prolonged drying under vacuum, giving the title compound (1.00 g, 90%). Mp 139.5–141.5 °C.

▶ *Isopropyl silver methylphosphonate Me(i-PrO)P(O)OAg* (39). Silver(I) nitrate (37.5 g, 0.22 mol) was dissolved in boiling water (250 ml) and treated slowly with 20% *w/v* aqueous sodium hydroxide until precipitation of silver(I) oxide was complete. The mixture was boiled until the oxide coagulated. The latter was washed four times by decanting with hot distilled water (200 ml), and isopropyl methylphosphonic acid (27.6 g, 0.20 mol) was added gradually with stirring. The mixture was heated to 100 °C for 15 min, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was twice distilled under slightly reduced pressure with benzene (100 ml each) and the remaining silver salt oven dried at 105–110 °C for 4 h. The drying was completed by keeping the salt under vacuum over anhydrous silica gel. This gave the pure salt (41.6 g, 85%). Mp 232 °C dec. Other silver salts of a similar constitution may be prepared by an identical procedure. Ethyl silver ethylphosphonate may be crystallised from anhydrous benzene.

▶ *Diisopropyl dimethylpyrophosphonate Me(i-PrO)P(O)OP(O)(O-i-Pr)Me* (**59**) (*Caution! Toxic*) (39). Isopropyl methylphosphonochloridate (15.6 g, 0.1 mol) dissolved in anhydrous benzene (15 ml) was added to a suspension of dry isopropyl silver(I) methylphosphonate (24.5 g, 0.1 mol) in the same solvent (60 ml). The mixture was heated to 100 °C under a reflux condenser, protected by a calcium chloride guard tube, for 1 h. At the end of this time, the mixture was cooled and the silver(I) chloride was filtered off. The benzene was recovered from the filtrate, and the residue was distilled under reduced pressure to leave the product as a colourless liquid (20.6 g, 80%). Bp 70 °C/0.06 mmHg. Other dialkyl dialkylpyrophosphonates may be made by a similar procedure starting with the appropriate silver salt and alkyl alkylphosphonochloridate. By substituting acetyl chloride for the latter, alkyl acetyl alkylphosphonates may be obtained.

▶ *Diisopropyl diethylpyrophosphonate i-PrO(Et)P(O)OP(O)(Et)OPr-i* (39). Isopropyl ethylphosphonochloridate (34.1 g, 0.2 mol) and diisopropyl ethylphosphonate (39.0 g, 0.2 mol) were heated in a 100-ml round-bottomed flask fitted with a short upright air condenser, the top of which was

connected to a downward spiral cooled in a mixture of chopped ice and hydrochloric acid. A reaction, accompanied by the distillation of isopropyl chloride, set in about 100–110 °C and appeared to be complete in about 2 h. Isopropyl chloride (9.5 g) was collected. The residue was fractionated under reduced pressure giving 14.5 g of material boiling at 60 °C/2 mmHg and 12.5 g boiling at 120–125 °C/2 mmHg. Decomposition set in towards the end of the distillation as shown by a rise in pressure. An undistillable residue (22 g) remained in the flask. The middle fraction was redistilled and collected at 120–121 °C/2 mmHg. This was the expected diisopropyl dimethylpyrophosphonate (yield not given).

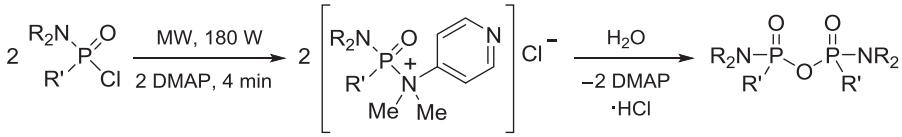
▶ 1-*Ethyl*-2-*isopropyl*-1-*methyl*-2-*ethylpyrophosphonate* *EtO(Me)P(O)OP(O)(Et)OPr-i* (*39*). Diethyl methylphosphonate (30.5 g, 0.2 mol) and isopropyl ethylphosphonochloridate (34.1 g, 0.2 mol) on heating evolved ethyl chloride at about 115 °C. The reaction seemed complete in about 1 h. The product, on fractionation, gave 8 g of a liquid boiling at 45–52 °C/1 mmHg and 17 g of a liquid boiling at 118–120 °C/1 mmHg. An undistillable residue (20 g) remained. Redistillation of the second fraction gave the pure title compound (yield not given). Bp 124 °C/2.5 mmHg.

▶ *Diethyl diethylpyrophosphonate* *EtO(Et)P(O)OP(O)(Et)OEt* (*39*). Diethyl ethylphosphonate (41.0 g, 0.25 mol) and ethyl ethylphosphorochloridate (38.5 g, 0.25 mol) were heated in a flask set in an oil bath and fitted with a short fractionating column attached to a downward coil surrounded with cardice and industrial spirit. A reaction set in at about 120 °C and ethyl chloride (10 g) distilled out. A small quantity of hydrogen chloride was also evolved. When the reaction ceased, the residue was fractionated under reduced pressure. Diethyl ethylphosphonate (9 g) distilled at about 70 °C/7 mmHg and the bulk of the product (42 g) consisting of the title compound was collected at 135–139 °C/3.5 mmHg. There was practically no residue. Redistillation gave the pure title compound (yield not given). Bp 137 °C/3.5 mmHg.

▶ *Diethyl dimethylpyrophosphonate* *EtO(Me)P(O)OP(O)(Me)OEt* (*microwave method*) (*497*). Ethyl methylphosphonochloridate (1.42 g, 10 mmol) was added to DMAP (1.22 g, 10 mmol) in a conical flask and mixed well. After irradiation in a domestic microwave (LG, Model MG-555F, New Delhi, India) at 180 W for 4 min, the formation of a salt was observed. This was dissolved by the addition of one drop of water. The mixture was further irradiated at 180 W for 1 min. Progress of reaction was monitored by ^{31}P NMR spectroscopy until the signal of ethyl methylphosphonochloridate disappeared. The reaction mixture was washed and extracted into pentane (4 × 25 ml), and the solvent was evaporated to afford the pure title compound (1.98 g, 86%). δ_P (162 MHz, $CDCl_3$; mixture of diastereoisomers) 22.5 and 22.2 ppm. The same method was used to prepare the other pyrophosphonates depicted in Fig. 2.30.5.

2.31 *N,N*-DIALKYL-*P*-ALKYLPHOSPHONAMIDIC ANHYDRIDES $R(R'_2N)P(O)OP(O)(NR'_2)R$

The chemistry of these compounds has not been that well explored. Several synthetic approaches are available (*500,501*). One of the best is a solvent-free and high-yielding method that involves the microwave-assisted reaction of an *N,N*-dialkyl alkylphosphonamidochloridate, DMAP and water in a 1:1:0.5 molar ratio (Fig. 2.31.1) (*501*).



N,N-Dialkyl-*P*-alkylphosphonamidic anhydrides

R	R'	Reaction time (min)	Yield (%) [a]	Mp (°C)	δ_P (ppm) [b]
n-Pr	Me	5	85	oil	27.1, 26.3
n-Bu	Me	5	90	oil	27.0, 26.2
n-Pr	*i*-Pr	6	91	38	34.0. 33.3
n-Bu	*i*-Pr	6	88	39	33.5, 32.8
i-Bu	*i*-Pr	6	87	40	33.0, 32.6
Et	Ph	7	90	42	16.5, 16.2
n-Pr	Ph	7	89	47	16.7, 16.5
i-Bu	Ph	7	93	50	18.2, 18.0

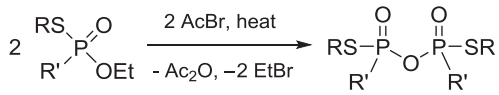
a. Isolated yield. *b*. ^{31}P NMR spectra were measured in $CDCl_3$ at 162 MHz.

Figure 2.31.1

▶ *N,N-Dialkyl-P-alkylphosphoramidic anhydrides* (*microwave method*) (*501*). The *N,N*-dialkyl alkylphosphonochloridate (10 mmol) and DMAP (1.22 g, 10 mmol) were mixed well. The resultant mixture was irradiated with microwaves at 180 W for 4 min, resulting in salt production. Water (900 µl, 5 mmol) was added to the salt, and the mixture was shaken until dissolution occurred. The mixture was further irradiated at 180 W for 1 min. The progress of reaction was monitored by ^{31}P NMR spectroscopy until the chloridate had been consumed. The reaction mass was washed and extracted with *n*-pentane (4 × 25 ml). The solvent was evaporated to afford the product that was triturated with *n*-pentane to yield a pure sample.

2.32 *S,S′*-DIALKYL DIALKYLDITHIOPYROPHOSPHONATES R(R′S)P(O)OP(O)(SR′)R

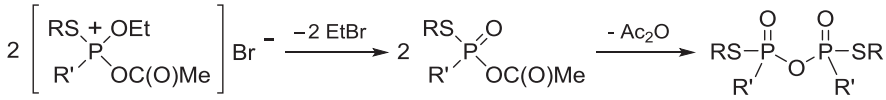
S,S′-Dialkyl dialkyldithiopyrophosphonates are prepared by the reaction of *O,S*-dialkyl alkylphosphonothiolates with acetyl bromide, with the concomitant formation of acetic anhydride and ethyl bromide (Fig. 2.32.1) (*502*). The starting materials are heated to 70–100 °C. It is important to use a threefold to fourfold molar excess of the phosphorus reagent. The mechanism is thought to involve a nucleophilic attack of the P═O oxygen atom of the *O*-ethyl *S*-alkyl alkylphosphonothiolate on acetyl bromide to yield a quasi-phosphonium intermediate (**299**) whose ethoxy group is dealkylated, with the loss of ethyl bromide, to provide the *O*-acetyl *S*-alkyl alkylphosphonothiolate (**300**) (Fig. 2.32.2). This then presumably undergoes an intermolecular reaction to provide the symmetrical pyrophosphonate (**301**) with the loss of acetic anhydride.



S,S'-dialkyl dialkyldithiopyrophosphonates

R	R'	Yield (%)	Bp (°C/mmHg)
Et	Me	54	120–124/0.040
n-Pr	Me	65	120–125/0.008
n-Bu	Me	69	125–130/0.005
Et	Et	61	115–120/0.005

Figure 2.32.1



299 **300** **301**

Figure 2.32.2

▶ *S,S'-Dialkyl dialkyldithiopyrophosphonates* (*general procedure*) (*502*). A mixture of *O*-ethyl *S*-alkyl alkylphosphonothiolate (0.4 mol) and acetyl bromide (12.3 g, 0.1 mol) was heated under reflux under nitrogen for 6—10 h at 70—100 °C. Ethyl bromide was collected (bp 38—40 °C). The residue was vacuum distilled. The first fraction collected was acetic anhydride (bp 138—140 °C), the second fraction was the starting material *O*-ethyl *S*-alkyl alkylphosphonothiolate and the third fraction was the title compound. Yields and boiling points appear in Fig. 2.32.1.

2.33 *O*-ALKYL *N*-ALKYL ALKYLPHOSPHONAMIDATES RP(O)(NR$_2$)OR

Two routes for converting methylphosphonic dichloride (**22**) to *O*-alkyl *N*-alkyl (or *N,N*-dialkyl) methylphosphonamidates (**167**) and (**181**) in adequate yield are shown in Fig. 2.33.1 (*259*).

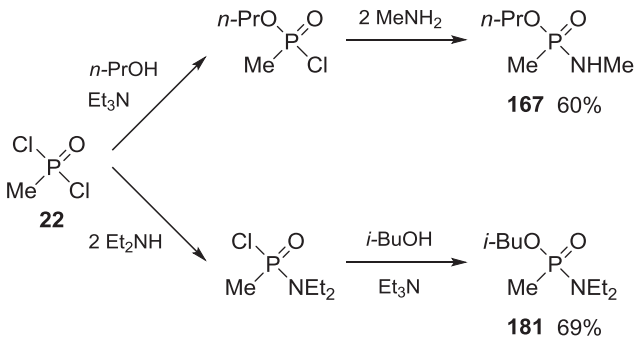
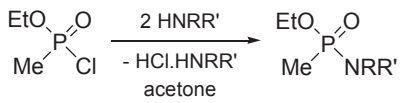


Figure 2.33.1

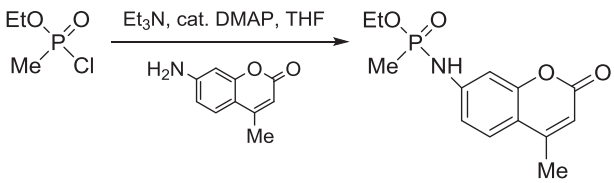
Alkyl alkylphosphonochloridates react efficiently with amines at velocities that depend on their electronic and steric character. Rates of reaction of ethyl methylphosphonochloridate with amines decrease in the order $NH_3 > RNH_2 > R_2NH$ (*503*). Reactions with ammonia, ethylamine, and *n*-butylamine are too quick to measure even at −50 °C. Relative rates for the following amines, given in brackets, demonstrate the strong influence of steric factors on the ease of combination: *s*-$BuNH_2$ (900) > Et_2NH (730) > *n*-Bu_2NH (540) > *t*-$BuNH_2$ (195) > $PhNH_2$ (57) > *s*-Bu_2NH (1). Yields and physical properties of the products appear in Fig. 2.33.2.



R	R'	Yield (%)	Bp (°C/mmHg)
H	*n* Bu	70	110–112/20
H	*s*-Bu	47	121–125/30
H	*t*-Bu	63	134–140/25
H	Ph	52	160–165/20
Et	Et	64	110–114/22
n-Bu	*n*-Bu	75	108–110/30
s-Bu	*s*-Bu	50	115–120/30

Figure 2.33.2

The aminocoumarin analogue (**302**) of the military nerve agent VX (Chapter 1) is prepared from ethyl methylphosphonochloridate and 7-amino-4-methylcoumarin, triethylamine and DMAP catalyst in THF (Fig. 2.33.3) (*9*). The yield is low due to the poor nucleophilicity of the coumarin amino group, which renders coupling problematic, and partial decomposition of the product during chromatography on silica gel.



302 25% δ_P 28.2

Figure 2.33.3

▶ *O-Ethyl N-substituted methylphosphonamidates EtO(Me)P(O)NRR′ (general method)* (*503*). Ethyl methylphosphonochloridate (1.42 g, 10 mmol) was added slowly to a stirred solution of the appropriate amine (22 mmol) in acetone (10 ml). After 72 h at room temperature, ether (20 ml) was added,

and the amine hydrochloride was collected by filtration and washed with ether. The solvent was removed from the combined filtrate and washings. Distillation of the residue under reduced pressure gave the amidates in Fig. 2.33.2.

▶ *O-n-Propyl N-methyl methylphosphonamidate n-PrO(Me)P(O)NHMe* (**167**) (*259*). A solution of *n*-propanol (30.0 g, 0.5 mol) and triethylamine (50.5 g, 0.5 mol) was added dropwise to a stirred solution of methylphosphonic dichloride (66.5 g, 0.5 mol) in anhydrous ether (600 ml) at −5 to −10 °C. After addition, the mixture was allowed to warm to room temperature and was stirred for 30 min. The mixture was cooled again to −5 to −10 °C, saturated with methylamine and then allowed to warm to room temperature. The precipitated amine hydrochloride salts were filtered off, the solvent was removed from the filtrate and the residue was distilled under reduced pressure to give a colourless liquid (45.25 g, 60%). Bp 115–118 °C/1.5 mmHg.

▶ *O-Isobutyl N,N-diethyl methylphosphonamidate i-BuO(Me)P(O)NEt*$_2$ (**181**) (*259*). Diethylamine (146 g, 2 mol) was added dropwise to a stirred solution of methylphosphonic dichloride (133 g, 1 mol) in anhydrous ether (600 ml) at −5 to −10 °C. After addition, the mixture was stirred for 25–30 min at room temperature and then cooled to 0–5 °C. A mixture of isobutanol (74 g, 1 mol) and triethylamine (101 g, 1 mol) was added dropwise. The temperature was raised to 30–35 °C and maintained as such for 1 h. The mixture was then cooled, and the amine hydrochloride was filtered off. The solvent was removed from the filtrate. The residue was distilled under vacuum to provide a colourless liquid (143 g, 69%). Bp 76–79 °C/2 mmHg.

▶ *O-Tert-butyl N-isopropyl methylphosphonamidate t-BuO(Me)P(O)NH-i-Pr* (*504*). Potassium *tert*-butoxide (108 mg, 0.97 mmol) was added to a solution of methylphosphonic dichloride (116 mg, 0.87 mmol) in *tert*-butanol. The mixture was shaken until all the *tert*-butoxide had dissolved. A large excess of isopropylamine (ca. 5 mmol) was then added. When the reaction was complete, as determined by ^{31}P NMR spectroscopy, the volatile material was evaporated, and the residue was partitioned between dichloromethane and water. Concentration of the organic layer and bulb-to-bulb distillation gave the title compound (yield not given). Bp 120 °C (oven temperature) at 1 mmHg. δ_P (36.2 MHz, CH_2Cl_2) 26.9 ppm.

▶ *O-Ethyl N,N-diethyl ethylphosphonamidate EtO(Et)P(O)NEt*$_2$ (*505*). Ethyl ethylphosphonochloridate (32 g, 0.20 mmol) in anhydrous light petroleum (bp 40–60 °C; 200 ml) was treated with diethylamine (35 g, 0.48 mol) in anhydrous light petroleum (50 ml). After 12 h, the precipitate was filtered off, and the filtrate was concentrated. Distillation gave the title compound as a colourless liquid (yield not reported). Bp 127–128 °C/25 mmHg.

▶ *O-Ethyl N-cyclohexyl ethylphosphonamidate EtO(Et)P(O)NHC*$_6$*H*$_{11}$ (*505*). This is prepared in the same way from ethyl ethylphosphonochloridate (32 g, 0.20 mol) and cyclohexylamine (48 g, 0.48 mol). Recrystallisation from light petroleum (bp 40–60 °C) gave the product as colourless prisms (yield not reported). Mp 75 °C.

▶ *O-Tert-butyl N-methyl isopropylphosphonamidate t-BuO(i-Pr)P(O)NHMe* (*504*). Anhydrous methylamine (390 mg, 12.5 mmol) in dichloromethane (5 ml) was added over 10 min to a stirred ice-cold solution of isopropylphosphonic dichloride (1.01 g, 6.27 mmol) in ether (16 ml). The mixture was filtered, and the filtrate was concentrated to yield crude *N*-methyl

isopropylphosphonamidochloridate [δ_P (36.2 MHz, $CDCl_3$) 56.2 ppm]. A portion of this was treated with potassium *tert*-butoxide (1 M, 1.5 mol equiv.) in *tert*-butanol to give, after Kugelrohr distillation, the title compound (yield not given). Bp 120 °C (oven temperature) at 1 mmHg. δ_P (36.2 MHz, CH_2Cl_2) 35.2 ppm.

▶ *O-Ethyl N-(2-oxo-4-methyl-2H-chromen-7-yl) methylphosphonamidate* (**302**) (*9*). A solution of 7-amino-4-methylcoumarin (0.5 g, 2.85 mmol) and triethylamine (0.4 ml, 2.86 mmol) in THF (50 ml) was added dropwise to a stirred solution of ethyl methylphosphonochloridate (0.41 g, 2.86 mmol) in THF (10 ml). A catalytic amount of DMAP (50 mg) was added, and the mixture was heated under reflux for 7 h under argon. The mixture was allowed to cool to room temperature. It was concentrated, dissolved in dichloromethane (100 ml) and washed with aqueous sodium bicarbonate (20 ml, 10% *w/v*). The organic layer was separated and dried ($MgSO_4$). Filtration of the drying agent and evaporation of the solvent from the filtrate gave the crude product. Chromatography on silica gel, eluting with 98:2 then 95:5 dichloromethane—isopropanol, gave a glassy syrup (0.2 g, 25%). δ_P ($CDCl_3$) 28.2 ppm.

2.34 *BIS*(*N,N*-DIALKYL) ALKYLPHOSPHONODIAMIDATES $RP(O)(NR_2)_2$

Substituted amides of alkenylphosphonic acids of the general formula $RP(O)(NR^1R^2)_2$, where R is an unsaturated group, and R^1 and R^2 represent the H atom or alkyl group, have been obtained by the reaction of the corresponding alkenylphosphonic dichlorides with ammonia, amines, amine hydrochlorides (*106*) or aziridine in the presence of triethylamine. They are usually stable viscous liquids that can be distilled under reduced pressure or white solids. They are generally insoluble in water but soluble in many organic solvents. Phosphonodiamidates of structure $(RNH)_2P(O)R'$ where R = H or alkyl, and R′ = alkyl or aryl, when slowly heated above 200 °C under a nitrogen atmosphere (*126*) or with urea and analogues (*506*) provide resinous polymers with useful properties.

Reaction of methylphosphonic dichloride (**22**) with ammonia in chloroform allows the preparation of methylphosphonodiamidate (**303**) (Fig. 2.34.1) (*507*). The mixture of this product and ammonium chloride formed cannot be separated by extraction with hot chloroform, even though the

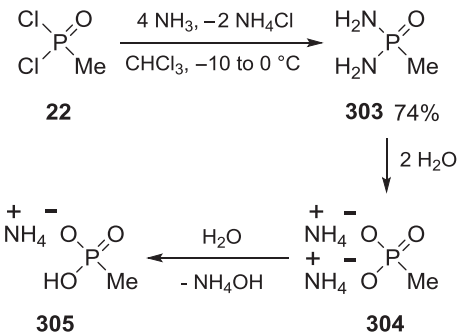


Figure 2.34.1

diamidate is fairly soluble in this solvent. Instead the ammonium chloride is best converted into diethylamine hydrochloride, which is very soluble in chloroform. Methylphosphonodiamidate crystallises from the chloroform solution in an almost pure state. The diamidate hydrolyses readily on exposure to the atmosphere; the crystals liquefy forming diammonium methylphosphonate (**304**) and then ammonium hydrogen methylphosphonate (**305**).

The higher alkylphosphonodiamidates (**306**) and (**307**) are prepared similarly, but in the absence of solvent, and appear to be slightly more hydrolytically stable than methylphosphonodiamidate. Treatment of ethylphosphonic dichloride (**22**) with an excess of methylamine gives *bis*(*N*-methyl) ethylphosphonodiamidate (**308**), which is also more hydrolytically stable. Thus, the ease of isolation of the pure materials decreases in the order $RP(O)(NR'_2)_2 > RP(O)(NHR')_2 > RP(O)(NH_2)_2$ in accord with their relative hydroscopicity and susceptibility to hydrolysis (Fig. 2.34.2).

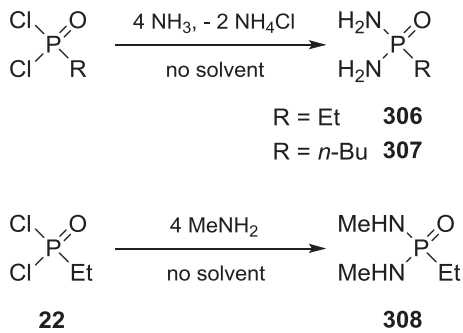
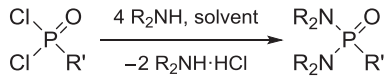


Figure 2.34.2

The higher homologues can be prepared by the reaction of alkylphosphonic dichlorides with secondary amines (*508*). The reaction of alkylphosphonic dichlorides with dimethylamine and diethylamine is conducted in refluxing heptane. The diamidate formed tends to increase the solubility of the amine hydrochloride in the reaction mixture so that complete removal of the salt by filtration is unachievable. Since distillation of the filtered reaction mixture, which retains some of the hydrochloride salt, can result in severe decomposition, it is advisable to eliminate the dissolved amine salt by treating the filtrate with aqueous sodium hydroxide, before distillation. Using this technique, it is possible to obtain consistent yields of 70–88% of the *bis*(*N*,*N*-dialkyl) alkylphosphonodiamidates (Fig. 2.34.3) (*39,505,509,510*). The reaction of the alkylphosphonic dichlorides with di-*n*-propylamine could not be forced to completion in refluxing heptane even after several days; replacement of this solvent by ethylbenzene overcame this problem, and the diamidates of methyl-, ethyl- and *n*-propylphosphonic acids were isolated in 25–30% yields. Appreciable quantities of amine hydrochlorides were retained in solution by these reaction mixtures and could not be completely precipitated by dilution with heptane. Washing these mixtures with sodium hydroxide prior to distillation was therefore imperative. The lower *bis*(*N*,*N*-dialkyl) alkylphosphonodiamidates derived



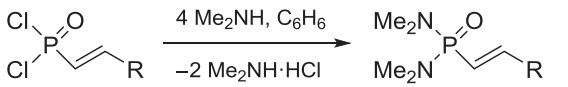
Bis(*N*,*N*-dialkyl) alkylphosphonodiamidates

R	R'	Bp (°C / mmHg)
Me	Me	138/32
Et	Me	166/33
n-Pr	Me	137/3.5
Me	Et	142/31
Et	Et	183/26
n-Pr	Et	137/1.2
Me	*n*-Pr	149/33
Et	*n*-Pr	189/28
n-Pr	*n*-Pr	141/1.2
Me	*n*-Bu	157/33
Et	*n*-Bu	137/3.5

Figure 2.34.3

from secondary amines are colourless liquids that are soluble in common organic solvents and infinitely soluble in water.

Addition of certain diamines to alkylphosphonic dichlorides gives cyclic diamidates, especially if formation of a five- or six-membered ring is possible (not shown) (*511*,*512*). Vinylphosphonic dichloride (**34**) and styrylphosphonic dichloride (**234**) react rapidly with 4 mol of dimethylamine to give diamidates (**309**) and (**310**), respectively (Fig. 2.34.4) (*106*).



R = H **34** R = H **309** 63%
R = Ph **234** R = Ph **310** 51%

Figure 2.34.4

Alkylphosphonic dichlorides can be characterised as their dianilides (*39*) by treatment with at least 4 molar equivalents of aniline, removing the aniline hydrochloride, together with any excess aniline, by treatment with dilute hydrochloric acid and crystallising the products from a suitable solvent or mixture of solvents. Addition of *O*-alkylhydroxylamines to alkyl- or arylphosphonic dichlorides gives derivatives of unusual structure, for example, $(MeONH)_2P(O)Ph$ (mp 70–72 °C) (not shown) (*513*).

▶ *Methylphosphonodiamidate* $(H_2N)_2P(O)Me$ (**303**) (*507*). Freshly distilled methylphosphonic dichloride (38 g, 0.29 mol) was added dropwise for 2 h at −10 to 0 °C to stirred absolute chloroform (800 ml) that had been saturated at −10 °C with dry ammonia gas. Passage of ammonia was continued during the addition. The precipitated mixture of methylphosphonodiamidate and ammonium chloride (48 g) was collected rapidly on a Büchner funnel with a sintered-glass disc and stored immediately in a vacuum desiccator over phosphorus pentoxide. The finely powdered material, suspended in a mixture of anhydrous chloroform (200 g) and anhydrous diethylamine (50 g), was refluxed gently until dissolution occurred. The hot solution was filtered to remove small quantities of impurities. When the filtrate had cooled to −15 °C, methylphosphonodiamidate crystallised as large plates, which were collected on a sintered-glass plate (21 g, 74%) and recrystallised from methanol containing 3% ether. Mp 128−129 °C (sealed capillary, dec.).

▶ *Ethylphosphonodiamidate* $(H_2N)_2P(O)Et$ (**306**) (*126*). Ethylphosphonic dichloride (15 g, 0.1 mol) was added dropwise to liquid ammonia (200 ml) in a flask equipped with a stirrer, dry ice-filled reflux condenser and a dropping funnel. After the addition, the excess ammonia was allowed to evaporate. The residue was removed by the addition of concentrated ammonium hydroxide (200 ml), which formed a slurry. This was filtered, and the filtered product was recrystallised from absolute ethanol to give the diamidate (yield not stated). Mp 180−185 °C. The analogue $(H_2N)_2P(O)Bu$-*n* (mp 170−175 °C) can be prepared similarly from *n*-butylphosphonic dichloride.

▶ *Bis(N-methyl) ethylphosphonodiamidate* $(MeNH)_2P(O)Et$ (**308**) (*126*). Ethylphosphonic dichloride (15 g, 0.1 mol) was added dropwise to methylamine (25 g, 0.8 mol) at −10 °C in a flask equipped with a stirrer, a dry ice-filled reflux condenser and a dropping funnel. After the addition, the excess methylamine was allowed to evaporate, and the mixture was diluted with ether (100 ml) and filtered to remove methylamine hydrochloride. The filtrate was concentrated to give a colourless liquid (yield not stated) that was shown to be pure by microanalysis.

▶ *Bis(N,N-dialkyl) phosphonodiamidates* $(R_2N)_2P(O)R'$ (Fig. 2.34.3) (*508*). A solution of the appropriate alkylphosphonic chloride (1 mol) in the same volume of solvent (heptane or ethylbenzene) was added dropwise to a stirred and cooled solution of the appropriate dialkylamine (4.1 mol) in the solvent (500−1000 ml). The resulting mixture was heated under reflux for either 24 h (dimethyl- and diethylamine) or 48 h (di-*n*-propylamine). The yields of *bis(N,N*-dimethyl) phosphonodiamidates were improved from 70−75% to 80−83% by the slow addition of the amine during the refluxing period to prevent volatilisation loss. The higher amines gave satisfactory yields without such a precaution. The mixture was cooled and filtered. The filtrate was treated with 30% *w/v* aqueous NaOH (25−30 ml) with cooling. After agitation for 2−3 h, the organic layer was separated, dried ($MgSO_4$) and distilled. The residue that remained after solvent removal usually had a red colour (origin unknown). The quantity of amine hydrochloride that separated from the reaction mixtures, involving the alkylphosphonic dichlorides and di-*n*-propylamine, was within a few grams of the theoretical amount. Nevertheless, distillation of the washed crude products gave disappointing yields of the phosphonodiamidates (generally <50%) with considerable amounts of dark undistillable residues.

▷ *Bis(N-cyclohexyl) ethylphosphonodiamidate* (*c-HexNH*)$_2$*P(O)Et* (*505*). Ethylphosphonic dichloride (29.4 g, 0.20 mol) in anhydrous benzene (200 ml) was treated with cyclohexylamine (43.6 g, 0.44 mol) in anhydrous benzene (50 ml). The precipitate was filtered off, and the filtrate was concentrated. Recrystallisation of the residue from acetone gave the title compound as colourless needles (yield not stated). Mp 160 °C.

▷ *N,N,N′,N′-Tetramethyl vinylphosphonodiamidate* (*Me*$_2$*N*)$_2$*P(O)CH═CH*$_2$ (**309**) (*106*). A solution of dimethylamine (7.7 g, 171 mol) in ether (50 ml) was added gradually with stirring to vinylphosphonic dichloride (6.0 g, 41 mmol) at −12 °C. The precipitate was filtered off, and the solvent was evaporated from the filtrate to leave a residue that was fractionated to give a colourless liquid (4.2 g, 63%). Bp 82 °C/3 mmHg.

▷ *N,N,N′,N′-Tetramethyl styrylphosphonodiamidate* (*Me*$_2$*N*)$_2$*P(O)CH═CHPh* (**310**) (*106*). Dimethylamine (9.00 g, 200 mmol) was added to a cooled stirred mixture of benzene (30 ml) and petroleum ether (70 ml) followed by the gradual addition of styrylphosphonic dichloride (11.05 g, 50.0 mmol). After addition, stirring was continued for 2 h. After 12 h, the mixture was heated to 30–35 °C for 2 h. The residue was filtered off and washed twice with petroleum ether. The combined filtrate and washings were treated with portions of saturated sodium bicarbonate solution to remove traces of dimethylamine hydrochloride, dried (NaOH) and distilled to give a colourless liquid (6.0 g, 51%). Bp 180 °C/2 mmHg.

▷ *Bis(N-phenyl) methylphosphonodiamidate* (*PhHN*)$_2$*P(O)Me* (*39*). A solution of aniline (37.2 g, 0.4 mol) in benzene (30 ml) was added to a stirred solution of methylphosphonic dichloride (13.3 g, 0.1 mol) in the same solvent (50 ml). A vigorous reaction set in, and a semisolid product resulted. After filtering, the solid was shaken with a mixture of chloroform and water, the latter extract being separated and discarded. The chloroform layer was extracted with dilute hydrochloric acid, separated and dried ($MgSO_4$). After concentration, it was treated with petroleum ether (bp 40–60 °C). The product, which separated as a liquid, rapidly crystallised. For analysis, it was crystallised first from chloroform, then from a mixture of this solvent and benzene, and finally from 1:4 *v/v* ethanol–water. It melted at 158 °C. Higher homologues were prepared similarly. In the preparation of the latter, however, the dianilide was found in the benzene filtrate from the aniline hydrochloride. This filtrate was worked up in a similar manner to that of the chloroform extract referred to in the preparation of *bis*(*N*-phenyl) methylphosphonodiamidate. Dianilides that can be isolated this way include *bis*(*N*-phenyl) ethyl- (mp 144 °C), *bis*(*N*-phenyl) *n*-propyl- (mp 150 °C), *bis*(*N*-phenyl) *n*-butyl- (mp 138 °C), *bis*(*N*-phenyl) *n*-pentyl- (mp 110 °C), *bis*(*N*-phenyl) hexyl- (mp 128 °C), *bis*(*N*-phenyl) heptyl- (mp 120 °C) and *bis*(*N*-phenyl) *n*-octylphosphonodiamidate (mp 98 °C).

2.35 *O,S*-DIALKYL ALKYLPHOSPHONOTHIOLATES RP(O)(OR)SR

O,S-Dialkyl alkylphosphonothiolates can be obtained by the reaction between alkyl alkylphosphonochloridates and sodium alkanethiolates (e.g. to give **311–313**), treatment of alkyl alkyl-*H*-phosphinates with triethylamine and sulfur and then an alkyl bromide (e.g. to give **311**), or from

the action of sodium salts of *O*-alkyl hydrogen alkylphosphonothioates on alkyl halides (e.g. to give **311** and **314**) (Fig. 2.35.1) (*514–517*). *O,S*-Dialkyl alkylphosphonothiolate products are useful for mass spectral studies (7,*253*).

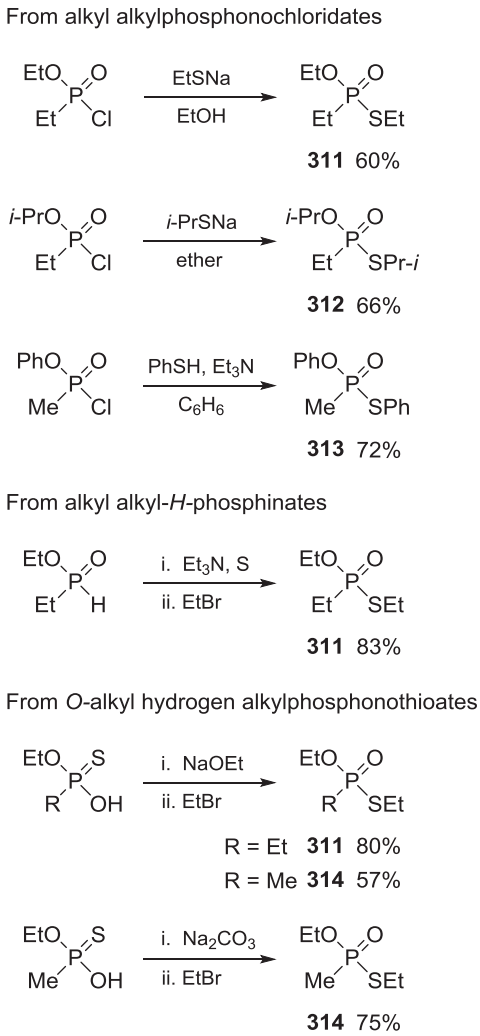


Figure 2.35.1

Other routes to *O,S*-dialkyl alkylphosphonothiolates include the Arbuzov reaction of dialkyl alkyl/arylphosphonites with dialkyl disulfides (e.g. to give **315**) (*518*) or alkyl thiocyanates (e.g. to give **316**) (*519*), the Pistchimuka isomerisation of dialkyl alkyl/arylphosphonothionates upon boiling with the appropriate alkyl iodide (e.g. to give **317**) (*520*), and the alkylation of *O*-alkyl alkyl/arylphosphonothioate salts with alkyl halides (e.g. to give **318**) (*521*) (Fig. 2.35.2).

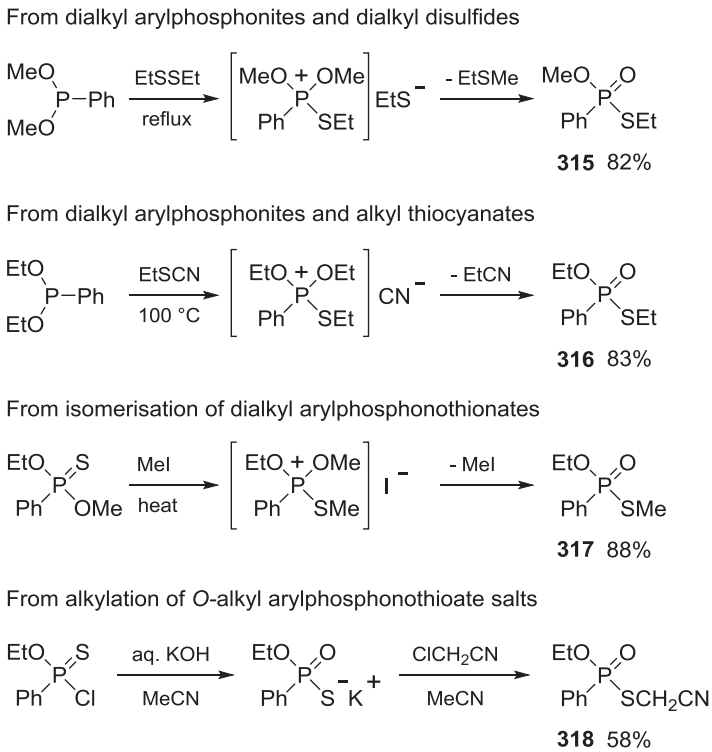


Figure 2.35.2

▶ *O-Cyclohexyl S-methyl methylphosphonothiolate c-HexO(MeS)P(O)Me* (**285**) (*262*). Methanethiol was bubbled into stirred anhydrous benzene (100 ml) containing sodium (3.00 g, 0.13 mol) heated to 40–50 °C. Once the sodium had dissolved, the mixture was heated under reflux for 1 h. Sodium methanethiolate precipitated. To this stirred suspension was added dropwise at room temperature cyclohexyl methylphosphonochloridate (19.65 g, 0.1 mol). After addition, the mixture was heated under reflux for 2 h. The sodium chloride was filtered off, the filtrate was concentrated and the residue was distilled under a current of nitrogen to provide the title compound (8.32 g, 40%). Bp 126 °C/5 mmHg.

▶ *O,S-Diethyl methylphosphonothiolate EtO(EtS)P(O)Me* (**314**) (*42*). To a solution of sodium ethoxide (0.05 mol, from 1.15 g of sodium and 25 ml of absolute ethanol) was added *O*-ethyl hydrogen methylphosphonothioate (7.00 g, 0.05 mol) and then ethyl bromide (7.63 g, 0.07 mol). The reaction mixture was heated under reflux for 3 h. The ethanol was removed, and the residue was treated with benzene (40 ml) and water (40 ml). The benzene layer was separated, dried ($MgSO_4$), the solvent removed and the residue vacuum distilled to provide the title compound as a colourless liquid (4.8 g, 57%). Bp 92–93 °C/9 mmHg. Under analogous conditions, the alkylation of the sodium salt of *O*-ethyl hydrogen methylphosphonothioate with *n*-butyl bromide gave *O*-ethyl *S*-*n*-butyl methylphosphonothiolate EtO(*n*-BuS)P(O)Me (56%, bp 112–114 °C/9 mmHg).

▶ *O,S-Diethyl methylphosphonothiolate EtO(EtS)P(O)Me* (**314**) (*522*). Sodium carbonate (42 g, 0.4 mol) was added in portions to a solution of *O*-ethyl hydrogen methylphosphonothioate (55 g, 0.4 mol) in ethanol (100 ml) with cooling. The solution was cooled and filtered, and ethyl bromide (60 g, 0.6 mol) was added. The mixture was heated under reflux for 1 h, and an equal volume of light petroleum (bp 40–60 °C) was added. The precipitated sodium bromide was filtered off, the solvent removed from the filtrate and the residue distilled to provide the title compound (56 g, 75%). Bp 63 °C/1 mmHg. The same substance was also prepared from ethyl methylphosphonochloridate, ethanethiol and triethylamine (no yield given). Bp 90 °C/12 mmHg (*420*).

▶ *O-Ethyl S-propyl methylphosphonothiolate EtO(n-PrS)P(O)Me* (*420*). This was prepared by boiling diethyl methylphosphonothionate with an excess of *n*-propyl iodide for 92 h, followed by distillation under reduced pressure (50%). Bp 106 °C/10 mmHg.

▶ *O,S-Diethyl ethylphosphonothiolate EtO(EtS)P(O)Et* (**311**) (*39*). Ethyl ethyl-*H*-phosphinate (6.1 g, 50 mmol) in triethylamine (5.05 g, 50 mmol) was treated with sulfur (1.6 g, 50 mmol) and warmed to 60 °C. Ethyl bromide (7.09 g, 65 mmol) and acetone (20 ml) were added, and the mixture was refluxed with stirring for 2.5 h. The base-hydrochloride was filtered off and washed with ether. The filtrate and washings were worked up to give the product as a colourless liquid (7.5 g, 83%). Bp 60 °C/1 mmHg. The same compound was prepared from ethanethiol, sodium wire and ethyl ethylphosphonochloridate. Bp 69–71 °C/2 mmHg (*40*).

▶ *O,S-Diethyl ethylphosphonothiolate EtO(EtS)P(O)Et* (**311**) (*39*). Sodium (1.4 g, 60 mmol) was dissolved in absolute ethanol (50 ml), and *O*-ethyl hydrogen ethylphosphonothioate (9.2 g, 60 mmol) in absolute ethanol (10 ml) was added. The sodium salt so obtained (Note) was treated with an excess of ethyl bromide (9.3 g, 85 mmol), and the mixture was refluxed gently for 1 h. After filtering off the sodium bromide, the ethanol was removed from the filtrate under reduced pressure, and the residue was shaken with 1% *w/v* sodium hydroxide solution (100 ml). The mixture was extracted with ether and the product, after removal of ether, was isolated by distillation under reduced pressure (8.7 g, 80%). Bp 81 °C/1 mmHg. A sample of the title compound prepared from ethyl ethylphosphonochloridate and sodium ethanethiolate was identical. Note: The sodium salt on isolation was found to be very hygroscopic, freely soluble in ethanol and acetone and readily soluble in warm benzene.

▶ *O,S-Diisopropyl ethylphosphonothiolate i-PrO(i-PrS)P(O)Et* (**312**) (*39*). 2-Propanethiol (3.5 g, 46 mmol) was added to sodium wire (1.1 g, 48 mmol) in anhydrous ether (75 ml). When the sodium had reacted completely, a solution of isopropyl ethylphosphonochloridate (7.8 g, 46 mmol) in ether (25 ml) was added. Heat was developed, and after refluxing for 1 h, the mixture was filtered and the ether was removed from the filtrate. Fractionation of the residue under vacuum gave the title compound (6.4 g, 66%). Bp 72 °C/1.5 mmHg.

▶ *O,S-Diphenyl methylphosphonothiolate PhO(PhS)P(O)Me* (**313**) (*429*). A solution of benzenethiol (5.76 g, 52 mmol) and triethylamine (5.30 g, 52 mmol) in benzene (50 ml) was added dropwise to a stirred solution of phenyl methylphosphonochloridate (10.0 g, 52 mmol) in benzene (50 ml) at 4–8 °C. The mixture was left for 12 h and was filtered. The filtrate was concentrated and then distilled twice to provide the title compound (10.0 g, 72%). Bp 137–138 °C/0.03 mmHg. δ_P (rel. to H_3PO_4) −46 ppm.

▷ *O-Methyl S-ethyl phenylphosphonothiolate MeO(Ph)P(O)SEt* (**315**) (*dialkyl disulfide method*) (*518*). A mixture of dimethyl phenylphosphonite (16.0 g, 94 mmol), diethyl disulfide (11.5 g, 94 mmol) and hydroquinone (220 mg, 2 mmol) was heated under reflux for 9 h. The pressure was then reduced gradually to 8 mmHg, whereupon volatile methyl ethyl sulfide (bp 65 °C) was collected in a cold trap. Distillation of the remaining reaction mixture through a 75 cm long Fenske column gave the title compound (16.3 g, 82%). Bp 117 °C/0.6 mmHg. Redistillation of this material provided a sample that was analytically pure. Bp 112 °C/2.2 mmHg.

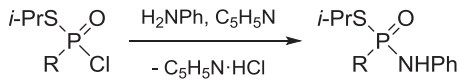
▷ *O,S-Diethyl phenylphosphonothiolate EtO(Ph)P(O)SEt* (**316**) (*alkyl thiocyanate method*) (*519*). A stirred equimolar mixture of diethyl phenylphosphonite and ethyl thiocyanate was heated slowly under an inert gas atmosphere (to suppress oxidation of the phosphonite) in an oil bath to about 100 °C. After the vigorous reaction was completed, the mixture was heated for 1 h by gradually raising the bath temperature from 160 to 180 °C, and the evolved ethyl cyanide was distilled off (bp 96 °C). The *O,S*-diethyl phenylphosphonothiolate remaining in the flask was purified by vacuum distillation (83%). Bp 96–97 °C/0.02 mmHg.

▷ *O-Ethyl S-methyl phenylphosphonothiolate EtO(Ph)P(O)SMe* (**317**) (*isomerisation method*) (*520*). Ethyl methyl phenylphosphonothionate (0.44 g, 2 mmol) and iodomethane (9.1 g, 64 mmol) were placed in a pressure vessel charged with 15 psi of nitrogen. The vessel was placed in an oil bath at 113 °C, and the mixture was stirred for 6 h. After cooling, the contents were filtered and concentrated under reduced pressure. Bulb-to-bulb distillation gave a product mixture (0.40 g) that was determined by NMR spectroscopy to contain the title compound (88%), starting thionate (8%) and *O,S*-dimethyl phenylphosphonothiolate (4%).

▷ *O-Ethyl S-cyanomethyl phenylphosphonothiolate EtO(Ph)P(O)SCH$_2$CN* (**318**) (*alkylation method*) (*521*). Water (50 ml) and subsequently a solution of potassium hydroxide (120 g, 2.14 mol) in water (200 ml) were added to a stirred solution of *O*-ethyl phenylphosphonochloridothionate (220.5 g, 1.00 mol). The temperature was allowed to rise to approximately 70 °C and was kept there for 1 h. The solvents were distilled off, and the residue was dissolved in absolute ethanol (800 ml). The undissolved potassium chloride was removed by suction filtration, and the clear filtrate was concentrated and dried to give a white solid (167 g, 70%). A portion of this salt (60 g, 0.25 mol) was dissolved in acetonitrile (100 ml). Chloroacetonitrile (18 g, 0.24 mol) was added with stirring at 50 °C. This temperature was maintained for 1 h. The reaction mixture was poured into ice water (200 ml). The oil that separated was dissolved in benzene (200 ml), dried ($MgSO_4$) and the solvent was removed by distillation under vacuum. The remaining residue was undistillable even at low pressure. The lower distilling impurities were removed at 70 °C at 1 mmHg within 1 h to provide the title compound (35 g, 58%).

2.36 *S*-ALKYL *N*-ALKYL (OR *N,N*-DIALKYL) ALKYLPHOSPHONAMIDOTHIOLATES RP(O)(NR$_2$)SR

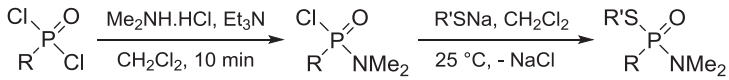
Two methods for the synthesis of *S*-alkyl *N*-substituted alkylphosphonamidothiolates are available. The first utilises the reaction between *S*-alkyl alkylphosphonochloridothiolates and amines, which proceeds facilely to generate the desired products (e.g. **319** and **320**) (Fig. 2.36.1) (*39*). The second starts with the



R = Me **319** 56%
R = Et **320** 60%

Figure 2.36.1

alkylphosphonic dichloride (**321**) whose treatment with an amine generates the *N*-substituted alkylphosphonamidochloridate (**322**) (Fig. 2.36.2) (*523*). Reaction of the chloridate with a sodium alkanethiolate provides the target compound (**323**) in an overall two-step one-pot sequence, ready for GC—MS to support the verification activities of the Chemical Weapons Convention (*524,525*).



321 **322** **323**

R = Me, Et, *n*-Pr ; R' = Me, Et, *n*- or *i*-Pr, *n*- or *i*-Bu, *n*- or *i*-pentyl, *n*-hexyl

Figure 2.36.2

▶ *S-Isopropyl N-phenyl methylphosphonamidothiolate i-PrS(Me)P(O)NHPh* (**319**) (*39*). *S*-Isopropyl methylphosphonochloridothiolate (2.2 g, 12.5 mmol) was added to aniline (1.1 ml, 12.5 mmol) and pyridine (2.0 ml, 25.0 mmol). Some heat was evolved, and the mixture was heated to 100 °C for 1 h. After cooling, it was poured into an excess of dilute hydrochloric acid. The anilide solidified at once and was recrystallised from benzene (1.6 g, 56%). Mp 143 °C. *S*-Isopropyl *N*-phenyl ethylphosphonamidothiolate *i*-PrS(Et)P(O)NHPh was made similarly and recrystallised from benzene (60%). Mp 118 °C.

▶ *S-Alkyl N,N-dimethyl alkylphosphonamidothiolates R′S(R)P(O)NMe*$_2$ (**323**) (*523*). Triethylamine (40.4 mg, 0.4 mmol) in dichloromethane (300 μl) was added dropwise to a stirred solution of the appropriate alkylphosphonic dichloride (0.2 mmol) and dimethylamine hydrochloride (16.3 mg, 0.2 mmol) in dichloromethane (300 μl). The mixture was stirred at room temperature for 10 min. Triethylamine hydrochloride was filtered off, and the resulting solution was added dropwise to a solution of the sodium alkanethiolate in dichloromethane (300 μl). The mixture was stirred for a further 10 min, sodium chloride filtered off and the solution analysed by GC—MS.

2.37 *S,S′*-DIALKYL ALKYLPHOSPHONODITHIOLATES RP(O)(SR$_2$)$_2$

S,S′-Dialkyl alkylphosphonodithiolates can in certain cases be obtained from alkylphosphonic dichlorides and lead(II) alkanethiolate salts. A disadvantage of methanethiol besides its obnoxious stench is its low volatility (bp 6 °C), which makes it difficult to add a precise amount. Lead(II) methanethiolate is more convenient and is prepared by bubbling methanethiol into a solution of lead(II) acetate in aqueous ethanol (*150*). The thiolate salt precipitates as a yellow solid and can be used

to convert alkylphosphonic dichlorides to the *S,S′*-dimethyl alkylphosphonodithiolates (e.g. **324**) (Fig. 2.37.1) (*121*). *Bis*(*S,S′*-dialkyl) alkylphosphonodithiolates (e.g. **325–327**) can also be prepared by the reaction of alkylphosphonic dichlorides with 2 molar equivalents each of an alkanethiol and triethylamine (*39,121*) or pyridine (*526*).

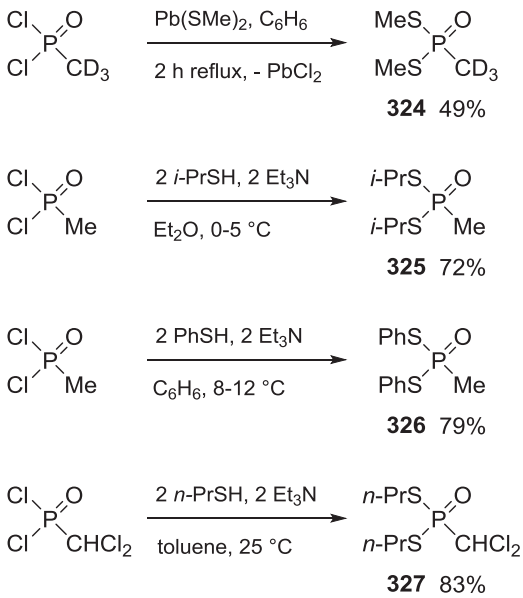


Figure 2.37.1

Measurements of the rate of hydrolysis of *S,S′*-diisopropyl methylphosphonodithiolate (**325**) by estimating the thiol and acid (**328**) produced show that P—S fission occurs both in acid and in alkaline solution (Fig. 2.37.2) (*527*). This is attributed to the low P—S bond strength, which is reflected in the high reactivity in alkaline solution (~10^4 times more reactive than diisopropyl methylphosphonate). The rate in acid solution is about 5 times less than that of the oxygen ester. Hydrolysis of *S*-isopropyl hydrogen methylphosphonothiolate (**328**) gives methylphosphonic acid (not shown).

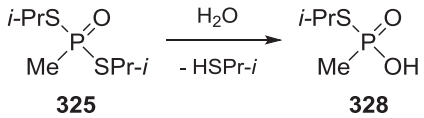


Figure 2.37.2

▶ *Preparation of lead(II) methanethiolate Pb(SMe)*$_2$ (*150*). Lead(II) acetate trihydrate (22.8 g, 60 mmol) was suspended in absolute ethanol (200 ml) maintained at 50 °C. Deionised water (~25 ml) was added, and the suspension was stirred until the solid dissolved. Methanethiol was bubbled through

the solution until a yellow precipitate formed. This was filtered off, washed with ethanol and dried under high vacuum (17.4 g, 96%). Mp 128 °C (dec.).

▶ *S,S′-Dimethyl d_3-methylphosphonodithiolate* $(MeS)_2P(O)CD_3$ (**324**) (*121*). Lead(II) methanethiolate (2.40 g, 8 mmol) was added in one portion to a solution of d_3-methylphosphonic dichloride (0.54 g, 4 mmol) in benzene (20 ml). The mixture was heated under reflux for 2 h. The dark yellow precipitate lightened in colour. An analysis of the solution by GC—MS showed the presence of the required product. The precipitate was filtered off, and the filtrate was concentrated to give a liquid. Column chromatography on silica gel, eluting with 7:3 hexane-acetone, gave a colourless liquid (0.31 g, 49%). δ_P ($CDCl_3$) 63.5 ppm.

▶ *S,S′-Diisopropyl methylphosphonodithiolate* $(i\text{-}PrS)_2P(O)Me$ (**325**) (*527*). Methylphosphonic dichloride (66.5 g, 0.5 mol) in ether (200 ml) was added dropwise to a stirred solution of 2-propanethiol (76.0 g, 1.0 mol) and triethylamine (101.0 g, 1.0 mol) in ether (1000 ml) at 0—5 °C. The mixture was left at room temperature for 12 h. The precipitate was filtered off and washed with ether. The solvent was removed from the combined filtrate and washings. Distillation of the residue under reduced pressure gave the title compound (76.3 g, 72%). Bp 94 °C/0.2 mmHg, 104 °C/2.5 mmHg (*39*). The related compounds $(EtS)_2P(O)Et$ (bp 120 °C/4.5 mmHg) and $(i\text{-}PrS)_2P(O)Et$ (bp 108 °C/2 mmHg) were prepared analogously (*39*).

▶ *S,S′-Diphenyl methylphosphonodithiolate* $(PhS)_2P(O)Me$ (**326**) (*429*). A solution of methylphosphonic dichloride (7.98 g, 60 mmol) in benzene (40 ml) was added dropwise to a stirred solution of benzenethiol (13.20 g, 120 mmol) and triethylamine (12.12 g, 120 mmol) in benzene (50 ml) at 8—12 °C. The mixture was left for 12 h, and the precipitate was filtered off. Removal of the solvent from the filtrate gave crystals, which were recrystallised from dichloromethane, to give the title compound (13.3 g, 79%). Mp 82—83 °C. δ_P (rel. 85% H_3PO_4) 56.0 ppm.

▶ *S,S′-Di-n-propyl dichloromethylphosphonodithiolate* $(n\text{-}PrS)_2P(O)CHCl_2$ (**327**) (*528*). 1-Propanethiol (9.12 g, 120.0 mmol) was added to a stirred solution of dichloromethylphosphonic dichloride (11.0 g, 54.5 mmol) maintained under nitrogen at room temperature. To this mixture was added dropwise a solution of triethylamine (13.23 g, 131 mmol) in toluene (35 ml). The resultant mixture was heated under reflux for 30 min. The mixture was allowed to cool to room temperature and was filtered. The filtrate was evaporated to leave a liquid. Bulb-to-bulb distillation gave a colourless mobile liquid (12.67 g, 83%). Oven temperature 100—120 °C/0.2 mmHg.

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CHAPTER 3

Thiophosphonyl Compounds

Christopher M. Timperley
Detection Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK

3.1 INTRODUCTION

Various thiophosphonyl compounds were developed in the 1960s–1970s as experimental and commercial pesticides. The majority had the *O*-alkyl *O*-alkyl/aryl alkylphosphonothionate structure in which the *O*-alkyl group (methyl, ethyl, *n*-propyl or isobutyl) and the *P*-alkyl group (methyl or ethyl) were kept small to confer effective anticholinesterase activity (Fig. 3.1.1) (*1*,*2*).

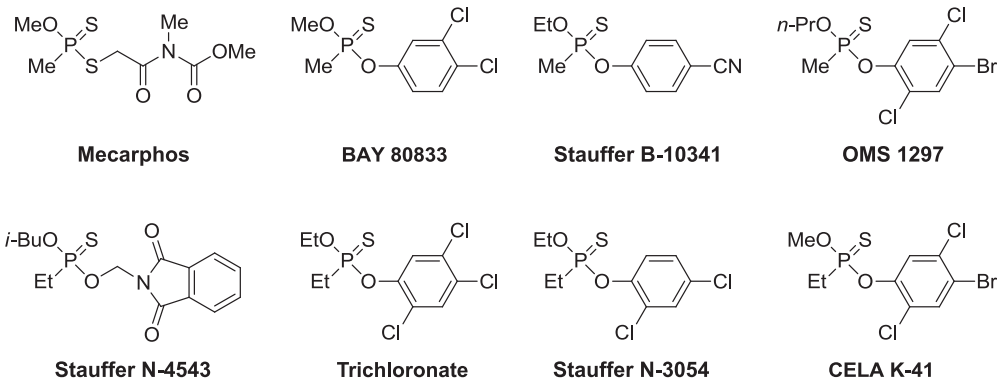

Figure 3.1.1 Some thiophosphonyl pesticides.

Mecarphos was introduced as an experimental insecticide by Murphy Chemical Limited (LD_{50} oral rat 57 mg/kg). BAY 80833 was an experimental soil insecticide made by Bayer AG, Stauffer B-10341 an insecticide that killed houseflies resistant to other insecticides, and OMS 1297 a promising poison of cattle grubs. Stauffer N-4543 was introduced by Stauffer Chemical Company in 1967 as an experimental foliar insecticide (LD_{50} oral rat 75 mg/kg); the variation of the *O*-alkyl group little affected the insecticidal activity but greatly affected mammalian toxicity; the lowest mammalian toxicity was achieved by the isobutyl ester. Trichloronate was developed by Bayer AG in 1960 as a soil insecticide (LD_{50} oral rat 50 mg/kg), while Stauffer N-3054 (LD_{50} oral rat 75 mg/kg) and CELA K-41 (LD_{40} rat 80 mg/kg) were researched as insecticides, but not marketed. The consumption of such materials in pest control nowadays is assumed to be low, due to toxicity and environmental

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concerns, and because some of the precursor chemicals and intermediates are covered by the Chemical Weapons Convention, as they can be used for prohibited purposes (*3*). All researchers performing practical work with such compounds should consult this legislation to ensure their planned activities are legal.

3.2 ALKYLPHOSPHONOTHIOIC DICHLORIDES RP(S)Cl$_2$

The reaction between an alkyl halide, phosphorus trichloride and aluminium trichloride to produce an ionic complex is called the Kinnear–Perren reaction (*4*) and is covered in detail in Chapter 2. The ionic complexes are able to react with various sources of sulfur to provide alkylphosphonothioic dichlorides. Although hydrogen sulfide has been used as a source of sulfur (*4*,*5*) the yields of the obtained alkylphosphonothioic dichlorides can be low due to competing formation of a symmetrical six-membered trimer of structure [RP(S)S]$_3$ (*6*). The use of ethanethiol or potassium thiocyanate (*7*) or dimethyl disulfide for larger scale work (*8*) as alternative sulfurising reagents allows efficient syntheses of methylphosphonothioic dichloride (**1**), ethylphosphonothioic dichloride (**2**) and isopropylphosphonothioic dichloride (**3**) (Fig. 3.2.1).

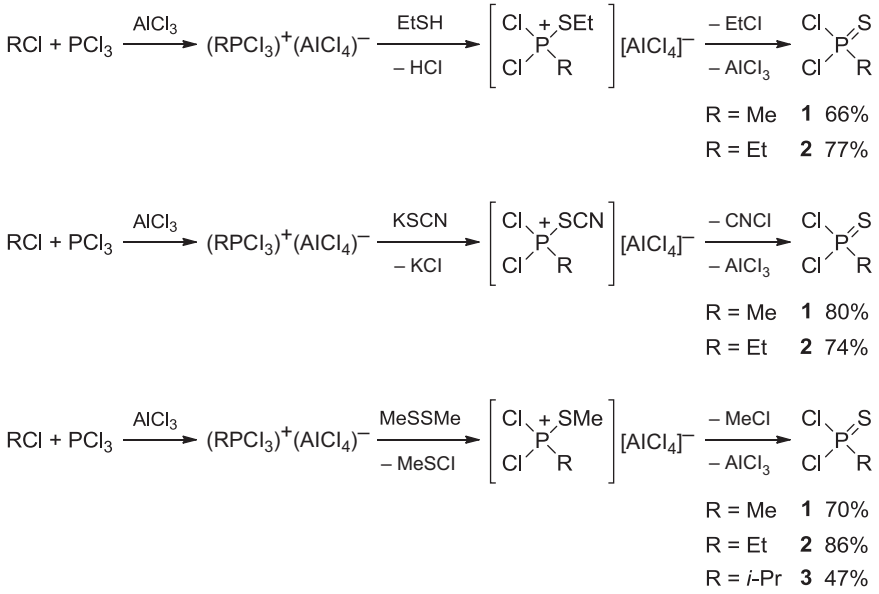


Figure 3.2.1

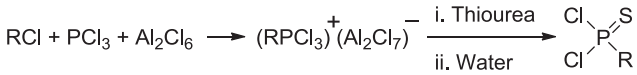
▶ *Methylphosphonothioic dichloride MeP(S)Cl$_2$* (**1**) *(from Kinnear–Perren complex and ethanethiol)* (*7*). Ethanethiol (9.6 g, 0.15 mol) was added dropwise to a stirred mixture of the $[MePCl_3]^+[AlCl_4]^-$ complex (50.0 g, 0.16 mol) and potassium chloride (11.6 g, 0.16 mol) at room temperature in

a three-necked flask equipped with a mechanical stirrer, dropping funnel and reflux condenser. The reaction mixture liquefied during the addition. After the ethanethiol had been added, the mixture was heated with stirring to 45–50 °C for 30 min. The reflux condenser was replaced by one set up for distillation, and the mixture was distilled. The products were collected in a cooled trap and receiver. Redistillation yielded ethyl chloride (6.5 g, 66%; boiling point (bp) 12 °C) and methylphosphonothioic dichloride (17.2 g, 74%). Bp 70–71 °C/50 mmHg, bp 148–150 °C. δ_P (24.3 MHz, CCl_4) −78 ppm (*9*). Ethylphosphonothioic dichloride (**2**) (bp 177–178 °C) was similarly obtained.

▷ *Methylphosphonothioic dichloride MeP(S)Cl$_2$* (**1**) *(from Kinnear-Perren complex and potassium thiocyanate)* (*7*). A well stirred mixture of the $[MePCl_3]^+[AlCl_4]^-$ complex (50.0 g, 0.16 mol) and potassium thiocyanate (15.0 g, 0.15 mol) was introduced into a Claisen flask. The mixture was heated under a vacuum and the reaction products were distilled off. Redistillation provided methylphosphonothioic dichloride (18.5 g, 80%). Bp 70–71 °C/50 mmHg. Ethylphosphonothioic dichloride (**2**) (bp 178 °C) was similarly obtained.

▷ *Methylphosphonothioic dichloride MeP(S)Cl$_2$* (**1**) *(from Kinnear–Perren complex and dimethyl disulfide)* (*8*). Aluminium chloride (1068 g, 8 mol) and phosphorus trichloride (1100 g, 8 mol) were introduced into a 4-l flask equipped with a stirrer and reflux condenser. Methyl chloride was passed into the stirred mixture at an internal temperature of 75 °C (oil bath temperature 90 °C). A clear solution formed after about 3 h. The mixture was stirred for a further 1 h. The reflux condenser was replaced by a descending Liebig condenser and the mixture was heated to an internal temperature of 110 °C. Excess (not complex-bound) phosphorus trichloride was distilled off – the recovered phosphorus trichloride weighed 160 g (therefore, the reacted phosphorus trichloride amounted to 940 g or 6.84 mol). The reaction mixture was allowed to cool to 90 °C and the following were added sequentially with stirring: dichloromethane (300 ml), potassium chloride (596 g, 8 mol) and dimethyl disulfide (483 g, 5.13 mol) were added dropwise over 1 h, without external heating, ensuring the internal temperature did not exceed 80 °C. The mixture was then heated cautiously until after 2.5 h an internal temperature of 200 °C was reached. This temperature was maintained for a further 1 h. The liquid distilling off at an internal temperature above 100 °C was collected and again distilled to yield the title compound (706 g, 70%). Bp 42–43 °C/11 mmHg. Ethylphosphonothioic dichloride (**2**) (86%, bp 56–60 °C/12 mmHg) and isopropylphosphonothioic dichloride (**3**) (47%, bp 71–75 °C/16 mmHg) were prepared similarly.

A modified Kinnear–Perren process where the chloroaluminate complex is treated with thiourea at room temperature followed by water provides pure alkylphosphonothioic dichlorides without the difficulties encountered using hydrogen sulfide as the source of sulfur. The starting alkyl chloride, products and yields appear in Fig. 3.2.2 (*10*). *n*-Butyl and 2-chloroethyl chlorides afforded rearranged products as expected from such reactions (refer to Chapter 2). The key step of the process is believed to be nucleophilic attack of the thiourea sulfur atom on the chloroaluminate complex followed by reaction with water to liberate the alkylphosphothioic dichloride and urea.



Alkylphosphonothioic dichlorides from Kinnear–Perren process

RCl	R in $RP(S)Cl_2$	Yield (%)	Bp (°C/mmHg)
EtCl	Et	32	62/15
i-PrCl	*i*-Pr	53	70/12
n-BuCl	*s*-Bu	54	80-82/8
BnCl	Bn	45	115/4
c-C_6H_{11}	*c*-C_6H_{11}	43	78/2
$ClCH_2CH_2Cl$	$ClCH_2CH_2$ [a]	43	85-92/10
$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2$	27	80/20

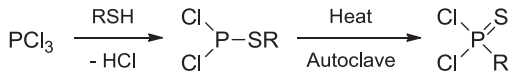
a. R = $ClCH_2CH_2$ (73%) and CH_3CHCl (27%) identified in crude product

Figure 3.2.2

▶ *Isopropylphosphonothioic dichloride i-PrP(S)Cl₂* (**3**) (*10*). Isopropyl chloride (15.7 g, 0.2 mol) was added dropwise to a stirred slurry of phosphorus trichloride (27.4 g, 0.2 mol) and anhydrous aluminium chloride (53.2 g, 0.4 mol) in dichloromethane (200 ml) at 20–25 °C. After completion of the addition, the mixture was stirred for 30 min. Powdered thiourea (30.4 g, 0.4 mol) was added in small portions while maintaining the temperature between 20 and 25 °C. The solution was stirred for a further 30 min, diluted with dichloromethane (200 ml), and cooled to −20 °C. Water was added in small portions with vigorous shaking. After about 65 ml of water was added, aluminium salts suddenly coagulated, leaving a clear solution. This was filtered, the solvent was removed and the residue was distilled to provide a colourless liquid (18.8 g, 53%). Bp 70 °C/12 mmHg. The infrared spectrum revealed a peak at 730/cm corresponding to the P═S bond.

Phosphorus trichloride reacts with alkanethiols and arylthiols slowly when warmed and provides the alkyl- or arylphosphorodichloridothioites (Cl_2PSR) after distillation under reduced pressure. These compounds when heated in an autoclave at temperatures around 300 °C and pressures up to 40 atm rearrange to give the alkyl- or arylphosphonothioic dichlorides (Fig. 3.2.3) (*11*). Other aliphatic phosphorus–sulfur compounds similarly rearrange when heated in sealed systems, such as Carius tubes or autoclaves, to provide alkylphosphonothioic dichlorides (*12*).

▶ *Methylphosphonothioic dichloride MeP(S)Cl₂* (*11*). Methanethiol (48.1 g, 1.0 mol) was bubbled over 90 min into stirred phosphorus trichloride (274.7 g, 2.0 mol) at 60–65 °C. Addition was set to a low rate at first and gradually increased as the thiol became more soluble in the reaction mixture. A dry ice condenser was used to prevent loss of the thiol. The reaction mixture was stirred for an additional 1 h at 65 °C. The temperature was then raised to 105–110 °C to complete the removal of hydrogen chloride. Upon fractionation methyl phosphorodichloridothioite $MeSPCl_2$ was collected



Alkylphosphonothioic dichlorides

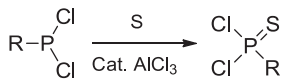
R	Temp (°C)	Time (h)	Yield (%)	δ_P (ppm)
Me	300	48	80	–79.4
Et	260	8	44	–95.4
n-Pr	300	21	60	–90.1
i-Pr	300	65	50	–107.0
n-Bu	290	8	45	–90.6
i-Bu	290	8	42	–89.0
c-C_6H_{11}	290	8	66	–101.8
CH_2=$CHCH_2$	140	60	50	–84.6
CH_2Ph	230	60	90	–85.0
Ph	265	70	90	–74.4

a. Yield is mole% of phosphorus in crude product by NMR analysis.

Figure 3.2.3

(72.2 g, 48%; bp 30 °C/9 mmHg; δ_P −206 ppm). Alternatively, in a separate experiment, crude methyl phosphorodichloridothioite (583 g) from the reaction of equimolar amounts of methanethiol and phosphorus trichloride was placed in a 1-l Parr-pressure reaction apparatus (Series 4500, stirred type) made of Hastelloy B and fitted with a Teflon gasket and stirrer bushing, Rulon Red™ shaft packing material and Viton A 'O' rings. The temperature was maintained at 300 °C for 6 h. The maximum pressure observed was approximately 40 atm. Gas chromatographic analysis of the reaction product, using authentic samples as standards, indicated the presence of 58% methylphosphonothioic dichloride and 16% dimethylphosphinothioic chloride. Distillation through a 1 m × 24 mm column packed with Berl saddles yielded 54% of the phosphonothioic dichloride (bp 67–70 °C/50 mmHg) and 14% of the phosphinothioic chloride (bp 58–61 °C/10 mmHg). Another experiment conducted at 300 °C for 72 h, without stirring, gave the phosphonothioic dichloride in 63% yield.

Alkylphosphonothioic dichlorides can be obtained in excellent yield by adding sulfur to alkylphosphonous dichlorides (Fig. 3.2.4). Addition, like that of sulfur to phosphorus trichloride, is strongly catalysed by aluminium trichloride (high-grade aluminium trichloride is recommended). The reaction once initiated proceeds with great vigour and if too much aluminium trichloride is added before it does start, as is sometimes the case with low-grade $AlCl_3$, it can easily become uncontrollable. An efficient fume cupboard should be used, for the vapour of the product, or possibly the starting materials, has a painful effect on the eyes (*13*). Lachrymation does not occur and the symptoms take 6–9 h to develop. Considerable pain is experienced for several days; fortunately, there appears to be no lasting effects once it subsides. Unlike methylphosphonous and ethylphosphonous dichlorides,



Alkylphosphonothioic dichlorides

R	Yield (%)	Bp (°C/mmHg)
Me	98	40/5
Et	88	47–48/3
i-Pr	no reaction	not applicable

Figure 3.2.4

isopropylphosphonous dichloride does not add sulfur even when heated to 100 °C with anhydrous aluminium trichloride (*14*).

▶ *Methylphosphonothioic dichloride MeP(S)Cl$_2$* (*14*). Methylphosphonous dichloride (196.4 g, 1.68 mol) and anhydrous aluminium trichloride (1.5 g, 11.24 mmol) were introduced into a three-necked flask fitted with a condenser, thermometer and magnetic stirring bar, under an atmosphere of dry nitrogen. Dried granular sulfur (53.8 g, 1.68 mol) was added in small portions with external water cooling in amounts sufficient to keep the reaction temperature at 60–65 °C. Addition took 50 min, the cooling bath was removed, and the mixture was heated to 85 °C for 5 min. Fractionation under reduced pressure gave methylphosphonothioic dichloride (244.5 g, 98%). Bp 68–69 °C/35 mmHg, 40 °C/5 mmHg.

▶ *Ethylphosphonothioic dichloride EtP(S)Cl$_2$* (*14*). Dried granular sulfur (26.1 g, 0.815 mol) was added to ethylphosphonous dichloride (107.0 g, 0.815 mol) in a manner similar to that already described for the preparation of methylphosphonothioic dichloride. The addition reaction was slower but proceeded smoothly at a temperature of 90 °C. Cooling was used to keep the temperature between 90 and 100 °C and the mixture was heated finally to 100 °C for 30 min, after all the sulfur had been added. Fractionation under reduced pressure gave ethylphosphonothioic dichloride (116.5 g, 88%). Bp 52 °C/6 mmHg, 47–48 °C/3 mmHg. A similar preparation (*13*) has been reported: Sulfur (5.5 g, 172 mmol) was added in one portion to ethylphosphonous dichloride (22 g, 168 mmol) in a three-necked flask fitted with a reflux condenser, a stirrer and a tube through which nitrogen was passed. The temperature was measured by a thermometer immersed in the liquid. After addition of the sulfur, the mixture was brought to the boil (temperature 112 °C). Stirring was continued until all the sulfur had dissolved. Heating was then discontinued, stirring was stopped, and a mixture of aluminium trichloride (0.6 g, 4.49 mmol) and sulfur (0.2 g, 6.25 mmol) was added quickly. A violent reaction set in and the temperature rose to 150 °C. The mass was heated for a further 2 h and the final temperature was 172 °C (it did not exceed this value). The product was vacuum distilled, yielding a colourless liquid having a pungent odour (22 g, 80%). Bp 82.5 °C/45.5 mmHg. It did not react with water at room temperature, but persisted as an oil in the bottom of the flask.

Alkenylphosphonothioic dichlorides are useful intermediates for the synthesis of monomers. Isooctenylphosphonothioic dichloride (**4**) is prepared in good yield by sulfur addition (Fig. 3.2.5) (*15*).

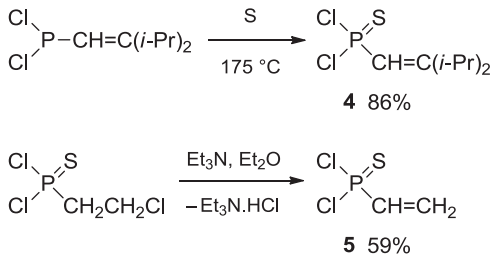


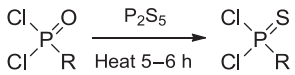
Figure 3.2.5

Vinylphosphonothioic dichloride (**5**) is obtained in modest yield by dehydrochlorination of 2-chloroethylphosphonothioic dichloride with triethylamine (*15*).

▶ *Isooctenylphosphonothioic dichloride (i-Pr)$_2$C═CHP(S)Cl$_2$* (**4**) (*15*). A mixture of isooctenylphosphonous dichloride and sulfur (equimolar proportions) was stirred and heated at 175 °C until an exothermic reaction commenced, when the reaction maintained itself at 175 °C. After the exotherm had subsided the mixture was again heated (to 175 °C) for 10 min, and then cooled. The title compound was isolated by distillation under reduced pressure (86%). Bp 95–100 °C/2 mmHg, 70–72 °C/3 mmHg.

▶ *Vinylphosphonothioic dichloride CH$_2$═CHP(S)Cl$_2$* (**5**) (*15*). Triethylamine (10.1 g, 0.1 mol) was added dropwise to a solution of 2-chloroethylphosphonothioic dichloride (19.8 g, 0.1 mol) in ether (70 ml) at 0–5 °C. After addition, the mixture was stirred for 30 min at 0–5 °C, for 1 h as the temperature was allowed to rise from 0 to 20 °C, and for 1 h at 40 °C. The triethylamine hydrochloride was filtered off and washed with ether, and the combined filtrate and washings were washed with a cold 1% solution of hydrochloric acid and with cold water. Afterwards, the solvent was evaporated and the residue was distilled under reduced pressure to give the title compound as a colourless liquid (9.5 g, 59%). Bp 54–55 °C/12 mmHg.

Heating alkylphosphonic dichlorides with phosphorus pentasulfide to 160 °C for 5–6 h results in their conversion to alkylphosphonothioic dichlorides (Fig. 3.2.6) (*16*). Despite the high yields claimed, it is the author's experience that such reactions rarely proceed fully, and after careful distillation,



Alkylphosphonothioic dichlorides

R	Yield (%)	Bp (°C/mmHg)
s-Bu	57	81.5–82/8
Et_2CH	60	88.5–89/7
n-C_5H_{11}	70	92–93/7
c-C_6H_{11}	51	122/8

Figure 3.2.6

a mixture of alkylphosphonic dichloride starting material and alkylphosphonothioic dichloride product is sometimes obtained, which is not easy to separate further, even by repeat fractionation.

▶ *Alkylphosphonothioic dichlorides RP(S)Cl$_2$ (from alkylphosphonic dichlorides and phosphorus pentasulfide)* (Fig. 3.2.6) (*16*). The appropriate alkylphosphonic dichloride (50 g) was heated under an atmosphere of carbon dioxide with an equimolar quantity of phosphorus pentasulfide for 5—6 h. The temperature of the mixture rose uniformly from 135 °C to 160 °C. The liquid part was vacuum distilled from the solid residue and diluted with ether. The solution was washed with cold water, the ether layer was separated, the residue was again extracted with ether, and the combined extract was dried (Na_2SO_4). The solvent was removed and the residue was fractionated to provide the alkylphosphonothioic dichloride.

Thiophosphoryl chloride can also be used as a starting material for the synthesis of alkylphosphonothioic dichlorides using autoclave technology. The high-temperature reaction of thiophosphoryl chloride with cyclohexane provides cyclohexylphosphonothioic dichloride (**6**) in modest yield (Fig. 3.2.7) (*17*).

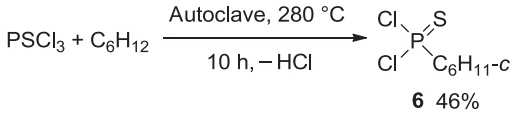


Figure 3.2.7

▶ *Cyclohexylphosphonothioic dichloride c-HexP(S)Cl$_2$* (**6**) (*17*). Thiophosphoryl chloride (68 g, 0.40 mol) and cyclohexane (67 g, 0.80 mol) were placed in a 300-mm 316 stainless steel autoclave. The autoclave was heated to 280 °C for 10 h with gentle rocking. After cooling, the autoclave was vented to expel hydrogen chloride (0.43 mol). The crude liquid (115 g) poured from the autoclave was distilled to provide unreacted cyclohexane (36 g) and the title compound (40 g, 46%). Bp 90—92 °C/0.2 mmHg.

Heating thiophosphoryl chloride with benzene and aluminium powder (*18*) or chlorobenzene and yellow phosphorus (*19*) in an autoclave provides two routes to phenylphosphonothioic dichloride (**7**) (Fig. 3.2.8). For such simple reactions, the yields are good.

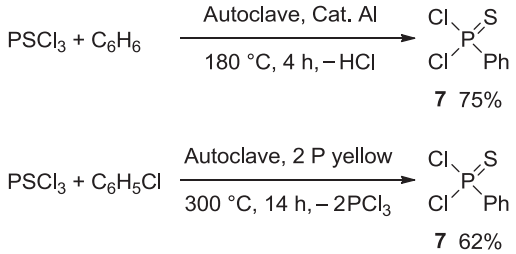


Figure 3.2.8

▶ *Phenylphosphonothioic dichloride PhP(S)Cl$_2$* (**7**) *(from thiophosphoryl chloride, benzene and aluminium trichloride)* (*18*). Thiophosphoryl chloride (42.35 g, 0.25 mol), benzene (19.53 g, 0.25 mol) and

aluminium powder (0.5 g) were added to a 100-ml autoclave. The reaction was initiated by heating to 180 °C for 4 h under the self-generated pressure of hydrogen chloride. After cooling to room temperature, the valve of the autoclave was opened to discharge the hydrogen chloride into a collector filled with an alkaline solution (e.g. aqueous sodium hydroxide). The reaction product was transferred to a flask and was fractionated under reduced pressure to obtain phenylphosphonothioic dichloride (39.6 g, 75%). Bp 115 °C/5 mmHg.

▶ *Phenylphosphonothioic dichloride PhP(S)Cl$_2$* (**7**) *(from thiophosphoryl chloride, chlorobenzene and yellow phosphorus)* (*19*). Thiophosphoryl chloride (51.0 g, 0.3 mol), chlorobenzene (34.0 g, 0.3 mol) and yellow phosphorus (6.0 g, 0.2 mol) were placed in a 300-mm 316 stainless steel autoclave with a 5000 pounds per square inch rupture disc. The autoclave was heated to 300 °C for 14 h with rocking for agitation. After cooling, a yellow liquid (87 g) was poured from the autoclave and distilled under reduced pressure to obtain the phenylphosphonothioic dichloride (39.0 g, 62%). Bp 90–100 °C/1.5 mmHg.

Alkylphosphonothioic dichlorides are stable colourless liquids that fume in air and have a rather pleasant smell. They dissolve in organic solvents but not in water; they are unaffected by cold water or dilute alkali. Prolonged boiling in water converts them into the alkylphosphonic acid with loss of hydrogen sulfide: $RP(S)Cl_2 + 3H_2O \rightarrow RP(O)(OH)_2 + 2HCl + H_2S$.

3.3 ALKYLPHOSPHONOTHIOIC DIFLUORIDES RP(S)F$_2$

Fluorination of methylphosphonothioic dichloride is accomplished by heating it with zinc fluoride or antimony trifluoride and distilling out the difluoride (**8**) (Fig. 3.3.1) (*20*). The lower yield achieved using antimony trifluoride results from formation of unknown volatile by-products. Methylphosphonothioic difluoride (bp 62 °C) has a much lower boiling point than methylphosphonic difluoride (bp 98 °C) probably due to weaker intermolecular interactions. Ethylphosphonothioic difluoride (**9**) can be obtained similarly using antimony pentachloride as a catalyst.

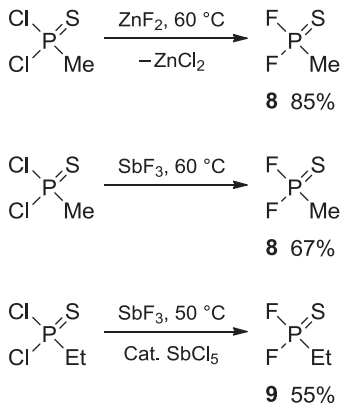


Figure 3.3.1

▶ *Methylphosphonothioic difluoride MeP(S)F_2* (**8**) *(from the phosphonothioic dichloride and zinc fluoride)* (*20*). Zinc fluoride (145 g, 1.4 mol) was placed in a three-necked flask equipped with a dropping funnel, thermometer and condenser set for distillation. Methylphosphonothioic dichloride (149 g, 1.0 mol) was introduced at such a rate that the temperature of the reaction mixture did not exceed 60 °C. After the addition was complete, the crude product was distilled. The distillate was fractionated twice using a short Vigreux column to give pure methylphosphonothioic difluoride (99 g, 85% based on methylphosphonothioic dichloride). Bp 62–63 °C.

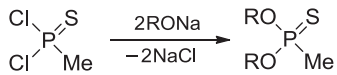
▶ *Methylphosphonothioic difluoride MeP(S)F_2* (**8**) *(from the phosphonothioic dichloride and antimony trifluoride)* (*20*). Methylphosphonothioic dichloride (44.7 g, 0.30 mol) was converted into the corresponding difluoride in the same way as described in the previous recipe, but using antimony trifluoride (44.7 g, 0.25 mol) instead of zinc fluoride. Fractionation of the crude distillate gave the desired product (19.3 g, 67% based on antimony trifluoride). Bp 61–63 °C.

▶ *Ethylphosphonothioic difluoride EtP(S)F_2* (**9**) *(from the phosphonothioic dichloride and antimony trifluoride)* (*13*). Antimony trifluoride (55 g, 0.3 mol) was added to a mixture of ethylphosphonothioic dichloride (68 g, 0.4 mol) and antimony pentachloride (3 ml, 24 mmol), preheated to about 50 °C, over a period of 15 min. The temperature rose to about 100 °C during the addition. The mixture was heated to 100 °C for 1 h, cooled and extracted with hydrochloric acid (density *d* 1.18 g/ml; 3 × 50 ml). The acid extracts were discarded, and the oil was dried with calcium chloride and distilled through a column to give the title compound (28 g, 55%). Bp 87–91 °C. On redistillation, it boiled at 89–90 °C and fumed very strongly on contact with air.

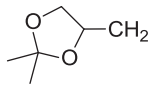
3.4 DIALKYL ALKYLPHOSPHONOTHIONATES $(RO)_2P(S)R$

The alkylphosphonothioic dichlorides are unreactive to nucleophiles, the compounds resembling in this regard *tert*-butylphosphonic dichloride rather than the general run of alkylphosphonic dichlorides. Unlike the latter, they do not easily react with 2 molar equivalents of an alcohol and two of triethylamine (the reaction stops at the mono-substitution stage). The diesters can only be obtained by heating the alkylphosphonothioic dichloride with a solution of 2 molar equivalents of sodium alkoxide in the alcohol (Fig. 3.4.1) (*21*). The yields of product depend very much on the nature of the alcohol. Ethylphosphonothioic dichloride reacts with sodium alkoxides, freshly prepared from the alcohols and sodium metal, to give the corresponding dialkyl ethylphosphonothionates in good yield (Fig. 3.4.2) (*22*).

Dialkyl methylphosphonothionates are prepared by heating methylphosphonothioic dichloride with a fivefold molar excess of an alcohol in the presence of a catalytic amount of boron trifluoride diethyl etherate (Fig. 3.4.3) (*23*). The role of the latter is not understood entirely. A plausible intermediate is a labile complex between the dichloride and the trifluoride, which might react more easily with the alcohol than the dichloride. In the absence of catalyst the reaction proceeds slowly and does not appear to be accelerated significantly by hydrochloric or sulfuric acid. With secondary alcohols such as isopropanol and *s*-butanol, higher boiling products were also obtained, but the results were erratic and fractionation of the crude products resulted in extensive decomposition; this was eliminated

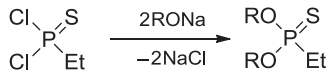


Dialkyl methylphosphonothionates

R	Yield (%)	Bp (°C/mmHg)
Me	92	52–53/8
Et	90	66–68/8
n-Pr	71	95–96/8
n-Bu	75	110–111/5
n-C_5H_{11}	68	124–125/3
i-$PrCH_2CH_2$	50	108–109/3
t-$BuCH_2$	40	90–92/2[a]
t-$BuCH(CH_3)$	50	99–100/3
c-C_6H_{11}	65	135–136/2
	61	155–156/0.3

a. Pure samples solidify at room temperature.

Figure 3.4.1

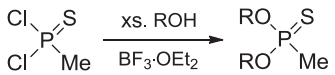


Dialkyl ethylphosphonothionates

R	Yield (%)	Bp (°C/mmHg)
Me	69	40/2.2
Et	75	42/1
n-Pr	83	42/0.1
i-Pr	67	48/0.5
n-Bu	86	58/0.09
n-C_5H_{11}	89	80–82/0.06

Figure 3.4.2

by removing the catalyst prior to distillation (Fig. 3.4.3) (*23*). The higher fractions were identified as the corresponding *O*-alkyl hydrogen methylphosphonothioates RO(Me)P(S)OH (R = *i*-Pr, *s*-Bu). It appears here that the reaction proceeds to the stage RO(Me)P(S)Cl and that further reaction with the alcohol is difficult due to steric hindrance, and is followed by dealkylation.



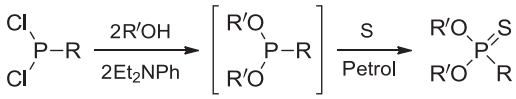
Dialkyl alkylphosphonothionates

R	Reflux (h)	Yield (%)	Bp (°C/mmHg)
Me	0.5	71	40–42/2–2.5
Et	1.5	80	89–92/25
n-Pr	3.0	70	71–73/0.45–0.5
n-Bu	4.0	81	93–94/0.7
i-Pr	6.0	39	42–44/0.25
s-Bu	6.0	35	58–60/0.6

Figure 3.4.3

The addition of sulfur to trivalent phosphorus esters is of general application. The reaction is generally vigorous and good to excellent yields are normally obtained (selenium behaves similarly, but tellurium does not appear to react). The dialkyl alkylphosphonite starting materials are very susceptible to oxidation. To prepare dialkyl alkylphosphonothionates from them, it is essential to protect them from oxidation. In this synthesis, however, it is unnecessary to isolate the alkylphosphonite; the required product can be obtained in good to excellent yield by adding sulfur to the reaction mixture from an alkylphosphonous dichloride, alcohol and tertiary base. The reaction occurs in a neutral diluent (petrol, benzene, etc.) that serves to moderate the vigour of the thionation.

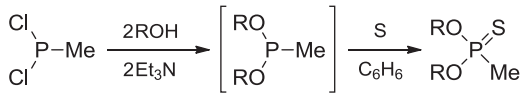
An alternative method consists of esterifying alkylphosphonous dichlorides (**10**) with the appropriate alcohol and a tertiary base (*N,N*-diethylaniline) in petroleum ether (petrol) (Fig. 3.4.4) (*13*). The dialkyl alkylphosphonite (**11**) obtained is not isolated nor is the base-hydrochloride filtered off. Sulfur is added to the mixture, and when the very vigorous reaction has subsided, dilute hydrochloric acid is introduced to dissolve the base-hydrochloride and remove any unreacted base. The petrol layer is separated, the petrol recovered and the product (**12**) purified by distillation under reduced pressure. The separated aqueous layer on basification gives a 95% recovery of *N,N*-diethylaniline.



10 **11** **12**

Figure 3.4.4

Several precautions must be observed. The dialkyl alkylphosphonites (**11**) are extremely sensitive to atmospheric oxidation (to the corresponding alkylphosphonates) so that not only must the whole operation, up to the completion of the addition of sulfur, be carried out in a stream of nitrogen but if the latter is slightly impure it must be passed through alkaline pyrogallol (1,2,3-trihydroxybenzene) to remove traces of oxygen (*13*). It is essential to interpose a drying bubbler containing sulfuric acid and glass wool between the pyrogallol and the reaction vessel. If this is not done, sufficient moisture is introduced from the aqueous pyrogallol to give pyro-esters as the main product. The addition of sulfur should be carried out with caution since the reaction between it and the dialkyl alkylphosphonite is very vigorous. The advantages of this method are obvious. The process is conducted in one pot, no filtration or catalyst is necessary and the whole operation can be carried out in less than 5 h, without diminution of yield. Attempts at replacing the petrol by benzene and the *N*,*N*-diethylaniline by *N*,*N*-dimethylaniline were unsuccessful. In the case of methylphosphonous dichloride, triethylamine in benzene solution can be used and the intermediates treated with sulfur to afford dialkyl methylphosphonothionates in acceptable yields (Fig. 3.4.5) (*21*).



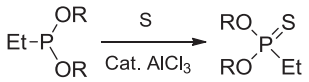
Dialkyl methylphosphonothionates

R	Yield (%)	Bp (°C/mmHg)
Et	70	66–68/8
n-Pr	72	95–96/8
i-Pr	71	60–62/4
n-Bu	57	110–111/5

Figure 3.4.5

Ethylphosphonous diesters can be used as precursors to disubstituted ethylphosphonothionates (*24*,*25*). However, the ethylphosphonous diesters are not easy to obtain or work with. They are colourless liquids of unpleasant odour. They oxidise readily in air to the dialkyl alkylphosphonates — oxidation being particularly vigorous in the case of the methyl and ethyl esters — which burst into flame on contact with filter paper. Hence, all operations with the diesters are best conducted under an inert atmosphere (e.g. carbon dioxide or nitrogen). The esters undergo a vigorous addition reaction with sulfur with the formation of the dialkyl ethylphosphonothionates (Fig. 3.4.6) (*24*). Alkylphosphonous diesters also react similarly with selenium to provide dialkyl alkylphosphonoselenonates (Chapter 6) (*25*).

Dialkyl alkylphosphonothionates are stable colourless liquids with a camphor-like odour. They are insoluble in water and miscible with organic liquids and emit faint grey fumes in contact with



Dialkyl ethylphosphonothionates

R	Yield (%)	Bp (°C/mmHg)
Et	74	80.5–81/10
n-Pr	57	69–70/1.5
Ph	66	144–144.5/1

Figure 3.4.6

air. They have a lower boiling point, density and refractive index than the isomeric *O,S*-dialkyl alkylphosphonothiolates.

▶ *Dialkyl methylphosphonothionates $(RO)_2P(S)Me$ (from methylphosphonothioic dichloride, an alcohol and boron trifluoride diethyl etherate)* (*23*). Primary alcohols: Methylphosphonothioic dichloride (1 mol) was added cautiously to the alcohol (5 mol) containing boron trifluoride diethyl etherate (10 ml). After the exothermic reaction had subsided, the mixture was heated under reflux for the period stated in Fig. 3.4.3. The excess of alcohol was removed under reduced pressure and the product distilled directly from the reaction flask. Secondary alcohols: Methylphosphonothioic dichloride (0.5 mol) was added to the alcohol (2.5 mol) containing boron trifluoride diethyl etherate (2 ml). The mixture was heated under reflux for approximately 6 h or to incipient turbidity, then cooled, and a solution of potassium hydroxide (3 g) in the appropriate alcohol was added cautiously. The excess of alcohol was removed under reduced pressure, the residue dissolved in anhydrous ether, and the ethereal solution filtered and fractionated. The yields and physical constants of the products appear in Fig. 3.4.3.

▶ *Diethyl methylphosphonothionate $(EtO)_2P(S)Me$ (from methylphosphonous dichloride, ethanol and N,N-diethylaniline, then sulfur)* (*13*). Anhydrous ethanol (92 g, 115 ml, 2 mol), *N,N*-diethylaniline (298 g, 318 ml, 2 mol) and light petrol (bp 40—60 °C, 1000 ml) were placed in a 5-l round-bottomed flask fitted with a dropping funnel, a sealed stirrer, a reflux condenser and an inlet tube (this should be as wide a bore as possible to avoid clogging with base-hydrochloride) for the introduction of dry oxygen-free nitrogen. The nitrogen gas from a cylinder was passed through alkaline pyrogallol (12 g pyrogallol in 100 ml of 50% *w/v* aqueous sodium hydroxide) and dried by passing it through sulfuric acid and glass wool. A stirrer was started and methylphosphonous dichloride (117 g, 98 ml, 1 mol) in light petrol (250 ml) was added dropwise over about 30 min. The mixture was then refluxed gently for a further 30 min to complete the esterification, a steady stream of purified nitrogen being maintained throughout the reaction. The dropping funnel was then replaced by a device for the slow introduction of sulfur (32 g, 1 mol) in small quantities at a time (the sulfur reacts with great vigour and care should be exercised in its addition. A slight excess does not seem to do any harm. It may conveniently be added by placing small quantities at a time in a small open-mouth dropping funnel, fitted with a tap of extra wide bore (7 mm diameter), and washing it into the reaction mixture with small quantities of petrol). After

the sulfur had been added, the mixture was stirred for 15 min and dilute hydrochloric acid (1000 ml water and 30 ml of hydrochloric acid, *d* 1.18 g/ml) run in. After stirring vigorously for 10 min, the upper petrol layer was decanted as far as possible and the remainder separated from the aqueous layer with the aid of a large tap funnel (the aqueous layer, on basification, gave an almost theoretical recovery of *N,N*-diethylaniline). The petrol extract was dried ($MgSO_4$), the petrol recovered and the residue distilled under reduced pressure (121 g, 72%). Bp 50 °C/1 mmHg or 43 °C/0.6 mmHg.

▶ *Diethyl methylphosphonothionate $(EtO)_2P(S)Me$ (from methylphosphonothioic dichloride and sodium ethoxide)* (*9*). Absolute ethanol (9.2 g, 0.2 mol) was added to sodium (4.6 g, 0.2 mol) in anhydrous benzene (50 ml) and the mixture boiled for 8 h. Methylphosphonothioic dichloride (14.9 g, 0.1 mol) was added dropwise to this suspension. This was accompanied by a rise in temperature. The mixture was stirred for 4 h and the sodium chloride filtered off. The solvent was removed and the residue fractionated to provide the title compound (9.1 g, 54%). Bp 77–79 °C/14 mmHg; δ_P (24.3 MHz, CCl_4) −96 ppm.

▶ *Di-n-propyl methylphosphonothionate $(n\text{-}PrO)_2P(S)Me$* (*26*). Prepared from methylphosphonothioic dichloride and sodium *n*-propoxide in propanol at 24 h at room temperature (no yield stated). Bp 62–64 °C/0.03 mmHg.

▶ *Diisopropyl methylphosphonothionate $(i\text{-}PrO)_2P(S)Me$* (*13*). This was prepared from isopropanol (150 ml), *N,N*-diethylaniline (318 ml), methylphosphonous dichloride (90 ml) and sulfur (32 g) in high yield (169 g, 86%). Bp 59 °C/1 mmHg. A modification involves treating methylphosphonous dichloride (117 g, 1 mol) with isopropyl alcohol (120 g, 2 mol) and triethylamine (202 g, 2 mol) in benzene under argon (*21*). Powdered sulfur (32 g, 1 mol) is added to the stirred mixture, which is then refluxed for 3 h until most of the sulfur has reacted. Removal of solvent and distillation provides the title compound (139 g, 71%). Bp 60–62 °C/4 mmHg.

▶ *Di-n-pentyl methylphosphonothionate $(n\text{-}C_5H_{11}O)_2P(S)Me$* (*21*). Sodium *n*-pentoxide was prepared from sodium (23 g, 1 mol) in *n*-pentanol (500 ml). After dissolution of the sodium, which took 2 h at an oil bath temperature of 150 °C, a solution of methylphosphonothioic dichloride (74.5 g, 0.5 mol) in *n*-pentanol (50 ml) was added and the resulting mixture heated under reflux for 4 h. The solvent was removed and distillation yielded the title compound (85.7 g, 68%). Bp 124–125 °C/2.5 mmHg.

▶ *Diethyl ethylphosphonothionate $(EtO)_2P(S)Et$* (*13*). Sodium (25 g, 1.1 mol) was dissolved in absolute ethanol (350 ml) under reflux with stirring. Ethylphosphonothioic dichloride (82 g, 60 ml, 0.5 mol) dissolved in ethanol (90 ml) was added to the hot sodium ethoxide from a dropping funnel over a period of 30 min. After refluxing for a further 1 h, the mixture was allowed to stand overnight and the excess alcohol removed under slightly reduced pressure, without filtering. Sufficient water was added to the residue to dissolve the sodium chloride and the mixture extracted with ether. The ether extract was separated, the solvent distilled and the residue fractionated under vacuum to yield the title compound (67 g, 74%). Bp 65 °C/3 mmHg. Like the dichloride, it emits greyish white fumes in contact with air. Diisopropyl ethylphosphonothionate was prepared similarly (bp 68 °C/2 mmHg).

▶ *Diethyl isopropylphosphonothionate $(EtO)_2P(S)Pr\text{-}i$* (*10*). Isopropylphosphonothioic dichloride (8.8 g, 50 mmol) was added dropwise to a stirred solution of sodium ethoxide made previously from sodium (2.3 g, 0.1 mol) and ethanol (80 ml). The reaction occurred immediately. Water was added and the mixture was extracted with petroleum ether (bp 40–60 °C). Removal of the solvent and

distillation gave the title compound (4.9 g, 50%). Bp 75 °C/5 mmHg. The infrared spectrum contained a band at 775/cm corresponding to the P═S bond.

▶ *Di(DL-1,2-isopropylideneglyceryl) methylphosphonothionate* (Fig. 3.4.1, *last entry*) (*21*). Sodium (11.5 g, 0.5 mol) was added to a stirred solution of DL-isopropylideneglycerol (solketal; 150 g, 1.1 mol) in anhydrous toluene (200 ml) and the mixture heated to 120 °C for 3 h to generate the alkoxide. To this was added a solution of methylphosphonothioic dichloride (37.2 g, 0.25 mol) in toluene (50 ml) and the mixture refluxed for 5 h. Solvent removal and distillation gave the title compound (51.9 g, 61%). Bp 155–156 °C/0.3 mmHg.

▶ *Diphenyl methylphosphonothionate $(PhO)_2P(S)Me$ (from methylphosphonothioic dichloride and sodium phenoxide)* (*9*). Phenol (18.8 g, 0.2 mol) was added to sodium (4.6 g, 0.2 mol) in anhydrous benzene (50 ml) and the mixture boiled for 8 h. Methylphosphonothioic dichloride (14.9 g, 0.1 mol) was added dropwise to this suspension. This was accompanied by a rise in temperature. The mixture was stirred for 4 h and the sodium chloride was filtered off. The solvent was removed and the residue was fractionated to provide the title compound (14.8 g, 56%). Bp 131–132 °C/0.04 mmHg. δ_P (24.3 MHz, CCl_4) −90 ppm.

▶ *Diphenyl ethylphosphonothionate $(PhO)_2P(S)Et$ (from diphenyl ethylphosphonite and sulfur)* (*25*). A stirred mixture of diphenyl ethylphosphonite (4.3 g, 17.48 mmol) and sulfur (0.6 g, 18.75 mmol) under a stream of nitrogen was heated to 40 °C at which point a reaction started. The temperature rose spontaneously to 120 °C and the whole of the sulfur dissolved. Distillation yielded diphenyl ethylphosphonothionate (3.4 g, 70%). Bp 144–145 °C/1 mmHg.

3.5 ALKYL ALKYLPHOSPHONOCHLORIDOTHIONATES RO(R')P(S)Cl

Dialkyl alkylphosphonothionates, unlike dialkyl alkylphosphonates, do not react with phosgene (to give a chloridothionate in this case), so alkyl alkylphosphonochloridothionates must be prepared by mono-addition of an alcohol and triethylamine, or the sodium alkoxide, to the alkylphosphonothioic dichloride (Fig. 3.5.1). When alkylphosphonothioic dichlorides are treated with a molar equivalent of the alcohol or sodium alkoxide, the product consists of the alkyl alkylphosphonochloridothionate (e.g. **13–15**), together with appreciable amounts of the dialkyl ester and unreacted dichloride. Separation of the alkyl alkylphosphonochloridothionate from the other products is only possible by repeat fractionation, and for this reason yields are generally low.

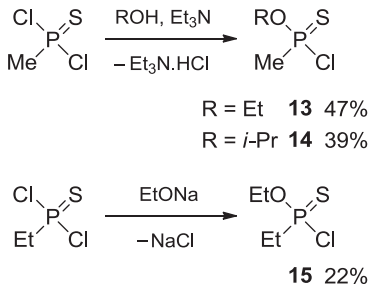
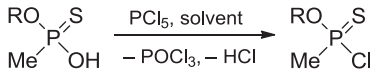


Figure 3.5.1

Treatment of *O*-alkyl hydrogen methylphosphonothioates with phosphorus pentachloride suspended in an inert solvent (e.g. ether, dichloromethane, light petroleum) also provides alkyl methylphosphonochloridothionates (Fig. 3.5.2) (*27*).



Alkyl methylphosphonochloridothionates

R	Yield (%)	Bp (°C/mmHg)
Me	54	55/13
Et	65	54/10
n-Pr	70	66/12
i-Pr	61	77/15
n-Bu	68	26/0.05

Figure 3.5.2

▷ *Ethyl methylphosphonochloridothionate EtO(Me)P(S)Cl* (**13**) (*9*). A solution of ethanol (22.1 g, 0.48 mol) and triethylamine (50 g, 0.49 mol) in anhydrous ether (100 ml) was added dropwise to a stirred solution of methylphosphonothioic dichloride (74.5 g, 0.5 mol) in ether (250 ml). The mixture was left for 12 h and was then heated for 1.5 h at 40 °C. The precipitate was filtered off. Fractionation of the residue gave the title compound as a colourless liquid (37.2 g, 47%). Bp 55–56 °C/10 mmHg. Phenyl methylphosphonochloridothionate PhO(Me)P(S)Cl was prepared similarly starting from phenol (45.1 g, 0.48 mol) also in 47% yield. Bp 121–123 °C/10 mmHg.

▷ *Isopropyl methylphosphonochloridothionate i-PrO(Me)P(S)Cl* (**14**) (*20*). A mixture of isopropanol (127 g, 2.12 mol) and triethylamine (72 g, 0.71 mol) in ether (50 ml) was added to a stirred solution of methylphosphonothioic dichloride (105 g, 0.71 mol) in ether (100 ml). The resulting mixture was heated under reflux for 20 h under nitrogen. After cooling, the triethylamine hydrochloride was filtered off and the filtrate concentrated under vacuum. The yield of once-distilled material was 63 g. This material was contaminated with unreacted methylphosphonothioic dichloride. Careful fractionation using a spinning band column provided the pure product (48 g, 39%). Bp 48 °C/5 mmHg.

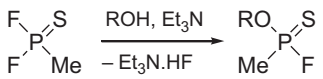
▷ *Ethyl ethylphosphonochloridothionate EtO(Et)P(S)Cl* (**15**) (*13*). Sodium (16 g, 0.7 mol) was dissolved in absolute ethanol (250 ml) with stirring and transferred to a dropping funnel. This warm solution of sodium ethoxide was added dropwise to a stirred solution of ethylphosphonothioic dichloride (115 g, 0.7 mol) in ethanol (90 ml) over 30 min. After refluxing for a further 1 h, the mixture was allowed to stand overnight and the excess alcohol removed under somewhat reduced pressure, without filtering. Sufficient water was added to the residue to dissolve the sodium chloride and the mixture was extracted with ether. The ether extract was separated and the solvent removed. The residue comprised unchanged dichloride, the diethyl ester and the required compound. The latter could only be isolated in a state of purity after repeated fractionation under vacuum (27 g, 22%). Bp 43 °C/1.5 mmHg. A further 17 g of

less pure material was also obtained. Isopropyl ethylphosphonochloridothionate *i*-PrO(Et)P(S)Cl was prepared similarly. Bp 56–57 °C/3 mmHg.

Alkyl methylphosphonochloridothionates RO(Me)P(S)Cl (from O-alkyl hydrogen methylphosphonothioates and phosphorus pentachloride) (*27*). A solution of the *O*-alkyl hydrogen methylphosphonothioate (1 mol equiv.) in a solvent (ether, dichloromethane, light petroleum) was added to a stirred suspension of phosphorus pentachloride (1 mol equiv.) in the same solvent at −10 °C. After stirring for 1 h at 0 °C, the mixture was filtered and solvent and phosphorus oxychloride were evaporated under reduced pressure. The residue was dissolved in ether and washed with dilute aqueous sodium bicarbonate and then with water. The ether solution was dried ($MgSO_4$). Removal of the solvent and distillation of the residue gave the title compounds, whose yields and boiling points appear in Fig. 3.5.2.

3.6 ALKYL ALKYLPHOSPHONOFLUORIDOTHIONATES RO(R')P(S)F

Treatment of methylphosphonothioic difluoride with alcohols in the presence of triethylamine provides alkyl methylphosphonofluoridothionates in acceptable yield (Fig. 3.6.1) (*20*). The reaction is conducted in ether for obtaining the products with the smaller alkyl groups, including the cyclopentyl group, and in benzene for obtaining those with the larger alkyl groups. The fluoridothionates are colourless liquids that fume in air to a certain extent depending of their vapour pressures. They have lower boiling points than their phosphonofluoridate counterparts, e.g. *i*-PrO(Me)P(S)F (bp 120 °C/760 mmHg) versus *i*-PrO(Me)P(O)F (sarin, bp 147 °C/760 mmHg).



Alkyl methylphosphonofluoridothionates

R	Yield (%)	Bp (°C/mmHg)
ethyl	54	46–49/23
n-propyl	68	59/19
isopropyl	56	45/14
n-butyl	80	63/10
cyclopentyl	55	68/5
cyclohexyl	47	61–65/1
cycloheptyl	52	73/0.4
1,3,3-trimethylpropyl	42	52/1
1,3-dimethylbutyl	67 [a]	53–55/3
1-methylheptyl	67 [a]	56/0.3

a. After one distillation; other products twice distilled

Figure 3.6.1

Isopropyl methylphosphonochloridothionate (**16**) reacts exothermically with antimony trifluoride to give isopropyl methylphosphonofluoridothionate (**17**) in good yield (Fig. 3.6.2) (*20*). This route is higher yielding than the one described in the previous paragraph. Antimony trifluoride is superior to other common fluorination reagents; isopropyl methylphosphonochloridothionate did not react with sodium fluoride in hot benzene, and in hot toluene, gave only a 10% yield of isopropyl methylphosphonofluoridothionate, which contained some toluene, even after careful fractionation.

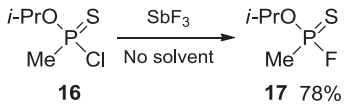


Figure 3.6.2

A mixture of the alkylphosphonothioic dichloride and alkylphosphonothioic difluoride does not constitute a reactive 'di—di' mixture, as in the case of the corresponding alkylphosphonic system, and no reaction with alcohols occurs even on heating (*13*).

▶ *Isopropyl methylphosphonofluoridothionate i-PrO(Me)P(S)F* (**17**) *(from methylphosphonothioic difluoride)* (*20*). A mixture of isopropanol (9.2 g, 0.15 mol) and triethylamine (15.5 g, 0.15 mol) in ether (10 ml) was added dropwise to a stirred solution of methylphosphonothioic difluoride (16.2 g, 0.14 mol) in ether (40 ml) at 0 °C. A slow stream of nitrogen was passed through the apparatus during the entire operation. The resulting mixture was stirred for an additional 3 h at room temperature and allowed to stand overnight to ensure complete reaction. The precipitated triethylamine hydrofluoride was filtered off and washed with multiple portions of ether. The combined filtrate and washings were concentrated under reduced pressure and the slightly coloured residual liquid was distilled twice using a Claisen flask with fractionating side-arm, yielding isopropyl methylphosphonofluoridothionate (12.2 g, 56%). Bp 45 °C/14 mmHg.

▶ *Isopropyl methylphosphonofluoridothionate i-PrO(Me)P(S)F* (**17**) *(from isopropyl methylphosphonochloridothionate)* (*20*). Antimony trifluoride (1.00 g, 6 mmol) was added in one portion to vigorously stirred isopropyl methylphosphonochloridothionate (2.32 g, 13 mmol). The temperature of the mixture immediately rose to 45 °C with dissolution of the antimony trifluoride and fell to its original value within 15 min. The colourless solution was stirred at room temperature for 30 min after which the volatile components were removed under vacuum (0.15 mmHg), the receiver being cooled with a dry ice-acetone slush. A yellow residue remained in the flask. The colourless distillate comprised the pure product (1.64 g, 78%).

▶ *Isopropyl ethylphosphonofluoridothionate i-PrO(Et)P(S)F* (*13*). Isopropyl ethylphosphonochloridothionate (12 g, 64 mmol), antimony trifluoride (4 g, 22 mmol), antimony pentachloride (1 ml, 8 mmol) and benzene (10 ml) were refluxed for 4 h. After cooling, the mixture was extracted with concentrated hydrochloric acid (2 × 10 ml), the extracts being discarded. The organic layer was separated and fractionated under reduced pressure after removal of the benzene to give the desired product (3 g, 28%). Bp 40—41 °C/2.5 mmHg.

3.7 *O*-ALKYL HYDROGEN ALKYLPHOSPHONOTHIOATES RO(R')P(S)OH

O-Alkyl hydrogen alkylphosphonothioates are strong acids and exist as a mixture of thiono (P═S) and thiolo (P—S) tautomers in equilibrium. Acid dissociation constants (pK_a) derived from experimental measurement for these compounds in 7% and 80% aqueous ethanol are shown in Fig. 3.7.1 (*28*). The lower the ethanol content the greater the ease of ionisation (proton loss) and the lower the pK_a value. Lengthening the R or R′ groups generally lowers the acidity, and raises the pK_a, due to the increased electron-donating effect to the P—OH/P—SH group caused by such changes. In both solvent systems, the thiono tautomer predominates over the thiolo tautomer and in 80% aqueous ethanol is virtually the only tautomer present.

Thiono **A** Thiolo **B**

pK_a data for selected *O*-alkyl hydrogen alkylphosphonothioates

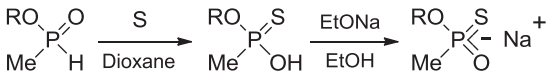
R	R′	pK_a [a]	%**A**	%**B**	pK_a [b]	%**A**	%**B**
Et	Me	1.82	81	19	3.51	98	2
n-Pr	Me	1.87	85	15	3.78	99	1
n-Bu	Me	1.95	88	12	3.77	99	1
i-Bu	Me	1.81	84	16	3.69	99	1
Et	Et	1.88	86	14	3.72	99	1
Et	*n*-Pr	2.00	88	12	3.81	99	1
Et	*n*-Bu	2.11	90	10	3.95	99	1

a. pK_a in 93% H_2O and 7% EtOH. *b*. pK_a in 80% EtOH and 20% H_2O.

Figure 3.7.1

One route to *O*-alkyl hydrogen alkylphosphonothioates involves the reaction of alkyl *H*-alkylphosphinates with sulfur (Fig. 3.7.2) (*29*). The rate depends on the solvent: the reaction occurs smoothly and with sufficient speed in dioxane (>80% conversion of *O*-ethyl *H*-methylphosphinate in 1—2 h) but in ether scarcely even under severe conditions (no change of the same phosphorus compound when heated in a sealed tube at 100 °C for 5.5 h). Alkyl *H*-alkylphosphinates in ether add sulfur only in the presence of bases such as triethylamine.

▶ *O-Ethyl hydrogen methylphosphonothioate EtO(Me)P(S)OH and its sodium salt* (*29*). Powdered sulfur (4.48 g, 0.14 mol) was added to a stirred solution of ethyl *H*-methylphosphinate (10.8 g, 0.1 mol) in anhydrous dioxane (50 ml) and the mixture heated under gentle reflux for 2 h. The mixture was allowed to cool to room temperature and the excess of sulfur filtered off. The solvent was



O-Alkyl hydrogen methylphosphonothioates

R	Yield (%)	Sodium salt mp (°C) [a]
Et	85	215–216
n-Bu	83	193–194
n-C_6H_{13}	89	161–163

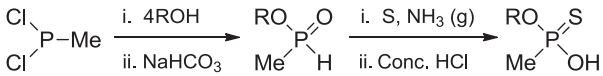
a. Recrystallised from petroleum ether.

Figure 3.7.2

removed to give a yellow homogeneous liquid from which sulfur precipitated after standing for several days. The product freed from sulfur was practically pure *O*-ethyl hydrogen methylphosphonothioate (11.9 g, 85%). Treatment with sodium ethoxide and recrystallisation from petroleum ether gave the sodium salt (melting point (mp) 215—216 °C). The other products in Fig. 3.7.2 were prepared similarly.

▶ *O-Ethyl hydrogen methylphosphonothioate EtO(Me)P(S)OH (13)*. Sulfur (3.2 g, 0.1 mol) was added in portions to a stirred mixture of ethyl *H*-methylphosphinate (10.8 g, 0.1 mol) and triethylamine (10.1 g, 0.1 mol). After the initial exothermic reaction had subsided, the mixture was heated to 60 °C for 15 min. Water and sulfuric acid (2.5 ml) were then added and the product extracted with ether. Purification by distillation at low pressure gave the title compound as a colourless liquid (9.6 g, 70%). Bp 88 °C/1.1 mmHg. Experiments on the same scale with other alkyl *H*-methylphosphinates yielded the following analogues in similar yield: *n*-PrO(Me)P(S)OH (bp 92 °C/0.9 mmHg), *n*-BuO(Me)P(S)OH (bp 100 °C/0.7 mmHg) and *n*-PentylO(Me)P(S)OH (bp 86 °C/0.05 mmHg).

Reaction of methylphosphonous dichloride and an aliphatic alcohol affords an *O*-alkyl *H*-methylphosphinate that can be treated, without isolation, with sulfur in the presence of ammonia to yield the ammonium *O*-alkyl methylphosphonothioate (Fig. 3.7.3) (*30*). The free acid is obtained by acidification of the salt and distillation. Apart from the easily dealkylated *O*-methyl compound (23%), the yields were satisfactory in all cases (56—72%). *O*-(*Tert*-butyl) hydrogen methylphosphonothioate could not be distilled: heating the crude acid to 150—200 °C resulted in complete decomposition, yielding a small amount of isobutene (identified as its dibromide), *tert*-butanethiol as the main distillable product, and a material of mp 115—125 °C whose infrared spectrum revealed the presence of P—Me (1300/cm), P═O (1200/cm) and P—O—P groups (940 and 980/cm). This was identified as the metaphosphonate $(MePO_2)_n$ as it reacted with ethanol to give *O*-ethyl hydrogen methylphosphonothioate EtO(Me)P(S)OH, with water to give methylphosphonic acid $MeP(O)(OH)_2$, or with thionyl chloride to give methylphosphonic dichloride $MeP(O)Cl_2$.



O-Alkyl hydrogen methylphosphonothioates

R	Yield (%)	Bp (°C/mmHg)
Me	23	77/0.45
Et	67	77–78/0.35
n-Pr	72	80–81/0.3
i-Pr	56	75–76/0.3
n-Bu	70	90/0.3
i-Bu	70	95/0.5
s-Bu	64	91/0.3
t-Bu	52	dec.

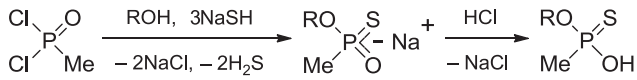
dec. = decomposed on heating (see text).

Figure 3.7.3

▶ *O-Alkyl hydrogen methylphosphonothioates RO(Me)P(S)OH (from methylphosphonous dichloride and an alcohol, then sodium hydrogen sulfide)* (Fig. 3.7.3) (*30*). Freshly distilled methylphosphonous dichloride (58.5 g, 0.5 mol) was added dropwise to the stirred appropriate alcohol (4.0 mol) at 0 °C. After 2 h solid sodium hydrogen carbonate was added. After removal of sodium chloride and the excess of sodium hydrogen carbonate, the remaining alcohol was distilled off under reduced pressure. Sublimed sulfur (16 g, 0.5 mol) was added and anhydrous ammonia passed into the mixture with stirring and cooling (if necessary). An exothermic reaction occurred and most of the sulfur disappeared. Ammonia was passed through the product for another 30 min, the semisolid mass dissolved in water (100 ml), and the filtered solution acidified with concentrated hydrochloric acid to pH 1. The free acid was extracted with ether (3 × 200 ml) and the combined extracts dried and concentrated under vacuum. The remaining acids were distilled at pressures below 1 mmHg. Yields and boiling points are given in Fig. 3.7.3.

Methylphosphonic dichloride reacts with a solution of 3 mol of sodium hydrogen sulfide in an alcohol to give sodium *O*-alkyl methylphosphonothioates, which after acidification provide the free acids (Fig. 3.7.4) (*30*).

▶ *O-Alkyl hydrogen methylphosphonothioates RO(Me)P(S)OH (from methylphosphonic dichloride, an alcohol and sodium hydrogen sulfide)* (Fig. 3.7.4) (*30*). Anhydrous hydrogen sulfide was passed with stirring into a solution of sodium (37.0 g, 1.6 mol) in the appropriate alcohol (600 ml) at 0–4 °C. Methylphosphonic dichloride (66.5 g, 0.5 mol) was added dropwise. Stirring was continued at room temperature for 30 min, and then the mixture was heated under reflux for 1 h to liberate the dissolved hydrogen sulfide. After cooling, sodium chloride was filtered off and the excess of alcohol removed under reduced pressure. The residue was dissolved in water, acidified with concentrated hydrochloric



O-Alkyl hydrogen methylphosphonothioates

R	Yield (%)	Bp (°C/mmHg)
Me	41	54–56/0.2
Et	55	63/0.22
n-Pr	48	74/0.35
i-Pr	34	61/0.2
n-Bu	55	83–84/0.1
i-Bu	54	95/0.5
s-Bu	28	91/0.3

Figure 3.7.4

acid, and extracted with ether (3 × 200 ml). After drying, the product was distilled, and yields and boiling points appear in Fig. 3.7.4.

Alkyl alkylphosphonochloridates react with freshly prepared sodium hydrogen sulfide in absolute ethanol to yield *O*-alkyl hydrogen alkylphosphonothioates (Fig. 3.7.5). The starting chloridates can contain primary or secondary alkyl groups bonded to the phosphorus atom. The transformations of isopropyl methylphosphonochloridate (**18**) to *O*-isopropyl hydrogen methylphosphonothioate (**19**) (*13*) and ethyl isopropylphosphonochloridate (**20**) to *O*-ethyl isopropylphosphonothioate (**21**) are examples of this approach (*31*).

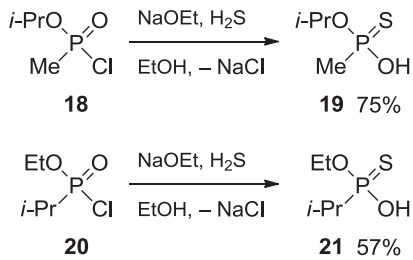


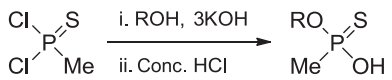
Figure 3.7.5

▶ *O-Isopropyl hydrogen methylphosphonothioate i-PrO(Me)P(S)OH* (**19**) (*13*). A solution of sodium ethoxide made from sodium (67.5 g, 2.935 mol) and absolute ethanol (1200 ml) was saturated with hydrogen sulfide. The solution was chilled to 15 °C and isopropyl methylphosphonochloridate (108 g, 0.690 mol) was added over 45 min. The resulting slurry was stirred for 2 h at room temperature and then ethanol was distilled off, while slowly adding water (800 ml), until the vapour temperature reached 99 °C. The aqueous residue was cooled, washed with ether (350 ml), acidified with

concentrated hydrochloric acid (350 ml), salted out and extracted with several portions of ether (3 × 250 ml). The ether extracts were combined and dried ($MgSO_4$). A second run was performed and the dried extracts from the two runs were combined and evaporated. Distillation of the residue through a short Vigreux column yielded the title compound as a colourless liquid (160 g, 75%). Bp 77–82 °C/0.5–1.0 mmHg.

▶ *O-Ethyl hydrogen isopropylphosphonothioate EtO(i-Pr)P(S)OH* (**21**) (*31*). Ethyl isopropylphosphonochloridate (34 g, 0.2 mol) was added dropwise to a stirred solution of sodium hydrogen sulfide prepared immediately beforehand by saturating sodium (9.2 g, 0.4 mol) dissolved in absolute ethanol (500 ml) with hydrogen sulfide gas. During addition, the temperature of the reaction mixture was not allowed to rise above 30 °C. The ethanol was stripped off to near dryness, water was added, and the solution was again evaporated to remove the residual ethanol. The residue was dissolved in water (~400 ml), washed with ether, and acidified with an excess of concentrated hydrochloric acid (~80 ml). The product was extracted with ether, and the combined extracts dried (Drierite™), filtered and concentrated. The residue was distilled under reduced pressure to give the title compound (19 g, 57%). Bp 82–85 °C/0.45–0.5 mmHg.

Treatment of methylphosphonothioic dichloride with an excess of an alcohol and 3 mol of potassium hydroxide enables the preparation of the *O*-alkyl methylphosphonothioate potassium salt, which is then neutralised with concentrated hydrochloric acid to provide the *O*-alkyl hydrogen methylphosphonothioate (*23*). The results are summarised in Fig. 3.7.6 for methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol and *s*-butanol; under these conditions, the last four alcohols give some of the diester (yields of neutral ester formed concurrently were, in the same order, 0, 0, 12.5%, trace, 13.4%, trace). The side-reaction is particularly pronounced for *n*-propanol and *n*-butanol. The first step is possibly the formation of the diester, which is hydrolysed by the alkali, a supposition supported by the observation that longer reaction times lower the yield of the diester and increase the yield of the salt of the monoester.



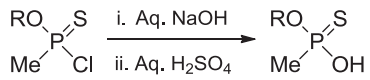
O-Alkyl hydrogen methylphosphonothioates

R	Yield (%)	Bp (°C/mmHg)
Me	71	75–83/0.4
Et	83	87–93/0.6
n-Pr	65	92–93/0.5
i-Pr	44	84–85/0.6
n-Bu	58	107–110/0.7
s-Bu	30	109–110/0.8

Figure 3.7.6

▶ *O-Alkyl hydrogen methylphosphonothioates RO(Me)P(S)OH (from methylphosphonothioic dichloride, an alcohol and potassium hydroxide)* (*23*). Methylphosphonothioic dichloride (74.5 g, 0.5 mol) was added dropwise to a stirred solution of 85% potassium hydroxide (1.5 mol) dissolved in the appropriate alcohol (500 ml) at 0–4 °C. After addition, stirring was continued at room temperature for 30 min and the mixture was then heated under reflux for 2 h. After cooling, potassium chloride was filtered off, and the excess of alcohol was removed under reduced pressure. The residue was dissolved in water, extracted with ether (2 × 200 ml) and acidified with concentrated hydrochloric acid. The *O*-alkyl hydrogen methylphosphonothioate was isolated by repeat extractions with ether (4 × 200 ml). After drying (Na_2SO_4) and removal of the solvent, the product was distilled at a pressure below 1 mmHg (Fig. 3.7.6).

Aqueous alkaline hydrolysis of alkyl methylphosphonochloridothionates can be used to obtain the *O*-alkyl hydrogen methylphosphonothioates (Fig. 3.7.7) (*32*). The chloridothionates are added dropwise with stirring to 2 molar equivalents of 5 M sodium hydroxide solution at 80–100 °C at sufficient rates to maintain a temperature of about 100 °C without further additional heating. The water-insoluble chloridothionates enter into solution rapidly under these conditions. The required *O*-alkyl hydrogen methylphosphonothioate is isolated from the resulting clear aqueous solution of the sodium salt of the thioacid and sodium chloride by acidification and extraction with benzene or ether.



O-Alkyl hydrogen methylphosphonothioates

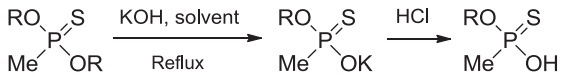
R	Yield (%)	Bp (°C/mmHg)
Et	89	63/0.22
n-Pr	75	74/0.35
i-Pr	65	61/0.2
n-Bu	55	83–84/0.1
n-C_5H_{11}	75	100–102/0.05

Figure 3.7.7

▶ *O-n-Pentyl hydrogen methylphosphonothioate n-C_5H_{11}O(Me)P(S)OH* (Fig. 3.7.7) (*32*). *O-n*-Pentyl methylphosphonochloridothionate (100 g, 0.5 mol) was added dropwise to a solution of sodium hydroxide (40 g, 1 mol) in water (200 ml) heated to 80 °C. Heating of the mixture was continued until the pot temperature reached 102 °C. At this temperature the reaction became self-sustaining and external heating was stopped. Addition of the chloridothionate was completed in 40 min at a pot temperature of 102–107 °C. After cooling to room temperature, the solution was extracted with ether, but no unreacted organic material was retrieved. The aqueous solution was then acidified with a 100% excess of 50% *v/v* sulfuric acid and extracted with ether (2 × 100 ml, then 2 × 50 ml). The

combined extracts were dried (Drierite™), the ether was removed, and the residual crude product was maintained at 40 °C at 0.4–0.5 mmHg for 6 h. Distillation under reduced pressure gave the title compound (69.4 g, 75%). The other thioacids listed in Fig. 3.7.7 were prepared similarly. In the distillation of the crude *O*-alkyl hydrogen alkylphosphonothioates, it is essential that the residues from the benzene or ether extracts are kept under high vacuum at temperatures not exceeding 45 °C for several hours to remove the last traces of moisture. If distillation is attempted without taking this precaution, the thioacids decompose with a considerable increase in viscosity of the charge, presumably because of intermolecular condensation to form the corresponding pyro-esters. For successful distillation of *O*-alkyl hydrogen alkylphosphonothioates a pressure below 1 mmHg is required to assure a minimum distillation temperature that does not result in such condensation reactions.

Heating dialkyl methylphosphonothionates with a molar equivalent of potassium hydroxide in an alcohol whose alkyl group is usually the same as that in the thionate, to prevent transesterification, yields the *O*-alkyl methylphosphonothioate potassium salt (Fig. 3.7.8) (*32*). Hydrolysis of the P–OR group proceeds much faster for the *n*-alkyl derivatives than for the diisopropyl ester. Acidification of the potassium salt with concentrated hydrochloric acid, extraction of the phosphonothioic acid into ether, and distillation yields the pure *O*-alkyl hydrogen methylphosphonothioate.



O-Alkyl hydrogen methylphosphonothioates

R	Yield (%)	Solvent	Reflux (h)	Bp (°C/mmHg)
Me	39	MeOH	1.5	54.5–56/0.2
Et	87	EtOH	1.5	63/0.22
n-Pr	57	*n*-PrOH	0.75	74/0.35
i-Pr	78	*i*-PrOH	5	61/0.2
n-C_5H_{11}	52	EtOH	2	100–102/0.05

Figure 3.7.8

▶ *O-Ethyl hydrogen methylphosphonothioate EtO(Me)P(S)OH (alkaline hydrolysis of diethyl methylphosphonothionate)* (Fig. 3.7.8) (*32*). Diethyl methylphosphonothionate (672 g, 4 mol) was added in one portion to a stirred solution of 85% potassium hydroxide (200 g, 3 mol) in absolute ethanol (1400 ml). The stirred mixture was heated under reflux for 90 min and cooled to room temperature. The solvent was removed under reduced pressure. The residual salt cake was dissolved in water (500 ml) and the aqueous solution extracted with ether (2 × 200 ml, then 1 × 100 ml). The combined ether-extracts were evaporated to leave the crude unreacted diester (160.5 g, ~0.96 mol). The aqueous solution was acidified with concentrated hydrochloric acid (340 ml) while being cooled in an ice bath. The organic layer of the resulting two-phase mixture was separated and the aqueous layer was

extracted with ether (2 × 200 ml). The washings and the organic layer were combined and dried (Drierite™) and the ether was removed under reduced pressure. The remaining crude product was distilled to give the title compound (293 g, 69%). Bp 63 °C/0.22 mmHg. This recipe is illustrative of this general procedure. Hydrolysis of dialkyl methylphosphonothionates with potassium hydroxide to *O*-alkyl potassium methylphosphonothioates is conducted in batches employing, in general, 1–4 mol of starting material and approximately 10–25% less than the equivalent amount of alkali in the appropriate alcohol (350–400 ml) per mole of the dialkyl methylphosphonothionate. The preparation of *O*-*n*-pentyl hydrogen methylphosphonothioate was conducted in ethanol instead of *n*-pentanol, but no transesterification was observed.

▶ *O-Ethyl hydrogen methylphosphonothioate EtO(Me)P(S)OH (13)*. Potassium hydroxide pellets (38.5 g, 0.69 mol) were dissolved in ethanol (200 ml) by gently heating under reflux, with occasional shaking by hand. Diethyl methylphosphonothionate (115 g, 0.68 mol) was added and the mixture heated to vigorous reflux for 12 h. At the end of this time, as much of the diluent as possible was removed under reduced pressure and the syrupy residue was dissolved in water (250 ml). The resulting turbid solution, which should be alkaline, was extracted with ether (2 × 100 ml), and the aqueous portion separated and made strongly acidic with concentrated hydrochloric acid. The oil that separated was extracted with ether (2 × 100 ml), the combined ether extracts dried ($MgSO_4$) and the ether recovered. The product was obtained from the residue by distillation under reduced pressure (64 g, 74% based on the ester consumed). Bp 90–91 °C/2.2 mmHg. The ether extract on concentration gave 11.5 g of unattacked starting material and this was taken into account while calculating the yield of title compound. *O*-Ethyl hydrogen ethylphosphonothioate, EtO(Et)P(S)OH (bp 87 °C/0.9 mmHg), was prepared similarly from diethyl ethylphosphonothionate.

O-Alkyl hydrogen alkylphosphonothioates form crystalline salts with achiral aliphatic amines (e.g. dicyclohexylamine) and with chiral aromatic amines (e.g. quinine or brucine) which allows their resolution for biochemical studies (*31*,*33*). The free acids are sparingly soluble in water, soluble in aqueous alkali and miscible with organic solvents. With the exception of isopropyl sodium methylphosphonothioate, which is sparingly soluble in cold ethanol and insoluble in acetone, the sodium salts are freely soluble in these solvents. Although the free acids, and in all probability their alkali salts as well, have been shown by infrared studies to have the thionate structure, they react with alkyl halides and substituted alkyl halides to give the *S*-esters (*34*), with apparently no trace of the *O*-ester being formed.

3.8 DIALKYL DIALKYLPYROPHOSPHONODITHIONATES RO(R')P(S)OP(S)(R')OR

(−)-Sodium *O*-ethyl methylphosphonothioate (**22**) reacts with racemic *O*-ethyl methylphosphonochloridothionate (**13**) to give the (+)-pyrophosphonodithionate (**23**) in modest yield (Fig. 3.8.1) (*35*).

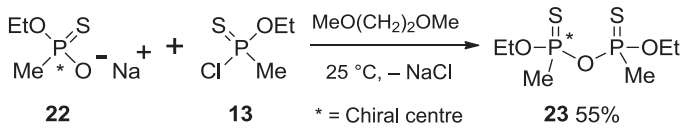


Figure 3.8.1

▶ (+)-*Diethyl dimethylpyrophosphonodithionate EtO(Me)P(S)OP(S)(Me)OEt* (**23**) (*35*). *O*-Ethyl hydrogen methylphosphonothioate (6.4 g, 46 mmol; $[\alpha]_D^{20}$ −8°) in anhydrous 1,2-dimethoxyethane (20 ml) was added dropwise to a stirred suspension of sodium hydride (50% in mineral oil, 2.19 g, 46 mmol) in 1,2-dimethoxyethane (75 ml). *O*-Ethyl methylphosphonochloridothionate (14.5 g, 91 mmol) in the same solvent (20 ml) was then added in one portion. The mixture was stirred overnight and the solvent was removed under reduced pressure. Ether (200 ml) was added and the precipitated sodium chloride was filtered off. Evaporation of the filtrate under reduced pressure and distillation of the residue gave unreacted phosphonochloridothionate (4 g) and diethyl dimethylpyrophosphonodithionate (10.4 g, 55%). Bp 80−81 °C/0.1 mmHg. $[\alpha]_D^{20}$ +24.2°.

3.9 *S*-ALKYL ALKYLPHOSPHONOCHLORIDOTHIOLOTHIONATES RS(R')P(S)Cl

Treatment of methylphosphonothioic dichloride with a molar equivalent each of benzenethiol and triethylamine in benzene gives *S*-phenyl methylphosphonochloridothiolothionate (**24**) and *S,S′*-diphenyl methylphosphonodithiolothionate (**25**), which can be separated by distillation (Fig. 3.9.1) (*9*). The lack of selective monosubstitution experienced here is due to the high reactivity of the monosubstituted product towards benzenethiol.

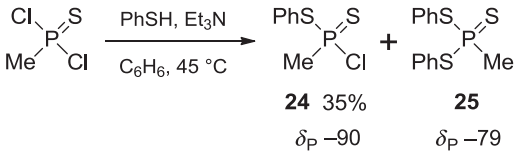


Figure 3.9.1

▶ *S-Phenyl methylphosphonochloridothiolothionate PhS(Me)P(S)Cl* (**24**) (*9*). A solution of benzenethiol (7.5 g, 68 mmol) and triethylamine (7.0 g, 69 mmol) in anhydrous benzene (20 ml) was added dropwise to a stirred solution of methylphosphonothioic dichloride (10.2 g, 68 mmol) in anhydrous benzene (30 ml) at 40−50 °C. After 12 h, the precipitate was filtered off. Fractionation under reduced pressure gave the title compound (5.3 g, 35%). Bp 106−107 °C/0.04 mmHg. δ_P (24.3 MHz, CCl_4) −90 ppm. Higher-boiling *S,S′*-diphenyl methylphosphonodithiolothionate (**25**) was also obtained. δ_P (24.3 MHz, CCl_4) −79 ppm.

3.10 *N,N*-DIALKYL *P*-ALKYLPHOSPHONAMIDOCHLORIDOTHIONATES $R_2N(R')P(S)Cl$

Treatment of alkylphosphonothioic dichlorides with 2 molar equivalents of an aliphatic amine in ether gives the respective *N,N*-dialkyl *P*-alkylphosphonamidochloridothionates in good to excellent yield (Fig. 3.10.1) (*9,36*). Monosubstitution is generally highly selective, unlike the case with thiol nucleophiles (see previous section), as the products are much less reactive to nucleophilic substitution.

Experimental procedures for *N,N*-dimethyl *P*-alkylphosphonamidochloridothionates (**26**) and (**27**), and *N,N*-diethyl *P*-methylphosphonamidochloridothionate (**28**), are provided.

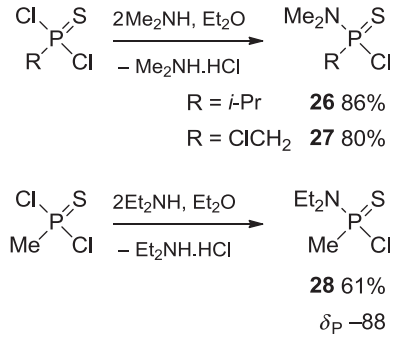


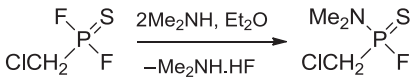
Figure 3.10.1

▶ *N,N-Dimethyl P-isopropylphosphonamidochloridothionate* $Me_2N(i\text{-}Pr)P(S)Cl$ (**26**) (*13,36*). A solution of dimethylamine (4.5 g, 100 mmol) in ether (50 ml) was added dropwise to a stirred solution of isopropylphosphonothioic dichloride (8.9 g, 50 mmol) in ether (100 ml) at 0–5 °C. After addition, the mixture was warmed to room temperature and left for 12 h. The precipitate of dimethylamine hydrochloride was filtered off. Concentration of the filtrate and distillation of the residue gave the title compound as a colourless liquid (8.0 g, 86%). Bp 73 °C/0.1 mmHg. The same protocol using dimethylamine (4.5 g, 100 mmol) and chloromethylphosphonothioic dichloride (9.2 g, 50 mmol) gave $Me_2N(ClCH_2)P(S)Cl$ (**27**) as a colourless liquid (7.7 g, 80%). Bp 62–64 °C/0.01 mmHg.

▶ *N,N-Diethyl P-methylphosphonamidochloridothionate* $Et_2N(Me)P(S)Cl$ (**28**) (*9*). A solution of diethylamine (73 g, 1 mol) in anhydrous ether (100 ml) was added dropwise to a stirred solution of methylphosphonothioic dichloride (74.5 g, 0.5 mol) in anhydrous ether (250 ml). The mixture was left for 12 h and then heated for 1.5 h under reflux. The precipitate was filtered off. Distillation gave the title compound as a colourless liquid (57 g, 61%). Bp 107–109 °C/8 mmHg. δ_P (24.3 MHz, CCl_4, rel. to H_3PO_4) −88 ppm.

3.11 *N,N*-DIALKYL *P*-ALKYLPHOSPHONAMIDOFLUORIDOTHIONATES $R_2N(R')P(S)F$

Treatment of chloromethylphosphonothioic difluoride with 2 molar equivalents of dimethylamine in ether gives *N,N*-dimethyl *P*-chloromethylphosphonamidofluoridothionate (**29**) in excellent yield (Fig. 3.11.1) (*36*). Substitution is highly selective: double substitution does not occur easily as the monosubstitution product is much less reactive to nucleophilic substitution than the starting difluoride.



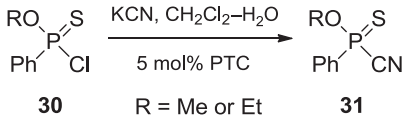
29 86%

Figure 3.11.1

▶ *N,N-Dimethyl P-chloromethylphosphonamidofluoridothionate* $Me_2N(ClCH_2)P(S)F$ (**29**) (*13*,*36*). A solution of dimethylamine (4.5 g, 100 mmol) in ether (50 ml) was added dropwise to a stirred solution of chloromethylphosphonothioic difluoride (made by heating the corresponding dichloride with antimony trifluoride at 60–70 °C in the absence of solvent; 7.5 g, 50 mmol) in ether (100 ml) at 0–5 °C. After addition, the mixture was warmed to room temperature and left for 12 h. The reaction mixture was washed with water (2 × 50 ml), the ether layer separated, dried ($MgSO_4$) and the drying agent filtered off. Concentration of the filtrate and distillation of the residue gave the title compound as a colourless liquid (7.5 g, 86%). Bp 43–46 °C/0.01 mmHg.

3.12 ALKYL ALKYLPHOSPHONOCYANIDOTHIONATES RO(R')P(S)CN

Alkyl alkyl/arylphosphonochloridothionates generally resist reaction with alkali metal cyanides indicating an apparent inertness of the system to nucleophilic substitution by cyanide. Partial thiono-thiolo isomerisation of *O*-alkyl phenylphosphonochloridothionates can occur upon prolonging heating in an effort to effect the displacement. Because of these difficulties, mild methods must be employed. A smooth way of effecting the transformation involves treating alkyl phenylphosphonochloridothionates (**30**) with potassium cyanide in dichloromethane-water in the presence of the phase-transfer catalyst cetyltrimethylammonium bromide (*37*). This provides the desired alkyl phenylphosphonocyanidothionates (**31**) in modest yields (Fig. 3.12.1).



30 R = Me or Et **31**

PTC = cetyltrimethylammonium bromide

Figure 3.12.1

▶ *Methyl phenylphosphonocyanidothionate MeO(Ph)P(S)CN* (**31**, R = Me) (*37*). A solution of methyl phenylphosphonochloridothionate (10.3 g, 0.05 mol) in dichloromethane (25 ml) was added to a stirred mixture of aqueous potassium cyanide (6.5 g, 0.10 mol in 40 ml of water), dichloromethane (125 ml) and cetyltrimethylammonium bromide (5 mol%) at room temperature. After stirring for 5 h, the organic layer was separated, washed with water (2 × 25 ml) and dried ($MgSO_4$). Evaporation of the solvent revealed a reddish brown liquid. Rapid distillation through a short-path apparatus using

a preheated oil bath gave the title compound (4.7 g, 48%). Ethyl phenylphosphonocyanidothionate (**31**, R = Et) was prepared similarly in 60% yield from ethyl phenylphosphonochloridothionate.

3.13 ALKYL ALKYL/ARYL ALKYLPHOSPHONOTHIONATES RO(R')P(S)OR"

Ethyl methylphosphonochloridothionate (**13**) reacts with 5-hydroxyquinoline in acetonitrile in the presence of potassium carbonate to provide *O*-ethyl *O*-(5-quinolinyl) methylphosphonothionate (**32**) in satisfactory yield (Fig. 3.13.1) (*38*). This method is applicable to many types of aryl and heterocyclic alcohols. Its chief advantage is the easy removal of the liberated hydrogen chloride by the potassium carbonate; the products — potassium chloride and potassium hydrogen carbonate — are easily removed by filtration.

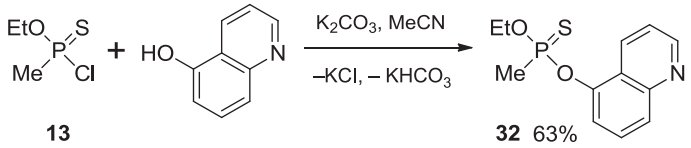


Figure 3.13.1

O-Ethyl O-(5-quinolinyl) methylphosphonothionate EtO(Me)P(S)O(5-quinolinyl) (**32**) (*38*). Ethyl methylphosphonochloridothionate (64 g, 0.4 mol) was added dropwise to a stirred mixture of 5-hydroxyquinoline (60 g, 0.4 mol) and potassium carbonate (56 g, 0.4 mol) in acetonitrile (150 ml) at 50 °C. After the exothermic reaction had subsided, the mixture was heated to 65—70 °C for a further 1 h, poured into ice water (300 ml), and the separated oil dissolved in benzene (200 ml). The benzene solution was dried (Na_2SO_4) and the solvent removed under vacuum. Distillation of the residue gave the title compound as a yellow liquid (67 g, 63%). Bp 125 °C/0.01 mmHg. It was scarcely soluble in water but dissolved in dilute acid. The compound is moderately toxic (LD_{50} oral rat 43 mg/kg).

3.14 *O*-ALKYL *N*-ALKYL/ARYL ALKYLPHOSPHONAMIDOTHIONATES RO(R')P(S)NR$_2$

Methylphosphonothioic dichloride (**1**) reacts with ethanol and triethylamine in boiling benzene to provide *O*-ethyl methylphosphonochloridothionate (**13**), which can be treated in the same pot with aniline and more triethylamine to give *O*-ethyl *N*-phenyl *P*-methylphosphonamidothionate (**33**) (Fig. 3.14.1) (*39*). For better yields of such products it is best to start with the pure alkyl alkylphosphonochloridothionates and perform the last step only.

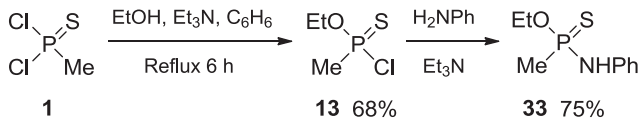


Figure 3.14.1

A trivalent phosphorus chemistry approach involving the addition of an alcohol and amine base to an iminophosphine, followed by addition of sulfur, namely $R^1P{=}NR^2 + ROH$ (+base) → $RO(R^1)P(NHR^2)$ (+S) → $RO(R^1)P(S)NHR^2$, is available but is rather specialised, and the starting iminophosphines are not readily available (*40*).

▶ *O-Ethyl N-phenyl P-methylphosphonamidothionate EtO(Me)P(S)NHPh* (**33**) (*39*). A solution of ethanol (3.1 g, 67 mmol) and triethylamine (6.8 g, 67 mmol) in anhydrous benzene (30 ml) was added dropwise to a stirred solution of methylphosphonothioic dichloride (10.0 g, 67 mmol) in anhydrous benzene (80 ml). After addition, the mixture was boiled under reflux for 6 h. On the next day, after filtration, the solution was washed with water (3 × 50 ml) and dried ($MgSO_4$). Distillation of the solution gave ethyl methylphosphonochloridothionate (7.2 g, 68%; bp 103 °C/70 mmHg). A mixture of aniline (4.1 g, 44 mmol) and triethylamine (4.5 g, 44 mmol) in anhydrous benzene (30 ml) was added to the aforementioned chloridothionate (7.2 g, 45 mmol) in benzene (80 ml). After addition, the mixture was heated under reflux for 3 h, allowed to cool to room temperature, filtered, washed with water (3 × 50 ml) and dried. Distillation gave the title compound (7.25 g, 75%). Bp 125 °C/0.05 mmHg.

3.15 *O*-ALKYL *S*-ALKYL ALKYLPHOSPHONODITHIOATES RO(R')P(S)SR

Treatment of *s*-butylphosphonothioic dichloride (**34**) with hydrogen sulfide at elevated temperature provides *s*-butylthionophosphine sulfide (**35**) (*41*) that undergoes ready alcoholysis to furnish the corresponding *O*-alkyl hydrogen *s*-butylphosphonodithioate (**36**) (Fig. 3.15.1) (*42*). The yields of both steps are excellent and they can be used to secure a range of thionophosphine sulfides (*43*) and *O*-alkyl hydrogen alkylphosphonodithioates (*44*).

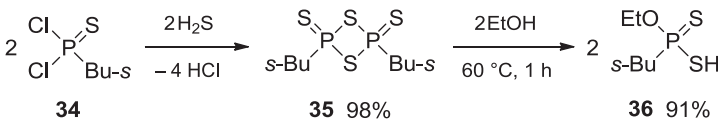


Figure 3.15.1

▶ *s-Butylthionophosphine sulfide* (**35**) (*41*). A vessel charged with *s*-butylphosphonothioic dichloride was heated gradually to 165–180 °C. At 135 °C hydrogen sulfide was passed into the liquid at a rate of 3–4 l/h for 18–24 h. The passage of hydrogen sulfide was stopped when the refractive index of the reaction mixture attained 1.62–1.64. The reaction product was removed from the vessel and the latter rinsed out with petroleum ether, from which the product crystallised (98%). Mp 92–93 °C.

▶ *O-Ethyl hydrogen s-butylphosphonodithioate EtO(s-Bu)P(S)SH* (**36**) (*42*). *s*-Butylthionophosphine sulfide was weighed into a three-necked flask fitted with a stirrer, a thermometer and a reflux condenser, under an anhydrous inert gas atmosphere. The solid was dissolved in benzene and a large excess of ethanol added. The stirred mixture was heated to 60–65 °C for 60–90 min. After cooling to room temperature, the solvent was removed and the residue distilled to give the product (91%). Bp 66–67 °C/0.18 mmHg.

O-Alkyl hydrogen alkylphosphonodithioates contain a nucleophilic thiolo sulfur atom and add to the double bonds of Michael acceptors. The reactions of *O*-ethyl hydrogen *s*-butylphosphonodithioate (**36**) with acrylonitrile and methyl acrylate provide *O*-ethyl *S*-(2-cyanoethyl) *s*-butylphosphonodithioate (**37**) and *O*-ethyl *S*-(2-methylcarboxyethyl) *s*-butylphosphonodithioate (**38**) respectively (Fig. 3.15.2) (*42*). The sodium salt of the dithioate also reacts with benzyl bromide to furnish *O*-ethyl *S*-benzyl *s*-butylphosphonodithioate (**39**).

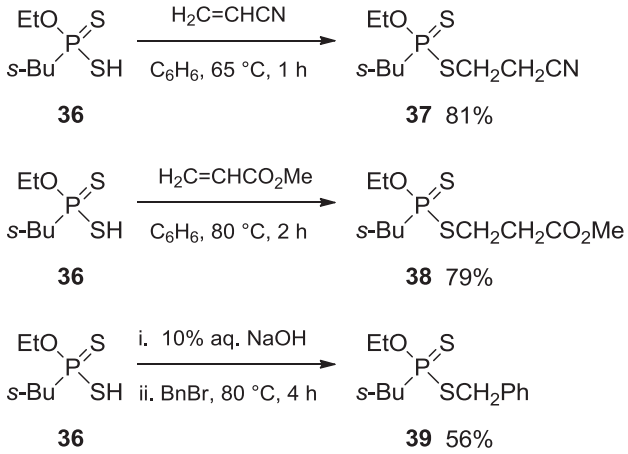


Figure 3.15.2

▶ *O-Ethyl S-(2-cyanoethyl) s-butylphosphonodithioate EtO(s-Bu)P(S)SCH$_2$CH$_2$CN* (**37**) (*42*). An equimolar amount of acrylonitrile was added dropwise to a stirred solution of *O*-ethyl *s*-butylphosphonodithioate in benzene. Heat was liberated. The mixture was heated to 60–65 °C for 1 h, the benzene was removed, and the residue was vacuum-fractionated to yield the title compound (81%). Bp 142.5 °C/0.2 mmHg.

▶ *O-Ethyl S-(2-methylcarboxyethyl) s-butylphosphonodithioate EtO(s-Bu)P(S)SCH$_2$CH$_2$CO$_2$Me* (**38**) (*42*). An equimolar amount of methyl acrylate was added dropwise to a stirred solution of *O*-ethyl *s*-butylphosphonodithioate in benzene. An exothermic reaction occurred. The mixture was heated to 70–80 °C for 2 h, the benzene was removed and the residue was vacuum-fractionated to yield the title compound (79%). Bp 116–117 °C/0.3 mmHg. To suppress polymerisation a little hydroquinone can be added to the reaction mixture (*45*).

▶ *O-Ethyl S-benzyl s-butylphosphonodithioate EtO(s-Bu)P(S)SCH$_2$Ph* (**39**) (*42*). Aqueous sodium hydroxide (10% *w/w*) was added dropwise to *O*-ethyl *s*-butylphosphonodithioate (1 M equiv.) until neutral (phenolphthalein indicator). Benzyl bromide (1 M equiv.) was added dropwise to the solution of the sodium salt of the dithioate and the mixture was heated to 70–80 °C for 3–4 h. The mixture was separated into aqueous and organic layers. The aqueous layer was extracted with benzene, the extract was combined with the organic layer, and the whole was dried (Na_2SO_4), and the solvent was removed. Fractionation of the residue under reduced pressure gave the title compound (56%). Bp 130 °C/0.01 mmHg.

3.16 *BIS*(*O*-ALKYL ALKYLPHOSPHINOTHIOYL) DISULFIDES RO(R')P(S)SSP(S)(R')OR

The potassium salt of *O*-ethyl hydrogen *s*-butylphosphonodithioate (**36**) is oxidised by iodine in the presence of potassium iodide to give the disulfide (**40**) (Fig. 3.16.1) (*42*).

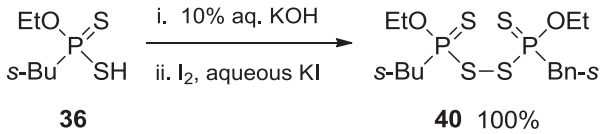


Figure 3.16.1

▶ *Bis(O-ethyl s-butylphosphinothioyl) disulfide EtO(s-Bu)P(S)SSP(S)(s-Bu)OEt* (**40**) (*42*). An equimolar amount of aqueous sodium hydroxide (10% *w/w*) was added dropwise to *O*-ethyl *s*-butylphosphonodithioate (1 M equiv.) until neutral (phenolphthalein indicator). The solution was treated with an equimolar amount of iodine in potassium iodide solution until a yellow colour appeared. Free iodine was removed by means of sodium thiosulfate solution. The precipitate was filtered off and crystallised from ethanol to yield the disulfide in quantitative yield. Mp 77–78.5 °C.

3.17 *BIS*(*N,N*-DIALKYL) ALKYLPHOSPHONODIAMIDOTHIONATES $(R_2N)_2P(S)R'$

Various uncomplicated methods are available for the synthesis of disubstituted alkylphosphonodiamidothionates (Fig. 3.17.1). Treatment of alkylphosphonothioic dichlorides with 4 molar equivalents of an alkylamine or dialkylamine in an inert solvent, such as benzene or ether, provides the target compounds. This approach works satisfactorily for *N,N,N′,N′*-tetraethyl methylphosphonodiamidothionate (**41**) (*9*). The stability of alkylphosphonothioic dichlorides to alkali and their greater reactivity towards nitrogen nucleophiles compared to oxygen nucleophiles allows them to

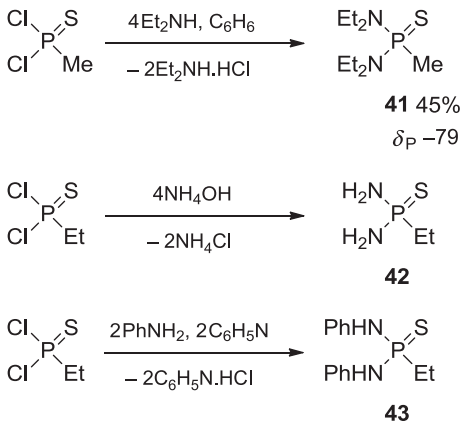


Figure 3.17.1

react with ice-cold aqueous ammonia (*d* 0.880 g/ml) to yield crystalline alkylphosphonodiamidothionates, e.g. ethylphosphonodiamidothionate (**42**) (*13*). They also undergo the Schotten—Baumann reaction with aniline in pyridine (or aqueous sodium hydroxide) to give the diamidothionate, e.g. *N,N′*-diphenyl ethylphosphonodiamidothionate (**43**) (*13*).

▶ *N,N,N′,N′-Tetraethyl methylphosphonodiamidothionate* $(Et_2N)_2P(S)Me$ (**41**) (*9*). A solution of methylphosphonothioic dichloride (7.45 g, 50 mmol) in anhydrous benzene (40 ml) was added dropwise to a stirred solution of diethylamine (14.6 g, 200 mmol) in benzene (50 ml) at room temperature. After 12 h, the precipitate was filtered off. The solvent was removed from the filtrate and the residue distilled to yield the title compound as a colourless liquid (5.0 g, 45%). Bp 149—151 °C/15 mmHg. δ_P (24.3 MHz, CCl_4) −79 ppm. *N,N′*-Dicyclohexyl methylphosphonodiamidothionate (mp 115 °C after recrystallisation from benzene-light petroleum) was prepared similarly in 53% yield from methylphosphonothioic dichloride (1 mol) and cyclohexylamine (4 mol) (*39*).

▶ *Ethylphosphonodiamidothionate* $(H_2N)_2P(S)Et$ (**42**) (*13*). Ethylphosphonothioic dichloride (13.6 g, 83 mmol) was added dropwise to ammonia (*d* 0.880 g/ml, 10 ml) contained in a flask cooled in ice and fitted with a mechanical stirrer. The white crystalline material that separated was filtered and crystallised from water. It separated in large prisms containing a half molar-equivalent of water of crystallisation: $C_2H_9N_2PS.0.5H_2O$ (mp 137 °C). The anhydrous substance was obtained by drying the latter at 70 °C over phosphorus pentoxide.

▶ *Ethylphosphonodianilidothionate* $(PhNH)_2P(S)Et$ (**43**) (*13*). Ethylphosphonothioic dichloride (4.1 g, 25 mmol) was added to a stirred mixture of aniline (4.6 g, 49 mmol) and pyridine (6 ml, 74 mol) and heated to 100 °C for 1 h. After cooling, the mixture was poured into an excess of dilute hydrochloric acid. The aqueous layer was decanted from the sticky pinkish organic material and the latter washed with aqueous sodium carbonate, water and carbon tetrachloride. It crystallised from benzene from which it separated with solvent of crystallisation. It melted indefinitely at 85—87 °C, solidified and remelted at 114 °C. The melting point of material recrystallised from carbon tetrachloride was 114 °C.

3.18 *S,S′*-DIALKYL ALKYLPHOSPHONODITHIOLOTHIONATES $(RS)_2P(S)R'$

Treatment of methylphosphonothioic dichloride with a molar equivalent of an aliphatic or aromatic thiol in the presence of triethylamine, with the intention of isolating the monosubstitution product, provides also the double substitution product (Fig. 3.18.1) (*9*). Distillation under reduced pressure provides the latter, and methods for *S,S′*-diethyl methylphosphonodithiolothionate (**44**) and *S,S′*-diphenyl methylphosphonodithiolothionate (**45**) are provided. The initial use of 2 molar equivalents of both the thiol and triethylamine would be expected to yield the *S,S′*-disubstituted methylphosphonodithiolothionates in greater yield.

Treatment of ethylphosphonous dichloride with 2 molar equivalents of an alkanethiol and triethylamine in ether provides *S,S′*-dialkyl ethylphosphonodithioites (**46**), which add sulfur to give *S,S′*-dialkyl ethylphosphonodithiolothionates (**47**) (Fig. 3.18.2) (*46*). The starting phosphonodithioites are mobile liquids with an unpleasant smell, are soluble in organic solvents (e.g. benzene, diethyl ether, petroleum ether) and are much less susceptible than the corresponding phosphonous esters $(RO)_2PEt$

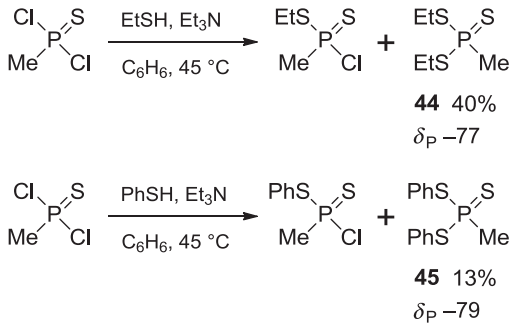
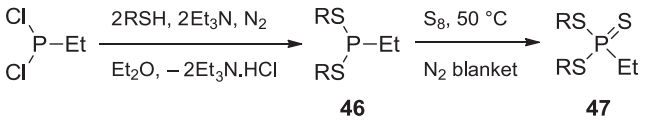


Figure 3.18.1



Dialkyl ethylphosphonodithioites **46** and -phosphonodithiolothionates **47**

R	Yield (%)	Bp (°C/mmHg)	Yield (%)	Bp (°C/mmHg)
n-Pr	73	86–88/0.1	87	94–96/0.05
i-Pr	62	95–97/9	77	76–78/0.05
n-Bu	84	92–94/0.07	81	109–110/0.05
i-Bu	57	154–157/120	84	103–105/0.05

Figure 3.18.2

to atmospheric oxidation. The addition of sulfur, as expected from their resilience to oxidation, proceeds less vigorously than in the case of the oxygen analogues. The reaction mixture must be heated to 50—80 °C to initiate the addition of sulfur, after which the reaction occurs with liberation of heat. The *S,S′*-dialkyl alkylphosphonodithiolothionate product is isolated by distillation under reduced pressure.

▶ *S,S′-Diethyl methylphosphonodithiolothionate* $(EtS)_2P(S)Me$ (**44**) (*9*). A solution of ethanethiol (4.2 g, 68 mmol) and triethylamine (7.0 g, 69 mmol) in benzene (20 ml) was added dropwise to a stirred solution of methylphosphonothioic dichloride (10.2 g, 68 mmol) in benzene (30 ml) at 40—50 °C. After 12 h, the precipitate was filtered off. Fractionation gave the title compound (5.4 g, 40%). Bp 131—133 °C/10 mmHg. δ_P (24.3 MHz, CCl_4) −77 ppm. The use of benzenethiol instead of ethanethiol gave $(PhS)_2P(S)Me$ (**45**) as a colourless liquid (13%). Bp 169—170 °C/0.03 mmHg. $^{31}P\{^1H\}$ NMR (24.3 MHz, CCl_4) −79 ppm.

▶ *S,S′-Di-n-propyl ethylphosphonodithiolothionate* $(n\text{-}PrS)_2P(S)Et$ (*46*). Ethylphosphonous dichloride (32.7 g, 0.25 mol) was added over 2 h to a vigorously stirred solution of *n*-propanethiol (38.0 g,

0.50 mol) and triethylamine (52.0 g, 0.51 mol) in ether (350 ml) in a four-necked flask equipped with a stirrer, a dropping funnel and a reflux condenser. During addition, the flask was cooled externally to 0–5 °C with ice and salt. The addition was performed under an atmosphere of nitrogen. Triethylamine hydrochloride was filtered off and washed with ether. Vacuum fractionation of the filtrate gave di-*n*-propyl ethylphosphonodithioite, $(n\text{-PrS})_2$PEt (38.2 g, 73%; bp 86–88 °C/0.1 mmHg). A mixture of this compound (5.4 g, 26 mmol) and sulfur powder (0.82 g, 26 mmol) was prepared in a flask fitted with a thermometer, calcium chloride tube and inlet for the passage of nitrogen. No reaction was observed in the cold; the stirred mixture was heated and the sulfur-addition reaction started at 50 °C. The application of heat was stopped but the temperature in the flask rose to 155 °C. All the added sulfur dissolved as it reacted. Vacuum distillation of the resulting liquid gave the title compound (5.4 g, 87%). Bp 94–96 °C/0.05 mmHg. The other compounds listed in Fig. 3.18.2 were prepared using the same methods.

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CHAPTER 4

Phosphoryl Compounds

Christopher M. Timperley,[a] Pierre-Yves Renard[b] and Catherine Gomez[b]
[a] *Detection Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK*
[b] *Normandie Univ, COBRA, UMR 6014 & FR 3038, UNIV Rouen, INSA Rouen, CNRS, 1 Rue Tesnières, 76821 Mont-Saint-Aignan Cedex, France*

4.1 INTRODUCTION

Organophosphates are essential for life and play a vital role as nucleic acids, nucleotide coenzymes, metabolic intermediates, and in many biochemical processes (Chapter 1). Man-made compounds in this class have found practical use as lubricants, oil additives, plasticisers and pesticides. Organophosphorus pesticides encompass insecticides, fungicides, and herbicides. The three substituents connected to the P═O group can modulate the chemical, physical, and biological properties of such species, and the seemingly endless possibilities fascinate the chemist some 190 years after the first phosphate esters were prepared by the French scientist, Jean Louis Lassaigne (1800–1859). This chapter describes some of the principal methods of synthesis of many representatives of the phosphate class.

4.2 ALKYL PHOSPHORODICHLORIDATES $ROP(O)Cl_2$

Mixing equimolar proportions of phosphorus oxychloride and aliphatic alcohols in the absence of solvent for 2 h, followed by vacuum fractionation, provides the alkyl phosphorodichloridates in acceptable yields (Fig. 4.2.1) (*1*). Alternatively, the alcohol can be added to phosphorus oxychloride in ether in the presence of a base such as triethylamine – this procedure gives isopropyl phosphorodichloridate and *n*-butyl phosphorodichloridate in modest yields (*2*,*3*). Alternatively, pyridine can be employed instead of triethylamine; e.g. to make 2,2,2-trichloroethyl phosphorodichloridate $CCl_3CH_2OP(O)Cl_2$ (bp 57.5 °C/0.1 mmHg) (*4*), a reagent used for oligonucleotide synthesis. The 2,2,2-trifluoro analogue, $CF_3CH_2OP(O)Cl_2$ (bp 59–61 °C/10 mmHg) (*5*), is potentially useful in this context.

Good yields of alkyl phosphorodichloridates are achieved by the reaction of phosphorus oxychloride with bulky alcohols in the presence of triethylamine. Such alcohols include *trans*-4-*tert*-butylcyclohexanol (*6*), *endo*-norborneol (*7*), and 2-adamantanol (*8*) which upon reaction yield the phosphorodichloridates **1–3** (Fig. 4.2.2). In these cases, the alcohols are sufficiently hindered to suppress the possibility of double nucleophilic substitution, providing clean passage to the desired compounds. The order of addition – alcohol to phosphorus oxychloride – ensures that the $POCl_3$ is always present in the reaction mixture in greater concentration than the alcohol, which lowers the

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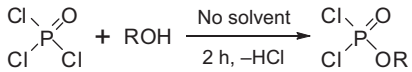


Alkyl phosphorodichloridates

R	Yield (%)	Bp (°C/mmHg)
Me	64	33–34/4
Et	62	34/2
n-Pr	64	56–58/3
i-Pr	61 [a]	40/4
n-Bu	54 [a]	50/1.5
CF_3CH_2	36 [a]	59–61/10

a. Diethyl ether added as solvent and triethylamine as base, 0–5 °C

Figure 4.2.1

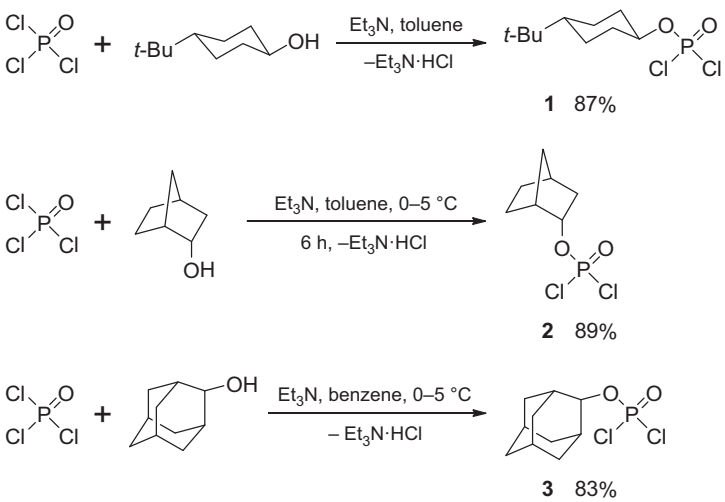


Figure 4.2.2

probability of polysubstitution. Heating methyl phosphorodichloridate with an excess of bromotrimethylsilane in ether provides in high yield trimethylsilyl phosphorodichloridate (**4**), a precursor useful for making various disubstituted hydrogen phosphates (Fig. 4.2.3) (*9*).

Alkyl phosphorodichloridates are corrosive liquids that react readily with moisture and alcohols (*10*); for example, the reaction of ethyl phosphorodichloridate $EtOP(O)Cl_2$ with ethanol to give diethyl phosphorochloridate $(EtO)_2P(O)Cl$ is much faster than the reaction of the latter compound with ethanol (*1*). The hydrolysis of ethyl phosphorodichloridate has also been studied (*11*). Methyl

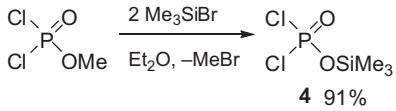


Figure 4.2.3

phosphorodichloridate and ethyl phosphorodichloridate are commercially available, but homologues are generally synthesised. Isopropyl phosphorodichloridate discolours on standing for several days in a refrigerator and is best used immediately for further transformations (*1*). Its vapour irritates the eyes and respiratory tract (*12*).

▶ *Alkyl phosphorodichloridates ROP(O)Cl$_2$ (general method)* (*1*). Equimolar amounts of phosphorus oxychloride and an alcohol were mixed at a temperature below 0 °C. The mixture was stirred for 2 h whereupon the hydrogen chloride formed was removed by bubbling dry nitrogen through the solution. Fractionation of the mixture under vacuum gave the alkyl phosphorodichloridates described in Fig. 4.2.1. Alternatively, an anhydrous alcohol (1 mol) was added to phosphorus oxychloride (1 mol) at below 20 °C. After addition, the cooling bath was removed and the solution was stirred at room temperature for 2 h. The solution was warmed under vacuum (60 °C/100 mmHg) to remove unreacted POCl$_3$ and HCl, and distilled to give the dichloridate (*13*).

▶ *Methyl phosphorodichloridate MeOP(O)Cl$_2$* (*14*). Phosphorus oxychloride (1177 g, 7.67 mol) was placed in a three-necked 1000-ml round-bottomed flask equipped with a thermometer, a stirrer, a dropping funnel, a gas inlet reaching beneath the surface of the liquid, and a vent. The phosphorus oxychloride was cooled to 5 °C, and anhydrous methanol (252 g, 7.88 mol) was added over 100 min while maintaining the temperature between 5 and 15 °C. Once the alcohol had been added, the cooling bath was removed and dry nitrogen was bubbled through the reaction mixture. Copious quantities of hydrogen chloride were evolved as the temperature rose; however, cooling due to the heat of vaporisation of HCl prevented the temperature rising above 15 °C, until practically all of this gas had been removed, when room temperature was reached. The product was fractionated and the fraction boiling at 85–92 °C/90 mmHg was collected. This was refractionated to yield methyl phosphorodichloridate (720 g, 63%). Bp 49 °C/13 mmHg (*15*).

▶ *Ethyl phosphorodichloridate EtOP(O)Cl$_2$* (*16*). Absolute ethanol (46.1 g, 1.0 mol) was added dropwise with stirring to phosphorus oxychloride (175 g, 1.1 mol) at 0–5 °C over 2 h. After addition, a dry inert gas (argon, nitrogen or carbon dioxide) was bubbled through the reaction mixture for several hours to remove the hydrogen chloride. The residue was then fractionated under reduced pressure to yield after two distillations ethyl phosphorodichloridate as a colourless liquid (135 g, 72%). Bp 56–61 °C/9–10 mmHg (lit. bp 58 °C/13 mmHg (*14*), 63 °C/19 mmHg (*17*)). It has a pungent smell and assumes a reddish colour when exposed to light. It can be stored in dark bottles for years without undergoing appreciable decomposition. Boiling points for other alkyl phosphorodichloridates

are as follows: *n*-PrOP(O)Cl_2 (bp 72 °C/13 mmHg), *i*-PrOP(O)Cl_2 (bp 60 °C/12 mmHg), and *n*-BuOP(O)Cl_2 (bp 84 °C/13 mmHg) (*15*).

▶ *2-Chloroethyl phosphorodichloridate* $ClCH_2CH_2OP(O)Cl_2$ (*18*). Phosphorus oxychloride (153.5 g, 1 mol) was added dropwise over 1.5 h to a stirred solution of 2-chloroethanol (80.5 g, 1 mol) in anhydrous carbon tetrachloride (100 ml). Stirring was continued while the flask was heated to 100 °C for 3 h. The mixture was then distilled very carefully under diminished pressure, the temperature being kept below 60 °C until the carbon tetrachloride was removed and hydrogen chloride was no longer evolved. Further distillation gave the title compound as a colourless mobile liquid of suffocating odour (93 g, 47%). Bp 108–110 °C/15 mmHg (lit. bp 50 °C/1 mmHg (*19*)). A similar method yielded 2-bromoethyl phosphorodichloridate $BrCH_2CH_2OP(O)Cl_2$ (bp 92–93 °C/5 mmHg) in 29% yield (*20*).

▶ *Isopropyl and n-butyl phosphorodichloridates i-PrOP(O)*Cl_2 *and n-BuOP(O)*Cl_2 (*2*). A solution of the appropriate alcohol (40 mmol) and triethylamine (40 mmol) in ether (50 ml) was added dropwise to a stirred solution of phosphorus oxychloride (60 mmol) in ether (75 ml) cooled to 0–5 °C. After addition, the mixture was allowed to warm to room temperature and was left for 14 h. The precipitate was removed by filtration and the filtrate concentrated to give a liquid. This was distilled under reduced pressure to give the dichloridate as a colourless liquid. Yields and boiling points for the title compounds are given in Fig. 4.2.1. Phosphorus nuclear magnetic resonance (NMR) chemical shifts (202 MHz, $CDCl_3$): *i*-PrOP(O)Cl_2 (δ_P 4.7 ppm) and *n*-BuOP(O)Cl_2 (δ_P 6.0 ppm).

▶ *2,2,2-Trifluoroethyl phosphorodichloridate* $CF_3CH_2OP(O)Cl_2$ (*5*). Triethylamine (25.25 g, 0.25 mol) was added dropwise to a stirred solution of phosphorus oxychloride (38.38 g, 0.25 mol) and 2,2,2-trifluoroethanol (25.00 g, 0.25 mol) in anhydrous ether (25 ml) cooled to 0–5 °C. After addition, the mixture was warmed to room temperature and heated under reflux for 2 h. The precipitate was removed by filtration and the filtrate concentrated to yield a liquid. Sometimes further triethylamine hydrochloride precipitated on standing. Filtration through a short column of silica gel, removal of solvent, and fractionation of the residue under reduced pressure gave a colourless liquid (19.53 g, 36%). Bp 59–61 °C/10 mmHg. δ_P (202 MHz, $CDCl_3$) 8.8 ppm.

▶ *Trans-4-tert-butylcyclohexyl phosphorodichloridate* (**1**) (*6*). *Trans*-4-*tert*-butylcyclohexanol (18.2 g, 0.12 mol) and triethylamine (14.1 g, 0.14 mol) were added to a stirred solution of phosphorus oxychloride (21.5 g, 0.14 mol) in anhydrous toluene (160 ml) for 3 h. Precipitated triethylamine hydrochloride was filtered off and the filtrate evaporated (75 °C/0.5 mmHg) to give a liquid (32.6 g, 87%).

▶ *Endo-bicyclo[2.2.1]heptyl phosphorodichloridate* (**2**) (*7*). A solution of *endo*-bicyclo[2.2.1]heptanol (*endo*-norborneol) (11.2 g, 0.10 mol) and triethylamine (12.1 g, 0.12 mol) in toluene (100 ml) was added gradually during 45 min to a stirred solution of phosphorus oxychloride (18.3 g, 0.12 mol) in toluene (50 ml) at 0–5 °C. After 6 h at 4 °C, precipitated triethylamine hydrochloride was collected and the filtrate evaporated at 40 °C/7 mmHg to give a fuming red liquid (18 g, 89%).

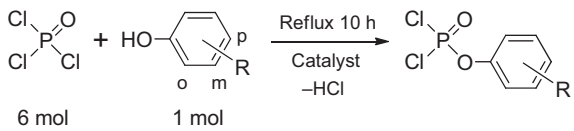
▶ *2-Adamantyl phosphorodichloridate* (**3**) (*8*). A solution of 2-adamantanol (3.06 g, 20 mmol) and triethylamine (2.02 g, 20 mmol) in benzene (150 ml) was added to a stirred solution of phosphorus oxychloride (3.07 g, 20 mmol) in benzene (30 ml) at 0–5 °C. The mixture was stirred at room

temperature for 2 h and then boiled under reflux for 6 h. Triethylamine hydrochloride was filtered off and the filtrate was evaporated to give a liquid (4.4 g, 83%).

▶ *Trimethylsilyl phosphorodichloridate* $Me_3SiOP(O)Cl_2$ (**4**) (*9*). Bromotrimethylsilane (12.6 g, 80.5 mmol) was added dropwise to a solution of methyl phosphorodichloridate (3.5 ml, 35 mmol) in anhydrous ether (60 ml) at room temperature. The mixture was heated under reflux for 2 h and was concentrated under reduced pressure. Distillation of the residue gave a colourless liquid (6.7 g, 91%). Bp 85–87 °C/29 mmHg.

4.3 ARYL PHOSPHORODICHLORIDATES $ArOP(O)Cl_2$

Aryl phosphorodichloridates can be prepared by heating under reflux a mixture of phosphorus oxychloride and aromatic alcohols (*21*). When equimolar quantities of reagents are used, the alcohols can react further with the desired dichloridate to give unwanted diaryl phosphorochloridates $(ArO)_2P(O)Cl$, lowering the yield of the dichloridate. Isolated yields of dichloridates exceeding 80% can be obtained by heating a 1:6 molar ratio of the alcohols with phosphorus oxychloride (Fig. 4.3.1). Phenols do not react with a large excess of $POCl_3$ which is partly explained by the comparatively low reaction temperature: a large excess of $POCl_3$ (bp 106 °C) does not allow the reaction mixture to be heated above 107–110 °C.



Aryl phosphorodichloridates

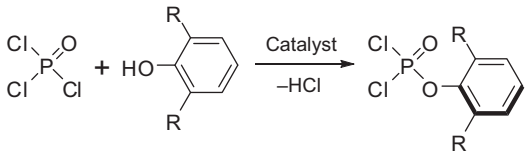
R	Catalyst	Yield (%)	Bp (°C/mmHg)
H	KCl	96	106–108/7
o-MeO	$FeCl_3$	89	120/2
m-MeO	KCl	89	123–124/1.5
p-MeO	NaCl	88	118–120/1.5
o-NO_2	KCl	83	138–139/1
m-NO_2	NaCl	87	144/1
p-NO_2	NaCl	88	144/1

Figure 4.3.1

The reaction is catalysed by certain ionic salts and the rate diminishes in the catalyst order $FeCl_3 > CsCl > RbCl > KCl > NaCl > BaCl_2$. The catalytic activity depends on the dissociation constant of the phenol used: the higher the dissociation constant, the more rapid the formation of the aryl phosphorodichloridate. The catalysts may work in two ways: by co-ordinating to the P═O oxygen atom and increasing the electrophilicity of the phosphorus atom, or by reacting with the

alcohol to produce an increased concentration of the more reactive ArO^- form. Using such catalysts, it is possible to prepare easily and in good yield aryl phosphorodichloridates that cannot be obtained by heating the phenol with a slight excess of phosphorus oxychloride; for example, *p*-nitrophenyl phosphorodichloridate, a useful intermediate for preparing analogues of the insecticide paraoxon (Section 4.35). Another catalyst reported to assist the preparation of phenyl phosphorodichloridate by the route discussed is aluminium trichloride (*22*).

Phosphorus oxychloride reacts upon heating with hindered aryl alcohols in the presence of catalysts (Fig. 4.3.2) (*23*). The efficiency of catalysts decreases in the order LiCl > Mg > Fe for coupling phosphorus oxychloride to 2,6-dimethylphenol. Using lithium chloride as the catalyst, it was possible to isolate 2,6-dimethylphenyl phosphorodichloridate in 81% yield. Similarly, the reaction of phosphorus oxychloride with 2,6-diisopropylphenol in the presence of lithium chloride after 24 h reflux gave 2,6-diisopropylphenyl phosphorodichloridate in 40% yield. Under the same conditions, the even more hindered alcohol, 2,6-di(*tert*-butyl)phenol, gave a negligible amount of the corresponding dichloridate after refluxing for 7 days, as the steric limit of reactivity was reached.



2,6-Dialkylaryl phosphorodichloridates

R	Catalyst	Time (h)	Yield (%)	Bp (°C/mmHg)
Me	Fe	24	33	110/1.5
Me	Mg	2.0–3.5	68	110/1.5
Me	LiCl	2.0–3.5	81	110/1.5
i-Pr	LiCl	72	82	138–140/0.1

Figure 4.3.2

▶ *Phenyl phosphorodichloridate $C_6H_5OP(O)Cl_2$ (stoichiometric alcohol, no catalyst)* (*24,25*). A round-bottomed flask fitted with a reflux condenser topped with a calcium chloride drying tube was charged with phosphorus oxychloride (170.6 g, 1.1 mol) and phenol (104.5 g, 1.1 mol). The mixture was heated under reflux for 10 h. The reaction mass obtained was distilled under vacuum and a fraction boiling at 97–103 °C/2 mmHg was collected. Redistillation gave the title compound as a colourless liquid (136.0 g, 58%). Bp 103–104 °C/2 mmHg. A similar experiment using 1 mol of each reactant gave a higher yield of phenyl phosphorodichloridate (168.0 g, 80%) (*21*). Bp 106–111 °C/8–9 mmHg.

▶ *Phenyl phosphorodichloridate $C_6H_5OP(O)Cl_2$ (excess phosphorus oxychloride, with catalyst)* (*21*). Potassium chloride (5.0 g, 67 mmol) was added to a solution of phenol (94 g, 1 mol) in phosphorus oxychloride (560 ml, 6 mol) and the mixture was heated under reflux until the evolution of hydrogen chloride ceased (after 10 h). The excess phosphorus oxychloride (bp 106 °C) was distilled off and the

residue was fractionated to give phenyl phosphorodichloridate (202.1 g, 96%). Bp 106.0–107.5 °C/7 mmHg (lit. bp 240 °C/760 mmHg (*26*)). This general method tolerates various substituents on the phenol (e.g. alkyl, alkoxy, hydroxy, and nitro). Sodium chloride and iron(III) chloride are also effective catalysts. The use of sodium chloride and *p*-nitrophenol gave *p*-nitrophenyl phosphorodichloridate *p*-$O_2NC_6H_4OP(O)Cl_2$ (88%; bp 144 °C/1 mmHg; mp 50 °C), a useful reagent for preparing analogues of the pesticide paraoxon (*27*).

▶ *2-Methylphenyl phosphorodichloridate 2-$MeC_6H_4OP(O)Cl_2$* (*13*). 2-Methylphenol (162 g, 1.50 mol) was added to phosphorus oxychloride (499 g, 3.25 mol) containing magnesium chloride (1 g) at 90 °C. After addition, the mixture was heated under reflux for 12 h. The excess $POCl_3$ was distilled off, followed by the title compound (172 g, 51%). Bp 110 °C/7 mmHg. When the magnesium chloride was absent, the yield fell to 33%.

▶ *2,6-Dimethylphenyl phosphorodichloridate 2,6-$(Me)_2C_6H_3OP(O)Cl_2$* (*23*). A mixture of phosphorus oxychloride (40 ml, 429 mmol), 2,6-dimethylphenol (17.4 g, 143 mmol) and lithium chloride (134 mg, 3 mmol) was heated under reflux for 24 h. Distillation under reduced pressure gave the title compound (27.7 g, 81%; bp 110 °C/1.5 mmHg). 2,6-Diisopropylphenyl phosphorodichloridate 2,6-$(i\text{-Pr})_2C_6H_3OP(O)Cl_2$ (82%; bp 138–140 °C/0.1 mmHg) was prepared similarly from 2,6-diisopropylphenol using a reflux time of 72 h.

▶ *Pentafluorophenyl phosphorodichloridate $C_6F_5OP(O)Cl_2$* (*28*). A solution of pentafluorophenol (72 g, 0.39 mol) in chloroform (100 ml) was added dropwise over 45 min to a stirred mixture of phosphorus oxychloride (109.4 ml, 1.17 mol) and powdered anhydrous calcium chloride (4.44 g, 0.04 mol). The resulting suspension was heated under reflux for 24 h, filtered, and the filter cake was washed several times with chloroform (200 ml in total). The solvent was removed from the combined extracts to give a yellow liquid (144 g). Distillation of this liquid under reduced pressure gave the title compound as a colourless liquid (50.8 g, 43%). Bp 50–51 °C/0.1 mmHg (lit. bp 112–125 °C/20 mmHg (*29*)). δ_P ($CDCl_3$) 6.3 ppm.

4.4 ALKYL PHOSPHORODIFLUORIDATES $ROP(O)F_2$

The lower members of the alkyl phosphorodifluoridate series are liquids that are difficult to handle due to their corrosive nature and low boiling points: $MeOP(O)F_2$ (bp 65 °C) (*30*) and $EtOP(O)F_2$ (bp 85 °C) (*31*). The latter can be prepared using trivalent phosphorus chemistry by treating diethyl phosphorochloridite (**5**) with 2-hydroperfluoropropyl azide (which is converted into 2-hydroperfluoroproprionitrile, bp 39–42 °C, and nitrogen) in the absence of solvent (Fig. 4.4.1). The postulated difluorophosphorane intermediate (**6**) is thought to lose ethyl chloride to provide the

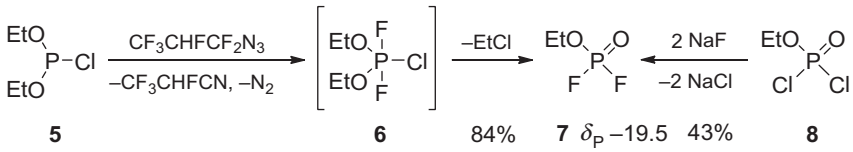


Figure 4.4.1

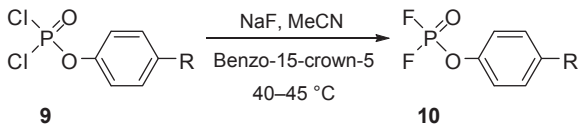
ethyl phosphorodifluoridate (**7**) (*32*). Alternatively, pentavalent phosphorus chemistry by reaction of ethyl phosphorodichloridate (**8**) with hot sodium fluoride provides the same product, although in lower yield (*33*). Alkyl phosphorodifluoridates are toxic and highly reactive (care must be taken to exclude moisture during storage as they hydrolyse quickly).

▶ *Ethyl phosphorodifluoridate EtOP(O)F_2 (trivalent route)* (*32*). Sodium azide (100 g, 1.54 mol) was placed into a three-necked flask (equipped with a mechanical stirrer, a gas inlet tube, and a Liebig condenser) and was suspended in anhydrous 2-methoxyethanol (1500 ml). The mixture was heated to 65 °C and a strong flow of perfluoropropene ($CF_3CF{=}CF_2$) was passed into the mixture. The crude 2-hydroperfluoropropyl azide was distilled off and purified by fractionation using a 50 cm Vigreux column and obtained as a colourless liquid (134 g, 45%; bp 51–53 °C). Diethyl phosphorochloridite (2.15 g, 13.7 mmol) was added dropwise to 2-hydroperfluoropropyl azide (2.65 g, 13.7 mmol) without solvent. The mixture was fractionated to provide ethyl phosphorodifluoridate (1.50 g, 84%). Bp 82–85 °C. δ_P ($CDCl_3$) −19.5 ppm (*t*, $^1J_{PF}$ 1008 Hz).

▶ *Ethyl phosphorodifluoridate EtOP(O)F_2 (pentavalent route)* (*33*). Sodium fluoride (84 g, 2.00 mol) was weighed into a 500 ml flask equipped with a dropping funnel, a sealed mechanical stirrer, and a large reflux condenser topped with a drying tube. The contents were heated under vacuum to expel traces of water and ethyl phosphorodichloridate (135 g, 0.85 mol) was then added to the hot sodium fluoride. Addition was carried out at a rate that maintained gentle refluxing. Finally, the mixture was refluxed for 30 min, and the product isolated by distillation. Redistillation of this product gave pure ethyl phosphorodifluoridate (46 g, 43%). Bp 84–85 °C. This highly reactive material was best preserved in sealed glass ampoules.

4.5 ARYL PHOSPHORODIFLUORIDATES ArOP(O)F_2

Aryl phosphorodichloridates (**9**) react with sodium fluoride and a catalytic amount of benzo-15-crown-5 in warm acetonitrile to provide aryl phosphorodifluoridates (**10**) in moderate yields (Fig. 4.5.1) (*34*).



Aryl phosphorodifluoridates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)
H	61	100/80	–28.3
Me	70	73–75/10	–26.9
MeO	68	103/10	–26.5
Cl	56	82/10	–26.9
NO_2 [a]	21	72–75/0.1	–27.5

a. Experiment performed at 25 °C

Figure 4.5.1

▶ *Aryl phosphorodifluoridates ArOP(O)F$_2$ (34)*. Powdered sodium fluoride (2.52 g, 60 mmol) was added in small portions via a powder funnel over 1 h to a stirred solution of the aryl phosphorodichloridate (30 mmol) and benzo-15-crown-5 (1.2 g, 4.5 mmol) in anhydrous acetonitrile (5 ml) heated to 40–45 °C. After addition was complete, the mixture was stirred at this temperature for a further 8 h. Anhydrous ether (30 ml) was added to the flask, which was topped with a calcium chloride guard tube and cooled to −15 °C. The precipitated solids were filtered off. Removal of the solvent and distillation of the residue gave the aryl phosphorodifluoridates listed in Fig. 4.5.1 as colourless liquids.

4.6 ALKYL *N,N,N′,N′*-TETRAALKYL PHOSPHORODIAMIDATES ROP(O)(NR$_2$)$_2$

These compounds can be prepared by treating alkyl phosphorodichloridates (**11a**) with 4 moles of a primary or secondary amine (Fig. 4.6.1, *Method A*). However, in some cases, the reaction may stop at the stage of the intermediate chloride R′O(R$_2$N)P(O)Cl, and in other instances, especially starting with methyl phosphorodichloridate, *O*-dealkylation may occur. The alternative procedure is to treat an *N,N,N′,N′*-tetraalkylphosphorodiamidic chloride (**11b**) with an alcohol in the presence of a base, or under more forcing conditions, with an alkali metal alkoxide (Fig. 4.6.1, *Method B*). Both routes can be used to convert 2,2,2-trifluoroethyl phosphorochloridate (**13a**) or *N,N,N′,N′*-tetramethylphosphorodiamidic chloride (**13b**) into the diamidate (**14**).

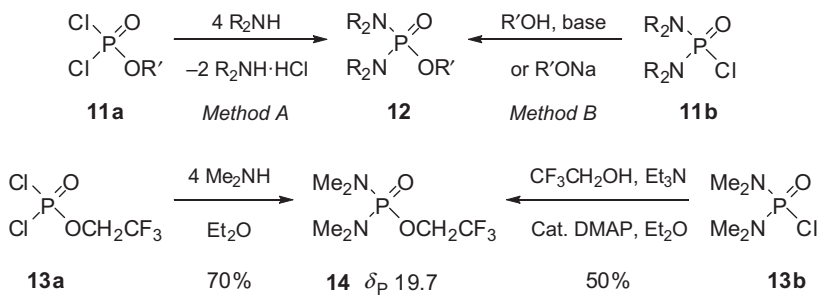


Figure 4.6.1

N,N,N′,N′-Tetraalkylphosphorodiamidic chlorides are fairly unreactive to nucleophilic substitution by virtue of two electron-donating amido groups which tend to make the phosphorus atom poorly electrophilic. One trick to overcome this problem is to add a catalytic amount of 4-(dimethylamino)pyridine (DMAP) (*5*). While the reaction between *N,N,N′,N′*-tetramethylphosphorodiamidic dichloride (**13b**) and fluoroalcohols in ether in the presence of triethylamine is slow, the rate is greatly accelerated by the addition of DMAP.

▶ *2,2,2-Trifluoroethyl N,N,N′,N′-tetramethylphosphorodiamidate (Me$_2$N)$_2$P(O)OCH$_2$CF$_3$* (**14**) *(from N,N,N′,N′-tetramethylphosphorodiamidic chloride)* (*5*). A solution of 2,2,2-trifluoroethanol (13.0 g, 0.13 mol) and triethylamine (13.1 g, 0.13 mol) in ether (50 ml) was added dropwise to a solution of

N,N,N′,N′-tetramethylphosphorodiamidic chloride (22.1 g, 0.13 mol) in ether (50 ml) cooled to 0–5 °C. After addition, the mixture was allowed to warm to room temperature and was heated under reflux for 2 h. Analysis by gas chromatography–mass spectrometry (GC–MS) showed that no reaction had occurred. DMAP (0.8 g, 6.5 mmol) was added and the mixture refluxed for another 26 h. Analysis by GC–MS showed 88% conversion to the product. The precipitate was filtered off and the filtrate concentrated. Fractionation of the residue gave the diamidate as a colourless liquid (15.2 g, 50%). Bp 45 °C/0.4 mmHg. δ_P (202 MHz, $CDCl_3$) 19.7 ppm.

▶ *2,2,2-Trifluoroethyl N,N,N′,N′-tetramethylphosphorodiamidate* $(Me_2N)_2P(O)OCH_2CF_3$ (**14**) *(from 2,2,2-trifluoroethyl phosphorodichloridate)* (*5*). A solution of dimethylamine (7.2 g, 0.16 mol) in anhydrous ether (10 ml) was added dropwise by cannula to a solution of 2,2,2-trifluoroethyl phosphorodichloridate (8.7 g, 0.04 mol) in anhydrous ether (15 ml) cooled to 0–5 °C. After addition, the mixture was allowed to warm to room temperature and was left for 5 days. Analysis by GC–MS showed 90% conversion to the desired product. The precipitate was filtered off and the filtrate concentrated and fractionated to give the diamidate (6.6 g, 70%). Bp 45 °C/0.4 mmHg. δ_P (202 MHz, $CDCl_3$) 19.7 ppm.

4.7 ALKYL PHOSPHORODIHYDRAZIDATES $ROP(O)(NHNHR)_2$

Alkyl phosphorodichloridates react readily with 4 molar equivalents of hydrazine or its substituted derivatives in an inert solvent to provide the alkyl phosphorodihydrazidates. This is illustrated for the conversion of *endo*-bicyclo[2.2.1]heptyl phosphorodichloridate (**2**) and phenylhydrazine to the corresponding phosphorodihydrazidate (**15**) (Fig. 4.7.1) (*7*). The chemistry of this product and related species has been described (*6,8*).

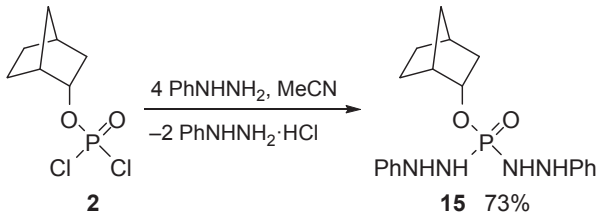
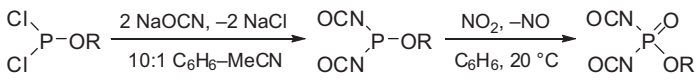


Figure 4.7.1

▶ *Endo-bicyclo[2.2.1]heptyl bis(2-N-phenyl)phosphorodihydrazidate* (**15**) (*7*). *Endo*-bicyclo[2.2.1]heptyl phosphorodichloridate (2.28 g, 10 mmol) was added dropwise to a stirred solution of phenylhydrazine (4.32 g, 40 mmol) in acetonitrile (25 ml) at 0–5 °C. After 10 h at 4 °C, the precipitate was filtered off and the solid was washed with water (500 ml) to remove phenylhydrazine hydrochloride. The remaining solid was stirred with water (150 ml), filtered and recrystallised from ethanol to give the title compound (2.7 g, 73%). Mp 170–172 °C.

4.8 ALKYL PHOSPHORODIISOCYANATIDATES $ROP(O)(NCO)_2$

Alkyl or aryl phosphorodichloridites (**16**) react readily with sodium cyanate in 10:1 benzene—acetone to give alkyl or aryl phosphorodiisocyanatidites (**17**) (Fig. 4.8.1) (*35*). The reaction proceeds with evolution of heat and is completed upon heating the mixture for 1—3 h. The diisocyanatidites are colourless, easily hydrolysed substances with a disagreeable odour. Treatment with nitrogen dioxide in benzene results in their oxidation to yield the alkyl or aryl phosphorodiisocyanatidates (**18**). These are colourless, easily hydrolysed liquids, or low-melting crystalline substances, that can be purified without decomposition by distillation under vacuum. The two-step method of preparation is preferable to the alternative one-step reaction of alkyl or aryl phosphorodichloridates with sodium cyanate that proceeds with difficulty. The two-step method gives a 78% yield of phenyl phosphorodiisocyanatidate, whereas boiling phenyl phosphorodichloridate with sodium cyanate for 10 h gives the same product in no more than 20% yield. Longer heating does not effect complete replacement of the chlorine atoms by the isocyanate group.



16 **17** **18**

	Alkyl phosphorodiisocyanatidites		Alkyl phosphorodiisocyanatidates	
R	Yield (%)	Bp (°C/mmHg)	Yield (%)	Bp (°C/mmHg)
Me	61	40–41/7	63	54–55/0.1
Et	60	64–65/22	77	59–60/0.5
n-Pr	60	75–76/14	81	57–58/0.1
i-Pr	62	54–55/10	65	47–48/0.1
n-Bu	53	80–82/19	70	61–62/0.1
Ph	65	60–61/0.07 [a]	78	87–88/0.15 [b]

a. Mp 17 °C. *b*. Mp 28 °C

Figure 4.8.1

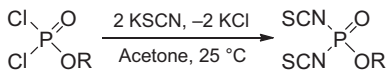
Alkyl or aryl phosphorodiisocyanatidates add 2 mol of an alcohol or aromatic amine to produce phosphorylated urethanes $ROP(O)(NHCO_2R')_2$ or ureas $ROP(O)(NHCONHAr)_2$, respectively (*35*). Infrared spectra of the phosphorodiisocyanatidates show an intense absorption band at 2260—2290/cm (NCO asymmetric stretching), a band at 1420—1450/cm (NCO symmetric stretching), and one around 600/cm (NCO deformation).

▶ *Alkyl or aryl phosphorodiisocyanatidites* $ROP(NCO)_2$ (**17**) (*35*). The alkyl or aryl phosphorodichloridite (70 mmol) was added to sodium cyanate (9.75 g, 150 mmol) in a 10:1 *v*/*v* mixture of anhydrous benzene and acetonitrile (550 ml) with vigorous stirring (heat evolution). The mixture was boiled for 1—3 h to complete the reaction. The precipitate of sodium chloride and excess sodium cyanate was removed, the solvent evaporated, and the residue fractionated to give the compounds shown in Fig. 4.8.1.

▶ *Alkyl or aryl phosphorodiisocyanatidates ROP(O)(NCO)$_2$* (**18**) (*35*). Nitrogen dioxide (23 g, 0.5 mol, dried over $CaCl_2$) in anhydrous benzene (50 ml) was added to a stirred solution of the alkyl or aryl phosphorodiisocyanatidate (0.5 mol) in anhydrous benzene (150 ml) at 5—10 °C. Alternatively, nitrogen dioxide was introduced until the mixture coloured yellow and the temperature ceased to rise. The mixture was allowed to stand for several hours, the solvent was removed, and the diisocyanatidate was distilled. Phenyl phosphorodiisocyanatidate crystallised on standing.

4.9 ALKYL PHOSPHORODIISOTHIOCYANATIDATES ROP(O)(NCS)$_2$

Treatment of alkyl phosphorodichloridates (**11a**) with 2 mol of potassium thiocyanate in acetone at room temperature provides alkyl phosphorodiisothiocyanatidates (**19**) as light-yellow mobile liquids (Fig. 4.9.1) (*36*). Selective attack of the nitrogen terminus of the ambident thiocyanate ion occurs: the chloridate contains a hard electrophilic phosphorus atom that prefers to react with the harder nitrogen centre instead of the soft sulfur terminus. Alkyl phosphorodiisothiocyanatidates are useful reagents and react with primary amines, for example, to yield phosphorylated thioureas of structure ROP(O)(NHCSNHR′)$_2$.



11a **19**

Alkyl phosphorodiisothiocyanatidates

R	Yield (%)	Bp (°C/mmHg)
Et	44	96–98/1.5
n-Pr	35	111–112/1
i-Pr	55	97–99/0.5
n-Bu	43	101–102/1

Figure 4.9.1

Acetone or other polar solvents such as acetonitrile dissolve alkali metal thiocyanates fairly readily and are the solvents of choice for exchange of P—Cl for P—NCS. Benzene or other non-polar solvents do not dissolve potassium thiocyanate, and reaction occurs very slowly in heterogeneous medium; sometimes the exchange occurs effectively without solvent, especially if the alkali metal thiocyanate dissolves in the alkyl phosphorodichloridate (*37*).

▶ *Alkyl phosphorodiisothiocyanatidates ROP(O)(NCS)$_2$* (**19**) (*36*). A solution of the alkyl phosphorodichloridate (1 mol) in acetone was added dropwise to a stirred solution of potassium thiocyanate (2 mol) in acetone. The mixture was stirred for 12 h at room temperature. The solids were filtered off. Removal of solvent from the filtrate and distillation under reduced pressure gave the products listed in Fig. 4.9.1.

4.10 ALKYL DIHYDROGEN PHOSPHATES ROP(O)(OH)$_2$

Alkyl dihydrogen phosphates can be prepared by phosphorylating an alcohol with dibenzyl phosphorochloridate or diphenyl phosphorochloridate (or a close analogue) in the presence of a base (e.g. pyridine), followed by catalytic hydrogenolysis of the benzyl or phenyl substituent. This approach has been used to furnish many alkyl dihydrogen phosphates for biological studies and two sequences are illustrated here. In the first, dibenzyl *H*-phosphonate (**20**) (*38*) is chlorinated with *N*-chlorosuccinimide to give dibenzyl phosphorochloridate (**21**) (*39*). This reagent is treated with cyclopropanemethanol in the presence of pyridine to give dibenzyl cyclopropylmethyl phosphate (**22**) (*40*). Catalytic hydrogenolysis using palladium on charcoal in ethanol provides the desired cyclopropylmethyl dihydrogen phosphate (**23**) (Fig. 4.10.1). This approach is often better than the alternative one of simple hydrolysis of alkyl (or aryl) phosphorodichloridates in neutral or alkaline aqueous media (*26*) from which it is often difficult to isolate the pure alkyl (or aryl) dihydrogen phosphates.

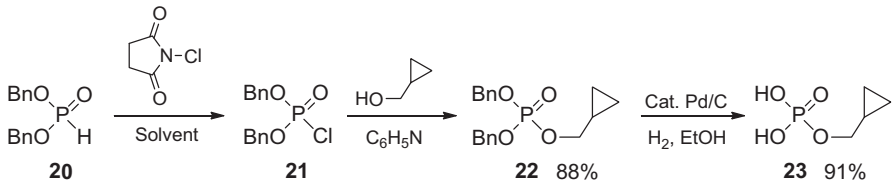


Figure 4.10.1

In the second example, di(2-*tert*-butylphenyl) phosphorochloridate treated with thymidine in pyridine solution provides the 5′-phosphate (*41*). Hydrogenolysis using platinum(IV) oxide (Adam's catalyst) in acetic acid, and neutralisation of the resulting alkyl dihydrogen phosphate with aqueous ammonia, gives thymidine 5′-phosphate ammonium salt (**24**) (Fig. 4.10.2). The same chemistry can be used to prepare other 5′-phosphates, for example, cytidine 5′-phosphate (**25**) or guanosine 5′-phosphate (**26**) ammonium salts.

Alkyl dihydrogen phosphates are strong acids that dissociate readily in water: the acid dissociation constant (pK_a) of MeOP(O)(OH)$_2$ is 1.54, and intermediate between that of phosphoric acid (HO)$_3$P═O (1.97) and dimethyl hydrogen phosphate (MeO)$_2$P(O)OH (1.25), when measured in water containing 7% *v*/*v* ethanol (*42*).

▷ *Dibenzyl cyclopropylmethyl phosphate (BnO)$_2$P(O)OCH$_2$—c—Pr* (**22**) (*40*). A solution of dibenzyl phosphorochloridate (19.6 g, 70 mmol) in anhydrous ether (75 ml) was added dropwise over 15 min to a stirred solution of cyclopropanemethanol (5.4 g, 75 mmol) and pyridine (5.93 g, 75 mmol) in ether (100 ml) at 0 °C. Pyridine hydrochloride precipitated immediately. After addition, the mixture was stirred at room temperature for 18 h. The precipitate was removed by filtration and the filtrate was evaporated to give the title compound (20.5 g, 88%). Attempted distillation at reduced pressure resulted in decomposition.

▷ *Cyclopropylmethyl dihydrogen phosphate (HO)$_2$P(O)OCH$_2$—c—Pr* (**23**) (*40*). A solution of dibenzyl cyclopropylmethyl phosphate (1.20 g, 3.6 mmol) was dissolved in absolute ethanol (30 ml) and 10%

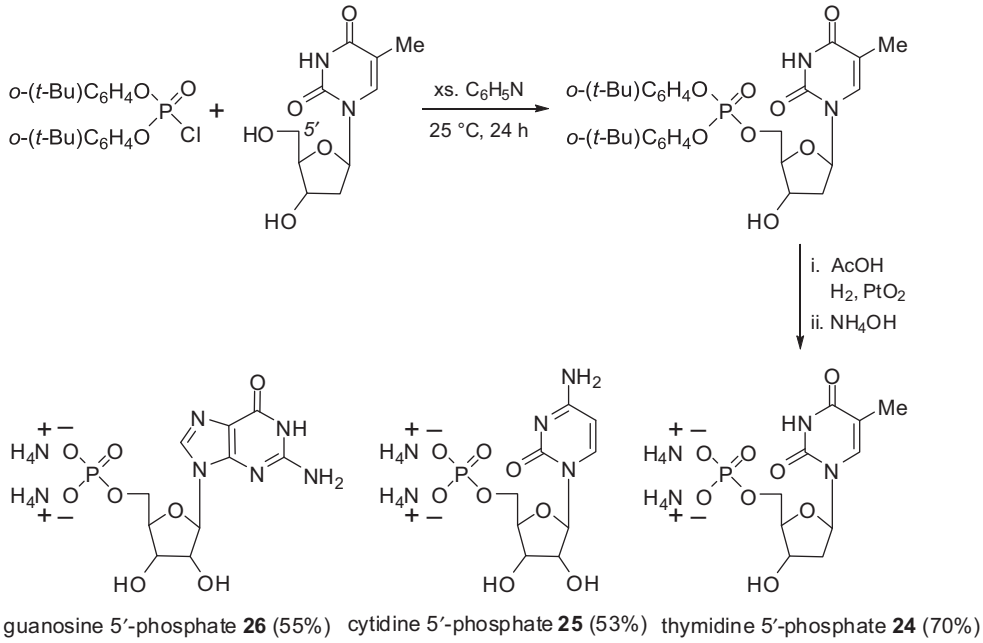


Figure 4.10.2

palladium on charcoal (0.5 g) was added. The mixture was hydrogenated for 30 min at 20–30 psi using a Parr hydrogenator. The catalyst was filtered off and the filtrate evaporated to afford the title compound as a liquid (0.50 g, 91%). Ethyl acetate can be used in place of ethanol. Once isolated, the product decomposes slowly at room temperature.

▷ *Thymidine 5′-phosphate ammonium salt* (**24**) (*41*). Thymidine (0.91 g, 3.75 mmol) was added to a stirred solution of di(2-*tert*-butylphenyl) phosphorochloridate (1.52 g, 4 mmol) in anhydrous pyridine (25 ml). The resulting mixture was stirred at room temperature for 24 h. The pyridine was removed under vacuum at 40 °C. The semisolid residue was dissolved in chloroform (70 ml), washed with water (30 ml) and then with saturated aqueous sodium bicarbonate (20 ml), and again with water (30 ml), and the chloroform layer was dried ($MgSO_4$). After evaporation, the residue (75% of theoretical) was dissolved in acetic acid (40 ml) and added to acetic acid (100 ml) containing prereduced platinum(IV) oxide (0.6 g). The mixture was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen was absorbed (8 mol equiv.). The catalyst was filtered and the solvent evaporated at 25 °C. The semisolid residue was washed several times with ether, dissolved in 2% aqueous ammonium hydroxide (30 ml), filtered, and freeze-dried to afford the product (70% yield).

▷ *Guanosine 5′-phosphate ammonium salt* (**26**) (*41*). Guanosine (240 mg, 0.85 mmol) was dissolved in anhydrous pyridine (20 ml) and anhydrous *N,N*-dimethylformamide (12 ml). The solution was acidified with acetic acid and cooled to 0 °C. Di(2-*tert*-butylphenyl) phosphorochloridate (380 mg, 1.00 mmol) was added and the mixture was stirred at 25 °C for 1 day. An identical work-up to that in

the previous procedure gave the title compound (55% yield). Adenosine 5′-phosphate and cytidine 5′-phosphate ammonium salts were prepared similarly in 62% and 53% yield, respectively.

4.11 *O,S,S′*-TRIALKYL PHOSPHORODITHIOLATES ROP(O)(SR)$_2$

Routes to these compounds focus on two reactions: an *S,S′*-dialkyl phosphorochloridodithiolate (**27**) reacting with 1 mol of an alcohol (*43*) or an alkyl phosphorodichloridate (**11a**) reacting with 2 mol of a thiol (*44*) in the presence of triethylamine (Fig. 4.11.1). In the latter case, the use of methyl phosphorodichloridate can be problematic as the methyl group is readily dealkylated by thiols. The rate of dealkylation of ethyl (and higher alkyl) phosphorodichloridates is much lower and these can be used without detriment to provide the *O,S,S′*-trialkyl phosphorodithiolate (**28**) in higher yield. Mixed *S,S′*-dialkyl phosphorochloridodithiolates give chiral species of structure RS(R′S)P(O)OR (*43*).

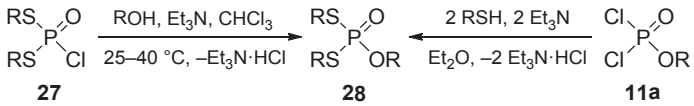


Figure 4.11.1

▶ *O,S,S′-Triethyl phosphorodithiolate (EtS)$_2$P(O)OEt* (*44*). Ethyl phosphorodichloridate (27 g, 0.17 mol) in anhydrous ether (50 ml) was added dropwise to a stirred solution of ethanethiol (20 g, 0.32 mol) and anhydrous triethylamine (50 ml, 0.36 mol) in anhydrous ether (100 ml). The mixture was boiled under reflux for 2 h and left at room temperature overnight. Evaporation of the filtered solution and distillation of the liquid residue gave the title compound (28 g, 77%). Bp 102—103 °C/0.3 mmHg.

4.12 *O,S*-DIALKYL PHOSPHOROCHLORIDOTHIOLATES RO(RS)P(O)Cl

Dialkyl phosphorochloridites react with alkylsulfenyl chlorides, prepared in situ from dialkyl disulfides and sulfuryl chloride, to provide *O,S*-dialkyl phosphorochloridothiolates (**29**) and (**30**) in acceptable yields (Fig. 4.12.1) (*45,46*).

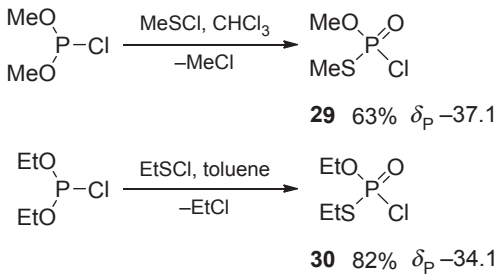


Figure 4.12.1

Many *O,O,S*-trisubstituted phosphorothiolates upon heating with phosphorus oxychloride yield *O,S*-disubstituted phosphorochloridothiolates and alkyl phosphorodichloridates (*47*). The progress of reaction is monitored by thin layer chromatography (TLC) as P—S compounds are usually visualised readily by iodine vapour. Advantage can be taken of the remarkable selectivity: the P—SR substituent is generally retained in the chloridate (e.g. **31** → **29** and **32** → **33**) (Fig. 4.12.2). Also, *O*-aryl groups are generally retained in preference to *O*-alkyl groups in the chloridate (e.g. **34** → **35**). The produced chloridate and dichloridate by-product usually have significantly different boiling points which permits their separation by vacuum fractionation. Alternatively the lower-boiling dichloridate can be removed by distillation under reduced pressure and the residue, the crude chloridate, isolated after column chromatography on silica gel. The original literature should be consulted for other examples of this versatile reaction (*47*). The *O,S*-disubstituted phosphorochloridothiolates react readily with amines to yield phosphoramidothiolates with insecticidal activity (*48*).

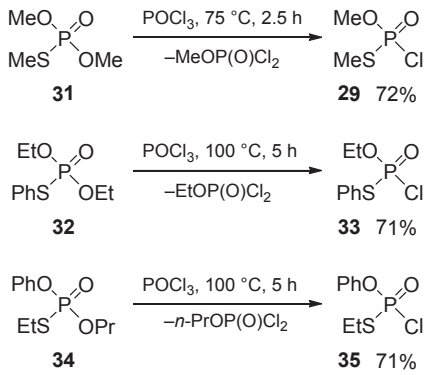


Figure 4.12.2

▶ *O,S-Dimethyl phosphorochloridothiolate MeO(MeS)P(O)Cl* (**29**) (*45*). Dimethyl phosphorochloridite (9.2 g, 72 mmol) in chloroform (10 ml) was added at −30 to −40 °C to methylsulfenyl chloride made from dimethyl disulfide (3.4 g, 36.2 mmol) and sulfuryl chloride (4.9 g, 36.2 mmol) in chloroform (30 ml). Vacuum distillation gave the crude product (7.3 g, 63%). Redistillation gave a 70% pure fraction. Bp 63—66 °C/3 mmHg. δ_P (neat) −37.1 ppm.

▶ *O,S-Diethyl phosphorochloridothiolate EtO(EtS)P(O)Cl* (**30**) (*45*). Diethyl phosphorochloridite (10.2 g, 65 mmol) in toluene (20 ml) was added at −30 to −40 °C to ethylsulfenyl chloride prepared from diethyl disulfide (4.0 g, 33 mmol) and sulfuryl chloride (4.4 g, 33 mmol) in toluene (20 ml). After evaporating the volatile products and solvent, the residue was distilled twice through a short Vigreux column to give the title compound (10.1 g, 82%). Bp 78 °C/1.5 mmHg (lit. 98—99 °C/7—8 mmHg) (*46*). δ_P (neat) −34.1 ppm.

▶ *O-Alkyl(aryl) S-alkyl(aryl) phosphorochloridothiolates RO(R′S)P(O)Cl* (*47*). A stirred equimolar mixture of the *O,O,S*-trisubstituted phosphorothiolate and phosphorus oxychloride was heated to

65–100 °C for 2.5–11 h until the thiolate disappeared from the mixture (as determined by TLC, eluting with 5:1 petroleum ether–ethyl acetate, with iodine vapour as the visualisation reagent). After the reaction was complete, the alkyl phosphorodichloridate by-product was removed by distillation under reduced pressure. The desired chloridate that remained was purified by column chromatography on silica gel, eluting with a gradient of petroleum ether–ethyl acetate.

4.13 *O*-ALKYL *N,N*-DIALKYLPHOSPHORAMIDOCHLORIDATES $RO(R_2N)P(O)Cl$

These compounds are best obtained by the reaction of an alkyl phosphorodichloridate with 2 mol of a primary or secondary amine, or 1 mol of the amine nucleophile and 1 mol of triethylamine or pyridine, in an inert solvent. The cyclic amidochloridate (**36**) is derived from phosphorus oxychloride and *N*-methylethanolamine (*49*) while the acyclic analogues (**37**,**38**) are prepared from ethyl phosphorodichloridate and dimethylamine and diethylamine (*16*), respectively (Fig. 4.13.1). Moderately electron-deficient amines, such as *bis*(2-chloroethyl)amine, react similarly to give the expected products (*50*).

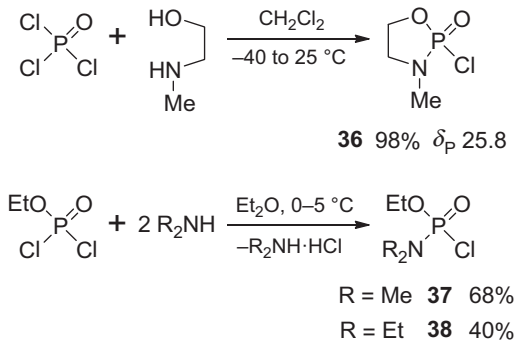


Figure 4.13.1

The preparation of *O*-methyl *N*-cyclohexylphosphoramidochloridate (**39**) and *O*-methyl *N*-morpholinophosphoramidochloridate (**40**) uses the same approach (Fig. 4.13.2) (*51*). *O,S*-Dialkyl *N,N*-dialkylphosphoramidothiolates, e.g. $MeO(Me_2N)P(O)SMe$, also provide *O*-alkyl

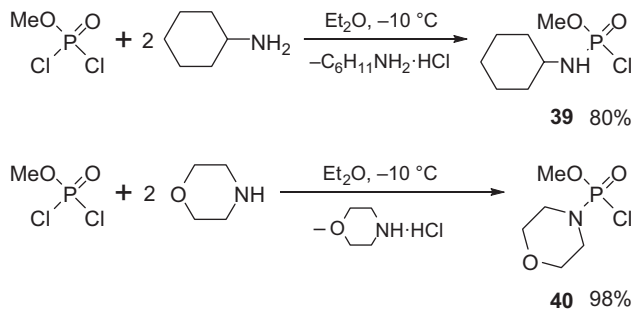


Figure 4.13.2

N,N-dialkylphosphoramidochloridates, e.g. $MeO(Me_2N)P(O)Cl$ (71%; bp 85 °C/9 mmHg), on treatment with sulfuryl chloride in benzene (*52*). *O*-Aryl *N,N*-dialkylphosphoramidochloridates of structure $ArO(Me_2N)P(O)Cl$ can be prepared by reaction of phenols with hexamethylphosphoramide $(Me_2N)_3P{=}O$ (HMPA) and hydrogen chloride (*53*).

▶ *2-Chloro-1-methyl-1,3,2-oxazaphosphacyclopentane-2-oxide* (**36**) (*49*). A solution of anhydrous *N*-methylethanolamine (0.23 g, 3.1 mmol) and triethylamine (0.9 ml, 6.5 mmol) in dichloromethane (50 ml) was added dropwise to stirred dichloromethane (100 ml) at −60 °C under nitrogen. Separately, but simultaneously, a solution of phosphorus oxychloride (0.47 g, 3.1 mmol) in dichloromethane (50 ml) was added dropwise. After addition, the reaction mixture was warmed to room temperature and stirred for 17 h. The solvent was removed and the residue extracted with ether (100 ml). The extract was filtered and the filtrate concentrated to yield a colourless liquid (0.47 g, 98%). δ_P ($CDCl_3$) 25.8 ppm.

▶ *O-Ethyl N,N-dimethylphosphoramidochloridate EtO(Me₂N)P(O)Cl* (**37**) (*16*). A solution of dimethylamine (90 g, 2 mol) in anhydrous ether (1000 ml) was added dropwise to a stirred solution of ethyl phosphorodichloridate (163 g, 1 mol) in anhydrous ether (3000 ml) at 0–5 °C over 2 h. After addition, the mixture was allowed to stand for 12 h. The precipitate of dimethylamine hydrochloride was removed by filtration and the filtrate concentrated by rotary evaporation. Vacuum distillation of the residue gave the title compound as a colourless fruity smelling liquid (116 g, 68%). Bp 70–74 °C/4–6 mmHg. It is soluble in most organic solvents and slightly soluble in water, hydrolysing slowly to the corresponding acid. It is also thermally unstable when heated. At 145 °C, a gas evolves and continues to be evolved up to 200 °C, whereupon the residue solidifies. The gas, which burns with a yellow-green flame, is ethyl chloride. These analogues were prepared similarly: *n*-$PrO(Me_2N)P(O)Cl$ (72%, bp 73 °C/2 mmHg) and *n*-$BuO(Me_2N)P(O)Cl$ (69%, bp 82–84 °C/1 mmHg) (*54*).

▶ *O-Ethyl N,N-diethylphosphoramidochloridate EtO(Et₂N)P(O)Cl* (**38**) (*16*). A solution of diethylamine (146 g, 2.00 mol) in anhydrous ether (450 ml) was added dropwise to a stirred solution of ethyl phosphorodichloridate (163 g, 1.00 mol) in anhydrous ether (850 ml) at −15 °C over 2 h. After addition, the mixture was allowed to stand for 12 h. The precipitate of diethylamine hydrochloride was filtered off and the filtrate rotary evaporated. Vacuum distillation of the residue gave the title compound as a colourless liquid with a strong aromatic smell (80 g, 40%). Bp 109–114 °C/17–18 mmHg. It is soluble in organic solvents but only very slightly soluble in water, hydrolysing slowly to the corresponding acid. On heating, it decomposes at 150 °C to form $Et_2NP({=}O)_2$ with elimination of ethyl chloride. *O-n*-Butyl *N,N*-diethylphosphoramidochloridate *n*-$BuO(Et_2N)P(O)Cl$ (bp 96 °C/1.3 mmHg) was prepared analogously (*54*).

▶ *O-Methyl N-cyclohexylphosphoramidochloridate* (**39**) (*51*). A solution of cyclohexylamine (4.0 g, 40 mmol) in anhydrous ether (50 ml) was added dropwise to a stirred solution of methyl phosphorodichloridate (3.0 g, 20 mmol) in anhydrous ether (100 ml) at −10 °C. After 2 h, the precipitated cyclohexylamine hydrochloride was filtered off and the filtrate was evaporated to give an oil (4.2 g). This was dissolved in petroleum ether (bp 40–60 °C) and, upon being cooled, deposited the crystalline product (3.4 g, 80%). Mp 49–52 °C. Recrystallisation gave crystals melting at 52–53 °C.

▶ *O-Methyl N-morpholinophosphoramidochloridate* (**40**) (*51*). This was prepared similarly from methyl phosphorodichloridate (7.5 g, 50 mmol) and morpholine (8.7 g, 100 mmol), the mixture being left for 1 h at room temperature after completion of the addition. The final liquid (9.8 g, 98%) was distilled under reduced pressure to give a main fraction boiling at 80–85 °C/0.01 mmHg.

4.14 *S*-ALKYL *N,N*-DIALKYLPHOSPHORAMIDOCHLORIDOTHIOLATES $RS(R_2N)P(O)Cl$

O,S-Dialkyl *N,N*-dialkylphosphoramidothiolates react with phosphorus oxychloride upon heating to provide *S*-alkyl *N,N*-dialkylphosphoramidochloridothiolates in reasonable yield (Fig. 4.14.1) (*47*). The *O*-alkyl group is removed preferentially to the *N,N*-dialkyl or *S*-alkyl group to provide the alkyl phosphorodichloridate as a by-product (e.g. **41** → **42** and **43** → **44**). The produced chloridate and dichloridate by-product usually have significantly different boiling points which permits their separation by vacuum fractionation. Alternatively the lower boiling dichloridate can be removed by distillation under reduced pressure and the residue, the crude chloridate, isolated by column chromatography on silica gel.

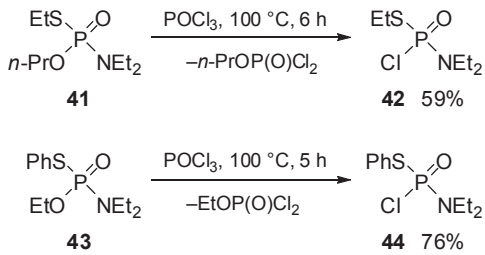
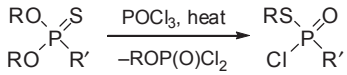


Figure 4.14.1

O,O-Dialkyl *N,N*-dialkylphosphoramidothionates (**45**) also react upon heating with phosphorus oxychloride to provide *S*-alkyl *N,N*-dialkylphosphoramidochloridothiolates (**46**) in isolated yields of typically around 50% (Fig. 4.14.2) (*55,56*). An *O*-alkyl group is usually removed preferentially to the *N,N*-dialkyl group and isomerisation of P═S to P–S occurs. The amidochloridothiolates are sufficiently insensitive to hydrolysis to enable purification by chromatography on silica gel. The same reaction scheme starting with amidothionates where R′ is NH_2 or NH-alkyl gives a complex mixture of products from which the desired amidochloridothiolates cannot be isolated easily.

▶ *S-Alkyl N,N-dialkylphosphoramidochloridothiolates* $R_2N(R'S)P(O)Cl$ (*47*). A stirred equimolar mixture of the *O,S*-dialkyl *N,N*-dialkylphosphoramidothiolate and phosphorus oxychloride was heated to 100 °C for 5–6 h until the thiolate disappeared from the reaction mixture (TLC eluting with 5:1 petroleum ether–ethyl acetate, with iodine vapour for visualisation). After the reaction was complete, the alkyl phosphorodichloridate by-product was removed by distillation under reduced pressure. The desired chloridate was purified by column chromatography on silica gel, eluting with petroleum ether–ethyl acetate.



45 **46**

N,N-Dialkyl *S*-alkyl phosphoramidochloridothiolates

R	R′	T (°C)	Time (h)	Yield (%)
Me		60	6.5	68
Me		60	12.5	84
Me		60	18.0	64
Et		100	60.0	79
Me	NEt_2	60	4.0	nd
Et	NEt_2	100	6.5	nd
n-Pr	NEt_2	100	10.0	52
n-Bu	NEt_2	100	15.0	nd

nd = not determined

Figure 4.14.2

▶ *S-n-Propyl N,N-diethylphosphoramidochloridothiolate* $Et_2N(n\text{-}PrS)P(O)Cl$ (*55*). A stirred mixture of *O,O*-di-*n*-propyl *N,N*-diethylphosphoramidothionate (18.6 g, 74 mmol) and phosphorus oxychloride (11.3 g, 74 mmol) was heated at 100 °C for 10 h, until the complete disappearance of the thionate was indicated by TLC (eluting with 10:1 petroleum ether—ether and visualising with iodine vapour). The by-product *n*-propyl phosphorodichloridate was removed under vacuum (1 mmHg) at 100 °C (oil bath). Column chromatography of the residue on silica gel (200—300 mesh), eluting with 10:1 petroleum ether—ethyl acetate, gave the title compound (8.8 g, 52%). Bp 86—88 °C/0.3 mmHg.

4.15 *S,S′*-DIALKYL PHOSPHOROCHLORIDODITHIOLATES $(RS)_2P(O)Cl$

O,S,S′-Trialkyl phosphorodithiolates react upon heating with phosphorus oxychloride to provide the *S,S′*-dialkyl phosphorochloridodithiolates in acceptable yield (Fig. 4.15.1) (*47*). The *O*-alkyl group is removed in preference to the *S*-alkyl groups to provide the alkyl phosphorodichloridate as a by-product (e.g. **47** → **48** and **49** → **50**). The produced chloridate and dichloridate by-product often have significantly different boiling points which permit their separation by vacuum fractionation. Alternatively the lower boiling dichloridate can be removed by distillation under reduced pressure and the residue, the crude chloridate, isolated after column chromatography on silica gel.

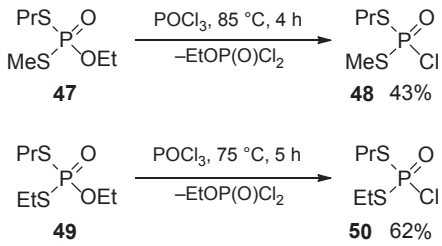
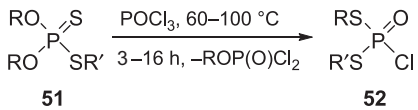


Figure 4.15.1

Chlorination of *O,O,S*-trialkyl phosphorothiolothionates (**51**) with a molar equivalent of phosphorus oxychloride at 60–100 °C can provide both symmetrical and mixed *S,S′*-dialkyl phosphorochloridodithiolates (**52**) (Fig. 4.15.2) (*43*). It takes 3–16 h for complete conversion as indicated by periodic TLC of the reaction mixture. The reaction time increases as the number of carbon atoms in the R group increases. The desired products cannot be obtained pure because of side reactions when R equals a branched alkyl (e.g. isopropyl or isobutyl) or a linear alkyl group with more than four carbon atoms.



S,S′-dialkyl phosphorochloridodithiolates

R	R′	Temp. (°C)	Time (h)
Me	Me	60	3.0
Me	*n*-Pr	60	4.0
Et	Et	100	5.5
Et	*n*-Bu	100	5.5
Et	Bn	80	16.0
Et	Ph	70	7.0
n-Pr	*n*-Pr	100	7.0
n-Bu	*n*-Bu	100	7.5

Figure 4.15.2

▶ *S,S′-Diethyl phosphorochloridodithiolate* $(EtS)_2P(O)Cl$ (*57*). A solution of ethanethiol (124 g, 2 mol) and pyridine (158 g, 2 mol) in benzene (200 ml) was added to a stirred solution of phosphorus oxychloride (154 g, 1 mol) in benzene (700 ml) while keeping the temperature below 20 °C with external cooling. After stirring for 3 h, the pyridine hydrochloride was filtered off and washed twice with anhydrous benzene. The filtrate and washings were combined and distilled through a 35 cm

vacuum-jacketed column packed with glass helices to give the title compound (49 g, 24%). Bp 145–150 °C/22 mmHg. *Caution!* This material is a mild vesicant.

▶ *S,S′-Dialkyl phosphorochloridodithiolates (RS)$_2$P(O)Cl* (*47*). A stirred equimolar mixture of the *O,O,S*-trialkyl phosphorothiolothionate and phosphorus oxychloride was heated to 65–100 °C for 3–16 h until the thiolothionate disappeared from the reaction mixture (TLC analysis eluting with 5:1 petroleum ether–ethyl acetate, with iodine vapour for visualisation). After the reaction was complete, the alkyl phosphorodichloridate by-product was removed by distillation under reduced pressure. The desired chloridate was purified by column chromatography on silica gel by eluting with petroleum ether–ethyl acetate.

4.16 *O,S*-DIALKYL PHOSPHOROFLUORIDOTHIOLATES RO(RS)P(O)F

Dialkyl phosphorofluoridites react with alkylsulfenyl chlorides, prepared in situ from dialkyl disulfides and sulfuryl chloride, to provide *O,S*-dialkyl phosphorofluoridothiolates in acceptable yields (*46*). The synthesis of *O,S*-diethyl phosphorofluoridothiolate (**53**) is a good example (Fig. 4.16.1).

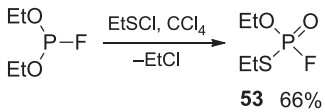


Figure 4.16.1

▶ *O,S-Diethyl phosphorofluoridothiolate EtO(EtS)P(O)F* (**53**) (*46*). A vigorously stirred equimolar mixture of diethyl phosphorochloridite and finely divided antimony trifluoride was heated at 60 °C for 15 min. Diethyl phosphorofluoridite was distilled from the reaction mixture and fractionated to give a pure sample (62%; bp 101–102 °C). A solution of ethylsulfenyl chloride (0.1 mol) prepared at −30 to −40 °C from diethyl disulfide (6.10 g, 0.05 mol) and sulfuryl chloride (6.8 g, 0.05 mol) in anhydrous carbon tetrachloride (30 ml) was then added slowly to a stirred solution of diethyl phosphorofluoridite (14.0 g, 0.10 mol) in the same solvent (30 ml). The reaction occurred with vigorous evolution of heat. When the addition was complete, the solvent was removed and the residue was fractionated to provide the title compound (11.4 g, 66%). Bp 71 °C/6 mmHg.

4.17 *O*-ALKYL *N,N*-DIALKYLPHOSPHORAMIDOFLUORIDATES RO(R$_2$N)P(O)F

The reaction of the nerve agent tabun with potassium hydrogenfluoride leads to substitution of the cyanide group and formation of the corresponding fluoridate (**54**) with production of potassium fluoride and hydrogen cyanide (Fig. 4.17.1) (*58*). This reaction provides an easy preparation of *O*-alkyl *N,N*-dialkylphosphoramidofluoridates in laboratories licensed and equipped to handle safely the nerve agent starting material. The fluoridate (**54**) is less toxic than the starting cyanidate.

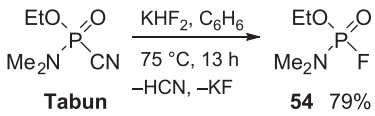


Figure 4.17.1

▶ *O-Ethyl N,N-dimethylphosphoramidofluoridate EtO(Me$_2$N)P(O)F* (**54**) (*58*). A solution of tabun (81 g, 0.5 mol) (*Caution! Neurotoxic*) in benzene (100 ml) was added to a suspension of potassium hydrogenfluoride (120 g, 1.5 mol) in benzene (400 ml) whilst stirring at 70–75 °C for 1 h. The reaction product was kept at 75 °C for 12 h. Removal of the salt and fractionation gave the title compound as a water-soluble colourless liquid (61 g, 79%). Bp 71 °C/14 mmHg. Tabun analogues can be fluorinated in the same way to provide MeO(Me$_2$N)P(O)F (bp 63 °C/14 mmHg), *n*- or *i*-PrO(Me$_2$N)P(O)F (bp 61 °C/4 mmHg or 50 °C/2 mmHg), *n*-, *i*- or *s*-BuO(Me$_2$N)P(O)F (bp 66 °C/3 mmHg, 64 °C/3 mmHg or 62 °C/4 mmHg), ClCH$_2$CH$_2$O(Me$_2$N)P(O)F (bp 69 °C/3 mmHg), EtO(EtMeN)P(O)F (bp 65 °C/4 mmHg), and EtO(Et$_2$N)P(O)F (bp 84 °C/3 mmHg).

4.18 SYMMETRICAL DIALKYL *H*-PHOSPHONATES (RO)$_2$P(O)H

Although these compounds are referred to in the literature as dialkyl phosphites (**A**), they have the phosphonate structure (**B**) (Fig. 4.18.1) and are more accurately named dialkyl *H*-phosphonates. The phosphonate structure is indicated by their infrared absorption spectra which are dissimilar to those of the neutral phosphite esters, but similar to those of the pentavalent alkylphosphonates, in that they contain a typical P═O frequency. Their chemical behaviour further supports their pentavalent structure (*59*).

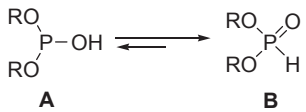
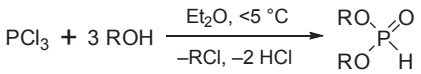


Figure 4.18.1

Treatment of phosphorus trichloride with 3 molar equiv. of an alcohol in the absence of a tertiary base provides a general route to dialkyl *H*-phosphonates (Fig. 4.18.2) (*27,60–68*). The transformation can be performed in an inert solvent (e.g. alkane, ether or chlorinated hydrocarbon) or neat. The by-product hydrogen chloride tends to react with the dialkyl *H*-phosphonate to form phosphorous acid and additional alkyl chloride: $(RO)_2P(O)H + 2\ HCl \rightarrow H_3PO_3 + 2\ RCl$. Various practices minimise the likelihood of this secondary reaction and include removing the hydrogen chloride rapidly by applying a vacuum or bubbling an inert gas through the mixture, or better still, introducing ammonia to neutralise it and precipitate ammonium chloride, which is easily removed by filtration. Bases other than ammonia, such as pyridine, can also be used. The preparation of diethyl *H*-phosphonate using refluxing hexane to remove the hydrogen chloride is also effective (*69*).

Only two-thirds of the alcohol used is incorporated into the dialkyl *H*-phosphonate, while the liberated alkyl halide serves as a coolant and diluent. The free hydrogen chloride evolved in the



Dialkyl *H*-phosphonates

R	Yield (%)	Bp (°C/mmHg)	R	Yield (%)	Bp (°C/mmHg)
Me	68	40/4	*i*-$PrCH_2CH_2$	85	75/0.2
Et	73	48/12.5	*i*-$PrCH_2CH(Me)$	89	81/0.2
n-Pr	72	59.5/1.5	Et_2CH	75	72/0.2
i-Pr	89	79/14	$ClCH_2CH_2$ [b]	72	129/0.6
n-Bu	52	94/3.5	$MeOCH_2CH_2$ [a,c]	60	125–128/1
i-Bu	82	87.5/4	$EtOCH_2CH_2$ [a,d]	57	132–134/3
s-Bu	70	111/15	*n*-$BuOCH_2CH_2$ [a,e]	35	158–161/3
n-C_5H_{11}	75	102–105/1.5–2	*n*-C_5H_{11} [a,f]	78	70–71/3

a. Reaction performed without solvent. δ_P shifts ($CDCl_3$): *b*. 8.3, *c*. 7.2, *d*. 5.4, *e*. 7.0, *f*. 4.0 ppm

Figure 4.18.2

reaction dealkylates the trialkyl phosphite formed, probably through a modified Arbuzov reaction (Fig. 4.18.3) (*70*). The use of 3 mol of [^{18}O]-ethanol gives the triply labelled diethyl *H*-phosphonate, $(Et^{18}O)_2P(^{18}O)H$ (*71*). The mechanism is supported by the reaction of trialkyl phosphites with hydrochloric acid, which also yields the dialkyl *H*-phosphonate and alkyl chloride. Treatment of phosphorus trichloride (1 mol) with deuterated alcohols (3 mol) in dichloromethane provides a convenient method of preparation of several species, e.g. $(CD_3O)_2P(O)H$ and $(CH_3CD_2O)_2P(O)H$, that are useful for reaction mechanism research (*72*).

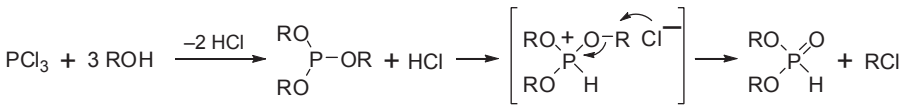
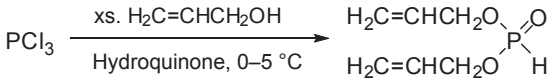


Figure 4.18.3

During the preparation of diallyl *H*-phosphonate (**55**) from allyl alcohol and phosphorus trichloride (Fig. 4.18.4) (*73*), the hydrogen chloride evolved can aid polymerisation of the product and must be removed as much as possible while keeping the temperature low. To achieve this, solid carbon dioxide can be added to the reaction mixture: the gaseous carbon dioxide evolved removes the

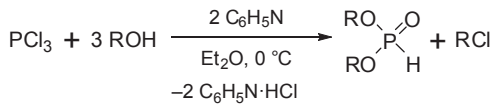


55 66% δ_P 8.2

Figure 4.18.4

hydrogen chloride as it forms. This trick may be used for preparing many dialkyl *H*-phosphonates as long as they are not too moisture sensitive.

Higher yields of dialkyl *H*-phosphonates can be obtained by neutralising the hydrogen chloride formed in such reactions by using 2 mol of pyridine in ether at the outset (Fig. 4.18.5) (*68*). Pyridine hydrochloride precipitates while the third mole of hydrogen chloride causes dealkylation.



Dialkyl *H*-phosphonates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)
n-Pr	99	undistilled	7.9 [a]
i-Pr	99	undistilled	7.3
i-Bu	95	undistilled	8.0
cyclohexyl	94	120–130/0.02	4.5
$MeOCH_2CH_2$	81	85/0.02	9.2

a. Measured in $CDCl_3$ at 101.3 MHz (others at 121.5 MHz)

Figure 4.18.5

Di-*tert*-butyl *H*-phosphonate (**56**) undergoes dealkylation under acidic conditions and is prepared satisfactorily from phosphorus trichloride, 3 mol of *tert*-butanol and 3 mol of pyridine, to trap the liberated hydrogen chloride (*74*,*75*), or by heating tri-*tert*-butyl phosphite under vacuum, which results in elimination of isobutene (Fig. 4.18.6) (*76*).

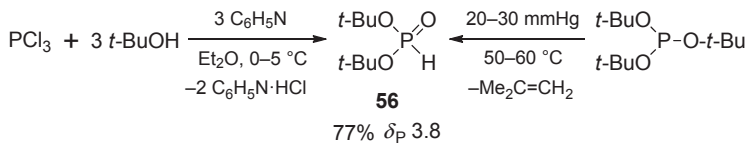


Figure 4.18.6

Dibenzyl *H*-phosphonate (**20**) is a liquid reagent useful for synthesising biological phosphates; such derivatives can be debenzylated by catalytic hydrogenation (Section 4.10) (*38*,*77*). The reagent is easily prepared from phosphorus trichloride and 3 mol of benzyl alcohol in the presence of 2 mol of *N*,*N*-dimethylaniline (Fig. 4.18.7). The mole of hydrogen chloride generated cleaves the intermediate $(BnO)_3P$ to give the product and benzyl chloride. Dibenzyl *H*-phosphonate decomposes upon heating and must be distilled with considerable care.

Dineopentyl *H*-phosphonate (**57**) cannot be prepared similarly from phosphorus trichloride and 3 mol of neopentyl alcohol as substitution does not proceed beyond addition of two ester groups due

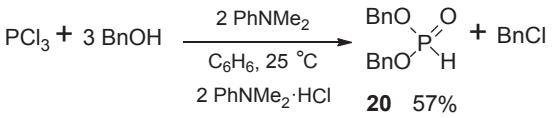


Figure 4.18.7

to their steric bulk. In this case, the controlled hydrolysis of the intermediate dineopentyl phosphorochloridite furnishes the desired product (Fig. 4.18.8) (*78*).

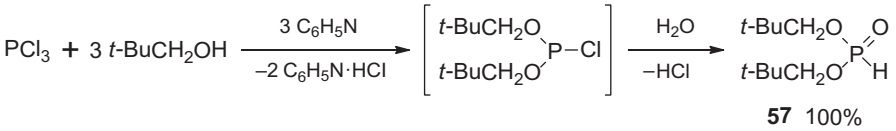


Figure 4.18.8

Bis(*p*-substituted benzyl) *H*-phosphonates are solid phosphorylating reagents that find application in the synthesis of biological phosphates (*79*). They are easily prepared by treating phosphorus trichloride with 2 mol of the *p*-substituted benzyl alcohol and 2 mol of *N*,*N*-dimethylaniline (Fig. 4.18.9). Hydrolysis of the intermediate diaryl phosphorochloridites (**58**) precipitates the *bis*(*p*-substituted benzyl) *H*-phosphonates (**59**–**61**) from solution.

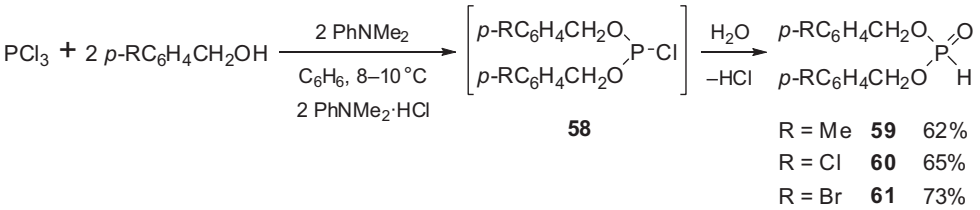


Figure 4.18.9

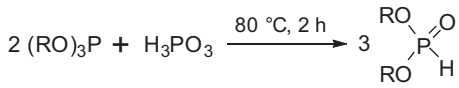
Addition of 3 mol of an alcohol to 1 mol of phosphorus trichloride sometimes provides an intermediate that the HCl liberated in the reaction cannot dealkylate. The difficulty forming compound (**62**) from an excess of 2,2-dimethyl-1,3-propanediol and phosphorus trichloride might result from the methyl groups blocking dealkylation (*80*). To overcome this, 2,2-dimethyl-1,3-propanediol, phosphorus trichloride, and a less hindered alcohol such as ethanol, can be employed to give the cyclic *H*-phosphonate (Fig. 4.18.10).

The action of phosphorus trichloride on 3 mol of an alcohol in the absence of a base to provide dialkyl *H*-phosphonates can fail in the case of alcohols substituted by strong electronegative groups, e.g. 2-nitroalcohols, 2-cyanoalcohols, 2,2,2-trichloro- or 2,2,2-trifluoroethanol. The trialkyl phosphites generated resist dealkylation by the hydrogen chloride formed. In such cases, treatment of the

R = ethyl, isobutyl, 2-ethyl-1-hexyl **62** 62–75%

Figure 4.18.10

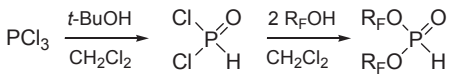
tertiary phosphite with phosphorous acid provides a satisfactory method of preparation of the target compounds, for example, *bis*(2-chloroethyl) *H*-phosphonate (**63**) and *bis*(2-chloropropyl) *H*-phosphonate (**64**) (Fig. 4.18.11) (*81*).



R = $ClCH_2CH_2$ **63** 92%
R = $CH_3CHClCH_2$ **64** 98%

Figure 4.18.11

Phosphorus trichloride reacts with a mole of *tert*-butanol to provide an intermediate that is able to undergo double nucleophilic substitution by 2 mol of a fluoroalcohol to provide the *bis*(fluoroalkyl) *H*-phosphonate (Fig. 4.18.12) (*82*). The lower *bis*(fluoroalkyl) *H*-phosphonates are colourless mobile



Bis(fluoroalkyl) *H*-phosphonates

R_F	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
HCF_2CH_2	42	79/1	7.6
$H(CF_2)_2CH_2$	77	119/0.06	7.4
$H(CF_2)_4CH_2$	59	104/0.1	7.3
CF_3CH_2	89	62/10	7.0
$C_2F_5CH_2$	74	76/10	7.2
$C_3F_7CH_2$	68	69/2	7.3
$(CF_3)_2CH$	71	62/8	7.9
$(FCH_2)_2CH$	86	116/1	6.7
$CF_3(CH_3)_2C$	55	71/10	–3.6
$(CF_3)_2CH_3C$	57	41/10	–4.1
$CF_3CH_2CH_2$	58	67/0.04	6.3
$C_4F_9CH_2CH_2$	73	42/5	6.3
$C_6F_{13}CH_2CH_2$	74	136/0.02	6.4

a. Recorded at 202 MHz in $CDCl_3$

Figure 4.18.12

liquids that are easily purified by distillation under reduced pressure. Like their unfluorinated analogues, they have the P(O)H structure. A doublet is observed in the ^{1}H NMR spectrum for the phosphorus-bonded hydrogen atom; the J_{PH} coupling constant is between 714 and 795 Hz. Phosphorus chemical shifts are between −3.6 and 7.9 ppm. Strong stretching vibrations for the P═O bond in the infrared spectra occur at 1288−1221/cm. Reactions of *bis*(fluoroalkyl) *H*-phosphonates are similar to those of non-fluorinated dialkyl *H*-phosphonates and are determined by the stereoelectronic effects of the fluoroalkyl groups (*83*).

Tris(dimethylamino)phosphine can be used as a starting material for accessing acid-sensitive dialkyl *H*-phosphonates such as dineopentyl *H*-phosphonate (**57**) (Fig. 4.18.13) (*68*). Addition of water and then 2 mol of neopentyl alcohol (2,2-dimethyl-1-propanol) to the phosphine reagent results in formation of the dineopentyl *H*-phosphonate with loss of 3 mol of dimethylamine. An attraction of this method is that the solution remains basic throughout the experiment.

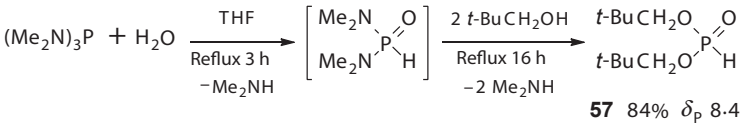


Figure 4.18.13

Dialkyl *H*-phosphonates, such as di-*n*-octyl *H*-phosphonate, can be produced by the usual method of allowing phosphorus trichloride (1 mol) to react with *n*-octanol (3 mol). This method has several disadvantages: first, about one-third of the octanol is converted to 1-chlorooctane; and, second, the removal of phosphorous acid, formed incidentally, requires several steps. The preferred process involves ester exchange in which a light alkyl or aryl group is replaced by a heavier alkyl or aryl group. Thus, transesterification of diethyl *H*-phosphonate (1 mol) with *n*-octanol (2 mol) proceeds smoothly upon heating (*69*) and provides di-*n*-octyl *H*-phosphonate (**65**) in excellent yield (Fig. 4.18.14). The process is driven in the desired direction by distillation of the more volatile departing alcohol from the reaction mixture. The method may be applied with slight modification to the preparation of other dialkyl *H*-phosphonates whose boiling points are too high to permit their purification by distillation. Dialkyl *H*-phosphonates can also be prepared cleanly by

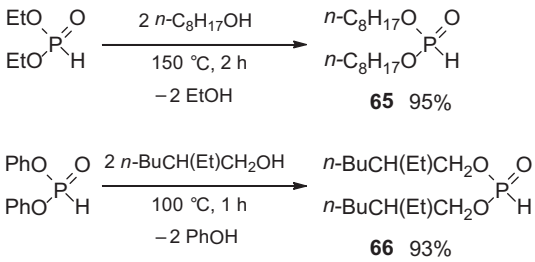


Figure 4.18.14

transesterification of diaryl *H*-phosphonates with aliphatic alcohols. Treatment of diphenyl *H*-phosphonate with 2-ethylhexanol at elevated temperature, followed by distillation, provides *bis*(2-ethylhexyl) *H*-phosphonate (**66**) in excellent yield (*81*).

The lower dialkyl *H*-phosphonates, such as diethyl *H*-phosphonate, are miscible with most organic solvents and are hydrolysed by water or moist air, forming phosphorous acid and the alcohol. The higher dialkyl *H*-phosphonates, with long hydrophobic alkyl chains, such as di-*n*-octyl *H*-phosphonate, are also soluble in common solvents, but are immiscible with water and therefore hydrolyse less easily. Since dialkyl *H*-phosphonates are derivatives of pentavalent phosphorus, they cannot undergo the Arbuzov reaction nor can they add sulfur (however, in the presence of a strong tertiary base, such as triethylamine, dialkyl *H*-phosphonates assume the trivalent "phosphite" structure and add sulfur, yielding after acidification dialkyl hydrogen phosphorothioates [$(RO)_2P(S)OH$ tautomeric with $(RO)_2P(O)SH$]). Dialkyl *H*-phosphonate properties (*59,84*), reactions (*85–88*), and metal salts (*89,90*) have been reviewed.

▶ *Dialkyl H-phosphonates $(RO)_2P(O)H$ (general procedure using pyridine as base)* (*68*). Phosphorus trichloride (12.5 ml, 0.14 mol) was added dropwise over 1 h to a stirred solution of the appropriate alcohol (0.43 mol) and pyridine (23.2 ml, 0.29 mol) in ether (50 ml) at 0 °C. After addition, the mixture was allowed to warm slowly to room temperature, and was stirred for 16 h. The white suspension was filtered under suction, the residual pyridinium chloride was washed with ether (2 × 50 ml), and the filtrates were combined and concentrated under reduced pressure. Drying under vacuum yielded the dialkyl *H*-phosphonates shown in Fig. 4.18.5. Distillation under reduced pressure gave purer specimens.

▶ *Dimethyl H-phosphonate $(MeO)_2P(O)H$ (no added base)* (*63*). A solution of phosphorus trichloride (413 g, 3.00 mol) in butane (265 ml) was added gradually over 2 h to a stirred solution of methanol (320 g, 10.00 mol) in butane (400 ml). Exterior cooling was applied, so that the temperature of the mixture was maintained around 0 °C, and a liquid cooling mixture was passed through the reflux condenser (if the condenser was not cooled, more butane was required to replenish that lost by evaporation). Volatile products were evaporated and the residue was distilled under reduced pressure to give the title compound (300 g, 91%). Bp 37–43 °C/6 mmHg (lit. 69–73 °C/25 mmHg (*65*)).

▶ *Dimethyl H-phosphonate $(MeO)_2P(O)H$ (with added base)* (*91*). Phosphorus trichloride (137.5 g, 1 mol) was added dropwise to a stirred solution of methanol (96.0 g, 3 mol) and quinoline (258.3 g, 2 mol) in ether (350 ml) at 0–5 °C. The ether layer was separated and saved; the quinoline hydrochloride precipitate was further extracted with ether (300 ml). The combined organic extracts were evaporated and the residue distilled under reduced pressure to yield the *H*-phosphonate (yield not stated). Bp 36–38 °C/1–1.5 mmHg.

▶ *Diethyl H-phosphonate $(EtO)_2P(O)H$* (*69*). Phosphorus trichloride (275 g, 2.0 mol) and hexane (275 g, 3.2 mol) were added to a 2-l three-necked round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser protected by a drying tube at the upper end. The contents of the flask were heated to reflux and a mixture of absolute ethanol (276 g, 6.0 mol) with an equal amount of hexane were added over 2–3 h with constant stirring and refluxing. After addition, the refluxing was continued for a further 30 min. The reaction mixture was cooled and transferred to

a distilling flask equipped with a short fractionating column, a thermometer, and a glass capillary (diethyl *H*-phosphonate tends to bump or boil over during distillation; this difficulty is alleviated by admitting a slow current of air through the capillary). A distilling head with a thermometer (to indicate the vapour temperature), a condenser, and a receiver was connected to the fractionating column, and a vacuum applied. Vigorous boiling of the liquid began, caused by the escape of the remaining ethyl chloride and hydrogen chloride, and after these substances had been expelled, the pressure dropped. At 25 mmHg, the vapour temperature of the distilling diethyl *H*-phosphonate was about 90 °C. The temperature in the flask increased slowly to about 100 °C, then rapidly to about 130 °C towards the end of the distillation, with an accompanying increase in pressure to 50–60 mmHg, which indicated the beginning of decomposition. Distillation was stopped when this occurred. The distillate comprised diethyl *H*-phosphonate (207–248 g, 75–90%). Bp 77–78 °C/13 mmHg. The residue had a deep yellow to orange colour and consisted of phosphorous acid and lower phosphorus oxides.

▶ *Diisopropyl H-phosphonate (i-PrO)$_2$P(O)H* (*14*). Dry isopropanol (180 g, 3 mol) was dissolved in dry ether (180 ml) contained in a flask fitted so that a stream of dry air could be drawn through the mixture. Phosphorus trichloride (137.5 g, 1 mol) dissolved in about half its volume of dry ether was slowly run into the alcohol solution with stirring at 0–5 °C. After addition, the flask was allowed to stand for 30 min with air bubbling through it. The remaining HCl was removed by passing a stream of anhydrous ammonia into the mixture and the ammonium chloride formed was removed by filtration. After a second treatment with ammonia, to ensure complete removal of hydrogen chloride, the ether was distilled off. Fractionation of the residue under reduced pressure gave the title compound as a colourless liquid (138–148 g, 83–89%). Bp 79 °C/14 mmHg, 82.5 °C/17 mmHg. The ether in the preparation may be replaced by carbon tetrachloride without alteration of yield. If a solvent is not used, the reaction mixture must be cooled by liberal addition of dry ice. This is a general method.

▶ *Di-n-butyl H-phosphonate (n-BuO)$_2$P(O)H* (*66*). *n*-Butanol (81 g, 1.09 mol) was added to a 125 ml round-bottomed flask equipped with an addition funnel and a reflux condenser both capped with calcium chloride guard tubes. Phosphorus trichloride (50 g, 367 mmol) was added dropwise to the stirred *n*-butanol. After addition, the mixture was heated at 50 °C for approximately 1 h. Distillation under reduced pressure gave the title compound as a colourless liquid (37 g, 52%). Bp 93.5 °C/3.5 mmHg (*27*).

▶ *Diisobutyl H-phosphonate (i-PrCH$_2$O)$_2$P(O)H* (*27*). A solution of phosphorus trichloride (125 g, 0.91 mol) in ether (65 ml) was added dropwise over 70 min to a stirred solution of isobutanol (2-methyl-1-propanol, 200 g, 2.70 mol) in ether (160 ml) at 0–5 °C. Dry air was passed through for 1 h to remove the liberated hydrogen chloride. Afterwards, the air was replaced by dry ammonia (temperature <20 °C) and the ammonium chloride precipitated was filtered off. Next, ammonia was passed through for 30 min and after a second filtration, the liquid was concentrated and finally distilled under reduced pressure to yield a colourless liquid (143 g, 82%). Bp 87–89 °C/5 mmHg. A second distillation gave very pure material. Bp 87.5 °C/4 mmHg.

▶ *Di-tert-butyl H-phosphonate (t-BuO)$_2$P(O)H* (**56**) (*74*). Phosphorus trichloride (45.4 g, 0.33 mol) in ether (60 ml) was dropped over 2 h into a stirred solution of *tert*-butanol (74.0 g, 1 mol) and

pyridine (79.0 g, 1 mol) in ether (400 ml) at 0–5 °C. The mixture was stirred for 1 h after addition and then filtered. The filtrate was warmed under reduced pressure to remove low-boiling liquids and the residue distilled rapidly to yield the title compound (50.0 g, 77%). Bp 66–68 °C/0.5 mmHg (lit. bp 70–75 °C/1 mmHg (*75*)). δ_P 3.8 ppm (*76*).

▷ *Di-tert-butyl H-phosphonate (t-BuO)$_2$P(O)H* (**56**) (*76*). A sample of tri-*tert*-butyl phosphite (17.7 g, 71 mmol) was heated to 50–60 °C at 20–30 mmHg. After isobutene evolution subsided, the pale yellow liquid, which weighed 14.3 g, was fractionated to yield di-*tert*-butyl *H*-phosphonate (yield not stated). Bp 42 °C/0.4 mmHg.

▷ *Diallyl H-phosphonate (CH$_2$=CHCH$_2$O)$_2$P(O)H* (**55**) (*73*). Phosphorus trichloride (91.9 g, 0.67 mol) was added dropwise over 2 h to stirred allyl alcohol (117 g, 2.01 mol) in a 250 ml flask. Nitrogen was bubbled through the mixture. Addition of each drop of phosphorus trichloride caused a crackling noise and evolution of hydrogen chloride. After addition was complete, the cooling bath was removed and replaced by an oil bath, and the flask was fitted with a reflux condenser connected via a cooled receiver to a vacuum pump. The oil bath was heated carefully and the allyl chloride and hydrogen chloride distilled off. After 3–5 h, the residue was distilled in a stream of nitrogen (*Caution!* Not more than two-thirds of the material should be distilled: otherwise an explosion may occur) at 8 mmHg to afford Fraction 1 (8 g, to 95 °C), Fraction 2 (52 g, 98 °C), and Fraction 3 (98–102 °C). Redistillation of Fractions 2 and 3 gave the title compound as a colourless mobile liquid (71 g, 66%). Bp 97.5–98.5 °C/8 mmHg. δ_P ($CDCl_3$) 8.2 ppm. It has a characteristic smell and is soluble in water and organic solvents. A small amount of hydroquinone can be added to crude diallyl *H*-phosphonate to suppress polymerisation during distillation.

▷ *Dibenzyl H-phosphonate (BnO)$_2$P(O)H* (**20**) (*38*). A mixture of benzyl alcohol (216 g, 2 mol) and *N*,*N*-dimethylaniline (242 g, 2 mol) was added dropwise over 2 h to a stirred solution of phosphorus trichloride (137.5 g, 1 mol) in anhydrous benzene (750 ml). Afterwards, stirring was continued for 30 min, more benzyl alcohol (108 g, 1 mol) was added dropwise over 20 min, and the mixture was left for 12 h at room temperature. Water (500 ml) was added to dissolve the precipitated *N*,*N*-dimethylaniline hydrochloride, and the benzene layer separated, washed in turn with water (2 × 500 ml), 5 M ammonium hydroxide (2 × 500 ml), and water (2 × 500 ml), and dried (Na_2SO_4). Evaporation of the benzene under reduced pressure left a pale-yellow liquid from which the remaining benzyl chloride was removed by rotary evaporation at 100 °C/0.1 mmHg. The residue (190 g) was subjected in portions (40–50 g) to slow distillation under 0.01 mmHg using an electric heating mantle. The main bulk of dibenzyl *H*-phosphonate distilled at 110–120 °C as a colourless liquid (149 g, 57%). At −5 °C, the pure compound set to a mass of crystals (mp 0–5 °C). Dibenzyl *H*-phosphonate decomposes when heated to 160 °C and prolonged heating at lower temperatures (~120 °C) can sometimes result in the same outcome. For this reason, care should be taken with regard to the purity of the starting materials used in its preparation, and distillation should be conducted under high vacuum, not more than 50 g being distilled in one operation. Distillation of larger quantities is a capricious and at times a rather hazardous operation, since decomposition of the ester is exothermic and produces a white resinous polymer and considerable quantities of phosphine.

▷ *Dineopentyl H-phosphonate (t-BuCH$_2$O)$_2$P(O)H* (**57**) *(from phosphorus trichloride)* (78). Phosphorus trichloride (2.29 g, 16.65 mmol) in ether (15 ml) was added to a stirred mixture of neopentyl alcohol (4.40 g, 50.00 mmol) and pyridine (3.95 g, 50.00 mmol) in ether (15 ml) at −15 °C. Pyridine hydrochloride formed immediately. Filtration, removal of ether from the filtrate, treatment with water, and distillation of the dried organic residue under vacuum gave the title compound (3.84 g, ∼100%). Bp 116−119 °C/13 mmHg.

▷ *Dineopentyl H-phosphonate (t-BuCH$_2$O)$_2$P(O)H* (**57**) (*from tris(dimethylamino)phosphine*) (68). Tris(dimethylamino)phosphine (9.79 g, 60 mmol) was added to a two-necked round-bottomed flask equipped with a teflon-coated magnetic stirrer bar, a reflux condenser, and a rubber septum, that was under argon. Tetrahydrofuran (THF) (25 ml) and distilled water (0.72 ml, 40 mmol) were added and the solution was heated to reflux for 3 h. Neopentyl alcohol (7.19 g, 81.6 mmol) in THF (30 ml) was introduced by syringe, and the mixture was refluxed for an additional 16 h. The mixture was cooled to room temperature. The solvent was removed to give a yellow oil. Distillation gave a colourless liquid (7.6 g, 84%). Bp 56 °C/0.015 mmHg. δ_P (121.5 MHz, $CDCl_3$) 8.4 ppm.

▷ *Di-n-octyl H-phosphonate (n-C$_8$H$_{17}$O)$_2$P(O)H* (**65**) (69). Diethyl *H*-phosphonate (114.5 g, 0.83 mol) and *n*-octanol (195.0 g, 1.5 mol) were added to a 1 l three-necked flask equipped with a thermometer, a glass capillary tube, and a short fractionating column. The flask was connected to a distilling head to which was attached a thermometer, a condenser and a receiver. The contents of the flask were heated at a sufficient rate such that the temperature reached 150 °C in 1−2 h. Ethanol began to distil when the temperature reached 125−135 °C. The vapour temperature at the top of the fractionating column rose slowly from 80 °C to about 105 °C. The flask contents were then permitted to cool, a vacuum was applied, and the distillation was started again. To prevent bumping and boiling over, air was allowed to bubble slowly through the contents of the distillation flask by means of the glass capillary. If the pressure was about 30 mmHg, the temperature was allowed to rise over 45 min to 150 °C with an accompanying vapour temperature of 90 °C. At this point, the excess of diethyl *H*-phosphonate had distilled over and the heating was stopped. This left a total distillate weighing about 64.0 g and residual di-*n*-octyl *H*-phosphonate (223.3 g, 95%). Further purification can be accomplished at lower pressure (bp 173 °C/0.5 mmHg; overall yield 74%). The product is a colourless liquid.

▷ *Bis(p-substituted benzyl) H-phosphonates (p-RC$_6$H$_4$CH$_2$O)$_2$P(O)H* (**59−61**) (79). A mixture of the *p*-substituted benzyl alcohol (0.764 mol) and *N,N*-dimethylaniline (99.83 g, 0.825 mol) in benzene (250 ml) was added to a stirred solution of phosphorus trichloride (53.52 g, 0.39 mol) in benzene (250 ml) at 8−10 °C. After addition, the mixture was stirred for 20 min. Water (100 ml) was added carefully followed by vigorous stirring for an additional 30 min. White platelets crystallised. They were filtered, washed with water (100 ml), and dried over phosphorus pentoxide. The combined filtrates and washings separated into two phases: the upper layer was washed with 5% aqueous potassium carbonate (100 ml) and water (100 ml), dried ($CaCl_2$) and concentrated by rotary evaporation to a volume of 150 ml. A second crop of crystals was obtained after addition of light petroleum ether (bp 60−90 °C). Another crop was harvested from the mother liquor that was concentrated and set aside in a refrigerator for several days. The crude product could be recrystallised from benzene,

ethanol, or cyclohexane to give *bis*(*p*-methylbenzyl) *H*-phosphonate (**59**, mp 62 °C), *bis*(*p*-chlorobenzyl) *H*-phosphonate (**60**, mp 75 °C) or *bis*(*p*-bromobenzyl) *H*-phosphonate (**61**, mp 93–94 °C).

▶ *2,2-Dimethyl-1,3-propanediol cyclic H-phosphonate* (**62**) (*80*). Phosphorus trichloride (41.3 g, 0.3 mol) was added dropwise to a stirred mixture of 2,2-dimethyl-1,3-propanediol (31.2 g, 0.3 mol) and ethanol (13.8 g, 0.3 mol). The flask was cooled externally so that the temperature did not rise above 25 °C. After all the phosphorus trichloride had been added and the exothermic reaction had subsided, the reaction mixture was stirred at 25 °C while nitrogen was introduced to remove the liberated ethyl chloride and hydrogen chloride. Next, the reaction mixture was warmed to 100 °C to complete the removal of by-products. The evolved ethyl chloride (14.0 g, theoretical 19.4 g) was collected in a dry ice trap. Vacuum distillation of the residue through a short Vigreux column gave a small forerun (2.5 g) followed by the title compound (28.0 g, 62%; bp 142–145 °C/2.9 mmHg). This solidified to give a white crystalline solid. Mp 48–50 °C. Repeating the above reaction with isobutanol or 2-ethyl-1-hexanol instead of ethanol gave, respectively, the title compound in 69% (bp 117–119 °C/1.3 mmHg) and 75% yield (bp 117–120 °C/0.8 mmHg). In these two cases, the temperature of the reaction mixture was moderated by the rate of addition of the phosphorus trichloride so that it never exceeded 70 °C. No cyclic *H*-phosphonate was obtained when 1-hexadecanol was used instead of ethanol.

▶ *Bis(2-chloroethyl) H-phosphonate* $(ClCH_2CH_2O)_2P(O)H$ (**63**) *(from phosphorous acid)* (*81*). Phosphorous acid (8.2 g, 0.1 mol) was added to stirred tris(2-chloroethyl) phosphite (53.9 g, 0.2 mol) at 25 °C under nitrogen. No sign of reaction was observed; the phosphorous acid crystals settled at the bottom of the flask. The reactants were heated slowly to 60 °C at which temperature the phosphorous acid dissolved within 10 min. No significant exotherm was observed. The mixture was heated to 80 °C for 2 h and cooled. Distillation gave the title compound (56.9 g, 92%). Bp 110 °C/0.5 mmHg. The following were prepared similarly: *bis*(2-chloropropyl) *H*-phosphonate (68.3 g, 98%; bp 120 °C/1 mmHg) and *bis*(phenyl-2-chloroethyl) *H*-phosphonate (107.7 g, 100% undistilled; the product decomposed during distillation).

▶ *Bis(fluoroalkyl) H-phosphonates* $(R_FO)_2P(O)H$ *(general method)* (*82*). A solution of anhydrous *tert*-butanol (1 mol) in anhydrous dichloromethane (100 ml) was added dropwise over 45 min to a stirred solution of phosphorus trichloride (1 mol) in dichloromethane (200 ml) at 0–5 °C. The mixture was stirred at this temperature for a further hour. The fluoroalcohol (2 mol) in dichloromethane (100 ml) was added dropwise over 30 min to the cooled solution. The mixture was left at room temperature for 12 h. It was heated under reflux for 3 h to drive out any dissolved hydrogen chloride. The solvent was removed. Distillation of the residue under reduced pressure gave a forerun of unreacted alcohol and a main fraction of the *bis*(fluoroalkyl) *H*-phosphonate as a colourless liquid. The compounds made by this method, their boiling points, and ^{31}P NMR spectroscopic shifts are given in Fig. 4.18.12.

▶ *Bis(2-ethylhexyl) H-phosphonate* $[n\text{-}BuCH(Et)CH_2O]_2P(O)H$ (**66**) *(transesterification method)* (*81*). 2-Ethylhexanol (78.0 g, 0.6 mol) was added to diphenyl *H*-phosphonate (70.2 g, 0.3 mol). The resulting solution was heated to 100 °C for 1 h, cooled and distilled. A forerun of phenol (52.3 g) was collected, boiling mainly at 55 °C/1 mmHg. The remaining product was distilled to give the title compound (85.2 g, 93%). Bp 148–151 °C/1 mmHg.

4.19 UNSYMMETRICAL DIALKYL *H*-PHOSPHONATES RO(R′O)P(O)H

Unsymmetrical dialkyl *H*-phosphonates are valuable reagents for the synthesis of chiral organophosphorus compounds. They are not often encountered and there is scope to improve the synthetic methodology beyond that available to increase the number of species known. Only a few preparative methods are presently available and their reliability is often poor; many of the procedures from the old literature that claim pure products may not withstand scrutiny using modern analytical methods. The stepwise reaction of phosphorus oxychloride with alcohols gives acceptable results only with secondary alcohols (*92–94*).

Unsymmetrical dialkyl *H*-phosphonates can be prepared by transesterification but this is rarely selective and often provides mixtures from which the desired product can be difficult to isolate pure (*95*). Nevertheless it is possible to isolate *n*-butyl ethyl *H*-phosphonate (**67**) and ethyl *n*-pentyl *H*-phosphonate (**68**) in acceptable yield using this approach (Fig. 4.19.1) (*94*). The departing alcohol must boil at a temperature lower than the incoming alcohol to enable its removal by distillation from the reaction mixture. This pushes the equilibrium towards the mixed *H*-phosphonate, which is isolated after repeat fractionation.

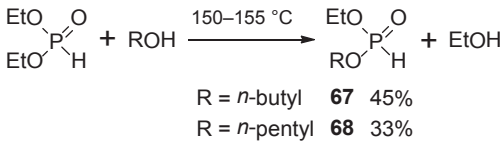
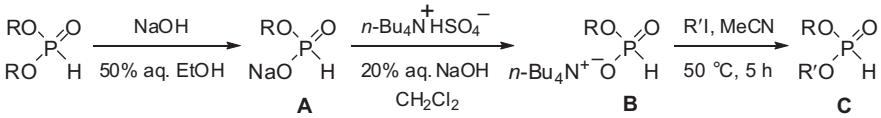


Figure 4.19.1

▶ *n-Butyl ethyl H-phosphonate n-$C_4H_9O(EtO)P(O)H$* (**67**) (*94*). A mixture of diethyl *H*-phosphonate (27.6 g, 0.2 mol) and *n*-butanol (14.8 g, 0.2 mol) was slowly heated in a distillation apparatus up to a bath temperature of 150 °C. A brisk reaction started and ethanol began to distil. The bath was kept at 150–155 °C for 55 min and ethanol (5.8 ml) was collected. Distillation of the reaction mixture under reduced pressure returned diethyl *H*-phosphonate (8 g), crude *n*-butyl ethyl *H*-phosphonate (16 g, bp 103–105 °C/13 mmHg), and crude dibutyl *H*-phosphonate (3 g, bp 110–115 °C/11 mmHg); the residue showed signs of decomposition after attempts at further distillation. Redistillation of the middle cut gave pure *n*-butyl ethyl *H*-phosphonate (15.0 g, 45%). Bp 99–100 °C/13 mmHg.

▶ *Ethyl n-pentyl H-phosphonate n-$C_5H_{11}O(EtO)P(O)H$* (**68**) (*94*). The previous procedure using diethyl *H*-phosphonate (27.6 g, 0.2 mol) and *n*-pentanol (17.6 g, 0.2 mol) gave unreacted diethyl *H*-phosphonate (11.5 g) and after two distillations pure ethyl *n*-pentyl *H*-phosphonate (12.0 g, 33%). Bp 109–110 °C/13 mmHg.

A reliable procedure for the synthesis of analytically pure unsymmetrical dialkyl *H*-phosphonates involves three stages (Fig. 4.19.2) (*96*). Step 1 involves the treatment of a symmetrical dialkyl *H*-phosphonate with aqueous ethanolic sodium hydroxide to give the sodium alkyl *H*-phosphonate (**A**). This is then treated with tetrabutylammonium hydrogen sulfate in aqueous sodium hydroxide. The use of dichloromethane as an effective extractant followed by evaporation of the solvent affords the



Sodium salts **A**			Salts **B**
R	Yield (%)	mp (°C)	Yield (%)
Et	95	182–183	80
i-Pr	97	128–130	73
n-Bu	93	175–177	92
t-Bu	99	not given	75

Mixed dialkyl *H*-phosphonates **C**			
R	R	Yield (%)	δ_P (ppm) [a]
Et	*n*-Pr	86	–5.4
Et	*n*-Bu	73	–6.6
Et	*i*-Bu	12	–6.3
Et	*s*-Bu	15	–5.2
Et	$CH_2{=}CHCH_2$	53	–6.7
i-Pr	Et	71	–6.9
i-Pr	*n*-Pr	65	–5.7
i-Pr	*s*-Bu	26	–4.9
i-Pr	$CH_2{=}CHCH_2$	69	–5.4
n-Bu	*n*-Pr	70	–7.4
n-Bu	*i*-Bu	17	–6.6
n-Bu	$CH_2{=}CHCH_2$	74	–7.7
t-Bu	Et	72	–1.6

a. Recorded at 24.3 MHz in CCl_4

Figure 4.19.2

tetrabutylammonium alkyl *H*-phosphonate (**B**). This is heated with an alkyl iodide in acetonitrile to provide the unsymmetrical dialkyl *H*-phosphonate (**C**).

The yield depends on the structure of the alkyl halide used and the character of its leaving group. The order of reactivity of the alkyl halide is RI > RBr > RCl > RF. Tetra-*n*-butylammonium ethyl *H*-phosphonate reacts with *n*-BuI and *n*-BuBr to give *n*-butyl ethyl *H*-phosphonate, *n*-BuO(EtO)P(O)H (**67**), in 73% and 18%, respectively. The ease of reaction also depends on the alkyl groups in both the ammonium alkyl *H*-phosphonate salt and alkyl halide (the order of reactivity for the latter being primary > secondary >> tertiary). Tetra-*n*-butylammonium isopropyl *H*-phosphonate and ethyl iodide, as opposed to tetra-*n*-butylammonium ethyl *H*-phosphonate and isopropyl iodide, constitute a better route to EtO(*i*-PrO)P(O)H (71 *vs* 30% yield). Proper selection of starting materials is essential for optimising the preparative procedure.

▶ *Sodium alkyl H-phosphonates RO(NaO)P(O)H* (*96*). These are prepared by hydrolysis of the corresponding dialkyl *H*-phosphonates with the stoichiometric quantity of sodium hydroxide in 50% *v*/*v* aqueous ethanol. The following can be obtained: sodium ethyl *H*-phosphonate (95% yield, mp 182–183 °C), sodium isopropyl *H*-phosphonate (97%, mp 128–130 °C), and sodium *n*-butyl

H-phosphonate (93% yield, mp 175–177 °C). Sodium *tert*-butyl *H*-phosphonate was obtained in 99% yield by slow addition of 50% *v/v* aqueous sodium hydroxide to an ethanolic solution of di-*tert*-butyl *H*-phosphonate at 50 °C followed by heating of the resultant mixture (pH 8) at 50–60 °C for 2 h and evaporating the solvent under vacuum.

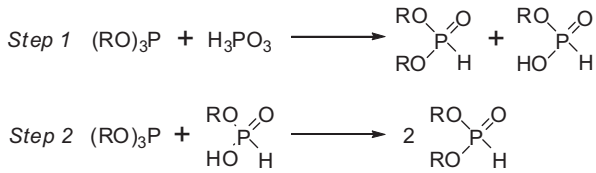
▶ *Tetra-n-butylammonium alkyl H-phosphonates* $RO(Bu_4N^+O^-)P(O)H$ (*96*). 20% *w/v* aqueous sodium hydroxide solution (25 ml) was added dropwise with stirring and external cooling (temperature <25 °C) to a solution of tetra-*n*-butylammonium hydrogen sulfate (33.9 g, 0.1 mol) in water (20 ml). A solution of sodium alkyl *H*-phosphonate (0.1 mol) in water (15 ml) was then added dropwise at room temperature. Stirring was continued for 15 min and the mixture then filtered if necessary (occasionally sodium sulfate precipitated). The filtrate was extracted with dichloromethane (4 × 50 ml) and the extracts were combined, dried ($MgSO_4$) and evaporated under vacuum (temperature <50 °C) to give the tetra-*n*-butylammonium alkyl *H*-phosphonate as a pale-yellow syrup. Products obtained this way were analytically pure: tetra-*n*-butylammonium ethyl *H*-phosphonate (80% yield), tetra-*n*-butylammonium isopropyl *H*-phosphonate (73%), tetra-*n*-butylammonium *n*-butyl *H*-phosphonate (92%), and tetra-*n*-butylammonium *t*-butyl *H*-phosphonate (75%).

▶ *Unsymmetrical dialkyl H-phosphonates* $RO(R'O)P(O)H$ (*96*). A mixture of the crude tetra-*n*-alkylammonium alkyl *H*-phosphonate (20 mmol), alkyl iodide (20 mmol) and acetonitrile (40 ml) was stirred at 50 °C for 5 h. The solvent was evaporated under reduced pressure and the residue diluted with petroleum ether (50 ml). The precipitated tetra-*n*-butylammonium iodide was filtered off, washed with petroleum ether, and the filtrate evaporated under vacuum. The residue was kept at 30–40 °C/2 mmHg for 15 min to remove traces of solvent. The crude unsymmetrical dialkyl *H*-phosphonates were obtained as colourless mobile liquids and were analytically pure.

4.20 DIARYL *H*-PHOSPHONATES $(ArO)_2P(O)H$

Treatment of triaryl phosphites with phosphorous acid at temperatures over 60 °C provides good yields of diaryl *H*-phosphonates (Fig. 4.20.1) (*81*). The reaction occurs in two stages. Step 1 entails the interaction of 1 mol of triaryl phosphite with 1 mol of phosphorous acid to provide 1 mol of diaryl *H*-phosphonate and 1 mol of aryl hydrogen *H*-phosphonate. This stage is rapid at 70 °C and occurs simultaneously with the disappearance of the phosphorous acid phase from the reaction mixture. Step 2 consists of reaction of 1 mol of triaryl phosphite with 1 mol of the aryl hydrogen *H*-phosphonate to form 2 mol of the diaryl *H*-phosphonate. The second stage is slower and requires heating to 70 °C for 5 h to approach completion.

▶ *Diphenyl H-phosphonate* $(PhO)_2P(O)H$ (*81*). Triphenyl phosphite (310 g, 1 mol) was added to a reactor equipped with a mechanical stirrer, a thermometer and a reflux condenser. While stirring at 25 °C (or above the melting point of the triaryl phosphite) under a current of dry nitrogen, phosphorous acid (41.0 g, 0.5 mol) was added. The phosphorous acid liquefied slowly forming a lower phase. The reaction was slightly exothermic. The stirred mixture was heated to 70 °C; at 55 °C the lower phosphorus acid-rich phase dissolved into the upper phase forming a clear homogeneous



Diaryl *H*-phosphonates

R	Yield (%)	Bp (°C/mmHg)
Ph	80	100/0.008
o-MeC_6H_4	98	100/0.005
m-MeC_6H_4	89	90–100/0.005
p-MeC_6H_4	99	110/0.005
o-ClC_6H_4	84	125/0.005
p-ClC_6H_4	85	125/0.005
p-*t*-BuC_6H_4	72	160/0.005 [a]

a. Mp 30–33 °C

Figure 4.20.1

solution. The phosphorous acid content of this solution was <1%; the triaryl phosphite content was between 30% and 40%. The remaining material was a mixture of phenyl hydrogen *H*-phosphonate and diphenyl *H*-phosphonate. The reaction mixture was held at 130 °C for 5 h to drive the reaction to completion. This step could be conducted at temperatures as high as 150 °C. The yield of the undistilled reaction mixture was 351 g. Of this, 10 g was distilled under reduced pressure to provide the title compound (9.6 g). Bp 100 °C/0.008 mmHg. The following diaryl *H*-phosphonates were prepared similarly from 0.1 mol of triaryl phosphite and 0.05 mol of phosphorous acid and yields are quoted for the distilled product: *bis*(2-methylphenyl) *H*-phosphonate (38.5 g, 98%; bp 100 °C/0.005 mmHg), *bis*(3-methylphenyl) *H*-phosphonate (34.7 g, 89%; bp 90—100 °C/0.005 mmHg), *bis*(4-methylphenyl) *H*-phosphonate (38.6 g, 99%; bp 110 °C/0.005 mmHg), *bis*(2-chlorophenyl) *H*-phosphonate (38.0 g, 84%; bp 125 °C/0.005 mmHg), *bis*(4-chlorophenyl) *H*-phosphonate (38.6 g, 85%; bp 125 °C/0.005 mmHg), and *bis*(4-*tert*-butylphenyl) *H*-phosphonate (37.3 g, 72%; bp 160 °C/0.005 mmHg) which crystallises slowly on standing (mp 30—33 °C).

4.21 DIALKYL PHOSPHOROFLUORIDATES $(RO)_2P(O)F$

The main results of investigations on the fluorides of phosphorus, including dialkyl phosphorofluoridates, summarising information spanning Moissan's discovery of phosphoryl oxyfluoride (POF_3) in the early days of fluorine chemistry, between 1875 and 1890, to 1964 have been compiled by Schmutzler (*97*). Another review on phosphorus fluorides by Drozd extends the coverage from 1965 to 1968 (*98*). Many dialkyl phosphorofluoridates, particularly those with small alkyl groups, are

neurotoxic (Chapter 1.5) (*58,99*) and should only be handled by chemists experienced in the manipulation of highly toxic and hazardous materials (otherwise serious accidents are likely to occur). Diisopropyl phosphorofluoridate (DFP, isoflurophate) used in ophthalmology (Chapter 1.8) is a potent anticholinesterase (*100*) having a lethal dose for half a group (LD_{50}) of mice injected intraperitoneally of 2.5 mg/kg (*101*). By contrast, dithymidyl-3′,5′-phosphorofluoridate having two large ester groups causes no mortality to mice in doses of 10 mg/kg by the same route of administration (*102*), presumably because it is too large to inhibit acetylcholinesterase (AChE).

Dialkyl phosphorofluoridates can be prepared by treatment of phosphoryl dichlorofluoride $POCl_2F$ (bp 53–54 °C) (*103–105*) with 2 mol equiv. of an alcohol in the absence or presence of 2 mol equiv. of a suitable base (*105,106*). Phosphoryl dichlorofluoride is hardly applicable to large-scale work owing to the difficulties of obtaining it in sufficient quantity. However, it is useful for preparing compounds containing the P(O)F group on a small scale, including trimethylsilyl phosphorochloridofluoridate $Me_3SiOP(O)FCl$ after reaction with hexamethyldisiloxane (*107*).

Alkyl phosphorodifluoridates react with certain alcohols in the absence of solvent to provide after distillation the dialkyl phosphorofluoridates in variable yields. Ethyl phosphorodifluoridate (**7**) combines with 2-iodoethanol to provide ethyl 2-iodoethyl phosphorofluoridate (**69**) (Fig. 4.21.1) (*33*). This approach allows access to unsymmetrical dialkyl phosphorofluoridates.

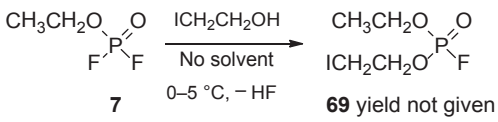


Figure 4.21.1

Treatment of dialkyl phosphorochloridates with various metal fluorides in an inert solvent in many instances leads to the corresponding fluoridates. Antimony trifluoride (*108*) was once a popular reagent for effecting this change although the yields were often low (*109*). Milder fluorinating systems include ammonium fluoride in warm acetone and more conventionally sodium fluoride in refluxing benzene (*110–112*) as illustrated for the synthesis of DFP (Fig. 4.21.2). DFP is highly toxic to man (*113,114*) and should be handled with great care to prevent accidental poisoning. [^{32}P]-Radiolabelled DFP has been prepared for biological studies (*115,116*). Like most dialkyl phosphorofluoridates, DFP is hydrolysed slowly in water, and rapidly in dilute alkali, to innocuous products (*117*).

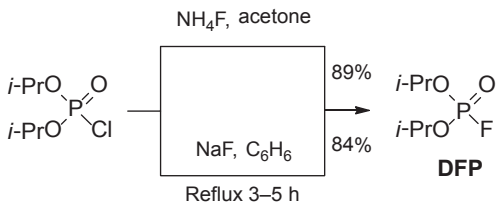


Figure 4.21.2

These classical methods of synthesis of dialkyl phosphorofluoridates are usually more efficient than one-pot multistep approaches in which the chloridate is constructed and then fluorinated promptly. Although shortcuts seem attractive, often poor conversion to the chloridate intermediate means a low yield of fluoridate. This is evident in the synthesis of di(cyclopropanemethyl) phosphorofluoridate (**70**) (Fig. 4.21.3). The first stage of the process involves double substitution of phosphorus oxychloride with an alcohol, an unselective reaction that usually provides a mixture of mono-, di- and trisubstituted organophosphorus products, and subsequent fluorination results in a poor isolated yield of the phosphorofluoridate.

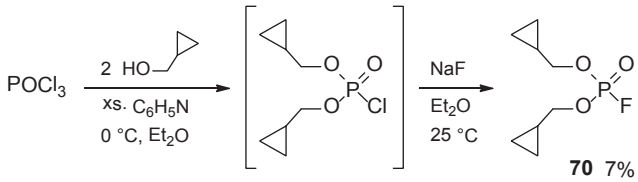
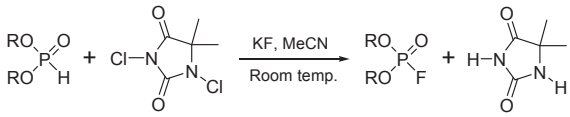


Figure 4.21.3

A mixture of 1,3-dichlorodimethylhydantoin (DCDMH) and potassium fluoride, ground together and then suspended in acetonitrile, converts disubstituted *H*-phosphonates into the corresponding fluoridates efficiently at room temperature (Fig. 4.21.4) (*118*). The reaction is presumed to proceed via an intermediate chloridate that transforms rapidly into the desired product.



Dialkyl phosphorofluoridates

R	Time (min)	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
Me	15	90	60–62/22	–8.5
Et	15	89	70–72/17	–8.3
n-Pr	20	90	78–80/20	–8.4
i-Pr	20	94	81–83/20	–10.2
n-Bu	30	91	80–82/10	–9.3
i-Bu	30	92	92–94/8	–10.2
s-Bu	30	95	95–97/5	–10.7
$CH_2{=}CHCH_2$	35	92	97–98/20	–8.8
n-C_5H_{11}	35	91	135–137/30	–9.5
i-C_5H_{11}	30	89	142–143/25	–9.1
i-PrCH_2CH(Me)	35	87	102–103/2.5	9.6
cyclohexyl	35	93	118–120/1.0	–9.1
phenyl	45	94	115–117/1.0	–20.3

a. Recorded at 162 MHz in $CDCl_3$ (85% H_3PO_4 external standard)

Figure 4.21.4

Biotinylated nerve agent mimics are useful for enzyme profiling. Fluorination of the unsymmetrical dialkyl *H*-phosphonate (**71**) with triethylamine tris(hydrogen fluoride), triethylamine and iodine in pyridine yields after column chromatography pure Nikolaev's probe (**72**) (Fig. 4.21.5, refer also to Chapter 1.12) (*119*). Iodination of the dialkyl *H*-phosphonate presumably yields the phosphoroiodidate, whose P—I bond is rapidly converted to a P—F bond under these conditions.

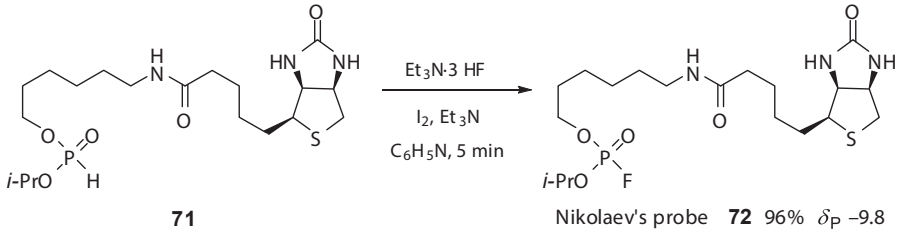
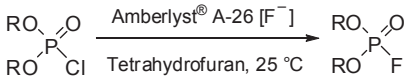


Figure 4.21.5

The use of solid-supported reagents in organic synthesis is of growing interest. Dialkyl phosphorochloridates are converted quantitatively to dialkyl phosphorofluoridates upon treatment with Amberlyst® A-26 fluoride resin in THF (Fig. 4.21.6) (*120*). Although convenient on a small scale, the resin is expensive and thus inappropriate for large-scale work.



Dialkyl phosphorofluoridates

R	Time (min)	Yield (%)	δ_F (ppm)	δ_P (ppm)	$^1J_{PF}$ (Hz) [a]
Me	30	82	–80	–8.5	984
Et	30	81	–77	–8.0	986
i-Pr	30	76	–77	–10.2	978
phenyl	60	70	–77	–21.0	1000

a. Average from ^{19}F and ^{31}P NMR measurements

Figure 4.21.6

The reaction of *bis*(2,2,2-trifluoroethyl) phosphorochloridate (**73**) with potassium fluoride in boiling dichloromethane is catalysed by trifluoroacetic acid (Fig. 4.21.7) (*82*) and provides the corresponding fluoridate (**74**) in good yield. The same product is also obtained in high yield by treating *bis*(2,2,2-trifluoroethyl) *S*-methyl phosphorothiolate (**75**) with silver(I) fluoride in acetonitrile (*121*).

Silver(I) fluoride, although expensive, is a convenient reagent for conversion of *O,O*-dialkyl *S*-alkyl phosphorothiolates to dialkyl phosphorofluoridates on a small scale (*122*).

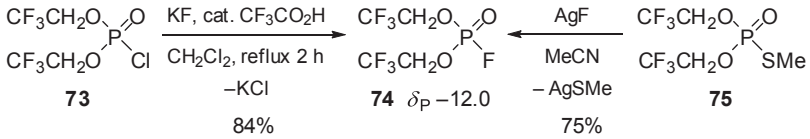


Figure 4.21.7

Treatment of *O,O,S*-trialkyl phosphorothiolothionates in acetonitrile or chloroform with a slight excess of 25% aqueous silver(I) fluoride at room temperature can in specific cases result in oxidation as well as fluorination; e.g. conversion of $(RO)_2P(S)SR$ to $(RO)_2P(O)F$ (*102,123*). *O,O*-Diethyl hydrogen phosphorodithioate (**76**) or *O,O*-diethyl *S*-butyl phosphorothiolothionate (**77**) reacts to form diethyl phosphorofluoridate (**78**) (Fig. 4.21.8) and a dark-grey precipitate (silver sulfides). After conversion is complete (^{31}P NMR control), the reaction mixture is diluted with dichloromethane, washed with brine, dried over magnesium sulfate, and purified usually by distillation. In such displacements, the Ag^+ ion is thought to complex with the sulfur atom, yielding an electrophilic species easily attacked at the phosphorus atom by the fluoride ion (*124,125*). An alternative fluorinating system for converting *O,O*-dialkyl hydrogen phosphorodithioates to dialkyl phosphorofluoridates comprises iodine (2.5 mol equiv.), triethylamine tris(hydrofluoride) (1 mol equiv.) and triethylamine (2 mol equiv.) in acetonitrile. In the case of dinucleoside hydrogen phosphorodithioates, fast and clean conversion to the fluoridate occurs (*126*).

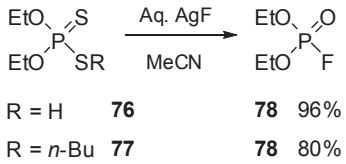


Figure 4.21.8

Heating *O,O*-dialkyl *S*-[2-(*N,N*-diethylamino)ethyl] phosphorothiolates (**79**) and (**80**) with 1-fluoro-2,4-dinitrobenzene results in production of diethyl phosphorofluoridates (**78**) and DFP (**81**), and [2-(*N,N*-diethylamino)ethyl]-2′,4′-dinitrophenyl sulfide (Fig. 4.21.9) (*127*). 2,4,6-Trinitrofluorobenzene in acetone can also effect the same type of fluorination (*128*).

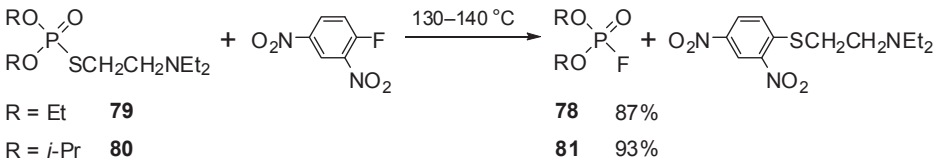


Figure 4.21.9

Competition reactions of organophosphorus fluorides with equimolar ratios of alcohols and amines, or alcohols and thiols, result in preferential formation of *O*-phosphylated products (*129*). This demonstrates that organophosphorus fluorides, such as dialkyl phosphorofluoridates, have a hard electrophilic phosphorus atom that prefers to react with hard electrophiles.

▶ *DFP (i-PrO)$_2$P(O)F (from sodium fluoride)* (*Caution!* Toxic) (*110*). Diisopropyl phosphorochloridate (295.0 g, 1.47 mol) was dissolved in dry benzene (150 ml) and heated gently with anhydrous powdered sodium fluoride (94.5 g, 2.25 mol) for 3.5 h in a flask provided with a mechanical stirrer and a reflux condenser. The temperature was adjusted so that the benzene boiled gently while vigorous stirring was maintained. At the end of the reaction time, a small quantity of kieselguhr was added, the mixture shaken and filtered. Removal of solvent and fractionation of the residue under reduced pressure gave a colourless liquid (229 g, 84%). Bp 48 °C/3 mmHg.

▶ *DFP (i-PrO)$_2$P(O)F (from ammonium fluoride)* (*110*). *Method A (with solvent)*: Diisopropyl phosphorochloridate (100.0 g, 0.5 mol) in dry acetone (200 ml) was treated with coarse-ground ammonium fluoride (55.5 g, 1.5 mol) previously dried by distillation with carbon tetrachloride. A mildly exothermic reaction set in and was completed by heating under reflux for 1 h. After cooling, the mixture was filtered and the filter cake was washed with anhydrous acetone. Removal of the diluent from the filtrate and distillation under reduced pressure gave the crude fluoridate (82 g, 89%). Bp 53 °C/4 mmHg. *Method B (without solvent)*: Diisopropyl phosphorochloridate (44.7 g, 0.24 mol) and dried ammonium fluoride (12.0 g, 0.32 mol) were heated under reflux in an oil bath. A vigorous reaction occurred at about 120 °C (bath temperature). When it had stopped, the mixture was cooled and filtered, the filter cake being washed with a small quantity of dichloromethane. The product was isolated by distillation (27 g, 61%). Bp 52–53 °C/4 mmHg.

▶ *DFP (i-PrO)$_2$P(O)F (from DCDMH and potassium fluoride)* (*118*). The fluorinating reagent was prepared by grinding a mixture of DCDMH (9.85 g, 0.05 mol) and potassium fluoride (6.38 g, 0.11 mol) in a pestle and mortar for 25–30 min until a fine homogeneous powder was obtained. It was dried under vacuum at 100 °C for 2 h and stored in a stoppered flask in a desiccator until use. Diisopropyl *H*-phosphonate (16.6 g, 0.10 mol) was added in one portion with stirring to the entire powdered fluorinating reagent suspended in anhydrous acetonitrile (40 ml) at room temperature. An exothermic reaction took place that was monitored by GC–MS and ^{31}P NMR spectroscopy. The mixture was filtered and the solid precipitate washed with anhydrous dichloromethane (2 × 10 ml). The filtrate and washings were combined and the solvent removed. Vacuum distillation of the residue gave the title compound (17.32 g, 94%). Bp 81–83 °C/20 mmHg. The other dialkyl phosphorofluoridates in Fig. 4.21.4 were prepared similarly.

▶ *Dialkyl phosphorofluoridates (RO)$_2$P(O)F (from dialkyl phosphorochloridates and fluoride resin)* (*120*). The dialkyl phosphorochloridate (2.8 mmol) was added to a stirred suspension of Amberlyst® A-26 fluoride resin (Aldrich Ltd., 1.0 g, 2.8 mmol) in THF (10 ml) at room temperature under argon. The mixture was stirred for the time given in Fig. 4.21.6, the resin filtered off, and the filtrate concentrated under reduced pressure to furnish the dialkyl phosphorofluoridate, whose yield and analytical data appear in the same figure.

▶ *Di(cyclopropanemethyl) phosphorofluoridate (c-PrCH$_2$O)$_2$P(O)F* (**70**) (*Caution!* Toxic) (*130*). A solution of cyclopropanemethanol (107.0 g, 1.49 mol) in ether (350 ml) was added to a stirred solution of phosphorus oxychloride (113.7 g, 0.74 mol) and dried pyridine (145 g, 1.83 mol) in ether (1400 ml) at 0 °C over 2 h. After addition, the mixture was stirred at 0 °C for 1 h, and then at 27–30 °C for 11 h. The solid that formed was removed by filtration under nitrogen and washed twice with ether (2 × 150 ml). The washings were combined with the filtrate. Sodium fluoride (120 g, 2.85 mol) was added and the mixture was stirred at room temperature for 22 h. The reaction mixture was filtered and the solid was washed with ether. The washings and filtrate were combined and transferred to a 3 l three-necked flask fitted with a thermometer, a gas inlet tube, a stirrer and a Drierite tube. Several drops of alcoholic bromophenol blue solution were added and anhydrous ammonia was introduced until a blue-violet colour appeared. The solid that formed was filtered off, and the filtrate was dried ($MgSO_4$) and filtered. The filtrate was concentrated under vacuum at 35–40 °C (bath temperature), leaving a residue (63 g). This material was distilled to give the title compound as a colourless liquid (11.7 g, 7%). The conditions used to prepare this phosphorofluoridate were modified from the literature method by keeping the temperature low throughout the procedure, including the distillation, and by using an acid acceptor to prevent ring expansion of the cyclopropylmethyl group to the cyclobutyl group.

▶ *6-N-Biotinylaminohexyl isopropyl phosphorofluoridate (Nikolaev's probe)* (**72**) (*119*). Triethylamine (72 ml, 0.52 mmol), triethylamine tris(hydrofluoride) (21 ml, 0.13 mol) and iodine (49 mg, 1.19 mmol) were added sequentially to a stirred solution of 6-*N*-biotinylaminohexyl isopropyl *H*-phosphonate (57 mg, 0.13 mmol) in pyridine (2 ml). The mixture was stirred for 10 min and diluted with dichloromethane (30 ml). The solution was washed successively with 1 M aqueous sodium thiosulfate (30 ml), saturated aqueous sodium bicarbonate (30 ml), and concentrated. Residual pyridine was removed from the residue by evaporation of toluene. Flash column chromatography of the residue on kieselguhr 60 (0.040–0.063 mm, Merck Ltd.), eluting with 2:3 isopropanol–ethyl acetate, gave a white waxy solid (57 mg, 96%). $[\alpha]_D^{21}$ +21.7 ($c = 0.9$, $CHCl_3$). NMR ($CDCl_3$) δ_F −78.4 ppm and δ_P −9.8 ppm ($^1J_{PF}$ 978 Hz).

▶ *Bis(2,2,2-trifluoroethyl) phosphorofluoridate (CF$_3$CH$_2$O)$_2$P(O)F* (**74**) *(from the phosphorochloridate)* (*82*). Finely divided potassium fluoride (1.7 g, 28.7 mmol) was added to a stirred solution of *bis*(2,2,2-trifluoroethyl) phosphorochloridate (4.0 g, 14.4 mmol) in dichloromethane (40 ml). The resulting suspension was heated under reflux for 2 h, and then analysed by GC–MS; only a trace of product was present. Trifluoroacetic acid (0.15 ml, 2 mmol) was added by syringe and the mixture heated under reflux for a further 2 h. A heavy white precipitate of potassium chloride formed. Analysis of the reaction mixture by GC–MS showed excellent conversion to the desired product. The solids were removed by filtration and the filtrate concentrated. Fractionation of the residue under reduced pressure gave a volatile colourless liquid (3.2 g, 84%). Bp 61 °C/40 mmHg.

▶ *Bis(2,2,2-trifluoroethyl) phosphorofluoridate (CF$_3$CH$_2$O)$_2$P(O)F* (**74**) *(from the phosphorothiolate)* (*121*). Silver(I) fluoride (1.68 g, 13.22 mmol), a brown powder, was added in one portion via a funnel to a stirred solution of *bis*(2,2,2-trifluoroethyl) *S*-methyl phosphorothiolate (1.93 g, 6.61 mmol) at room temperature. The solution assumed a yellow colour. The suspension was stirred for 12 h. The

solids were removed by filtration through a short column of silica gel. The filtrate was concentrated to give a liquid. Distillation under reduced pressure gave the title compound as a colourless liquid (1.30 g, 75%). Bp 46–47 °C/10 mmHg (oil bath temperature ~100 °C).

Diaryl phosphorochloridates (e.g. **82**) react with sodium fluoride and a catalytic amount of benzo-15-crown-5 in warm acetonitrile to provide the diaryl phosphorofluoridates (e.g. **83**) in modest yields (Fig. 4.21.10) (*34*). Caution must be taken while handling such products because of their potential neurotoxic properties (*131*).

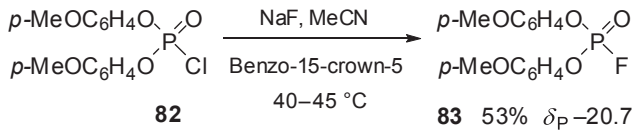


Figure 4.21.10

▶ *Bis(p-methoxyphenyl) phosphorofluoridate (p-MeOC$_6$H$_4$O)$_2$P(O)F* (**83**) (*34*). A stirred mixture of *bis*(*p*-methoxyphenyl) phosphorochloridate (6.56 g, 20 mmol), sodium fluoride (0.84 g, 20 mmol) and benzo-15-crown-5 (0.8 g, 3 mmol, 15 mol%) in acetonitrile (5 ml) was heated to 40–45 °C for 8 h. Anhydrous ether (30 ml) was added to the flask, which was topped with a calcium chloride guard tube and cooled to −15 °C. The precipitated solids were filtered off. Removal of the solvent and distillation of the residue gave the title compound (3.3 g, 53%). Bp 155 °C/0.001 mmHg. δ_P −20.7 ppm (d, $^1J_{PF}$ 1005 Hz).

4.22 DIALKYL PHOSPHOROCHLORIDATES (RO)$_2$P(O)Cl

Dialkyl phosphorochloridates are among the most important organophosphorus reagents. They contain a single chlorine atom that can be replaced by a large variety of nucleophiles to provide compounds of diverse structure. Such substitution products are of economic importance and constitute many classes of compounds with useful applications, several of which are described in Chapter 1. For this reason, their preparation is covered here in detail. The major routes generally start from trialkyl phosphites or dialkyl *H*-phosphonates and minor ones from phosphorus oxychloride or alkyl phosphorodichloridates.

Treatment of trialkyl phosphites with chlorine neat or with added solvent, with cooling, provides high yields of dialkyl phosphorochloridates, e.g. **84**–**85** (Fig. 4.22.1). The by-product is the alkyl halide which escapes from the reaction mixture in the case of lower alkyl halides, or is easily removed by rotary evaporation prior to fractionation of the residue. Trialkyl phosphites also react under modified Todd–Atherton conditions to provide after distillation acceptable yields of dialkyl phosphorochloridates, e.g. **84** and **86** (*132*). An alternative system for converting trialkyl phosphites into dialkyl phosphorochloridates is tellurium tetrachloride ($TeCl_4$) in dichloromethane. Tellurium metal and the alkyl chloride are produced as by-products, and 75–90% yields of the desired chloridate result (*133*).

Trialkyl phosphites react with phosgene to give the dialkyl phosphorochloridates, carbon monoxide and the alkyl chloride (not shown) (*14*). A safer alternative that avoids the use of the toxic

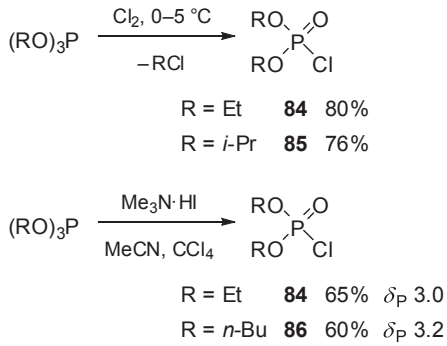
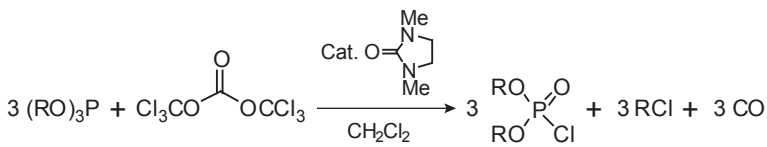


Figure 4.22.1

gas phosgene is to treat the trialkyl phosphites with the less hazardous *bis*(trichloromethyl) carbonate (triphosgene). Using 1,3-dimethyl-2-imidazolidinone catalyst in dichloromethane at 30–35 °C, this reagent provides within 2 h the dialkyl phosphorochloridates in excellent yields (Fig. 4.22.2) (*134*). The by-products are the alkyl chloride and carbon monoxide, and their non-acidic nature does not cause the chloridates to degrade.



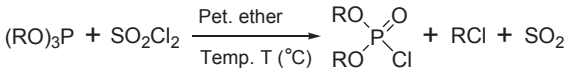
Dialkyl phosphorochloridates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
Me	97	52–54/3	8.1
Et	95	68–71/4	5.8
n-Pr	94	76–78/2	5.5
i-Pr	95	89–92/10	2.8
n-Bu	92	94–97/3	6.3
n-C_5H_{11}	93	134–136/3	5.4
i-C_5H_{11}	92	104–106/2	4.7
n-C_6H_{13}	92	148–152/3	6.3
cyclohexyl	91	143–146/2	5.1
n-C_8H_{17}	92	168–171/2	6.3
phenethyl	90	undistilled	5.0
phenyl	93	122–124/2	–17.1

a. Recorded in $CDCl_3$ on 262 MHz NMR instrument

Figure 4.22.2

Trialkyl phosphites also react with sulfuryl chloride in petroleum ether to give dialkyl phosphorochloridates (Fig. 4.22.3) (*135*). The reaction proceeds vigorously even at temperatures as low as −20 °C in a variety of solvents at low dilution. The alkyl chloride and sulfur dioxide are by-products. The order of adding the reactants does not affect the results obtained. However, addition of the trialkyl phosphite to the sulfuryl chloride is recommended as the reverse addition could prompt an Arbuzov reaction between the trialkyl phosphite and the liberated alkyl chloride, possibly producing the dialkyl alkylphosphonate as an unwanted impurity. The use of thionyl chloride instead of sulfuryl chloride is not recommended as the conversion of the trialkyl phosphite to the dialkyl phosphorochloridate proceeds in much lower yield with attendant formation of the trialkyl phosphate, trialkyl phosphorothionate, sulfur dioxide, and the alkyl chloride (*136*).



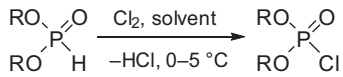
Dialkyl phosphorochloridates

R	Temp. T (°C)	Yield (%)	Bp (°C/mmHg)
Et	0	87	52–54/0.8
i-Pr	10	73	87–91/11–12
n-Bu	–10	89	121–126/8
$ClCH_2CH_2$	0	48	118–125/0.4

Figure 4.22.3

One of the most versatile and high yielding methods of preparation of dialkyl phosphorochloridates involves the chlorination of dialkyl *H*-phosphonates with elemental chlorine (Fig. 4.22.4) (*27*,*38*,*60*–*62*,*78*). The reaction proceeds smoothly at ice-cold temperatures and is self-indicating, that is, the appearance of the green colour of chlorine in the reaction mixture signals that chlorination is complete. Early examples employed carbon tetrachloride as the diluent, but this solvent can be replaced by dichloromethane or chloroform with little or no effect on the yield. It is customary at the end of the reaction to remove the liberated hydrogen chloride from the crude product by passing dry air or an inert gas through the reaction mixture prior to solvent removal. Distillation of a crude product free from hydrogen chloride ensures a higher yield of the dialkyl phosphorochloridate as traces of acid present during heating can lead to dealkylation of the more acid-sensitive chloridates. Di-*tert*-butyl phosphorochloridate is a particularly heat- and acid-sensitive species and differs from other chloridates shown in Fig. 4.22.4 in that it cannot be distilled. The same limitation applies to dibenzyl phosphorochloridate prepared the same way: it cannot be distilled even under reduced pressure without decomposition and is therefore best used in the crude state for phosphorylation reactions (*38*).

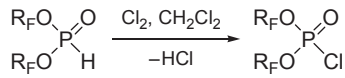
Bis(fluoroalkyl) *H*-phosphonates also react with chlorine in dichloromethane or chloroform solution to provide *bis*(fluoroalkyl) phosphorochloridates often in excellent yield (Fig. 4.22.5) (*82*).



Dialkyl phosphorochloridates

R	Yield (%)	Bp (°C/mmHg)
Me	90	70–71/15
Et	93	76–78/8
n-Pr	91	78/2
i-Pr	89	78–80/7–7.5
n-Bu	90	80.5–81/0.5
i-Bu	80	62/0.18
s-Bu	70	84/0.8
n-C_5H_{11}	76	71–72/0.4
t-$BuCH_2$	84	90/2
Bn	100	not distilled

Figure 4.22.4



Bis(fluoroalkyl) phosphorochloridates

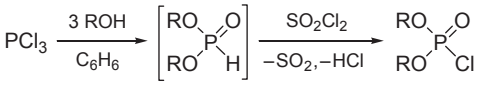
R_F	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
HCF_2CH_2	91	76/0.1	4.6
$H(CF_2)_2CH_2$	83	115/0.08	4.5
$H(CF_2)_4CH_2$	89	100/0.1	4.7
CF_3CH_2	94	62/10	4.7
$C_2F_5CH_2$	84	71/10	4.6
$C_3F_7CH_2$	90	68/2	4.8
$(CF_3)_2CH$	82	48/10	8.9
$(FCH_2)_2CH$	79	154/0.2	4.2
$CF_3(CH_3)_2C$	88	80/10	–7.2
$(CF_3)_2CH_3C$	62	54/10	–7.7
$CF_3CH_2CH_2$	76	77/0.08	2.7
$C_4F_9CH_2CH_2$	49	141/6	3.0
$C_6F_{13}CH_2CH_2$	96	solid (mp 27 °C)	2.3

a. Recorded at 202 MHz in $CDCl_3$

Figure 4.22.5

Simple rotary evaporation of the reaction mixture at the end-point of chlorination suffices to remove sufficient hydrogen chloride to allow these acid-resistant chloridates to be distilled smoothly and without significant decomposition. These chloridates are useful reagents in drug discovery and medicinal chemistry (*137*,*138*) and in synthesis (*139*). Their reactions are similar to those of non-fluorinated dialkyl phosphorochloridates and are determined by the stereoelectronic effects of the fluoroalkyl groups (*83*).

A one-pot method starting from phosphorus trichloride can be used to good effect for the synthesis of dialkyl phosphorochloridates (*140*,*141*). Treatment of phosphorus trichloride with 3 mol of an alcohol in an inert solvent provides the dialkyl *H*-phosphonate that is then chlorinated with sulfuryl chloride (Fig. 4.22.6). The large quantity of hydrogen chloride generated makes this approach unsuitable for the synthesis of dialkyl phosphorochloridates bearing acid-sensitive alkoxy groups (e.g. di-*tert*-butyl phosphorochloridate) as their dealkylation lowers the yield and complicates purification.



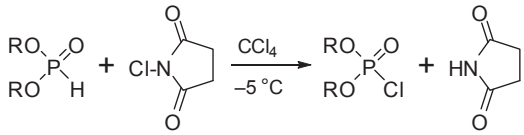
Dialkyl phosphorochloridates

R	Yield (%)	Bp (°C/mmHg)
Me	85	80/25
Et	66	42/0.2
n-Pr	50	74/0.3
i-Pr	78	48/1
n-Bu	92	98/0.3
i-Bu	60	111/12
$ClCH_2CH_2$	86	132/0.5

Figure 4.22.6

For small-scale work, chlorination of dialkyl *H*-phosphonates can conveniently be effected by *N*-chlorosuccinimide (Fig. 4.22.7) (*111*). This method has the advantage that none of the products of the reaction is acidic. The partial degradation of the dialkyl phosphorochloridate observed with other chlorinating agents that produce acid by-products is circumvented and the method is particularly useful for the synthesis of acid-sensitive dialkyl phosphorochloridates.

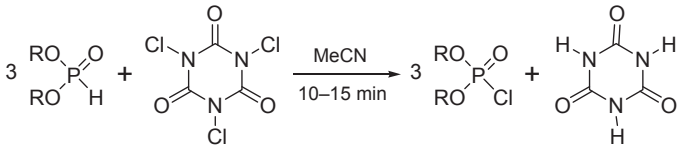
Trichloroisocyanuric acid can be used instead of *N*-chlorosuccinimide and produces the neutral by-product cyanuric acid (Fig. 4.22.8) (*142*). *N*,*N*-Dichloro poly(styrene-co-divinyl benzene) sulfonamide polymeric beads bearing $-SO_2NCl_2$ groups (1 mol) also convert the same set of disubstituted *H*-phosphonates (2 mol) into the corresponding chloridates (*143*). The by-product in this case is a resin containing non-acidic $-SO_2NH_2$ groups. However, the unavailability of the resin reagent prevents this chlorination method from finding widespread use at present.



Dialkyl phosphorochloridates

R	Yield (%)	Bp (°C/mmHg)
Me	85	54.5/2
Et	88	93/18
i-Pr	87	94–95/14
CH_2=$CHCH_2$	38	89–90/0.9
EtOC(O)CH(Me)	75	158–160/1

Figure 4.22.7



Dialkyl phosphorochloridates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
Me	96	75–77/20	6.3
Et	98	85–87/10	4.1
n-Pr	94	102–103/10	5.5
i-Pr	98	90–92/10	2.8
n-Bu	95	120–122/9	4.6
i-Bu	92	122–124/10	4.2
s-Bu	96	95–97/2	4.7
n-C_5H_{11}	95	129–132/1	4.6
i-C_5H_{11}	94	133–135/1	3.6
n-C_6H_{13}	96	undistilled	4.3
cyclohexyl	96	130–132/1	5.5
benzyl	94	undistilled	4.7
phenyl	96	133–135/0.5	–6.2

a. Recorded in $CDCl_3$ on 400 MHz instrument

Figure 4.22.8

Di-*tert*-butyl phosphorochloridate (**87**) is an attractive reagent for the phosphorylation of alcohols and amines and the *tert*-butyl groups in the products can be removed under mildly acidic conditions. The sensitivity of the chloridate to acid conditions does not permit its preparation from di-*tert*-butyl *H*-phosphonate by the halogenation methods already described; even the *N*-chlorosuccinimide method gives an impure sample (*74*). Purification of di-*tert*-butyl phosphorochloridate by distillation is not possible due to its thermal instability. A method for obtaining it pure involves the reaction of di-*tert*-butyl *H*-phosphonate with carbon tetrachloride in a two-phase system consisting of dichloromethane, dilute aqueous sodium hydroxide, and a catalytic amount of benzyltriethylammonium chloride (BTAC) (Fig. 4.22.9) (*144*). The reaction mixture is kept constantly alkaline, thus preventing acid-catalysed dealkylation. Substantial steric hindrance at the phosphorus atom due to the bulky *tert*-butyl groups prevents conversion of the chloridate product into the tetra-*tert*-butyl pyrophosphate. Di-*tert*-butyl phosphorochloridate is an unstable liquid that decomposes at room temperature after several hours. It stores at 5 °C for about 12 h without decomposition and remains stable at −10 °C for at least 3 days. It is best used immediately for further synthetic transformations.

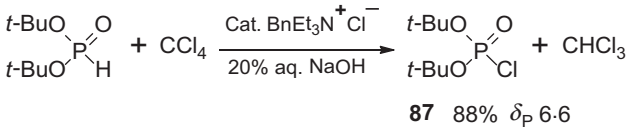


Figure 4.22.9

The methods described already are generally superior to the reaction of 2 mol of an alcohol with phosphorus oxychloride in the presence of 2 mol of a suitable base (e.g. pyridine or triethylamine). In the case of unbranched small aliphatic alcohols, this approach provides pure dialkyl phosphorochloridates in low yields usually only after repeat fractionation. For example, the reaction of ethanol with phosphorus oxychloride in the presence of pyridine yields a mixture of mono-, di- and trisubstituted products, from which diethyl phosphorochloridate (**84**) can be isolated (Fig. 4.22.10) (*57*). However the approach does have merit when the aliphatic alcohol used is bulky, which suppresses triple substitution, and provides a higher proportion of the requisite dialkyl phosphorochloridate. A good example of this is the reaction of 2,2-dimethyl-1,3-propanediol with phosphorus oxychloride, without the addition of a base, which provides the cyclic dialkyl

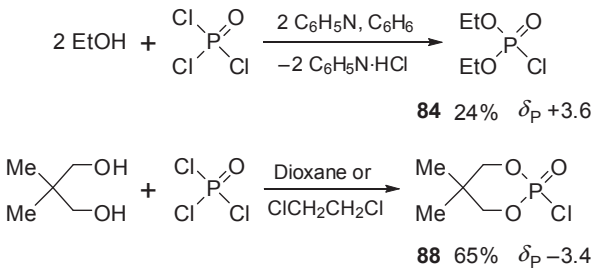


Figure 4.22.10

phosphorochloridate (**88**) (*80*). The phosphorus NMR shifts in Fig. 4.22.10 are taken from a paper describing the reactions of the chloridates with strong amine bases (*145*).

Treatment of phosphorus trichloride with ethylene glycol in dichloromethane provides ethylene phosphorochloridite (**89**) (*146*) which dinitrogen tetroxide vapour oxidises to ethylene phosphorochloridate (**90**) (*147*) (Fig. 4.22.11). The by-products are N_2O and N_2 with predominance of the former. The phosphorochloridate yield after vacuum distillation (30%) is low as it polymerises during purification.

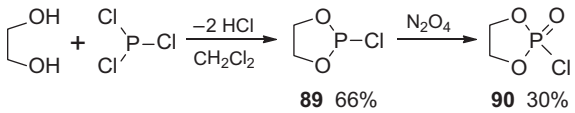


Figure 4.22.11

Unsymmetrical dialkyl phosphorochloridates are usually prepared by treatment of an alkyl phosphorodichloridate with a molar equivalent of an alcohol in the presence of a base, as in the synthesis of ethyl *n*-propyl phosphorochloridate (**91**) (Fig. 4.22.12) (*148*).

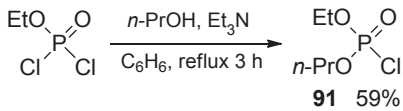


Figure 4.22.12

Dialkyl phosphorochloridates undergo ready bimolecular substitution by a variety of nucleophiles (NuH) at the phosphorus atom (S_N2P) process (*149*). Reaction proceeds via a trigonal bipyramidal intermediate $(RO)_2P(OH)(Nu)Cl$. The nucleophile adopts an apical position and the leaving group (chloride) departs from an apical position. The rate of substitution depends on the size and electronegativity of the alkoxy groups in the phosphorochloridate. Small or electronegative alkoxy groups increase the rate, whereas large or electropositive groups slow it down. Sufficient is known about the comparative reactivity of nucleophiles to predict that for a given phosphorochloridate the order of reactivity will decline in the order: fluoride ion > primary and secondary amines > aromatic amines > aliphatic alcohols > aromatic alcohols > aliphatic thiols > aromatic thiols (*129,150–152*).

▶ *Dimethyl phosphorochloridate $(MeO)_2P(O)Cl$ (from trimethyl phosphite and triphosgene)* (*134*). Triphosgene (5.0 g, 17 mmol) in dichloromethane (5 ml) was added to a stirred solution of trimethyl phosphite (6.2 g, 50 mmol) and 1,3-dimethyl-2-imidazolidinone (0.2 g, 3% mol, 1.5 mmol) in dichloromethane (15 ml) below 5 °C. The mixture was stirred for 2 h at 30–35 °C. The solvent was removed and the residue was distilled under vacuum to afford dimethyl phosphorochloridate (7.0 g, 97%). Bp 52–54 °C/3 mmHg. δ_P ($CDCl_3$) 8.1 ppm. The same method was used to prepare the other phosphorochloridates shown in Fig. 4.22.2.

▷ *Dimethyl phosphorochloridate $(MeO)_2P(O)Cl$ (from dimethyl H-phosphonate and N-chlorosuccinimide)* (*91*). Equimolar quantities of dimethyl *H*-phosphonate and *N*-chlorosuccinimide in anhydrous benzene were stirred at room temperature overnight. The product (bp 45 °C/ ~ 2 mmHg) was recovered by vacuum distillation of the benzene layer and showed only minor impurities by gas chromatography.

▷ *Diethyl phosphorochloridate $(EtO)_2P(O)Cl$ (from triethyl phosphite and chlorine)* (*60*). Anhydrous chlorine was bubbled into stirred triethyl phosphite (16.6 g, 0.1 mol) until a faint permanent green colour persisted. Excess chlorine was removed by bubbling dry air through the liquid under reduced pressure for 3 h. After treatment with lead(II) carbonate and filtration through kieselguhr, the product was distilled to yield the chloridate (13.7 g, 80%). Bp 93–95 °C/18 mmHg.

▷ *Diethyl phosphorochloridate $(EtO)_2P(O)Cl$ and di-n-butyl phosphorochloridate $(n\text{-}BuO)_2P(O)Cl$ (from the trialkyl phosphite, trimethylammonium iodide and carbon tetrachloride)* (*132*). A solution of the trialkyl phosphite (0.10 mol) and trialkylammonium iodide ($Me_3N \cdot HI$ or $Et_3N \cdot HI$, 0.15 mol) in acetonitrile (50 ml) was stirred vigorously, taking precautions to exclude moisture, and warmed to 45–50 °C. Carbon tetrachloride (0.10 mol) was added. After 5 h, the mixture was cooled to room temperature, any solid material was filtered off, and the filtrate was rotary evaporated. The liquid residue was distilled under reduced pressure to give colourless liquids: $(EtO)_2P(O)Cl$ (65% yield; bp 50 °C/1 mmHg; δ_P 3.0 ppm) and $(n\text{-}BuO)_2P(O)Cl$ (60% yield; bp 78 °C/1 mmHg; δ_P 3.2 ppm).

▷ *Diethyl phosphorochloridate $(EtO)_2P(O)Cl$ (from triethyl phosphite and phosgene)* (*14*). Triethyl phosphite (83 g, 0.5 mol) was placed in a 250 ml three-necked flask carrying a sleeved mechanical stirrer, a gas inlet opening at the bottom of the flask, a calcium chloride guard tube and a thermometer (bulb in liquid). The stirrer was started and a stream of phosgene (*Caution!* toxic gas) introduced at a rate of about 500 ml/min. The reaction was exothermic but could easily be kept at 30 ± 2 °C by surrounding the flask with a bath of cold water. Some frothing took place and the reaction was considered complete when this had ceased, the gas passed freely through the liquid and the temperature fell. This occurred in about 1 h. The stirrer was stopped and the contents of the flask were transferred to a pear-shaped distilling flask fitted with an integral 75 cm Vigreux column. The flask carried a capillary air-bleed protected by a calcium chloride guard tube and was surrounded by an oil bath at about 70 °C. Volatile materials (dissolved phosgene and ethyl chloride) were removed with the aid of a water pump until the pressure no longer fell. The water pump was replaced by an oil pump and the product distilled under reduced pressure (bath temperature ~ 100 °C). Except for a very small forerun and residue, the whole material distilled over and was collected as a colourless liquid (81 g, 94%). Bp 54 °C/1 mmHg. A rapidly revolving stirrer was advisable to minimise "slip" of phosgene and to avoid local overheating. It was essential that the mixture was saturated with phosgene: otherwise any unattacked phosphite may have reacted with the phosphorochloridate during distillation to produce tetraethyl pyrophosphate (*Caution!* neurotoxic), thereby reducing the yield.

▷ *Diethyl phosphorochloridate $(EtO)_2P(O)Cl$ (from triethyl phosphite and sulfuryl chloride)* (*135*). Triethyl phosphite (166 g, 1.0 mol) in anhydrous petroleum ether (200 ml) was added dropwise over 5 h to a stirred solution of sulfuryl chloride (135 g, 1.0 mol) in anhydrous petroleum ether (300 ml) at 0 °C

under nitrogen. Sulfur dioxide was evolved. After addition, the reaction mixture was allowed to warm to room temperature (over 1 h). The solvent, ethyl chloride and sulfur dioxide were removed by rotary evaporation at room temperature. Distillation of the residue under reduced pressure gave diethyl phosphorochloridate (149.5 g, 87%). Bp 52–54 °C/0.8 mmHg. The other dialkyl phosphorochloridates shown in Fig. 4.22.3 were prepared similarly.

▶ *Ethyl n-propyl phosphorochloridate EtO(n-PrO)P(O)Cl (from ethyl phosphorodichloridate, n-propanol and triethylamine)* (*148*). A solution of ethyl phosphorodichloridate (8.1 g, 50 mmol) in anhydrous benzene (25 ml) was added dropwise to a stirred solution of *n*-propanol (3.0 g, 50 mmol; dried by distillation from calcium hydride) and triethylamine (5.05 g, 50 mmol) in anhydrous benzene (100 ml). The mixture was heated under reflux for 3 h and cooled and anhydrous ether (100 ml) was added. The precipitated triethylammonium chloride (6.6 g, 96%) was filtered off. Distillation of the filtrate yielded ethyl *n*-propyl phosphorochloridate (5.5 g, 59%). Bp 89 °C/8 mmHg.

▶ *Diisopropyl phosphorochloridate (i-PrO)$_2$P(O)Cl (from triisopropyl phosphite and chlorine)* (*153*). Chlorine was added dropwise via a condenser cooled to −78 °C to a stirred solution of triisopropyl phosphite (20.0 g, 96 mmol) in ether (150 ml) at −78 °C until the formed white slurry retained a green tint. The mixture was allowed to warm slowly to room temperature, and the solvent, excess chlorine and isopropyl chloride were removed by rotary evaporation. The liquid residue was distilled to yield the pure chloridate (16.1 g, 84%). Bp 50–54 °C/0.1 mmHg. The product is a volatile liquid with a flowery odour. Another synthetic variation involves a different work-up (*14*): a slow stream of chlorine was passed through stirred diisopropyl *H*-phosphonate (100 g, 0.6 mol) contained in a flask cooled by ice water until the yellow colour persisted. After allowing the mixture to stand for 5 min, a current of nitrogen was passed through it, until the liquid was colourless, and afterwards for 1 h more. Anhydrous powdered lead(II) carbonate (15–20 g) was then added and nitrogen drawn through with stirring for a further 3 h. Complete removal of the HCl was usually indicated by the tendency of the lead salts to settle after stirring. They were removed by the addition of a little kieselguhr followed by filtration. Distillation of the filtrate under reduced pressure gave the title compound as a colourless corrosive liquid (85 g, 71%). Bp 95 °C/14 mmHg. It was essential to remove all traces of hydrogen chloride before attempting to distil it. If this was not done, extensive decomposition took place during distillation.

▶ *Diisopropyl phosphorochloridate (i-PrO)$_2$P(O)Cl (from triisopropyl phosphite and phosgene)* (*110*). Triisopropyl phosphite (104 g, 0.5 mol) was treated with a fairly rapid stream of phosgene, with stirring, the temperature being kept at 30–35 °C. Reaction was complete in about 1 h, when the temperature had stopped rising and the effervescence had ceased. The next morning the product was degassed using a water pump and then distilled under reduced pressure to give the chloridate (92 g, 92%). Bp 63 °C/1 mmHg.

▶ *Diisopropyl phosphorochloridate (i-PrO)$_2$P(O)Cl (from diisopropyl H-phosphonate and sulfuryl chloride)* (*14,110*). Diisopropyl *H*-phosphonate (66.4 g, 0.4 mol) diluted with carbon tetrachloride (100 ml) was treated with sulfuryl chloride (54.0 g, 0.4 mol). The product was isolated by distillation (68.2–72.2 g, 85–90%). Bp 68 °C/2 mmHg.

▷ *Diisopropyl phosphorochloridate (i-PrO)$_2$P(O)Cl (from diisopropyl H-phosphonate and trichloroisocyanuric acid)* (*142*). A solution of diisopropyl *H*-phosphonate (1.66 g, 10 mmol) in anhydrous acetonitrile (5 ml) was added in one portion to a stirred solution of trichloroisocyanuric acid (0.76 g, 3.33 mmol) in anhydrous acetonitrile (15 ml) at room temperature. Cyanuric acid precipitated after 10 min and indicated the end of the reaction. The mixture was stirred for another 5 min and filtered to remove the precipitate. Removal of the solvent from the filtrate and vacuum distillation of the residue gave diisopropyl phosphorochloridate (1.96 g, 98%). Bp 90–92 °C/10 mmHg. δ_P ($CDCl_3$) 2.8 ppm. The other phosphorochloridates in Fig. 4.22.8 were prepared similarly.

▷ *Diisopropyl phosphorochloridate (i-PrO)$_2$P(O)Cl (from diisopropyl H-phosphonate and N-chlorosuccinimide)* (*111*). *N*-Chlorosuccinimide (13.4 g, 0.1 mol) was added in portions (0.5 g) to a stirred solution of diisopropyl *H*-phosphonate (16.6 g, 0.1 mol) in anhydrous carbon tetrachloride (30 ml) with cooling. The solution was cooled to −5 °C and the precipitated succinimide filtered off. Removal of the solvent and fractionation of the residue gave diisopropyl phosphorochloridate (17.5 g, 87%). Bp 94–95 °C/14 mmHg. The other chloridates shown in Fig. 4.22.7 were prepared similarly.

▷ *Diisobutyl phosphorochloridate (i-BuO)$_2$P(O)Cl (from diisobutyl H-phosphonate and chlorine)* (*27*). Chlorine was passed through a solution of diisobutyl *H*-phosphonate (121 g, 0.63 mol) in carbon tetrachloride (250 ml) at a temperature not exceeding −5 °C. After 45 min, the liquid had become yellow, and dry air (or nitrogen or argon) was passed through for 1 h, after which the solvent was removed under reduced pressure. Carbon tetrachloride (120 ml) was added and the evaporation repeated; this was done four times to remove the hydrogen chloride completely. Finally the product was distilled to provide diisobutyl phosphorochloridate (115.5 g, 80%; bp 64–66 °C/0.5 mmHg). Redistillation gave a very pure sample (bp 62 °C/0.18 mmHg) [the first distillation usually provides good quality material]. This general method was used to make the dialkyl phosphorochloridates shown in Fig. 4.22.4.

▷ *Di-tert-butyl phosphorochloridate (t-BuO)$_2$P(O)Cl (from di-tert-butyl H-phosphonate and carbon tetrachloride)* (*144*). A solution of di-*tert*-butyl *H*-phosphonate (9.7 g, 50 mmol) in dichloromethane (15 ml) was added dropwise to a stirred two-phase system of carbon tetrachloride (30 ml), 20% aqueous sodium hydroxide (30 ml) and BTAC (0.5 g). The temperature of the slightly exothermic reaction was maintained at 20–25 °C. After addition, stirring was continued for 3 h at room temperature. The mixture, now coloured dark brown, was diluted with dichloromethane (50 ml). The organic layer was separated, washed with water (3 × 30 ml) and dried ($MgSO_4$). The solvent was evaporated and the residue kept at 20 °C/0.6 mmHg for 1 h to remove volatile impurities. The residual pale-yellow liquid was the analytically pure title compound (10.1 g, 88%). δ_P (CCl_4) 6.6 ppm.

▷ *Bis(fluoroalkyl) phosphorochloridates (R_FO)$_2$P(O)Cl (from the bis(fluoroalkyl) H-phosphonates and chlorine)* (*82*). Chlorine was bubbled into a solution of *bis*(fluoroalkyl) *H*-phosphonate (0.2 mol) in dichloromethane or chloroform (50 ml) until a yellow colour persisted in the reaction mixture. The solvent was removed. Distillation of the residue gave the *bis*(fluoroalkyl) phosphorochloridate as a colourless liquid (Fig. 4.22.5). *Bis*(*1H,1H,2H,2H*-perfluoro-1-octyl) phosphorochloridate was not distilled; removal of solvent gave the pure material as a white solid (mp 27 °C).

▶ *Dialkyl phosphorochloridates (from phosphorus trichloride, an alcohol and sulfuryl chloride)* (*140*). A solution of phosphorus trichloride (184 g, 1.34 mol) in anhydrous benzene (350 ml) was added dropwise to a stirred solution of the alcohol (4.00 mol) in anhydrous benzene (350 ml). The mixture was stirred for 1 h after the addition and then a solution of sulfuryl chloride (180 g, 1.33 mol) in benzene (350 ml) was added dropwise at 8–10 °C. The mixture was warmed to room temperature, concentrated, and distilled to provide the dialkyl phosphorochloridates shown in Fig. 4.22.6.

▶ *Dineopentyl phosphorochloridate (t-BuCH$_2$O)$_2$P(O)Cl* (*78*). Chlorine was passed into dineopentyl *H*-phosphonate (4.0 g, 18 mmol) at room temperature for 15 min, after which the liquid coloured yellow. During this period, the liquid warmed and hydrogen chloride was evolved. Distillation of the residue gave the chloridate which on cooling crystallised to give a white solid (3.9 g, 84%). Bp 90 °C/2 mmHg. Mp 42.5 °C.

▶ *Dibenzyl phosphorochloridate (BnO)$_2$P(O)Cl (from dibenzyl H-phosphonate and chlorine)* (*38*). A solution of chlorine in carbon tetrachloride (200 ml, 1.4 M) was added dropwise to a stirred solution of dibenzyl *H*-phosphonate (39.3 g, 0.15 mol) in carbon tetrachloride (200 ml) at −15 to −10 °C. After addition, nitrogen was passed through the liquid for ~1.5 h to remove the excess of chlorine and the hydrogen chloride produced. For phosphorylation purposes, the solution thus obtained was normally used, as removal of the solvent under vacuum at room temperature gave dibenzyl phosphorochloridate as a viscous liquid (this decomposed on standing or on attempted distillation). The same product was obtained when chlorination was conducted in ether or chloroform solution.

▶ *Dibenzyl phosphorochloridate (BnO)$_2$P(O)Cl (from dibenzyl H-phosphonate and sulfuryl chloride)* (*140*). A solution of sulfuryl chloride (13.5 g, 0.1 mol) in carbon tetrachloride (50 ml) was added to a solution of dibenzyl *H*-phosphonate (26.2 g, 0.1 mol) in carbon tetrachloride (300 ml) at 16–19 °C under nitrogen. After addition, nitrogen was passed rapidly through the mixture for 90 min. The solution was concentrated to give dibenzyl phosphorochloridate (28.5 g, 96%).

▶ *2,2-Dimethyl-1,3-propanediol cyclic phosphorochloridate* (*80*). Phosphorus oxychloride (153 g, 1 mol) was added dropwise to a stirred solution of 2,2-dimethyl-1,3-propanediol (104 g, 1 mol) in anhydrous 1,4-dioxane (400 ml). After a short induction period, the temperature of the reaction mixture rose to about 80 °C. The temperature was not allowed to exceed 80 °C and was controlled by occasional external cooling using chilled water. After the phosphorus oxychloride had added and the mixture had cooled to room temperature, stirring was continued for 8 h while anhydrous nitrogen gas was introduced through a fritted glass disc, to flush out the liberated hydrogen chloride. The solvent was removed by distillation at atmospheric pressure, leaving a liquid that crystallised as it cooled. This material was washed with cold cyclohexane and then recrystallised from a 1:1 mixture of cyclohexane and benzene (or from a 3:1 mixture of cyclohexane and 1,2-dichloroethane). The purified material was obtained as white crystals (115 g, 63%). Mp 102–103 °C. It was soluble in acetone, benzene and 1,2-dichloroethane and insoluble in water, ether, and cyclohexane. The target compound can be prepared using 1,2-dichloroethane as the solvent instead of 1,4-dioxane; in this case, the yield of recrystallised product is 65%.

4.23 DIARYL PHOSPHOROCHLORIDATES $(ArO)_2P(O)Cl$

Diphenyl *H*-phosphonate can be chlorinated with chlorine or sulfuryl chloride to form diphenyl phosphorochloridate (**92**) (Fig. 4.23.1) (*81*). In the case of diaryl *H*-phosphonates that contain alkyl substituents on the phenyl group, sulfuryl chloride is the preferred chlorination agent, since chlorine attacks both the P—H and the hydrocarbon group. Both methods are higher yielding than an alternative route to diaryl phosphorochloridates that involves heating 2 mol of an aromatic alcohol with phosphorus oxychloride, as in the synthesis of di(2-alkylphenyl) phosphorochloridates (**93**) and (**94**) (*41*).

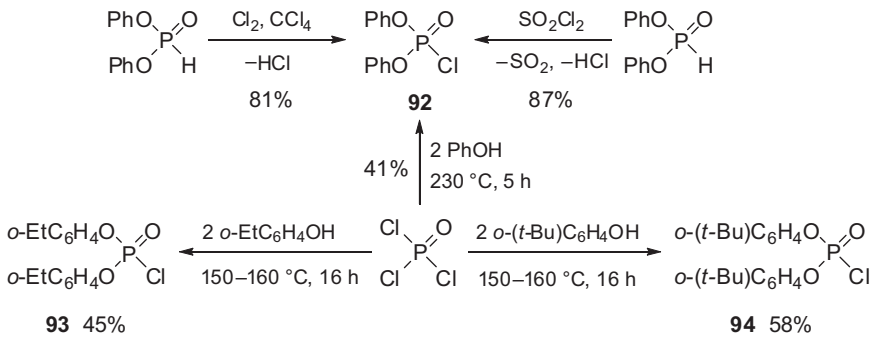


Figure 4.23.1

Phenyl reacts with *p*-nitrophenyl phosphorodichloridate (**95**) upon heating in the presence of a catalytic amount of sodium chloride to give the corresponding unsymmetrical diaryl phosphorochloridate (**96**) in modest yield (Fig. 4.23.2) (*154*).

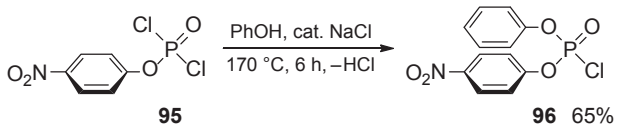


Figure 4.23.2

▶ *Diphenyl phosphorochloridate $(PhO)_2P(O)Cl$ (from diphenyl H-phosphonate and chlorine)* (*81*). Chlorine (28.4 g, 0.4 mol) was passed into a solution of diphenyl *H*-phosphonate (93.5 g, 0.4 mol) in carbon tetrachloride (400 ml) at 0—5 °C. A vigorous exothermic reaction ensued and the by-product hydrogen chloride escaped through the exhaust vent. The end-point was signalled by the green colour of chlorine persisting in the mixture. Distillation gave the product (87.5 g, 81%). Bp 141 °C/1 mmHg. A similar preparation on a 0.136 mol scale gave *bis*(2-chlorophenyl) phosphorochloridate $(2\text{-}ClC_6H_4O)_2P(O)Cl$ (47.7 g, 80%; bp 156 °C/1 mmHg). An analogous experiment conducted with *bis*(methylphenyl) *H*-phosphonates $(MeC_6H_4O)_2P(O)H$ resulted in considerable chlorination of the hydrocarbon group.

▶ *Diphenyl phosphorochloridate $(PhO)_2P(O)Cl$ (from diphenyl H-phosphonate and sulfuryl chloride)* (*81*). Sulfuryl chloride (42.0 g, 0.31 mol) was added dropwise during 30 min to diphenyl *H*-phosphonate (70.2 g, 0.30 mol) at 0–5 °C. The reaction was exothermic and within 10 min, hydrogen chloride was liberated. The mixture was stirred at 5 °C for another 20 min and the temperature was allowed to rise to 25 °C. The reaction was no longer exothermic. The pressure was reduced as quickly as possible and distillation gave the product (70.1 g, 87%). Bp 141 °C/1 mmHg.

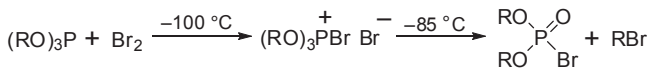
▶ *Diphenyl phosphorochloridate $(PhO)_2P(O)Cl$ (from phosphorus oxychloride)* (*140*). A stirred mixture of phosphorus oxychloride (15.4 g, 0.1 mol) and phenol (18.8 g, 0.2 mol) were heated to 230 °C for 5 h. The brown oil obtained was distilled to give diphenyl phosphorochloridate (11.0 g, 41%). Bp 102–105 °C/0.05 mmHg.

▶ *Di(alkylphenyl) phosphorochloridates $(RC_6H_4O)_2P(O)Cl$ (from phosphorus oxychloride)* (*41*). A stirred mixture of phosphorus oxychloride (78 g, 0.5 mol) and the alkylphenol (1 mol) was heated to 150–160 °C for 16 h under nitrogen. The mixture was distilled and the forerun to 84 °C/0.4 mmHg comprising unreacted $POCl_3$, alkylphenol and alkylphenyl phosphorodichloridate was discarded. The residue was distilled to give di(2-ethylphenyl) phosphorochloridate **93** (45% yield, bp 66 °C/0.03 mmHg). Di(2-*tert*-butylphenyl) phosphorochloridate **94** (58% yield) was isolated similarly.

▶ *Phenyl p-nitrophenyl phosphorochloridate $PhO(p\text{-}O_2NC_6H_4O)P(O)Cl$* (**96**) (*154*). A mixture of *p*-nitrophenyl phosphorodichloridate (28.0 g, 0.11 mol), phenol (9.5 g, 0.10 mol) and anhydrous sodium chloride (0.5 g) was heated slowly to 170 °C. After 6 h, the volatile products were evaporated (18 mmHg) at a temperature that was raised slowly to 200 °C. The fraction boiling at 203–209 °C/1 mmHg was collected and the title compound was crystallised by cooling and scratching, and obtained as fine needles (20 g, 65%). Mp 78–80 °C. Pure samples are stable in a refrigerator for more than 6 months.

4.24 DIALKYL PHOSPHOROBROMIDATES $(RO)_2P(O)Br$

Trialkyl phosphites react at low temperatures with bromine vapour (*155*) or bromine dissolved in ether (*156*) to produce bromophosphonium salts that decompose at −85 °C to give the dialkyl phosphorobromidates and alkyl bromide (Fig. 4.24.1).

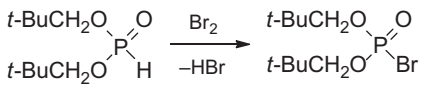


R = Et	δ_P 11.5	δ_P −9.7
R = *t*-$BuCH_2$	δ_P 13.0	δ_P −8.5
R = CCl_3CH_2	δ_P 6.5	δ_P −12.7
R = Me_3Si	δ_P nm	δ_P −34.0

^{31}P NMR data recorded in EtCl. nm = not measured

Figure 4.24.1

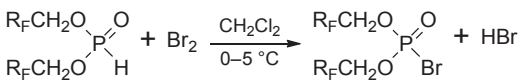
The reaction of dialkyl *H*-phosphonates that are easily dealkylated with bromine provides impure samples of dialkyl phosphorobromidates due to subsequent reaction with the liberated hydrogen bromide: $(RO)_2P(O)H + Br_2 \rightarrow (RO)_2P(O)Br + HBr \rightarrow RO(HO)P(O)Br + RBr$ and $RO(HO)P(O)Br + HBr \rightarrow (HO)_2P(O)Br + RBr$. Dialkyl *H*-phosphonates with alkoxy groups resistant to dealkylation can however be used to furnish pure dialkyl phosphorobromidates, albeit often in low yield. Dineopentyl *H*-phosphonate, for example, reacts with bromine to provide dineopentyl phosphorobromidate (**97**) in modest isolated yield (Fig. 4.24.2) (*78*).



97 33%

Figure 4.24.2

Treatment of *bis*(2,2,2-trifluoroethyl) *H*-phosphonate or *bis*(2,2,3,3,3-pentafluoropropyl) *H*-phosphonate with bromine in dichloromethane allows the isolation of the corresponding bromidates (**98**) or (**99**) (Fig. 4.24.3) (*82,149*). These compounds can be isolated because they have superior thermal stability compared to their non-fluorinated counterparts and because their ester groups are not as easily dealkylated by the released hydrogen bromide. The *bis*(fluoroalkyl) phosphorobromidates are potent phosphorylating agents and react readily with nucleophiles to give a variety of interesting products (*82,149*).



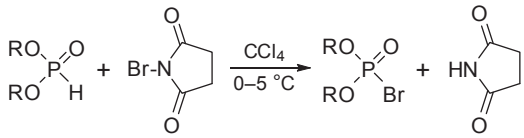
$R_F = CF_3$ **98** 51% δ_P −8.6

$R_F = C_2F_5$ **99** 87% δ_P −8.9

Figure 4.24.3

The reaction of dialkyl *H*-phosphonates with *N*-bromosuccinimide in carbon tetrachloride proceeds smoothly and gives pure phosphorobromidates in acceptable yields (Fig. 4.24.4) (*157–159*). The lower members of the series are liquids that can be purified by distillation under reduced pressure. However, they are not too thermally stable and decompose easily; diethyl phosphorobromidate converts quantitatively to ethyl bromide and a polymeric bromine-free residue after storage for 3 days at room temperature or after 20 min at 100 °C (the compound can however be stored for long periods without change at −40 °C) (*157*). The dialkyl phosphorobromidates are easily hydrolysed and react readily with aniline to yield the corresponding dialkyl *N*-phenylphosphoramidates.

Di-*tert*-butyl phosphorobromidate (**100**) is obtained pure from the reaction of di-*tert*-butyl *H*-phosphonate with carbon tetrabromide in a two-phase system comprising dichloromethane, dilute

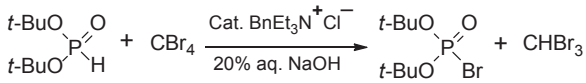


Dialkyl phosphorobromidates

R	Yield (%)	Bp (°C/mmHg)
Me	67	45–47/0.8
Et	65	75/1.5
n-Pr	45	88–90/0.4
i-Pr	65	77–78/0.4

Figure 4.24.4

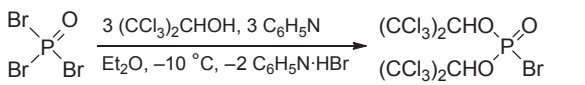
aqueous sodium hydroxide, and a catalytic amount of BTAC (Fig. 4.24.5) (*144*). The reaction mixture is alkaline, preventing acid-catalysed dealkylation, and steric hindrance by the bulky *tert*-butyl groups prevents conversion of the bromidate into the corresponding tetra-*tert*-butyl pyrophosphate. Di-*tert*-butyl phosphorobromidate is an unstable liquid that decomposes at room temperature within hours. It stores at 5 °C for about 12 h without decomposition and remains stable at −10 °C for at least 3 days, and can be used to phosphorylate amines (*74*).



100 90% δ_P 22.9

Figure 4.24.5

Another starting material for the synthesis of dialkyl phosphorobromidates is phosphorus oxybromide. It is unusual to attempt to substitute this reagent with 2 mol of an alcohol due to a tendency to form intractable mixtures of the mono-, di- and trisubstituted species. However, the use of a bulky alcohol such as hexachloroisopropanol stops the reaction at the *bis*-substitution stage, presumably for steric reasons, and this allows *bis*(hexachloroisopropyl) phosphorobromidate (**101**) to be isolated in excellent yield (Fig. 4.24.6) (*160*). This bromidate shows much lower reactivity to nucleophiles than



101 89% mp 120 °C

Figure 4.24.6

the less-hindered analogues already described. Only 10% of a sample in contact with water and acetone for 4 h at room temperature hydrolysed; the remainder was recovered unchanged.

The chemistry of dialkyl phosphorobromidates is not that well explored. When generated by the Todd—Atherton reaction of the dialkyl *H*-phosphonate, carbon tetrabromide, and a tertiary amine, they can react subsequently with amines (*74,161*) or thiols (*149*).

▷ *Dialkyl phosphorobromidates $(RO)_2P(O)Br$ (from the dialkyl H-phosphonate and N-bromosuccinimide)* (*157*). *N*-Bromosuccinimide (8.9 g, 50 mmol) was added in portions (0.5 g) to a stirred solution of the dialkyl *H*-phosphonate (50 mmol) in anhydrous carbon tetrachloride (20 ml) at 0—5 °C. After addition, the insoluble succinimide was filtered off. Removal of solvent from the filtrate and distillation of the residue under reduced pressure gave the dialkyl phosphorobromidates shown in Fig. 4.24.4.

▷ *Di-tert-butyl phosphorobromidate $(t\text{-}BuO)_2P(O)Br$ (from di-tert-butyl H-phosphonate and carbon tetrabromide)* (*144*). A solution of di-*tert*-butyl *H*-phosphonate (9.7 g, 50 mmol) in dichloromethane (15 ml) was added dropwise to a stirred two-phase system of dichloromethane (30 ml), carbon tetrabromide (8.3 g, 25 mmol), 20% aqueous sodium hydroxide (20 ml) and BTAC (0.5 g, ~5 mol%) at 20—25 °C. The mixture was stirred at this temperature for a further 3 h. The pale-yellow solution was diluted with dichloromethane (50 ml), the organic layer was separated, washed with water (2 × 50 ml), and dried ($MgSO_4$). The solvent was evaporated and the residue kept at 20 °C/0.5 mmHg for 1 h to remove any volatile impurities. The residual liquid was an analytically pure sample of the title compound (12.2 g, 90%). δ_P (CCl_4) 22.9 ppm.

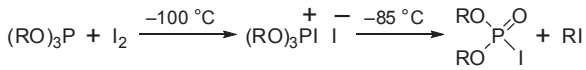
▷ *Dineopentyl phosphorobromidate $(t\text{-}BuCH_2O)_2P(O)Br$* (*78*). Bromine vapour (3.6 g, 22.5 mmol) was passed into dineopentyl *H*-phosphonate (4.4 g, 20.0 mmol) at room temperature. The mixture warmed up and was cooled, and hydrogen bromide was copiously evolved. Distillation afforded the bromidate as a white solid (2.0 g, 33%). Bp 90 °C/1 mmHg.

▷ *Bis(2,2,2-trifluoroethyl) phosphorobromidate $(CF_3CH_2O)_2P(O)Br$ (from the bis(fluoroalkyl) H-phosphonate and bromine)* (*82*). A solution of bromine (3.2 g, 20 mmol) in dichloromethane (20 ml) was added dropwise to a stirred solution of bis(2,2,2-trifluoroethyl) *H*-phosphonate (4.9 g, 20 mmol) in dichloromethane (30 ml) at 0—5 °C. After addition, the solution was warmed to room temperature and was left for 14 h; the yellow colour of residual bromine faded. The dichloromethane was removed. Fractionation of the residue under reduced pressure gave the title compound as a colourless liquid (3.3 g, 51%). Bp 38 °C/0.8 mmHg. A similar bromination of *bis*(2,2,3,3,3-pentafluoropropyl) *H*-phosphonate gave the corresponding phosphorobromidate $(C_2F_5CH_2O)_2P(O)Br$ (87%; bp 88 °C/1 mmHg) (*149*).

▷ *Bis(hexachloroisopropyl) phosphorobromidate $[(CCl_3)_2CHO]_2P(O)Br$ (from phosphorus oxybromide, hexachloroisopropanol and pyridine)* (*160*). A solution of hexachloroisopropanol (8.00 g, 30 mmol) and pyridine (2.37 g, 30 mmol) in ether (40 ml) was added to a stirred solution of phosphorus oxybromide (2.87 g, 10 mmol) in ether (40 ml) at −10 °C. After addition, the mixture was warmed to room temperature and the solids filtered off. The solvent was removed from the filtrate to give a solid. Recrystallisation from *n*-hexane gave the phosphorobromidate as white needles (5.87 g, 89%). Mp 120 °C (lit. 51—53 °C from petroleum ether and a different synthetic route (*161*)).

4.25 DIALKYL PHOSPHOROIODIDATES $(RO)_2P(O)I$

The existence of dialkyl phosphoroiodidates in solution after treating trialkyl phosphites with iodine dissolved in ether was first reported in 1945 (*70*). In dichloromethane or ether at −100 °C, the iodophosphonium salt forms instantaneously, and on warming to −85 °C decomposes to the dialkyl phosphoroiodidate and alkyl iodide (Fig. 4.25.1) (*156,162*). Dialkyl phosphoroiodidates prepared this way decompose upon removal of solvent and cannot be isolated. The reaction of diethyl *H*-phosphonate with iodoform and triethylamine in toluene at room temperature also results in rapid formation of diethyl phosphoroiodidate (*163*). However, this unstable product decomposes completely in the solution after 3 h.



R = Et	δ_P −15.1	δ_P −41.0
R = *t*-BuCH$_2$	δ_P −14.0	δ_P −40.0
R = CCl$_3$CH$_2$	δ_P nm	δ_P −50.0
R = Me$_3$Si	δ_P nm	δ_P −76.0

^{31}P NMR data recorded in EtCl. nm = not measured

Figure 4.25.1

The first dialkyl phosphoroiodidates obtained pure and free of solvent contain fluoroester groups that increase their stability. They are accessed in two ways (Fig. 4.25.2) (*164*). Treatment of *bis*(2,2,2-trifluoroethyl) *H*-phosphonate (**102**) with a solution of iodine in toluene, with argon blowing through the reaction mixture, yields *bis*(2,2,2-trifluoroethyl) phosphoroiodidate (**103**). Argon is passed into the mixture to help remove the liberated hydrogen iodide whose presence can cause dealkylation of the ester groups and therefore a reduced yield of the phosphoroiodidate. The use of *N*-iodosuccinimide as the iodination reagent in acetonitrile yields the neutral product succinimide, which

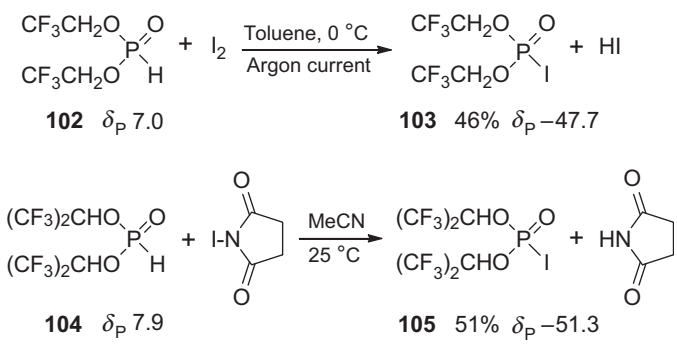


Figure 4.25.2

is unable to react with the phosphoroiodidate, and precipitates from solution. This method allows *bis*(hexafluoroisopropyl) *H*-phosphonate (**104**) to be converted into *bis*(hexafluoroisopropyl) phosphoroiodidate (**105**). The phosphoroiodidates (**103**) and (**105**) are sufficiently thermally stable to be purified by vacuum fractionation.

▶ *Bis(2,2,2-trifluoroethyl) phosphoroiodidate* $(CF_3CH_2O)_2P(O)I$ *(164)*. A solution of iodine (5.08 g, 20 mmol) in anhydrous toluene (100 ml) was added dropwise to a stirred solution of *bis*(2,2,2-trifluoroethyl) *H*-phosphonate (4.92 g, 20 mmol) in anhydrous toluene (75 ml) at 0–5 °C with passage of argon through the solution. After addition, the purple solution was left for 2 h. Residual iodine was removed by filtration through a small plug of silica gel. Removal of toluene and double distillation of the residue gave the iodidate as a pale yellow liquid (3.42 g, 46%). Bp 40 °C/0.02 mmHg. δ_P (202 MHz, $CDCl_3$) −47.7 ppm.

▶ *Bis(hexafluoroisopropyl) phosphoroiodidate* $[(CF_3)_2CHO]_2P(O)I$ *(164)*. A solution of *N*-iodosuccinimide (2.62 g, 11.65 mmol) in anhydrous acetonitrile (20 ml) was added dropwise by cannula to a stirred solution of *bis*(hexafluoroisopropyl) *H*-phosphonate (4.45 g, 11.65 mmol) in anhydrous acetonitrile (30 ml). After 2 h, analysis by GC–MS showed good conversion to product. Removal of solvent and double distillation of the oily residue gave the iodidate as a pale-yellow liquid (3.00 g, 51%). Bp 46 °C/2 mmHg. δ_P (202 MHz, $CDCl_3$) −51.3 ppm.

4.26 DIALKYL PHOSPHOROCYANIDATES $(RO)_2P(O)CN$

Diethyl phosphorocyanidate (**106**) was the first member of these compounds to be isolated, around 1948, by reaction of triethyl phosphite with cyanogen iodide (Fig. 4.26.1) *(165)*. Cyanogen iodide can be prepared from 1 mol of mercury(II) cyanide and 2 mol of iodine ($Hg(CN)_2 + 2\ I_2 \rightarrow HgI_2 + 2\ ICN$). It reacts readily with trialkyl phosphites to give the dialkyl phosphorocyanidates and the alkyl iodide. The more readily available cyanogen bromide can be used instead of cyanogen iodide, and returns the alkyl bromide instead of the alkyl iodide. The cyanidates are usually isolated in a pure state by vacuum fractionation.

Schrader reported that the reaction of dialkyl phosphorochloridates with sodium cyanide was sluggish and gave poor yields *(58)*. Nonetheless he managed to convert diethyl phosphorochloridate to

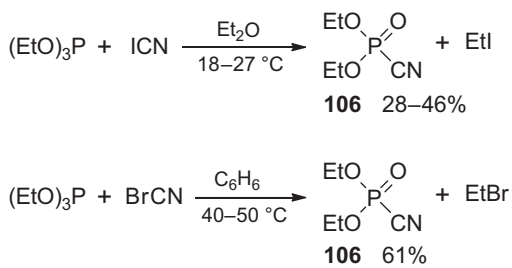
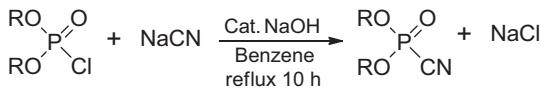


Figure 4.26.1

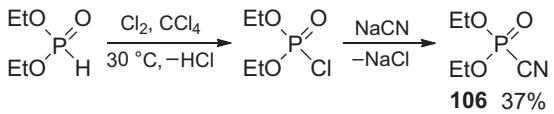
diethyl phosphorocyanidate in 22% yield by heating it with sodium cyanide in carbon tetrachloride (see recipes at the end of this section). Later investigation of this type of reaction revealed that an aged sample of sodium cyanide gave an improved yield of diethyl phosphorocyanidate (*166*). This suggested that sodium hydroxide, formed by partial hydrolysis of sodium cyanide in the old sample, might have catalysed the reaction. When the experiment was repeated with fresh sodium cyanide mixed with a small quantity of sodium hydroxide, consistent yields of both dimethyl and diethyl phosphorocyanidates (up to 46%) were obtained (Fig. 4.26.2). The species that combined with the cyanide in this case may have been the tetraalkyl pyrophosphate formed as an intermediate. Inclusion of a phase-transfer catalyst did not improve the yield and employment of polar aprotic solvents — acetonitrile, *N,N*-dimethylformamide, or dimethyl sulfoxide (DMSO) — suppressed the reaction totally.



R = Et **106** 46%
R = Me **107** 30%

Figure 4.26.2

The dialkyl phosphorochloridate can be prepared in one pot from the readily available dialkyl *H*-phosphonates using chlorine in carbon tetrachloride (Fig. 4.26.3) (*58*). The reaction mixture containing a dialkyl phosphorochloridate and hydrogen chloride is heated to 60—70 °C with an excess of sodium cyanide and a small quantity of water. The yield of the dialkyl phosphorocyanidate after distillation is however still modest.

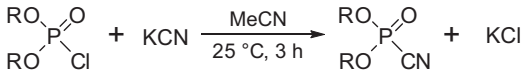


106 37%

Figure 4.26.3

Screening of a variety of solvents and temperatures for cyanidation of disubstituted phosphorochloridates resulted in the discovery of a general and mild method applicable to both dialkyl and diaryl phosphorochloridates (*167*). The chloridates react with potassium cyanide in acetonitrile at room temperature to give the cyanidates in high yield after vacuum distillation (Fig. 4.26.4). Prolonged boiling of diisopropyl phosphorochloridate with potassium cyanide for 16 h in acetone also provides diisopropyl phosphorocyanidate, but only in 42% isolated yield (*168*).

Higher yields of dialkyl phosphorocyanidates are obtained from dialkyl phosphorochloridates and hydrogen cyanide in ether in the presence of triethylamine (Fig. 4.26.5) (*169*). A white precipitate of triethylamine hydrochloride forms during the reaction. Filtration and distillation of the concentrated filtrate gives the desired cyanidates. Much lower yields are obtained when acetonitrile, benzene, dichloromethane, *N,N*-dimethylformamide, or THF are used instead of ether.

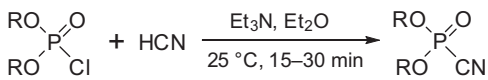


Dialkyl phosphorocyanidates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
Et	81	54–55/0.7	–20.6
n-Pr	86	76–78/1.0	–19.9
i-Pr	86	50–51/0.2	–23.4
n-Bu	80	90–94/0.8	–19.9
i-Bu	82	86–88/1.0	–19.6
s-Bu	82	68–69/0.3	–22.1
n-C_5H_{11}	83	130–131/1.2	–19.9
phenyl	47	128–130/0.4	–29.2

a. In $CDCl_3$ (85% H_3PO_4 external standard)

Figure 4.26.4



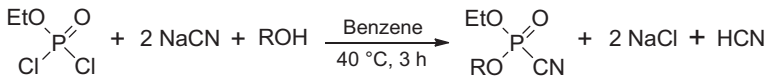
Dialkyl phosphorocyanidates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)[a]
Et	94	52–54/0.6	–20.5
n-Pr	95	62–64/0.4	–19.6
i-Pr	88	53–55/0.2	–23.1
n-Bu	90	70–71/0.2	–20.1
i-Bu	92	69–71/0.1	–19.5
s-Bu	85	70–71/0.2	–22.1
n-C_5H_{11}	87	102–104/0.5	–19.9

a. In $CDCl_3$ (85% H_3PO_4 external standard)

Figure 4.26.5

A high-yielding and versatile method of synthesis of dialkyl phosphorocyanidates involves the reaction of an alkyl phosphorodichloridate with an alkali metal cyanide and an equimolar amount of an alcohol in the presence of an inert solvent at about 40–45 °C (Fig. 4.26.6) (*58*). The discovery of this method by Schrader allowed him to prepare the first unsymmetrical dialkyl phosphorocyanidates (**108–109**); few such species are currently known.



R = Et **106** 80%
R = *n*-Pr **108**
R = *i*-Pr **109**

Figure 4.26.6

Dialkyl phosphorocyanidates are relatively non-toxic. The lower members are soluble in water and hydrolyse easily to give dialkyl hydrogen phosphates and hydrogen cyanide. Diethyl phosphorocyanidate is available commercially. It has many uses: for example, as a precursor to phosphorocyanidate salts, e.g. $(NaO)_2P(O)CN$ (*170*), in synthesis (*171–174*), or in combination with triethylamine for the conversion of carboxylic acids to amides, esters and thioesters (after reaction with amines, alcohols or thiols) (*175*). The P–CN bond in dialkyl phosphorocyanidates is weak and easily broken upon nucleophilic attack. The phosphorus atom in such species, in contrast to that in phosphorofluoridates or to an extent phosphorochloridates, is a soft electrophile and in competition reactions prefers to react with thiols rather than alcohols (*129*).

▶ *Cyanogen iodide ICN* (*16*). Mercury(II) cyanide (126 g, 0.5 mol) was added in portions to a stirred solution of iodine (254 g, 1 mol) in anhydrous ether (1500 ml). The mixture was stirred for 3 h. Mercury(II) iodide was separated by filtration and washed with ether. The filtrate and ether washings were combined and the solvent was removed by rotary evaporation (water bath at room temperature). The cyanogen iodide obtained was purified by vacuum sublimation at 40–45 °C to give a pure sample (12.7 g, 8%).

▶ *Diethyl phosphorocyanidate $(EtO)_2P(O)CN$ (Arbuzov reaction with cyanogen iodide: small scale)* (*165*). A solution of cyanogen iodide (38.75 g, 0.25 mol) in anhydrous ether (100 ml) was added to a stirred solution of triethyl phosphite (41.50 g, 0.25 mol) in anhydrous ether (500 ml). At first a vigorous reaction took place, but no free iodine was produced until the addition was complete; a brown colour then developed slowly. The volatile material was removed at room temperature using a water pump over 90 min and almost the entire residue was distilled at 93–98 °C/14 mmHg. Redistillation gave diethyl phosphorocyanidate (18.70 g, 46%; bp 90–91 °C/11 mmHg). This compound dissolves in water whereupon it hydrolyses to diethyl hydrogen phosphate and hydrocyanic acid.

▶ *Diethyl phosphorocyanidate $(EtO)_2P(O)CN$ (Arbuzov reaction with cyanogen iodide: large scale)* (*16*). A solution of cyanogen iodide (153 g, 1 mol) in anhydrous ether (400 ml) was added dropwise to a stirred solution of triethyl phosphite (166 g, 1 mol) in ether (2000 ml) over 30 min. After addition,

the reaction mixture was stirred at room temperature for 1 h. A rise in temperature from 18 °C to 27 °C was observed. After the addition was complete, the reaction mixture had a brown colour. The ether was removed and the residue fractionated through a Vigreux column to yield a colourless liquid (45 g, 28%). Bp 91–94 °C/10 mmHg.

▷ *Diethyl phosphorocyanidate $(EtO)_2P(O)CN$ (Arbuzov reaction with cyanogen bromide)* (58). A solution of cyanogen bromide (23 g, 0.22 mol) in benzene (50 ml) was added dropwise to a stirred solution of triethyl phosphite (34 g, 0.20 mol) in benzene (100 ml) at 40–50 °C. The product obtained after the vigorous reaction had subsided was distilled to provide diethyl phosphorocyanidate (20.0 g, 61%). Bp 78 °C/5 mmHg.

▷ *Diethyl phosphorocyanidate $(EtO)_2P(O)CN$ (cyanidation with sodium cyanide in carbon tetrachloride)* (58). Diethyl phosphorochloridate (87 g, 0.5 mol) was added to sodium cyanide (150 g, 3.0 mol) in carbon tetrachloride (300 ml) at 56 °C. After addition, the mixture was heated to 70 °C for 3 h. Filtration followed by distillation gave diethyl phosphorocyanidate (18 g, 22%). Bp 67–68 °C/1 mmHg.

▷ *Diethyl phosphorocyanidate $(EtO)_2P(O)CN$ (from the dialkyl H-phosphonate)* (58). Chlorine (35 g, 0.5 mol) was introduced over a period of 1 h into a stirred solution of diethyl *H*-phosphonate (70 g, 0.5 mol) in carbon tetrachloride (300 ml) at 30 °C. Sodium cyanide (150 g, 3.0 mol) and water (0.4 ml) were added. The mixture was stirred for 3 h at 60–70 °C. The usual work-up gave diethyl phosphorocyanidate (30 g, 37%). Bp 75 °C/2 mmHg.

▷ *Dialkyl/diaryl phosphorocyanidates $(RO)_2P(O)CN$ (cyanidation with potassium cyanide in acetonitrile)* (167). The dialkyl/diaryl phosphorochloridate (20 mmol), potassium cyanide (2.6 g, 40 mmol) and anhydrous acetonitrile (20 ml) was added to a 50 ml round-bottomed flask. The mixture was stirred vigorously at room temperature for 3 h and then filtered. The solvent was removed and the residue was distilled under reduced pressure.

▷ *Dialkyl phosphorocyanidates $(RO)_2P(O)CN$ (cyanidation with sodium cyanide and sodium hydroxide in benzene)* (166). A solution of dialkyl phosphorochloridate (0.10 mol) in benzene (20 ml) was added over 15 min to a stirred suspension of finely powdered sodium cyanide (7.35 g, 0.15 mol) and sodium hydroxide (0.20 g, 5 mmol) in benzene (50 ml). After addition, the mixture was heated under reflux with stirring for 10 h. Filtration and removal of the solvent gave a reddish brown liquid. Distillation gave the pure products: dimethyl phosphorocyanidate $(MeO)_2P(O)CN$ (30%, bp 90–91 °C/17 mmHg) or diethyl phosphorocyanidate $(EtO)_2P(O)CN$ (46%, bp 104–106 °C/14 mmHg). These turned brown on standing, but redistillation after 10 weeks returned the pure cyanidates.

▷ *Diisopropyl phosphorocyanidate $(i\text{-}PrO)_2P(O)CN$ (cyanidation with potassium cyanide in acetone)* (168). Diisopropyl phosphorochloridate (25.0 g, 0.12 mol) was dissolved in anhydrous acetone (50 ml) containing potassium cyanide (12.5 g, 0.19 mol) and stirred and boiled for 16 h. The solvent was removed and the material was distilled to provide the cyanidate (9.6 g, 42%). Bp 58–60 °C/1 mmHg. δ_P (D_2O) 24.2 ppm.

▷ *Dialkyl phosphorocyanidates $(RO)_2P(O)CN$ (cyanidation with hydrogen cyanide and triethylamine)* (169). A solution of hydrogen cyanide (0.16 g, 6 mmol) in ether (0.5 ml) was added to a stirred solution of the dialkyl phosphorochloridate (5 mmol) and triethylamine (0.51 g, 5 mmol) in ether

(2 ml) at 10–20 °C. After addition, the mixture was stirred for 15 min, then filtered, and the filtrate was concentrated and distilled under vacuum.

▶ *Diethyl phosphorocyanidate (EtO)$_2$P(O)CN (from ethyl phosphorodichloridate)* (*58*). Ethyl phosphorodichloridate (82 g, 0.50 mol) was added over 15 min to a stirred mixture of sodium cyanide (100 g, 2.04 mol), absolute ethanol (12 g, 0.26 mol) and benzene (100 ml) at 25 °C. A temperature of 40 °C was reached in 3 min. The reaction temperature was kept at 40 °C by cooling. After the dichloridate had been run in, additional absolute ethanol (12 g, 0.26 mol) was added over a period of 7 min while keeping the temperature at 40 °C. The reaction mixture was stirred for 3 h. The solids were filtered off and the filtrate concentrated. Vacuum distillation of the residue gave diethyl phosphorocyanidate (65 g, 80%; bp 93–95 °C/10 mmHg). A second distillation gave a sample of 98% purity (bp 72 °C/2 mmHg) as determined by titration with silver(I) nitrate. Repeating this experiment with *n*-propanol or isopropanol instead of ethanol gave ethyl *n*-propyl phosphorocyanidate EtO(*n*-PrO)P(O)CN (bp 88 °C/25 mmHg) or ethyl isopropyl phosphorocyanidate EtO(*i*-PrO)P(O)CN (bp 77 °C/3 mmHg).

4.27 *O*-ALKYL DIALKOXYPHOSPHINYLFORMATES (RO)$_2$P(O)C(O)OR

The reaction of triethyl phosphate with benzoyl chloride in the presence of triethylamine catalyst gives benzoyl diethyl phosphate (**110**) in low yield (Fig. 4.27.1) (*176*). Such compounds are potent phosphorylating agents and react with nucleophiles with loss of benzoic acid.

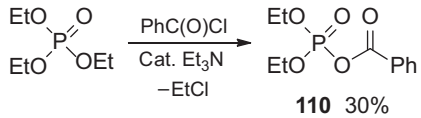


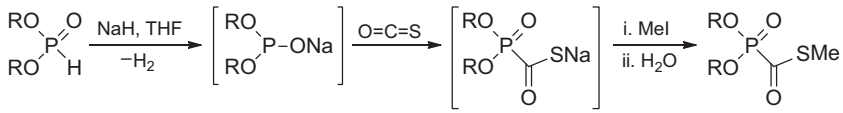
Figure 4.27.1

▶ *Benzoyl diethyl phosphate (EtO)$_2$P(O)OC(O)Ph* (**110**) (*176*). A stirred mixture of triethyl phosphate (364.0 g, 2 mol), benzoyl chloride (140.5 g, 1 mol) and triethylamine (1.0 g, 10 mmol) was heated at 140–145 °C for 7 h. Distillation gave the title compound (77.4 g, 30%). Bp 128–140 °C/0.1 mmHg.

4.28 *S*-ALKYL DIALKOXYPHOSPHINYLTHIOFORMATES (RO)$_2$P(O)C(O)SR

Dialkyl phosphite sodium salts suspended in THF add carbonyl sulfide to give thioformate salts that react with alkyl iodides (*177*). Aqueous work-up and distillation of the product provides *S*-alkyl dialkoxyphosphinylthioformates in modest to good yields (Fig. 4.28.1).

▶ *S-Methyl diethoxyphosphinylthioformate (EtO)$_2$P(O)C(O)SMe* (**111**) (*177*). Diethyl *H*-phosphonate (27.6 g, 0.2 mol) was added dropwise to a slurry of sodium hydride (51% dispersion in mineral oil, 9.6 g, 0.2 mol) in THF (200 ml) at 25–30 °C in a dry atmosphere. The mixture was stirred and heated under reflux until hydrogen evolution ceased. The mixture was cooled to 6 °C and carbonyl sulfide gas was passed into the mixture at 2–5 °C until the mixture had absorbed sufficient gas (13.3 g,



R = Et **111** 48% δ_P 4.6
R = *i*-Pr **112** 70% δ_P 6.5

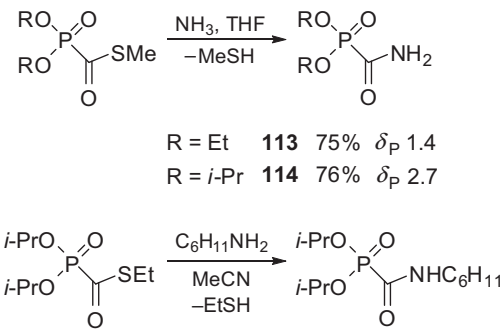
Figure 4.28.1

0.22 mol). Iodomethane (28.4 g, 0.2 mol) was added over 10 min to the stirred mixture at 3–5 °C. The mixture was poured into ice water (1000 ml) whereupon a liquid separated. This was extracted into ether (200 ml). The water layer was saturated with sodium chloride and extracted with ether (200 ml). The ether extracts were combined, dried ($MgSO_4$), filtered, and evaporated to yield a colourless liquid whose distillation gave the thioformate (20.5 g, 48%). Bp 80–81 °C/0.1 mmHg. δ_P (neat) 4.6 ppm.

▶ *S-Methyl diisopropoxyphosphinylthioformate (i-PrO)$_2$P(O)C(O)SMe* (**112**) (*177*). The previous procedure was followed using diisopropyl *H*-phosphonate (33.2 g, 0.2 mol), sodium hydride (51% dispersion in mineral oil, 9.6 g, 0.2 mol), carbonyl sulfide (25.1 g, 0.43 mol), iodomethane (28.4 g, 0.2 mol) and THF (200 ml). The title compound was obtained (33.8 g, 70%). Bp 100–101 °C/0.5 mmHg. δ_P (neat) 6.5 ppm.

4.29 *N*-ALKYL DIALKOXYPHOSPHINYLFORMAMIDES $(RO)_2P(O)C(O)NR_2$

S-Methyl dialkoxyphosphinylthioformates react with ammonia in THF at the carbonyl rather than the phosphonyl group. Methanethiol is lost and the formed dialkoxyphosphinylformamides (**113**) and (**114**) precipitate from solution in good yield (Fig. 4.29.1) (*177*). *S*-Alkyl dialkoxyphosphinylthioformates also react with primary amines in acetonitrile to yield *N*-alkyl dialkoxyphosphinylformamides (**115**) (*178*). The driving force for these reactions is presumably the formation of a resonance-stabilised peptide bond.



R = Et **113** 75% δ_P 1.4
R = *i*-Pr **114** 76% δ_P 2.7

115 78% δ_P −2.5

Figure 4.29.1

▶ *Diethoxyphosphinylformamide* $(EtO)_2P(O)C(O)NH_2$ (**113**) (*177*). Ammonia was passed into a solution of *S*-methyl diethoxyphosphinylthioformate (4.24 g, 20 mmol) in THF (30 ml) at room temperature for 3 h. The white crystals were filtered off and the filtrate was concentrated to yield more solid. The crystalline solids were combined, washed with ether, filtered, and dried at 70 °C/20 mmHg to yield the product (2.80 g, 75%). Mp 138–139 °C. A sample was recrystallised from hot ethyl acetate and dried under vacuum to yield crystals (mp 138–139 °C). δ_P (15.9% solution in acetone) 1.4 ppm.

▶ *Diisopropoxyphosphinylformamide* $(i\text{-}PrO)_2P(O)C(O)NH_2$ (**114**) (*177*). The previous procedure was followed using *S*-methyl diisopropylphosphinylthioformate (4.9 g, 21 mmol). The title compound was isolated as a white solid (3.3 g, 76%). Mp 94–96 °C. A sample was recrystallised from hot ethyl acetate to yield colourless needles (mp 95–97 °C.) δ_P (15.9% solution in acetone) 2.7 ppm.

▶ *N-Cyclohexyl diisopropoxyphosphinylformamide* $(i\text{-}PrO)_2P(O)C(O)NHC_6H_{11}$ (**115**) (*178*). *S*-Ethyl diisopropylphosphinylthioformate (2.1 g, 8.2 mmol) was added to a stirred mixture of cyclohexylamine (0.81 g, 8.2 mmol) and triethylamine (1.66 g, 16 mmol) in acetonitrile (10 ml) under nitrogen. The reaction was monitored by ^{31}P NMR spectroscopy. After 8 h, the mixture was concentrated and the residue dissolved in ethyl acetate, filtered and washed successively with 1 M hydrochloric acid, water, 10% aqueous sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated under vacuum to give the title compound as a white solid (1.85 g, 78%). Mp 78–80 °C. δ_P ($CDCl_3$) −2.5 ppm.

4.30 [(DIALKOXYPHOSPHINYL)FORMYL]-*O*-ALKYLHYDROXAMATES $(RO)_2P(O)C(O)NHOR$

S-Ethyl diisopropylphosphinylthioformate reacts with *O*-methylhydroxylamine in pyridine to provide a mixture of [(diisopropoxyphosphinyl)formyl]-*O*-methylhydroxamate (**116**) and diisopropyl phosphoramidate (**117**) (Fig. 4.30.1) (*178*). The two are separable by chromatography on silica gel.

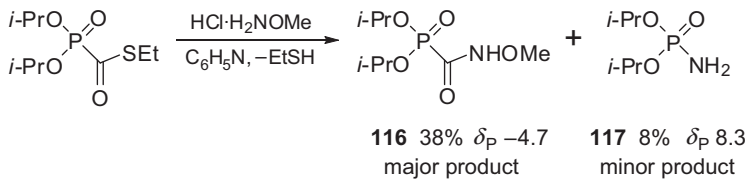


Figure 4.30.1

▶ *[(Diisopropoxyphosphinyl)formyl]-O-methylhydroxamate* $(i\text{-}PrO)_2P(O)C(O)NHOMe$ (**116**) (*178*). *S*-Ethyl diisopropylphosphinylthioformate (2.540 g, 0.01 mol) was added to a stirred mixture of *O*-methylhydroxylamine hydrochloride (0.835 g, 0.01 mol) in pyridine (10 ml) at 25 °C under nitrogen. The reaction was monitored by ^{31}P NMR spectroscopy. After 72 h the mixture was concentrated and the residue was taken up in ethyl acetate, filtered, and chromatographed on silica gel, eluting with 2:1 ethyl acetate–petroleum ether, to give a colourless liquid (0.908 g, 38%). δ_P ($CDCl_3$) −4.7 ppm.

4.31 *S*-ALKYL DIALKOXYPHOSPHINYLDITHIOFORMATES $(RO)_2P(O)C(S)SR$

Dialkyl phosphite sodium salts suspended in THF add carbonyl disulfide to give thioformate salts that react readily with alkyl iodides (*177*). Aqueous work-up and distillation of the product provides the *S*-alkyl dialkoxyphosphinyldithioformates (**118**) and (**119**) in acceptable yields (Fig. 4.31.1).

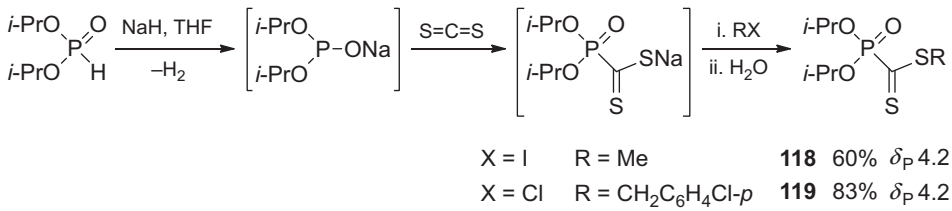


Figure 4.31.1

▶ *S-Methyl diisopropoxyphosphinyldithioformate (i-PrO)$_2$P(O)C(S)SMe* (**118**) (*177*). Diisopropyl *H*-phosphonate (33.2 g, 0.2 mol) was added dropwise to a slurry of sodium hydride (51% dispersion in mineral oil, 9.4 g, 0.2 mol) in THF (200 ml) at 25–30 °C in a dry atmosphere. The mixture was stirred and heated under reflux until hydrogen evolution ceased. The resulting solution was added over 15 min to stirred carbon disulfide (76.0 g, 1 mol) at 2–8 °C. The solution coloured red. Iodomethane (30.0 g, 0.21 mol) was added over 5 min to the stirred solution at 5 °C. The mixture was stirred for an additional 5 min at 5 °C. The homogeneous dark-red mixture was poured into ice water (750 ml) and the organic phase was extracted into ether (300 ml). The ether layer was washed with water (4 × 500 ml), dried ($MgSO_4$), filtered, and the filtrate evaporated to yield an oil. Distillation through a 22 cm vacuum-jacketed Vigreux column gave a dark red-coloured liquid (30.8 g, 60%). Bp 116–117 °C/0.4 mmHg. δ_P (neat) 4.2 ppm.

▶ *S-(4-Chlorobenzyl) diisopropoxyphosphinyldithioformate (i-PrO)$_2$P(O)C(S)SCH$_2$C$_6$H$_4$Cl-p* (**119**) (*177*). Sodium hydride (51% dispersion in mineral oil, 4.7 g, 0.10 mol) was freed of mineral oil by washing with hexane (3 × 300 ml). The supernatant liquor was removed and sodium diisopropyl phosphite (0.10 mol) was prepared in THF (100 ml) in the usual manner. The THF solution of sodium diisopropyl phosphite was added to carbon disulfide (38.0 g, 0.50 mol) as before. A solution of 4-chlorobenzyl chloride (14.5 g, 0.09 mol) in THF (100 ml) was added over 5 min to the reaction mixture at 1–3 °C, which was then stirred for 19 h under nitrogen. The mixture was heated under reflux for 1 h. Ether (300 ml) was added and the mixture was washed with water (3 × 500 ml). The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated at 80 °C to leave a dark red oil. The oil was dried at 80 °C/0.1 mmHg for 1 h and then at room temperature at 0.1 mmHg for 20 h to yield a deep-red liquid (27.4 g, 83%). The ^{31}P NMR spectrum showed three shifts at 4.2, 0.0 and −16.1 ppm. The peak at 4.2 ppm accounted for >95% of the combined areas under the peaks.

4.32 SYMMETRICAL DIALKYL HYDROGEN PHOSPHATES $(RO)_2P(O)OH$

The lower dialkyl hydrogen phosphates $(RO)_2P(O)OH$, where R = Me, Et and *i*-Pr, are prepared satisfactorily by oxidising the dialkyl *H*-phosphonates, $(RO)_2P(O)H$, with aqueous chloramine T (*N*-chloro-*p*-toluenesulfonamide sodium salt, $MeC_6H_4SO_2NClNa$) (*179*). They are also readily prepared by hydrolysis of species $(RO)_2P(O)X$ where X is a good leaving group that includes the halogens, azide, cyanide, alkylthiolate (*180*), enolates (*181*), electronegative aromatic groups, e.g. 4-nitrophenoxy (*182–184*), amino groups under acidic conditions, or hydrazine groups in aqueous iodine (*185*). Dialkyl hydrogen phosphates are strong acids. Acidity decreases with increasing size of the alkyl substituents: $(MeO)_2P(O)OH$ pK_a 1.3 (*186*) and $(EtO)_2P(O)OH$ pK_a 1.5 (*187*).

Unsymmetrical and symmetrical dialkyl phosphorochloridates are often the most accessible and convenient reagents for conversion to the dialkyl hydrogen phosphates (**120–122**), which can be achieved by addition of the chloridate to water or aqueous ethanol (Fig. 4.32.1) (*148,188,189*).

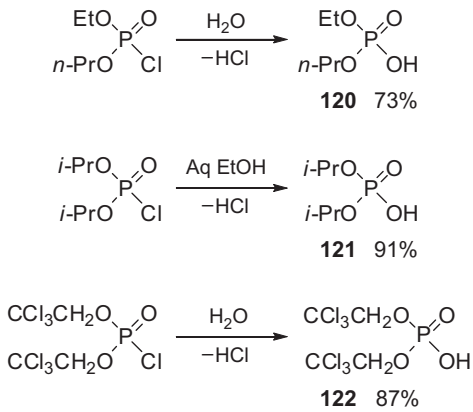


Figure 4.32.1

Cyclic dialkyl hydrogen phosphates are also known (*190*). The cyclic phosphorochloridate (**88**) does not hydrolyse readily as it is insoluble in water, but can be converted into the acid (**123**) by dissolving it in aqueous acetone (Fig. 4.32.2) (*80*).

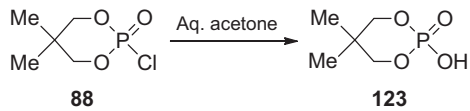


Figure 4.32.2

Treatment of purified dibenzyl *H*-phosphonate with aqueous bromine in the presence of pyridine and carbon tetrachloride provides the dibenzyl hydrogen phosphate (**124**) in good yield (Fig. 4.32.3) (*77*). *O,O*-Diethyl hydrogen phosphorothioate (**125**) is converted into the sulfur-free analogue (**126**) when allowed to stand with an equimolar amount of DMSO for 1 week at 20 °C (Fig. 4.32.4) (*191*).

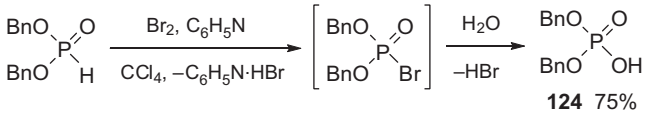


Figure 4.32.3

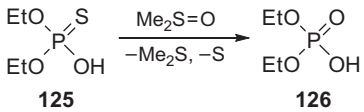


Figure 4.32.4

▶ *Ethyl n-propyl hydrogen phosphate EtO(n-PrO)P(O)OH* (**120**) (*148*). Ethyl *n*-propyl phosphorochloridate (5.0 g, 27 mmol) was added dropwise with stirring to water (25 ml) cooled in an ice bath. Distillation gave the title compound (3.3 g, 73%). Bp 128 °C/0.2 mmHg.

▶ *Diisopropyl hydrogen phosphate (i-PrO)$_2$P(O)OH* (**121**) (*188*). Diisopropyl phosphorochloridate (4.0 g, 20 mmol) was mixed with water and ethanol (9:1) and the solvents evaporated at 50 °C under reduced pressure, first with a water pump and finally for several hours under high vacuum. The residual colourless oil, crystallised by freezing with liquid air [nitrogen is safer], formed white crystals (3.3 g, 91%). Mp 34 °C.

▶ *Bis(2,2,2-trichloroethyl) hydrogen phosphate (CCl$_3$CH$_2$O)$_2$P(O)OH* (**122**) (*189*). Water (0.80 ml, 44.5 mmol) was added with stirring to *bis*(2,2,2-trichloroethyl) phosphorochloridate (15.17 g, 40.0 mmol) that had been melted and maintained at 80–85 °C. After 30 min the mixture was evacuated leaving a crystalline mass. Crystallisation from hexane gave the product (12.58 g, 87%). Mp 81–84 °C.

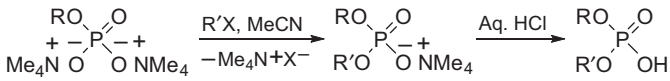
2,2-Dimethyl-1,3-propanediol cyclic hydrogen phosphate (**123**) (*80*). A small sample of 2,2-dimethyl-1,3-propanediol cyclic phosphorochloridate was dissolved in 1:1 *v/v* acetone–water and left for 2 days. Some of the solvent evaporated and a white crystalline material deposited. Recrystallisation of this from a mixture of benzene and ethanol gave the title compound as a monohydrate, as long slender needles. Mp 174–176 °C.

▶ *Dibenzyl hydrogen phosphate (BnO)$_2$P(O)OH* (**124**) (*77*). A solution of bromine (110 g, 0.69 mol) in carbon tetrachloride (150 ml) was added over 3 h dropwise to a stirred solution of crude dibenzyl *H*-phosphonate (225 g of 80% purity, 0.69 mol), carbon tetrachloride (50 ml), pyridine (200 g, 2.53 mol) and water (600 ml) at 0–5 °C. After addition, stirring was continued for a further 1 h, concentrated hydrochloric acid (250 ml) was added, and the layers were separated. The carbon tetrachloride layer was washed with water and then neutralised with 10% aqueous sodium hydroxide (170 ml) using phenolphthalein as the pH indicator. Acidification of the neutral aqueous layer with hydrochloric acid precipitated dibenzyl hydrogen phosphate, which was extracted with chloroform (3 × 150 ml), the extract evaporated, and the product crystallised from ether. Colourless prisms were obtained (100 g, 52%). Mp 79–80 °C. The impurities present in crude dibenzyl *H*-phosphonate had an adverse effect on yield, as a comparable experiment starting with distilled material gave more product (144 g, 75%).

4.33 UNSYMMETRICAL DIALKYL HYDROGEN PHOSPHATES RO(R′O)P(O)OH

Various options are available for the synthesis of mixed dialkyl hydrogen phosphates. These include replacement of one alkyl group of a dialkyl hydrogen phosphate by another alkyl group (*192*) or selective monodealkylation of a trialkyl phosphate (*193–195*). Conversion of an alkyl dihydrogen phosphate to a dialkyl hydrogen phosphate has been accomplished in nucleotide synthesis using an alcohol and dicyclohexylcarbodiimide as a condensing agent (*196*), but this method is unsatisfactory for the production of simple aliphatic derivatives. Low yields of the desired products are obtained and these require purification by chromatography. Hydrolysis of unsymmetrical dialkyl phosphorochloridates is another possibility and can give good yields of the hydrogen phosphate (Section 4.32), although rarely are the starting chloridates readily available.

Mixed dialkyl hydrogen phosphates can be made by selective monoalkylation of the *bis*(tetramethylammonium) salts of alkyl dihydrogen phosphates with long-chain alkyl halides (Fig. 4.33.1) (*197*). The starting alkyl dihydrogen phosphates are prepared by phosphorylation of alcohols with pyrophosphoric acid (*198*). Selective monoalkylation is possible because of the greater nucleophilicity of the alkyl phosphate dianion compared to the anion of the dialkyl hydrogen phosphate product. An excess of alkyl halide carries the reaction on to the trialkyl phosphate, but with equimolar amounts of alkyl dihydrogen phosphate and alkyl halide, the yields are consistently about 80% dialkyl hydrogen phosphate and <5% trialkyl phosphate.



Unsymmetrical dialkyl hydrogen phosphates

R	R′	X	Reaction time (h)	Yield (%)
C_8H_{17}	$C_{14}H_{29}$	Cl	24	81
$C_{10}H_{21}$	$C_{16}H_{33}$	Cl	20	78
$C_{10}H_{21}$	C_6H_{13}	Br	16	81
$C_{12}H_{25}$	C_6H_{13}	Br	2.5	79

Figure 4.33.1

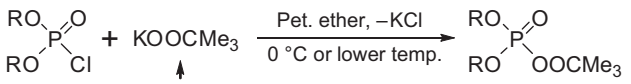
When the product dialkyl hydrogen phosphate is a solid, it can be purified by recrystallisation. Otherwise it is necessary to convert it into the sodium salt by neutralisation with NaOH in ethanol, which causes precipitation of the unreacted monoalkyl phosphate disodium salt, allowing its removal. The reactivity of the alkyl halides follows the customary order (I > Br > Cl > F). It is possible to use the cheaper alkyl chlorides by heating the reaction mixture under reflux overnight to give yields comparable to those obtained in several hours from the corresponding bromides. Also the difference in halide reactivity can be exploited to produce mixed dialkyl hydrogen phosphates having a halogen in one of the ester groups; 1-bromo-3-chloropropane, for example, reacts with *bis*(tetramethylammonium) dodecyl

phosphate to give the product with the 3-chloropropyl side-chain. Secondary halides are less reactive and generally give low yields.

▶ *Dialkyl hydrogen phosphates RO(R′O)P(O)OH* (*197*). The alkyl dihydrogen phosphate (21 mmol) was dissolved in 20% methanolic tetramethylammonium hydroxide (determined by titration to contain 42 mmol of base) and the solvent removed by vacuum evaporation at 40 °C for 30 min. The tacky solid was dissolved in acetonitrile (50 ml) and an alkyl halide (21 mmol) was added. The reaction mixture was stirred and heated under reflux for 1—2 h in the case of bromides (or 24 h for chlorides). The solvent was removed and the residue dissolved in water (100 ml), acidified with concentrated hydrochloric acid (5 ml), and extracted with ether (3 × 60 ml). The combined ether layers were washed with water (3 × 25 ml) and dried ($MgSO_4$). The solvent was removed to produce a residue that was weighed and analysed by titration with 1 M aqueous NaOH (which distinguishes between the starting alkyl dihydrogen phosphate and the dialkyl hydrogen phosphate, the neutral remainder being taken as trialkyl phosphate). For isolation of the pure dialkyl hydrogen phosphate, the mixture was dissolved in isopropanol and neutralised with the calculated quantity of 50% *w/v* aqueous sodium hydroxide. After centrifugation, the supernatant contained the sodium dialkyl phosphate, which was isolated by evaporation, and if necessary reconverted to the acid by the above procedure. Purity was assessed by TLC on silica gel, eluting with 60:35:5 chloroform—methanol—water; this solvent system allowed separation of mono-, di- and trialkyl esters, which were visualised using bromophenol blue.

4.34 DIALKYL ALKYLPEROXY PHOSPHATES $(RO)_2P(O)OOR$

Two methods for the synthesis of these species are available (Fig. 4.34.1) (*140*). The first is reaction of a dialkyl phosphorochloridate with *tert*-butyl hydroperoxide in cold anhydrous pyridine to yield the peroxy phosphates (**127—129**). The second involves treating dialkyl phosphorochloridates with aqueous potassium hydroxide and *tert*-butyl hydroperoxide in petroleum ether (bp 20—40 °C). No general protocol for the preparation of the peroxy phosphates exists and the original literature (*140*)



R = Me	**127**	53%
R = Et	**128**	53%
R = *n*-Pr	**129**	70%
R = *i*-Pr	**130**	52%
R = *n*-Bu	**131**	77%
R = *i*-Bu	**132**	47%
R = Bn	**133**	- [a]
R = Ph	**134**	- [b]

a. Decomposes rapidly at 25 °C. *b*. Decomposes violently at 0 °C (*caution!*).

Figure 4.34.1

should be consulted for experimental methods for products **128–134** (some of the original methods are reproduced at the end of this section). The choice of solvent is critical: when benzene, diethyl ether, or *n*-pentane is substituted for petroleum ether, little or no product forms.

The dialkyl phosphorochloridate is added dropwise as rapidly as possible while keeping the temperature between 8 and 12 °C. If the temperature rises sharply above 15 °C, or if the pH falls below 8, the corresponding dialkyl hydrogen phosphate, $(RO)_2P(O)OH$, forms, but not with the peroxy phosphate, as its decomposition is catalysed by dialkyl hydrogen phosphate impurities. The disubstituted *tert*-butylperoxy phosphates have varying stability according to the nature of the ester groups attached to the phosphorus atom. Dimethyl *tert*-butylperoxy phosphate (**127**) is a low-melting white solid that decomposes rapidly at room temperature, but stores without decomposition for a few days at 5 °C and for several weeks at −20 °C. Diethyl *tert*-butylperoxy phosphate (**128**) and di-*n*-propyl or diisopropyl *tert*-butylperoxy phosphates (**129**) and (**130**) are liquids and can be purified in quantities of 5 g or less by short-path distillation under reduced pressure; pure samples store indefinitely at room temperature. Di-*n*-butyl or diisobutyl *tert*-butylperoxy phosphates (**131**) and (**132**) can be purified by chromatography on neutral alumina and are stable indefinitely at −20 °C. Dibenzyl *tert*-butylperoxy phosphate (**133**) decomposes at room temperature and has not been isolated pure. Diphenyl *tert*-butylperoxy phosphate (**134**) is hazardous to work with as it decomposes violently even at 0 °C under high vacuum. The chemistry of the dialkyl *tert*-butylperoxy phosphates is largely uncharted.

Distillation of dialkyl *tert*-butylperoxy phosphates of sufficient stability is greatly facilitated by washing the distillation vessel with 30% *w/v* aqueous sodium hydroxide solution, water, and then acetone before each distillation; and by washing the peroxy ester in petroleum ether with a cold 50% *v/v* aqueous ammonium hydroxide solution before distillation.

▶ *Dimethyl tert-butylperoxy phosphate* $(MeO)_2P(O)OO$*-t-Bu* (**127**) (*140*). *Tert*-butyl hydroperoxide (9.01 g, 0.10 mol) was added in one portion followed by petroleum ether (bp 20–40 °C, 60 ml) to a stirred solution of potassium hydroxide (6.16 g, 0.11 mol) in water (29 ml) at 0 °C. The mixture was cooled to 13 °C and dimethyl phosphorochloridate (12.9 g, 0.09 mol) was added in one portion. The mixture was held at 20 °C for 10 min. The organic layer was washed successively with ice-cold 5% *w/w* aqueous NaCl (50 ml) and ice water (50 ml), dried ($MgSO_4$) and concentrated at 10 °C. The oily residue was crystallised repeatedly from Skellysolve B to give the title compound (9.44 g, 53%). Mp 26 °C.

▶ *Diethyl tert-butylperoxy phosphate* $(EtO)_2P(O)OO$*-t-Bu* (**128**) *(pyridine method)* (*140*). *Tert*-butyl hydroperoxide (36 g, 0.4 mol) in anhydrous pyridine (24 g, 0.3 mol) was added to a stirred solution of diethyl phosphorochloridate (35 g, 0.2 mol) in petroleum ether (bp 20–40 °C, 100 ml) at −20 °C. The mixture was warmed to 25 °C and filtered. The filtrate was concentrated and the residual oil was dissolved in benzene. The benzene solution was washed with ice-cold water and concentrated. Distillation of the residue under reduced pressure gave the title compound (yield not stated). Bp 66–67 °C/0.15 mmHg.

▶ *Diethyl tert-butylperoxy phosphate* $(EtO)_2P(O)OO$*-t-Bu* (**128**) *(potassium hydroxide method)* (*140*). Diethyl phosphorochloridate (31.0 g, 0.18 mol) was added over 5 min to a stirred mixture of potassium hydroxide (12.3 g, 0.22 mol), water (58 ml), *tert*-butyl hydroperoxide (36.1 g, 0.4 mol) and petroleum ether (bp 20–40 °C, 120 ml) at 9 °C. The mixture was stirred at 9–15 °C for 30 min and

the organic layer was washed with water (100 ml), dried ($MgSO_4$) and concentrated. The residual liquid was held at ambient temperature under vacuum until TLC and NMR analyses showed that all the *tert*-butyl hydroperoxide had been removed. The title compound remained (21.6 g, 53%).

▶ *Di-n-propyl tert-butylperoxy phosphate (n-PrO)$_2$P(O)OO-t-Bu* (**129**) (*140*). Freshly distilled di-*n*-propyl phosphorochloridate (18.05 g, 0.09 mol) was added to a stirred mixture of potassium hydroxide (6.16 g, 0.11 mol), water (29 ml), *tert*-butyl hydroperoxide (9.01 g, 0.10 mol) and petroleum ether (bp 20–40 °C, 100 ml) at 10 °C. The mixture was stirred at room temperature for 2.5 h. The organic layer was washed with cold water (50 ml), dried (Na_2SO_4), concentrated and distilled to give the title compound (16 g, 70%). Bp 85–87 °C/0.3 mmHg.

4.35 TRIALKYL PHOSPHATES $(RO)_2P(O)OR$

These organophosphorus compounds were among the earliest researched (*199,200*). Often dialkyl phosphorochloridates react with alcohols in the absence of base to give trialkyl phosphates in good yields. The phosphorohalidate can be generated in situ or used pure. Bromine can be added to a mixture of the trialkyl phosphite and an alcohol until its brown colour persists, signifying that the formed dialkyl phosphorobromidate has reacted, or the pure dialkyl phosphorochloridate or dialkyl phosphoroiodidate can be stirred with an excess of the alcohol (*201*). These routes to trimethyl phosphate (**135**) are summarised in Fig. 4.35.1. Dialkyl phosphorofluoridates also react with alcohols to furnish trialkyl phosphates; the reaction of diethyl trichloromethylphosphonate with potassium fluoride in methanol results in P–C bond cleavage and fluorination, to give diethyl phosphorofluoridate,

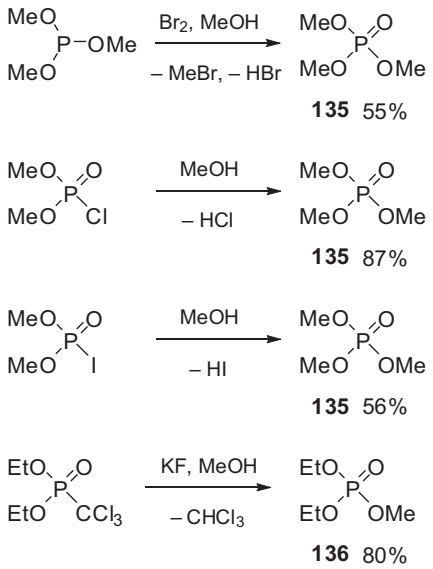


Figure 4.35.1

which undergoes prompt methanolysis. Diethyl methyl phosphate (**136**) is thus obtained in high yield (*202*).

▶ *Trimethyl phosphate* (**135**) *(from trimethyl phosphite, bromine and methanol)* (*201*). Bromine was added dropwise to a solution of trimethyl phosphite (24.8 g, 0.2 mol) in methanol (250 ml) at 0–10 °C until the bromine colour was no longer discharged. The solution was allowed to warm to room temperature and the solvent was removed. Distillation of the residue gave trimethyl phosphate (15.3 g, 55%). Bp 73–78 °C/10 mmHg.

Oxidation of trialkyl phosphites by an oxidising agent such as mercury(II) oxide (e.g. to give **137**) or atmospheric oxygen (e.g. to give **138**) is one of the oldest routes to trialkyl phosphates (*76*). Yellow mercury(II) oxide oxidises non-cyclic and cyclic trialkyl phosphites, the latter without ring opening, to the phosphates **139** and **140** (Fig. 4.35.2) (*203*). Five-membered phosphate esters are useful synthetic intermediates (*204*). Dinitrogen tetroxide, prepared by reaction of nitric oxide with oxygen, also oxidises non-cyclic and cyclic phosphites (*203*,*205*). Oxygen under photolytic conditions (*206*) or nitrosobenzene in benzene (*207*) effect the same transformation.

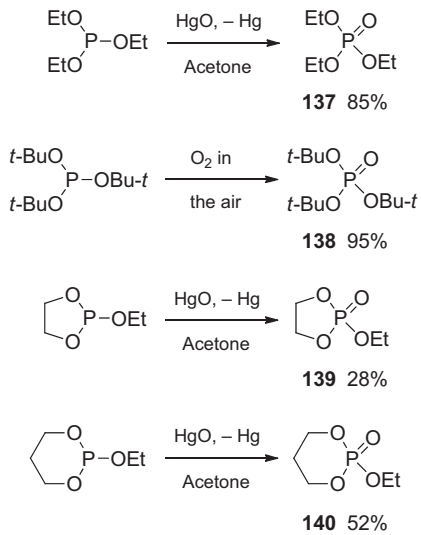


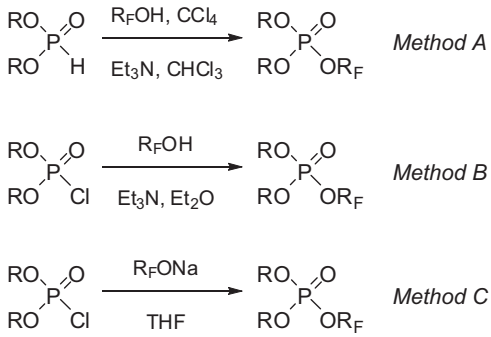
Figure 4.35.2

▶ *Tri-tert-butyl phosphate* $(t\text{-}BuO)_3P{=}O$ (**138**) *(from oxidation of the phosphite with air)* (*76*). Introduction of air into tri-*tert*-butyl phosphite (8.0 g, 32 mmol) caused a mildly exothermic reaction, and the temperature rose to 35 °C. The sample solidified after about 1 h. Recrystallisation from pentane yielded large colourless plates (8.3 g, 98%). Mp 72–74 °C.

▶ *Ethyl ethylene phosphate* (**139**) *(from oxidation of the phosphite with mercuric oxide)* (*203*). Ethyl ethylene phosphite (27.2 g, 0.20 mol) was oxidised by addition of yellow mercury(II) oxide (75 g, 0.35 mol) in small portions with cooling. After attaining room temperature overnight, the mixture was

filtered, the solvent removed, and the residual liquid distilled to yield the phosphate (8.5 g, 28%). Bp 106–108 °C/0.7–0.8 mmHg.

The synthesis of dialkyl fluoroalkyl phosphates illustrates three common approaches to unsymmetrical phosphates of general structure $(RO)_2P(O)OR'$. The first involves the reaction of a dialkyl *H*-phosphonate with a fluoroalcohol, carbon tetrachloride and triethylamine in chloroform (*Method A*) (Fig. 4.35.3) (*208*). This is a modified Todd–Atherton procedure (Section 4.41) where the dialkyl phosphorochloridate intermediate couples with the alcohol. The second route involves the reaction of a dialkyl phosphorochloridate with a fluoroalcohol and triethylamine in ether (*Method B*). The third route involves the reaction between a dialkyl phosphorochloridate and the sodium salt of a fluoroalcohol in THF (*Method C*).



Dialkyl fluoroalkyl phosphates

R	R_F	Method	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
Me	CH_2CF_3	A	54	54/1.8	–0.4
Me	$CH_2C_2F_5$	B	40	61/1	–0.6
Me	$CH(CF_3)_2$	B	39	50/6	–1.1
Me	$CH_2(CF_2)_3CF_2H$	C	30	66/0.08	–0.4
Et	CH_2CF_3	A	30	60–66/0.05	–2.6
Et	$CH_2C_2F_5$	A	49	90/12	–2.9
Et	$CH(CF_3)_2$	B	60	56/0.5	–3.4
Et	$CH_2(CF_2)_3CF_2H$	B	41	111/3.5	–0.3

a. NMR data acquired at 202 MHz and measured in $CDCl_3$ solvent

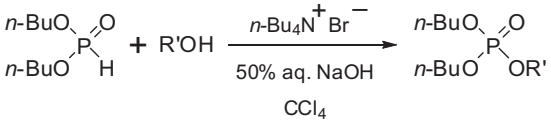
Figure 4.35.3

▶ *Dialkyl fluoroalkyl phosphates* $(RO)_2P(O)OR_F$ (Fig. 4.35.3) (*208*). *Method A*. A solution of the fluoroalcohol (0.2 mol) and triethylamine (0.2 mol) in ethanol-free chloroform (50 ml) was added dropwise over 2–3 h to a stirred solution of the dialkyl *H*-phosphonate (0.2 mol) in carbon

tetrachloride (0.2 mol) cooled to 0–5 °C. A white precipitate of triethylamine hydrochloride formed. The mixture was stirred for 2 h at 0–5 °C and allowed to stand for 16 h at room temperature. The mixture was washed with water (2 × 25 ml), the organic layers combined, dried ($MgSO_4$), filtered, and the solvent removed from the filtrate to leave a liquid. This was distilled, initially at 12–15 mmHg with gentle heating to remove any unreacted fluoroalcohol. The temperature was then increased and the pressure adjusted to between 0.5 and 12 mmHg depending on the boiling point of the product (Fig. 4.35.3). *Method B.* A mixture of the fluoroalcohol (0.1 mol) and triethylamine (0.1 mol) was added dropwise to a stirred solution of the dialkyl phosphorochloridate (0.1 mol) in anhydrous ether (100 ml) cooled to 0–5 °C. After addition, the solution was stirred for 4 h and filtered. The filtrate was concentrated to a liquid which was distilled as described in the previous method. *Method C.* A solution of the fluoroalcohol (40 mmol) in anhydrous THF (30 ml) was added dropwise to a stirred suspension of sodium hydride (48 mmol) in THF (30 ml) at room temperature. After addition, the mixture was cooled to 0–5 °C and to it was added dropwise a solution of the dialkyl phosphorochloridate (40 mmol) in THF (50 ml). The mixture was allowed to warm to room temperature and was left to stand for 16 h. It was treated carefully with water (50 ml) and extracted with ethanol-free chloroform (3 × 50 ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed to give a liquid that was distilled.

The Todd–Atherton phosphorylation method (*209–211*) is a versatile means of accessing trisubstituted phosphates. The triple component system – dialkyl *H*-phosphonate, carbon tetrachloride, and triethylamine – first reported by Steinberg (*212,213*) was developed further by Kenner and Williams (*214*) to access dialkyl aryl phosphates. There are some drawbacks to such methodology. One molar equivalent of triethylamine is essential to obtain a reasonable yield of phosphate (and triethylamine hydrochloride can sometimes contaminate the phosphate product) and long reaction times and heating under reflux are often required. The phosphorylation of alcohols by dialkyl *H*-phosphonates in carbon tetrachloride and aqueous sodium hydroxide using a phase-transfer catalyst (tetra-*n*-butylammonium bromide or BTAC) offers a milder alternative (Fig. 4.35.4) (*215*). The conditions are not optimised. Substantial changes of reaction temperature, order of mixing of reagents, and lower concentrations of aqueous sodium hydroxide yield considerable amounts of dialkyl hydrogen phosphate, $(RO)_2P(O)OH$, and toxic tetraalkyl pyrophosphate, $(RO)_2P(O)OP(O)(OR)_2$. The preparative value is restricted to the use of lower dialkyl *H*-phosphonates and primary alcohols. Secondary and tertiary alcohols exhibit much lower reactivity and furnish poor yields of impure products. Dialkyl *H*-phosphonates derived from higher alcohols, e.g. dibenzyl *H*-phosphonate, provide the trisubstituted phosphates, but contaminated with appreciable impurities (from partial dealkylation of the *H*-phosphonate in the aqueous alkaline medium), and their purification is laborious and difficult.

▶ *Trisubstituted phosphates $(RO)_2P(O)OR'$ (general method)* (*215*). A solution of dialkyl *H*-phosphonate (0.25 mol, 25% excess) in carbon tetrachloride (60 ml) was added dropwise to a stirred mixture of an alcohol (0.2 mol), 50% *w/v* aqueous sodium hydroxide (60 ml), carbon tetrachloride (120 ml) and tetra-*n*-butylammonium bromide (1.6 g, 5 mol%) at 0–5 °C. After addition, the mixture was allowed to warm to room temperature and was stirred for a further 3 h. The mixture was diluted



Di-*n*-butyl alkyl phosphates

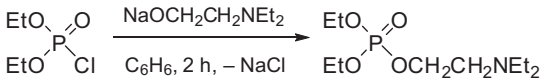
R'	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
Et	71	60–61/0.1	0.8
i-Bu	62	78–79/0.2	0.6
i-Pr	35	88–90/0.3	0.6
Bn	95	115–118/0.2	0.7
Ph	94	106–108/0.4	6.5

a. Measured at 24.3 MHz as neat liquids

Figure 4.35.4

with dichloromethane (50 ml) and filtered; the precipitate was washed with dichloromethane (50 ml) and the layers were separated. The organic layer was washed with 2% *v/v* aqueous hydrochloric acid (25 ml) and water (2 × 25 ml), dried ($MgSO_4$) and evaporated. The residue was kept at 30–40 °C/0.1 mmHg for 1 h to remove residual solvent. Analytical samples were distilled under reduced pressure although this treatment was not necessary because they were analytically pure even in the crude state.

Dialkyl phosphorochloridates react with alcohols in the absence (*188,216*) or presence of a base. Sodium alkoxides can be used effectively as in the synthesis of compound (**141**), an analogue of the pesticide amiton (Fig. 4.35.5) (*44*).



141 53%

Figure 4.35.5

▶ *Diethyl 2-diethylaminoethyl phosphate* $(EtO)_2P(O)OCH_2CH_2NEt_2$ (**141**) *(from the dialkyl phosphorochloridate and sodium alkoxide)* (*44*). Sodium (14.5 g, 630 mmol) in anhydrous benzene (250 ml) was boiled with 2-diethylaminoethanol (72.0 g, 620 mmol) for 2 h. The solution of the sodium salt was decanted from unchanged sodium, and diethyl phosphorochloridate (104.0 g, 600 mmol) in anhydrous benzene (200 ml) was added over 1 h at room temperature. Precipitation of sodium chloride was induced by addition of light petroleum (bp 40–60 °C) and the mixture was filtered through kieselguhr. Removal of solvent and then distillation gave a forerun of triethyl phosphate followed by a fraction (bp 75–80 °C/0.01 mmHg) that on redistillation gave the title compound (80.0 g, 53%). Bp 87 °C/0.02 mmHg.

Alcoholysis of alkyl phosphorodichloridates (Section 4.2) in ether in the presence of triethylamine and a catalytic amount of DMAP also provides dialkyl alkyl phosphates, (**142**) and (**143**), in acceptable yield (Fig. 4.35.6) (*2*).

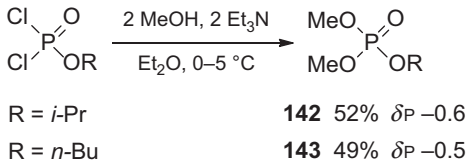


Figure 4.35.6

▶ *Dimethyl alkyl phosphates $(MeO)_2P(O)OR$* (**142**) and (**143**) *(from the alkyl phosphorodichloridate, alcohol, and triethylamine)* (*2*). A solution of methanol (25 mmol) and triethylamine (25 mmol) in ether (15 ml) was added dropwise to a stirred solution of the alkyl phosphorodichloridate (11 mmol) in ether (35 ml) cooled to 0–5 °C under argon. The mixture was allowed to warm to room temperature and was left for 14 h; analysis by GC–MS showed varying extents of reaction. To ensure full conversion to the phosphate, a catalytic amount of DMAP was added before refluxing the mixture (15 h for dimethyl isopropyl phosphate and 5 h for dimethyl *n*-butyl phosphate). The precipitate was removed and the filtrate concentrated to give a mobile liquid that was distilled using a Kugelrohr apparatus to give the products as colourless liquids: **142** (52%, bp 61 °C/0.03 mmHg; δ_P (202 MHz, $CDCl_3$) −0.6 ppm) and **143** (49%, bp 70 °C/0.02 mmHg; δ_P (202 MHz, $CDCl_3$) −0.5 ppm).

Bis(fluoroalkyl) phosphates $(R_FO)_2P(O)OR$ can be prepared in 18–75% yield by treating phosphorochloridates $(R_FO)_2P(O)Cl$, where R_F is HCF_2CH_2, $HCF_2CF_2CH_2$, $H(CF_2)_4CH_2$, $C_2F_5CH_2$, $C_3F_7CH_2$, $(CF_3)_2CH$, $(FCH_2)_2CH$ and $(CH_3)_2CF_3C$ with methanol, ethanol, propanol and isopropanol in ether in the presence of triethylamine (*217*). The bulky chloridate $[(CH_3)_2CF_3CO]_2P(O)Cl$ reacts with methanol, ethanol and propanol, but not with isopropanol – even on heating in the presence of DMAP – due to steric hindrance at the phosphorus atom. Fluoroalkyl-substituted phosphates have physical (*2*) and biological (*218*) properties that favour their development as fire extinguishants to replace halogenated substances banned under the Montreal Protocol (Chapter 1.9). 2,2,2-Trifluoroethyl phosphorodichloridate (*5*) and *bis*(2,2,2-trifluoroethyl) phosphorochloridate (*82*) react with fluoroalcohols when heated in the presence of a catalytic amount of calcium chloride (Fig. 4.35.7) (*219*). The phosphates (**144**–**147**) are isolated by distillation from the reaction vessel.

▶ *Bis(fluoroalkyl) 2,2,2-trifluoroethyl phosphates $(R_FCH_2O)_2P(O)OCH_2CF_3$* (**144** and **145**) (*219*). 2,2,2-Trifluoroethyl phosphorodichloridate (2.17 g, 10 mmol) was weighed into a 25 ml round-bottomed flask equipped with a magnetic flea and a Liebig condenser with a calcium chloride guard tube. Finely powdered anhydrous calcium chloride (0.06 mg, 0.5 mmol) was added in one portion to the dichloridate, followed by the appropriate fluoroalcohol (20 mmol). This mixture was stirred and maintained at 150 °C for 2 h. Evolution of hydrogen chloride was observed; beads of hydrochloric acid formed on the inner surface of the guard tube. The products were isolated by

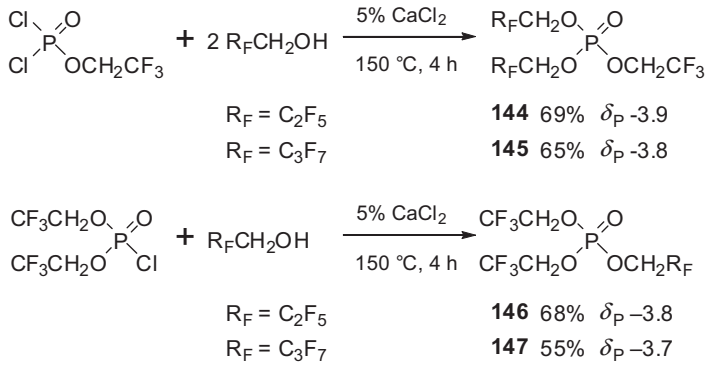
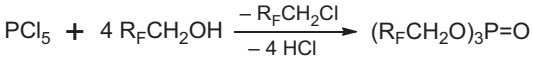


Figure 4.35.7

fractionation under reduced pressure: **144** (bp 100 °C/10 mmHg) and **145** (bp 100 °C/1 mmHg). Similarly, *bis*(2,2,2-trifluoroethyl) phosphorochloridate (2.81 g, 10 mmol) and the appropriate fluoroalcohol (10 mmol) gave the phosphates **146** (bp 82 °C/10 mmHg) and **147** (bp 85 °C/10 mmHg).

Phosphorus pentachloride can be used as a starting material for the synthesis of symmetrical trisubstituted phosphates, providing the latter resist cleavage by the large amount of hydrogen chloride evolved. Four moles of an appropriate fluoroalcohol combine with a mole of phosphorus pentachloride to furnish the tris(fluoroalkyl) phosphates (Fig. 4.35.8) (*219*).



Tris(fluoroalkyl) phosphates

R_F	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
CF_3	73	40/0.6	–3.7
C_2F_5	69	64/0.9	–4.0
C_3F_7	76	63/0.08	–3.4

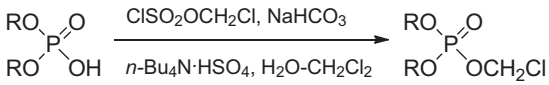
a. NMR data acquired at 202 MHz and measured in $CDCl_3$

Figure 4.35.8

▶ *Tris(fluoroalkyl) phosphates* $(R_FCH_2O)_3P{=}O$ (*219*). The fluoroalcohol (0.20 mol) was added dropwise, using a pressure-equalising dropping funnel equipped with a calcium chloride guard tube, to finely divided stirred phosphorus pentachloride (0.05 mol) in a round-bottomed flask cooled to 0–5 °C. Contact of the fluoroalcohol with the solid phosphorus pentachloride resulted in dissolution, producing a colourless solution that effervesced, due to liberation of hydrogen chloride and the respective fluoroalkyl chloride. After addition, the mixture was warmed to room temperature and left for 12 h. An aliquot was analysed by GC–MS. In cases where good conversion to the required product

had occurred, residual phosphorus pentachloride was removed by filtration. Fractionation under reduced pressure gave the tris(fluoroalkyl) phosphates as colourless liquids (Fig. 4.35.8).

Several methods for the synthesis of trialkyl phosphates start from dialkyl hydrogen phosphates. A problem with this approach is that few dialkyl hydrogen phosphates are readily available (Sections 4.32 and 4.33). Nonetheless, dialkyl chloromethyl phosphates can be prepared from dialkyl hydrogen phosphates and chloromethyl chlorosulfate under alkaline phase-transfer conditions (Fig. 4.35.9) (*220*).



Dialkyl chloromethyl phosphates

R	Yield (%)	δ_P (ppm) [a]
n-Bu	84	–0.9
Bn	90	–1.1
CH_2=$CHCH_2$	36	–1.6
t-Bu	72	–11.2

a. NMR data measured in $CDCl_3$ solvent

Figure 4.35.9

▶ *Dialkyl chloromethyl phosphates* $(RO)_2P(O)OCH_2Cl$ (*220*). The dialkyl hydrogen phosphate (4.76 mmol), sodium bicarbonate (19.04 mmol), and tetra-*n*-butylammonium hydrogen sulfate (0.48 mmol) were dissolved in water (40 ml). Dichloromethane (25 ml) was added and the mixture was stirred vigorously at 0 °C for 10 min. A solution of chloromethyl chlorosulfate (5.70 mmol) in dichloromethane (15 ml) was added next and stirring was continued overnight at room temperature. The organic layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. Column chromatography of the residue on silica gel eluting with 3:1 hexane—ethyl acetate gave the products listed in Fig. 4.35.9.

The synthesis of alkyl di-*tert*-butyl phosphates can be achieved efficiently using a three-stage method starting from potasssium di-*tert*-butyl phosphate (**148**) (Fig. 4.35.10) (*221*,*222*). This is treated with tetra-*n*-butylammonium hydrogen sulfate in a two-phase system of dilute aqueous sodium hydroxide and dichloromethane to provide tetra-*n*-butylammonium di-*tert*-butyl phosphate (**149**), a colourless crystalline non-hygroscopic solid that can be stored for an indefinite time at room temperature. When kept in an open vessel, it transforms slowly into the monohydrate (mp 73—75 °C) from which the anhydrous salt (mp 108—110 °C) can be recovered upon drying under vacuum over phosphorus pentoxide. Esterification of the tetra-*n*-butylammonium salt provides phosphates (**150—154**) in good yields (*222*).

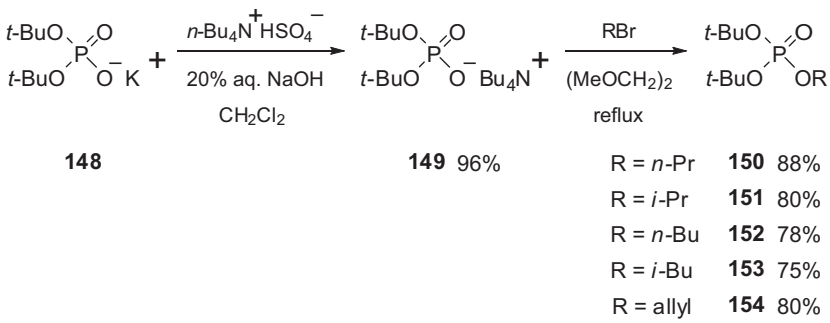


Figure 4.35.10

▶ *Potasssium di-tert-butyl phosphate (t-BuO)$_2$P(O)O$^-$K$^+$* (**148**) (*221*). Finely powdered potassium permanganate (23.1 g, 0.14 mol) was added portionwise over 1 h to a stirred mixture of di-*tert*-butyl *H*-phosphonate (38.8 g, 0.2 mol) and potassium bicarbonate (12.2 g, 0.12 mol) in water (170 ml) cooled with an efficient ice-salt bath. The temperature of the strongly exothermic reaction was kept at 0 °C. After addition was complete, stirring was continued for 30 min at room temperature. The mixture was then heated for 15 min at 60 °C to coagulate the colloidal suspension of MnO_2, filtered, and the solution decolourised by boiling with charcoal (3 g). Evaporation of the filtered solution afforded the title compound as a colourless crystalline mass (47.1 g, 95%). The potassium salt can be maintained indefinitely at room temperature in aqueous solution of known concentration and converted to di-*tert*-butyl hydrogen phosphate (mp 83–84 °C) on treatment with concentrated hydrochloric acid (95% yield).

▶ *Tetra-n-butylammonium di-tert-butyl phosphate (t-BuO)$_2$P(O)O$^-$Bu$_4$N$^+$* (**149**) (*222*). 20% *w/v* aqueous sodium hydroxide solution (12.5 ml) was added dropwise at 20 °C with stirring and external cooling to a solution of tetra-*n*-butylammonium hydrogen sulfate (17.0 g, 50 mmol) in water (10 ml). A solution of potassium di-*tert*-butyl phosphate (12.4 g, 50 mmol) in water (6 ml) was then added dropwise at 20 °C. The mixture was stirred for 30 min and then extracted with dichloromethane (4 × 25 ml). The combined extracts were dried over anhydrous potassium carbonate and evaporated under reduced pressure to give a colourless crystalline solid (21.7 g, 96%). Mp 108–110 °C.

▶ *Alkyl di-tert-butyl phosphates (t-BuO)$_2$P(O)OR* (**150–154**) (*222*). A mixture of tetra-*n*-butylammonium di-*tert*-butyl phosphate (9.0 g, 20 mmol), the corresponding alkyl bromide (22 mmol) and 1,2-dimethoxyethane (50 ml) was heated under reflux with stirring for 3 h and then cooled to room temperature. The precipitated tetra-*n*-butylammonium bromide was filtered off and washed with petroleum ether (20 ml). The filtrate was diluted with petroleum ether (30 ml) and the resultant solution washed with 20% *w/v* aqueous potassium carbonate (5 ml). The organic layer was dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was kept at 35–40 °C/2 mmHg for 30 min to remove traces of solvent. The products were colourless mobile liquids and were analytically pure.

Routes to dialkyl aryl phosphates mirror those already described and often start from the dialkyl *H*-phosphonate or the dialkyl phosphorochloridate. A Todd–Atherton procedure provides the dialkyl coumarinyl phosphate (**155**) in high yield (Fig. 4.35.11) (*223*). Dialkyl coumarinyl phosphates and phosphonates are useful fluorogenic substrates for enzymes (Section 1.11) and have several biological applications (*224–229*).

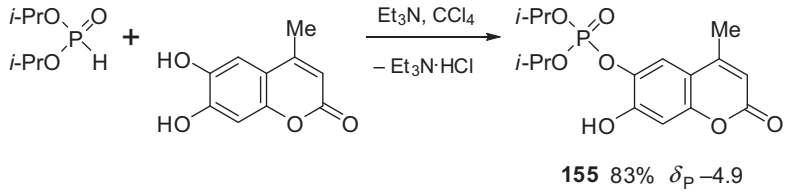


Figure 4.35.11

▶ *Diisopropyl 6-oxy-7-hydroxy-4-methylcoumarinyl phosphate* (**155**) (*223*). A solution of diisopropyl *H*-phosphonate (0.17 g, 1.0 mmol) in carbon tetrachloride (5 ml) was added dropwise to a stirred solution of 6,7-dihydroxy-4-methylcoumarin (0.19 g, 1.0 mmol) in acetone (20 ml) and triethylamine (2 ml, 14.3 mmol) at 0 °C. After addition, the mixture was warmed to room temperature and stirred for 12 h. The solid triethylamine hydrochloride was removed by filtration and the filtrate evaporated. The crude product was extracted with ethyl acetate, washed with water (4 × 15 ml) and dried ($MgSO_4$). Evaporation of the solvent and column chromatography of the residue on silica gel, eluting with 3:7 hexane–ethyl acetate, gave the title compound (0.30 g, 83%). Mp 166–167 °C. δ_P (400 MHz, $CDCl_3$) −4.9 ppm. Related phosphorylated coumarins were prepared similarly.

Schrader prepared the insecticide paraoxon using four methods (Fig. 4.35.12) (*58*). Three started from diethyl phosphorochloridate and *p*-nitrophenol under basic conditions and gave the pesticide in modest yields. An excellent yield was obtained by nitration of diethyl phenyl phosphate with red fuming nitric acid; a high preference for *para* substitution resulted. Ethanolysis of *p*-nitrophenyl phosphorodichloridate also produces paraoxon (*21*). The preparation of other dialkyl *p*-nitrophenyl phosphates (methyl; *n*- and *iso*-propyl; *n*-, *iso*- and *sec*-butyl; and *n*-pentyl esters) has been described (*27*). The *p*-nitrophenoxy group in such compounds is easily displaced by nucleophiles; in competition reactions between amino and hydroxyl nucleophiles, the *O*-ester forms virtually exclusively (*129*).

▶ *Diethyl p-nitrophenyl phosphate (paraoxon) (p-nitrophenol and pyridine, or sodium cyanide, method)* (*58*). Diethyl phosphorochloridate (52 g, 0.3 mol) was added to a stirred solution of *p*-nitrophenol (42 g, 0.3 mol) in anhydrous pyridine (50 ml) at 55–60 °C and the mixture heated for 1 h at 60 °C. The mixture was cooled and diluted with water. The pyridine hydrochloride dissolved and the insoluble reaction product was taken up in ether. Work-up in the usual manner gave paraoxon (23 g, 28%). Bp 173 °C/1 mmHg. The use of sodium cyanide instead of pyridine to neutralise the acid liberated gave paraoxon in 55% yield.

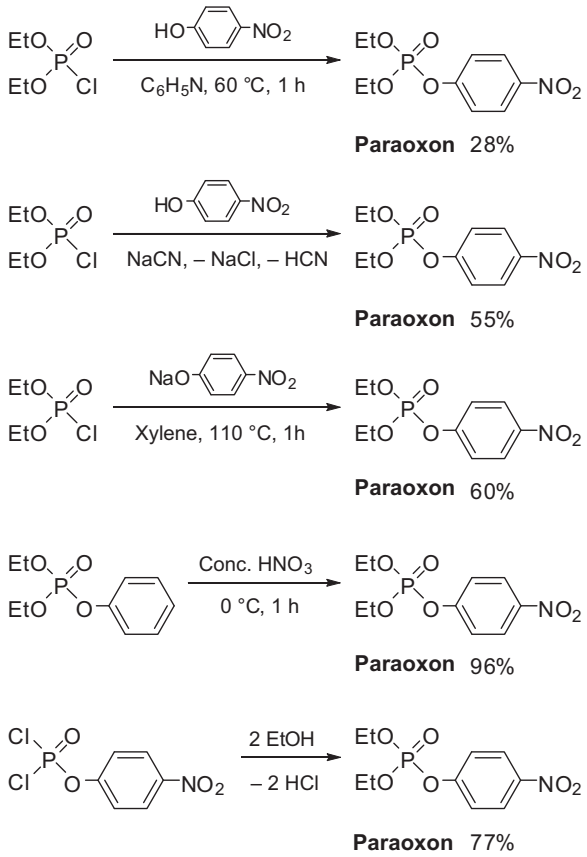


Figure 4.35.12

▷ *Diethyl p-nitrophenyl phosphate (paraoxon) (sodium p-nitrophenolate method)* (*58*). Diethyl phosphorochloridate (86 g, 0.5 mol) was added to a stirred suspension of sodium *p*-nitrophenolate (81 g, 0.5 mol) in xylene (250 ml) and the mixture heated for 1 h at 110 °C. The salt was filtered off and the filtrate distilled to provide paraoxon (83 g, 60%). Bp 173 °C/1 mmHg.

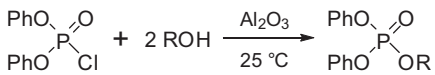
▷ *Diethyl p-nitrophenyl phosphate (paraoxon) (nitration method)* (*58*). Red fuming nitric acid (186 g, 3.0 mol) was added slowly at a temperature not exceeding 0 °C to stirred diethyl phenyl phosphate (138 g, 0.6 mol). After addition, the mixture was stirred for 1 h and then poured onto ice. The *p*-nitro compound was insoluble in water and could thus be separated; it was washed twice with water, dissolved in ether, dried, and finally freed from solvent, to provide paraoxon (158 g, 96%).

▷ *Diethyl p-nitrophenyl phosphate (paraoxon) (ethanolysis method)* (*21*). Absolute ethanol (30 ml, 0.51 mol) was added slowly with cooling and stirring to *p*-nitrophenyl phosphorodichloridate (33.6 g, 0.13 mol) in a round-bottomed flask via a dropping funnel fitted with a calcium chloride tube to prevent entry of moisture. After 12 h, the excess of ethanol and the hydrogen chloride liberated were

removed by rotary evaporation. The residual liquid was washed with water and aqueous sodium acetate, extracted with 1,2-dichloroethane, and dried ($MgSO_4$). After filtration, the solvent was removed from the filtrate and the residue was distilled to provide paraoxon (27.90 g, 77%). Bp 170–171 °C/1 mmHg.

4.36 DIARYL ALKYL PHOSPHATES $(ArO)_2P(O)OR$

The reaction of diaryl phosphorochloridates with alcohols can be assisted by Lewis acids such as alumina or titanium tetrachloride. Reaction of diphenyl phosphorochloridate with alcohols in the presence of alumina at room temperature allows diphenyl alkyl phosphates to be accessed (Fig. 4.36.1) (*230*).



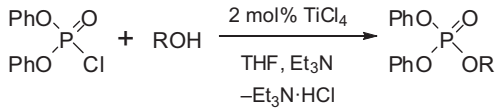
Diphenyl alkyl phosphates

R	Yield (%)	Bp (°C/mmHg)	δ_p (ppm)
Me	84	158/0.3	–14.5
Et	84	162/0.2	–14.1
n-Pr	82	166/0.2	–13.5
i-Pr	82	165/0.2	–13.9
n-Bu	81	174/0.2	–12.8
i-Bu	80	173/0.2	–12.3
$CH_2{=}CHCH_2$	75	162/0.2	–18.3
cyclopentyl	78	178/0.2	–12.1
cyclohexyl	79	181/0.2	–11.4
Bn	67	201/0.2	–17.7
Ph	41	195/0.3	–18.9

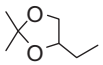
Figure 4.36.1

▶ *Diphenyl alkyl phosphates $(PhO)_2P(O)OR$ (from diphenyl phosphorochloridate, alcohols and alumina)* (*230*). An alcohol (2.2 mmol) was added to neutral activated alumina (0.306 g, 3.0 mmol) in a single-necked 25 ml round-bottomed flask. This was sealed with a rubber septum and diphenyl phosphorochloridate (0.269 g, 1.0 mmol) was added by syringe at 0 °C. The resulting suspension was shaken occasionally at room temperature. The progress of reaction was monitored by TLC and gas chromatography after withdrawing a few milligrams of the mixture and suspending it in ether (1 ml). After the reaction was complete, which took 5–15 min, the mixture was extracted with ether (3 × 5 ml) and filtered. The solvent was removed from filtrate and the residue was distilled under vacuum to furnish the pure phosphate (Fig. 4.36.1).

Another method of constructing diphenyl alkyl/aryl phosphates consists of treating diphenyl phosphorochloridate with alcohols in THF in the presence of titanium tetrachloride catalyst and a stiochiometric amount of triethylamine (Fig. 4.36.2) (*231*). The procedure is mild enough to enable isolation of products with ketal-containing ester groups.



Diphenyl alkyl/aryl phosphates

R	Yield (%)	Mp (°C)	δ_p (ppm) [a]
$C_7H_{15}CH_2$	94	liquid	–10.7
$PhCH_2$	96	47–49	–10.7
$HC{\equiv}CCH_2$	97	liquid	–10.7
	84	liquid	–10.8
i-Pr	90	liquid	–11.8
cyclohexyl	97	36–38	–11.6
phenyl	98	47–49	–16.6

a. Measured at 121.5 MHz in $CDCl_3$

Figure 4.36.2

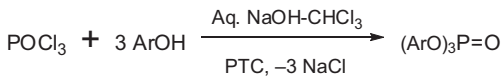
▶ *Diphenyl alkyl phosphates $(PhO)_2P(O)OR$ (from diphenyl phosphorochloridate, alcohols and titanium tetrachloride)* (*231*). Titanium tetrachloride (0.02 ml, 0.17 mmol) was added to THF (20 ml), followed by addition of the alcohol (8.5 mmol), triethylamine (1.8 ml, 12.75 mmol), THF (10 ml) and diphenyl phosphorochloridate (2.65 ml, 12.75 mmol). The solution was stirred for 1 h at room temperature. Water (10 ml) was added, the mixture was extracted with dichloromethane (3 × 20 ml), and the combined organic layers were dried ($MgSO_4$), and filtered. The filtrate was concentrated to give a residue that was purified by chromatography on silica gel (Fig. 4.36.2).

4.37 TRIARYL PHOSPHATES $(ArO)_3P{=}O$

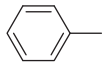
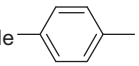
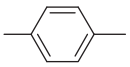
Triaryl phosphates find a variety of uses as plasticisers, flame retardants, non-flammable fluids in hydraulic systems, and additives for lubricating oils. They can be synthesised by several procedures. Large-scale production often involves prolonged heating of phosphorus oxychloride and an aromatic alcohol. Catalysts such as calcium, magnesium, aluminium, or their chlorides, or phosphorus pentachloride, are often employed to accelerate product formation. The liberated hydrogen chloride presents a corrosion problem in industrial reactors and low pressures are usually maintained to facilitate

its removal. A tertiary base such as pyridine or an *N,N*-dialkylaniline can be used to neutralise it, but this increases the cost of the process. High temperatures, although required, can lead to the formation of unacceptable amounts of by-products. Plasticiser-grade triaryl phosphates need to be very pure. The product has invariably to be distilled at low pressure (at least 1 mmHg) to provide material of the desired purity. Distillation at low pressure poses a problem for large-scale industrial synthesis and also lowers the yield.

A mild method that overcomes some of these problems comprises the reaction of phosphorus oxychloride with the sodium salt of the aromatic alcohol in a two-phase system consisting of chloroform, water, and the phase-transfer catalyst Aliquat™ 336 (tricaprylmethylammonium chloride) (Fig. 4.37.1) (*232*). The reaction proceeds smoothly at room temperature and furnishes trialkyl phosphates in high yields (82–96%). Products are purified by crystallisation, the catalyst and mother liquor are recycled, and hydrogen chloride accumulation is avoided. Other phase-transfer catalysts, such as benzyltriethylammonium chloride (BTAC) and dibenzo-18-crown-6, can also be used (*233*).



Triaryl phosphates

Ar	Yield from Method A [a]	Yield from Method B [b]	Yield from Method C [c]	Mp (°C)
	82	89	90	49
Me 	86	93	91	77
Cl 	88	96	92	117

PTC = phase transfer catalyst. *a*. PTC = Aliquat™ 336; 30–50 °C, 2 h (*232*) *b*. PTC = Aliquat™ 336; 30–45 °C, 1 h (*232*). *c*. PTC = BTAC and dibenzo-18-crown-6, room temperature, 20 min (*233*)

Figure 4.37.1

▶ *Triphenyl phosphate (PhO)$_3$P=O (Method A)* (*232*). Aqueous sodium phenolate, made by treating phenol (48.5 g, 0.516 mol) with sodium hydroxide (20.6 g, 0.516 mol) in water (300 ml), was added to ethanol-free chloroform (75 ml) containing Aliquat™ 336 (2.84 g, 7.027 mmol). The heterogeneous system was stirred mechanically and phosphorus oxychloride (24.9 g, 0.162 mol) was added dropwise over 75 min. The reaction was highly exothermic, but slow addition of the phosphorus

reagent ensured a controlled reaction. After addition, the mixture was stirred for a further 45 min. The organic layer was separated, washed with 2% *w/w* aqueous sodium hydroxide (2 × 250 ml), then with water (250 ml), and dried (Na_2SO_4). The solvent was removed. The yield of crude product containing the catalyst was 50.4 g (95% based on $POCl_3$). Crystallisation from a mixture of petroleum ether (bp 60–80 °C) and ethanol gave a white solid (43.6 g, 82%). Mp 49 °C. The product was pure when checked by TLC on silica gel plates and visualised with iodine vapour.

▶ *Triphenyl phosphate $(PhO)_3P{=}O$ (Method B)* (*232*). An aqueous solution (150 ml) of sodium phenolate (0.17 mol) prepared as in Method A was added to ethanol-free chloroform (250 ml) containing Aliquat™ 336 (2.5 g, 6.19 mmol). The two-phase system was stirred. Phosphorus oxychloride (8.3 g, 54 mmol) was added dropwise over 20 min. After addition, the mixture was stirred for a further 40 min. The organic layer was worked up as before and the solvent removed to give the crude product (20.0 g, pure by TLC). Crystallisation as described before afforded pure material (15.6 g, 89%).

▶ *Triaryl phosphates $(ArO)_3P{=}O$ (Method C)* (*233*). An aqueous solution of the sodium phenolate derivative prepared by treating the aryl alcohol (1.13 g, 12 mmol) with sodium hydroxide (0.48 g, 12 mmol) in distilled water (20 ml) was added to chloroform (20 ml) containing BTAC (0.46 g, 2 mmol) and dibenzo-18-crown-6 (5 mg). The heterogeneous mixture was stirred and phosphorus oxychloride (0.60 g, 3.9 mmol) was added dropwise over 10 min. An exothermic reaction occurred. After addition, the mixture was stirred for another 10 min. The organic layer was separated, washed with 2% aqueous sodium hydroxide, and dried ($MgSO_4$). The solvent was removed under reduced pressure and the products recrystallised from petroleum ether–ethyl acetate.

Perhalogenated triaryl phosphates can be synthesised by heating phosphorus oxychloride and 3 molar equivalents of an aromatic alcohol or mixing the same chemicals at room temperature in the presence of a suitable base (Fig. 4.37.2). Tris(pentafluorophenyl) phosphate (**156**), having a high autoignition temperature, good thermal and hydrolytic stability, and a high fire resistance, is a useful lubricant and additive for aircraft hydraulic systems (*234*). Tris(pentachlorophenyl) phosphate (**157**) has antiseptic and antifungal properties (*235*).

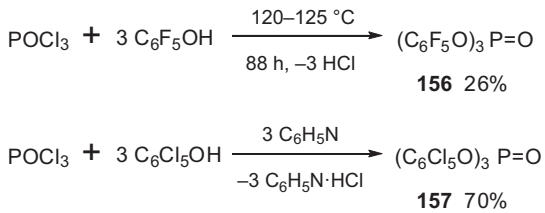


Figure 4.37.2

▶ *Tris(pentafluorophenyl) phosphate $(C_6F_5O)_3P{=}O$* (**156**) (*234*). Phosphorus oxychloride (153.5 g, 1.00 mol) was added dropwise to stirred pentafluorophenol (97.5 g, 0.53 mol) at room temperature and the mixture then heated under reflux at 129 °C for 1 h, cooled to 120 °C, and maintained at 120 °C for 66 h. The mixture was heated to 125 °C for 22 h and then cooled. Phosphorus

oxychloride (bp 106 °C) was removed by distillation at atmospheric pressure. Further distillation gave the phosphate (26.8 g, 26%). Bp 164–168 °C/1 mmHg.

▶ *Tris(pentachlorophenyl) phosphate* $(C_6Cl_5O)_3P{=}O$ (**157**) (*235*). Phosphorus oxychloride (6.5 g, 42 mmol) was added to a stirred solution of pentachlorophenol (26.6 g, 100 mmol) in pyridine (110 ml) while maintaining the temperature at 15–20 °C. After addition, the mixture was heated under reflux for 1 h after which the liquid was evaporated to one-third of its original volume. After cooling, the mixture was poured into water. The precipitate was filtered, washed with 5% aqueous sodium carbonate, and recrystallised from aqueous ethanol to give the phosphate (19.7 g, 70%). Mp 322–326 °C (dec.).

4.38 DIALKYL ALKYLIDENEAMINO PHOSPHATES $(RO)_2P(O)ON{=}CR_2$ (ALLEN REACTION)

Dialkyl alkylideneamino phosphates such as diethyl species (**158**) can be prepared by treating a dialkyl phosphorochloridate with an oxime under basic conditions, or by treating a trialkyl phosphite with a suitable α-halonitro compound (Fig. 4.38.1). The latter reaction, furnishing an alkyl halide and oxime ester of the corresponding pentavalent phosphorus acid, was discovered in the mid-1950s by J. F. Allen and now bears his name (*236*). Phosphorylated oximes are highly reactive towards oxygen nucleophiles, readily losing the oxime group, and are easily hydrolysed.

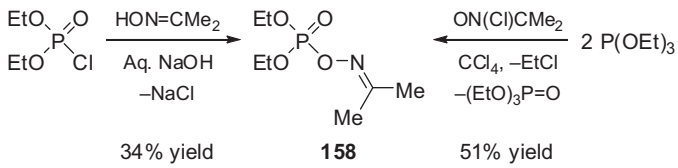


Figure 4.38.1

▶ *Diethyl isopropylideneamino phosphate* $(EtO)_2P(O)ON{=}CMe_2$ (**158**) *(dialkyl phosphorochloridate route)* (*236*). Diethyl phosphorochloridate (34.5 g, 0.2 mol) was added gradually at 15–17 °C to acetone oxime (14.6 g, 0.2 mol) and sodium hydroxide (12.0 g, 0.3 mol) dissolved in water (100 ml). The mixture was stirred for 30 min, the two layers separated, and the aqueous layer extracted with ether. After drying the combined organic layers, the ether was removed and the product distilled to give the product (14.0 g, 34%). Bp 95–98 °C/0.2 mmHg.

▶ *Diethyl isopropylideneamino phosphate* $(EtO)_2P(O)ON{=}CMe_2$ (**158**) *(trialkyl phosphite route)* (*236*). Crude 2-chloro-2-nitrosopropane was obtained by adding chlorine (35.5 g, 1 mol) to acetone (58.0 g, 1 mol) and sodium hydroxide (40.0 g, 1 mol) dissolved in water (400 ml). The product was separated from the aqueous solution, dried ($CaSO_4$), and used without further purification. The resulting nitroso compound (53.8 g, 0.5 mol) in carbon tetrachloride (200 ml) was cooled to 0 °C and triethyl phosphite (83.0 g, 0.5 mol) added with stirring. After addition, the temperature was raised to 75 °C and ethyl chloride (21 g) containing a small quantity of carbon tetrachloride was collected in the cold trap. The remaining volatile matter was removed and the product fractionated to yield the oxime ester (53.0 g, 51%). Bp 88–96 °C/0.1 mmHg.

4.39 DIALKYL ENOLPHOSPHATES $(RO)_2P(O)OCR{=}CR_2$ (PERKOW REACTION)

W. Perkow discovered in 1952 that trialkyl phosphites react with α-haloaldehydes to give dialkyl enol phosphates, rather than the isomeric dialkyl alkylphosphonates from the Arbuzov reaction, as reported repeatedly up to that point (Fig. 4.39.1) (*237*). As evidence for the enol phosphate structure, Perkow demonstrated that chlorine or bromine added to the double bond, and that the products failed to undergo reactions characteristic of the carbonyl group. Perkow's discovery was confirmed rapidly in other laboratories and the scope of the reaction extended to α-haloketones and α-haloesters (*238*,*239*).

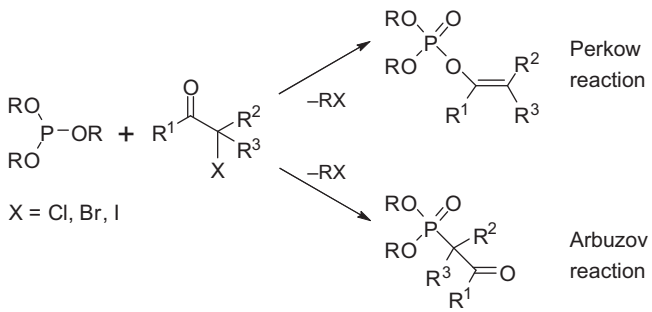


Figure 4.39.1

The reactivity of α-halocarbonyl reactants decreases in the order: α-haloaldehydes > α-haloketones > α-haloesters. In the case of α-haloaldehydes, the Perkow reaction is favoured, whereas with α-haloketones and α-haloesters both the Perkow reaction and the Arbuzov reaction can occur simultaneously, producing enol phosphate and phosphonate mixtures that are sometimes difficult to separate. The nature of the α-halogen atom X also determines the pathway, the Perkow reaction being favoured in the order Cl > Br > I, although the chlorides are the least reactive (*237–239*). The exact mechanism of the Perkow reaction has been controversial and is not understood fully. It is generally accepted that it is ionic, and at some point in the overall scheme, valency expansion of phosphorus occurs.

Two mechanisms are commonly invoked (*240*). The most common involves attack of the phosphite lone pair on the carbonyl group to form intermediate (**159**) that rearranges to an enolphosphonium salt (**160**). Alternatively, the phosphite lone pair attacks the halogen atom to provide a halophosphonium species (**161**) that undergoes nucleophilic attack by the enolate anion. The enolphosphonium salt common to both mechanisms undergoes rapid dealkylation by the halide ion (c.f. the last stage of the Arbuzov reaction) to provide the enol phosphate (**162**) (Fig. 4.39.2).

The Perkow reaction is used to prepare various insecticides having the enol phosphate structure (*241*). These include those shown in Fig. 4.39.3.

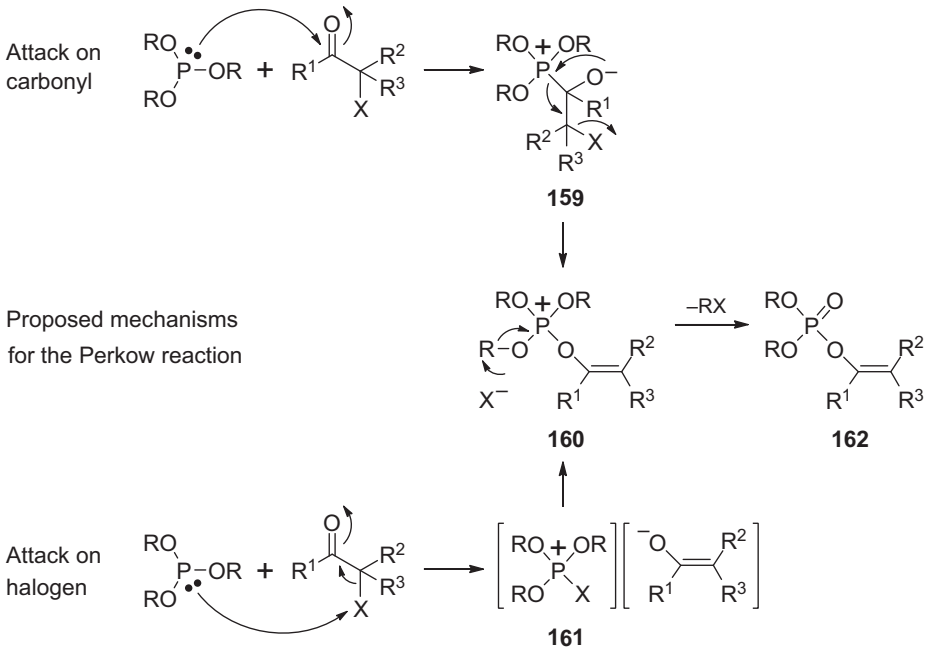


Figure 4.39.2

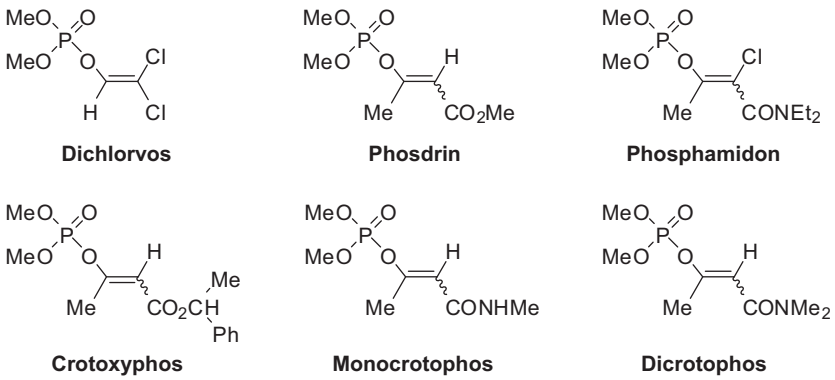


Figure 4.39.3

Triethyl phosphite and chloral react to give diethyl 2,2-dichlorovinyl phosphate (**163**) (*238*). The reaction proceeds readily; it is strongly exothermic and external cooling must be applied. The rate of reaction with different aldehydes decreases with fewer halogen atoms next to the carbonyl group, in the order $CCl_3CHO > HCCl_2CHO > ClCH_2CHO$, to give enol phosphates **163–165** (Fig. 4.39.4) (*238*). Triethyl phosphite and chloral yield the dichlorovinyl phosphate uniformly and spontaneously,

whereas dichloroacetaldehyde reacts exothermically but less vigorously, and chloroacetaldehyde requires heating to 110 °C for reaction to occur.

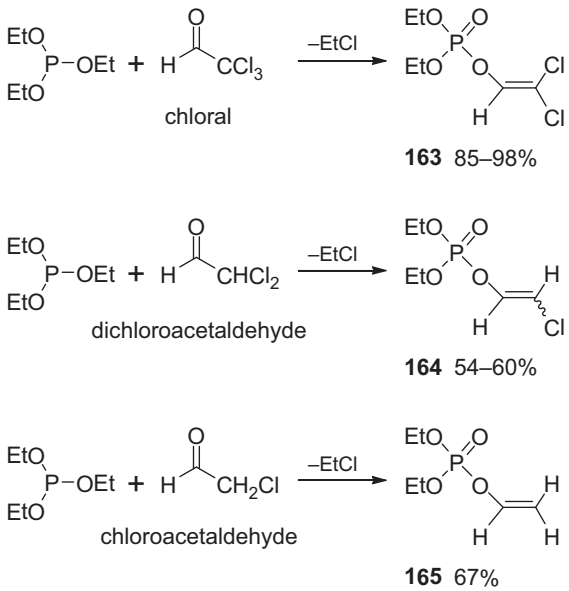


Figure 4.39.4

The reaction is not restricted to the chloral series. Using carbonyl reactants of structure $R^1C(O)CR^2R^3H$ can yield mixtures of geometric isomers due to the disposition of the different R groups in the enol phosphate product (*242*). For example, trimethyl phosphite and methyl α-chloroacetoacetate yield the insecticide phosdrin usually as a 3:2 mixture of *cis*- and *trans*-isomers (Fig. 4.39.5) (*241*). The *cis*-isomer is much more insecticidal — about 100 times more active — than the *trans*-isomer.

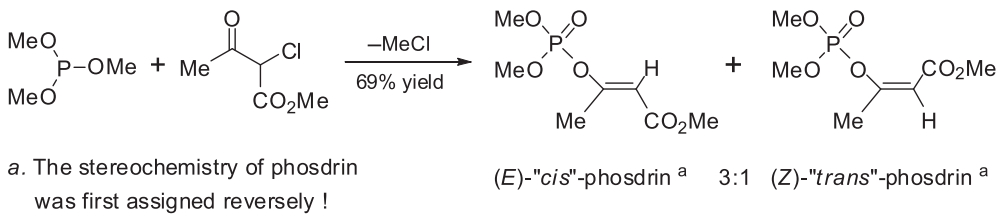


Figure 4.39.5

Vinyl phosphates can also be prepared from dialkyl *H*-phosphonates and α-halo systems in the presence of bases. This method is attractive because of the greater accessibility of dialkyl *H*-phosphonates compared to trialkyl phosphites. One example is the reaction of diethyl *H*-phosphonate with 2,2-dichloroacetophenone to give (*E*)-(**166**) in good yield (Fig. 4.39.6) (*243*).

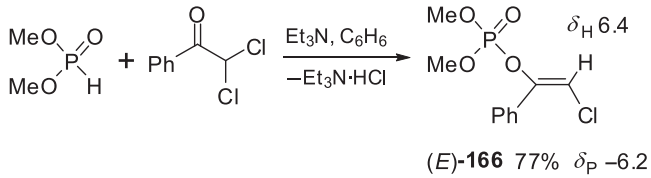


Figure 4.39.6

Dialkyl phosphorochloridates add alkali metal enolates to provide enol phosphates, as exemplified by the reaction of diethyl phosphorochloridate with the enolate derived from sodium ethoxide and ethyl acetoacetate, which yields product (**167**) (Fig. 4.39.7) (*58*).

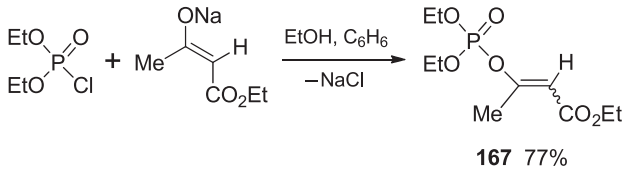
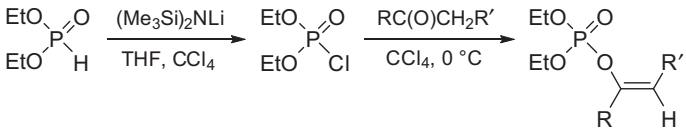


Figure 4.39.7

A one-pot variation of the previous reaction can be used to isolate a range of enol phosphates (Fig. 4.39.8) (*244*). In this case, the dialkyl phosphorochloridate is generated in situ and treated with the lithium enolate salt derived from the aldehyde (or ketone) and lithium *bis*(trimethylsilyl) amide.



Enol phosphates

R	R′	Yield (%)	*E*:*Z*
Ph	H	90%	-
Ph	Ac	65%	0:100
Ph	$P(O)(OEt)_2$	85%	0:100
Me	Ph	74%	7:3
Me	Ac	95%	0:100
Me	CO_2Et	90%	0:100

Figure 4.39.8

Enol phosphates readily add chlorine or bromine across the C═C double bond. Hydrogenation of this bond can be effected by hydrogen in the presence of catalysts, although reductive

cleavage of the enol ester bond may also result. Hydrogenation of the C=C enol bond proceeds generally at a slightly lower rate than that of an isolated double bond in the same molecule, and often allows benzyl ester groups to be removed, while leaving the vinyl ester group intact. The enol phosphate bond is readily hydrolysed under acidic conditions to yield the dialkyl hydrogen phosphate and the aldehyde.

▷ *Dimethyl 1-carbomethoxy-1-propen-2-yl phosphate* $(MeO)_2P(O)OC(Me){=}CHCO_2Me$ *(Phosdrin)* (*245*). Trimethyl phosphite (100.0 g, 0.8 mol) was added dropwise over 1 h to methyl α-chloroacetoacetate (121.5 g, 0.8 mol) in a flask fitted with a reflux condenser. The temperature rose to 85 °C and methyl chloride was evolved. The product was isolated by distillation as a colourless liquid (123.0 g, 69%). Bp 107 °C/1 mmHg.

▷ *(E)-Dimethyl 2-chloro-1-phenylvinyl phosphate* $(MeO)_2P(O)OC(Ph){=}CHCl$ (**166**) (*243*). A solution of triethylamine (8.2 g, 81.2 mmol) in benzene (10 ml) was added dropwise to a stirred mixture of dimethyl *H*-phosphonate (8.8 g, 80.0 mmol) and 2,2-dichloroacetophenone (15.0 g, 79.4 mmol). The reaction mixture was stirred for 3 h and then left overnight at room temperature. Triethylamine hydrochloride was filtered off. Vacuum distillation of the filtrate gave the vinyl phosphate (16.1 g, 77%). Bp 158–160 °C/5 mmHg. δ_P (16.2 MHz, CCl_4) −6.2 ppm.

▷ *Diethyl vinyl phosphate* $(EtO)_2P(O)OCH{=}CH_2$ (*246,247*). Triethyl phosphite (665 g, 4 mol) was added over 40 min to chloroacetaldehyde (314 g, 4 mol) with external cooling to keep the temperature in the range 50–60 °C. The mixture was then warmed to 110 °C and ethyl chloride (178 g, 70%) was distilled off. The residue was fractionated through a 60 cm column packed with glass rings to give diethyl vinyl phosphate (482 g, 67%). Bp 79 °C/6 mmHg.

▷ *Diethyl 1-carbethoxy-1-propen-2-yl phosphate* $(EtO)_2P(O)OC(Me){=}CHCO_2Et$ (**167**) (*58*). Small pieces of sodium (12 g, 0.52 mol) were added to anhydrous benzene (450 ml). Absolute ethanol (25 g, 0.54 mol) was added under agitation at 40–50 °C. After the sodium had reacted to generate sodium ethoxide, ethyl acetoacetate (65 g, 0.50 mol) was added slowly at 30 °C and the reaction product heated to 50 °C for 1 h. Diethyl phosphorochloridate (86 g, 0.50 mol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The separated sodium chloride was filtered off and the filtrate fractionated to give a colourless liquid (103 g, 77%). Bp 138 °C/2 mmHg.

▷ *Diethyl Z-(1-acetyl-2-methylvinyl) phosphate* $(EtO)_2P(O)OCH(Me){=}CHC(O)Me$ (*244*). Acetylacetone (0.1 g, 1.00 mmol) was added slowly to a stirred solution of lithium *bis*(trimethylsilyl)amide (1.2 ml, 1.0 M solution in THF, 1.20 mmol) and carbon tetrachloride (5 ml) at 0 °C. After addition, the mixture was stirred for 30 min, and then a solution of diethyl *H*-phosphonate (0.16 g, 1.16 mmol) in carbon tetrachloride (5 ml) was added dropwise. The resultant mixture was stirred at room temperature and the progress of reaction was monitored by TLC. When the reaction was complete, about 30 min after adding the diethyl *H*-phosphonate, the mixture was neutralised with acetic acid and filtered. The filtrate was washed with water, dried ($MgSO_4$) and concentrated to reveal a brown liquid. Chromatography on silica gel, eluting with 2:1 *v*/*v* petrol–ethyl acetate, gave the title compound (0.225 g, 95%).

4.40 DIALKYL PHOSPHORAZIDATES $(RO)_2P(O)N_3$

The literature on the synthesis and properties of phosphorus acid azides has been reviewed (*248*). Preparation of dialkyl phosphorazidates proceeds readily upon treatment of dialkyl phosphorochloridates with an excess of sodium azide in acetonitrile at room temperature (*249*) or in refluxing acetone (*250*). These approaches yield dimethyl phosphorazidate (**168**) and diethyl phosphorazidate (**169**) in reasonable yields (Fig. 4.40.1). The former was isolated pure after filtration and removal of solvent, and the latter likewise but after distillation at 10—11 mmHg. Although phosphoryl azides with one $P—N_3$ group tend to be thermally stable (*248*), their distillation is best avoided to reduce the risk of rapid decomposition and/or explosion.

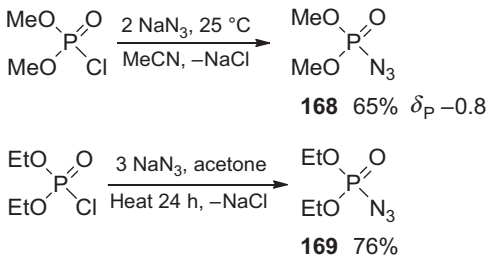


Figure 4.40.1

The reaction between *bis*(2,2,2-trifluoroethyl) phosphorochloridate and an excess of sodium azide in acetonitrile proceeds smoothly at room temperature and provides pure *bis*(2,2,2-trifluoroethyl) phosphorazidate (**170**) in excellent yield after removal of the inorganic salts by filtration and evaporation of the solvent (Fig. 4.40.2) (*251*).

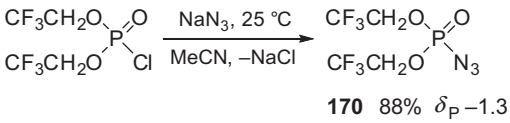


Figure 4.40.2

The azide group attached to the phosphorus atom behaves like a chlorine atom and is often referred to as a pseudohalogen; it is easily displaced by nucleophiles, especially oxygen- or nitrogen-based ones. In the case of bidentate nucleophiles having both a hydroxyl and an amino substituent, no selectivity is observed (*129*) (in contrast with phosphorochloridates which react preferentially with an amino group).

▶ *Dimethyl phosphorazidate* $(MeO)_2P(O)N_3$ (**168**) (*249*). A solution of dimethyl phosphorochloridate (2.89 g, 20 mmol) in acetonitrile (30 ml) was added dropwise to a stirred suspension of

sodium azide (2.60 g, 40 mmol) in acetonitrile (25 ml) and the mixture stirred for 36 h at room temperature. The inorganic salts were filtered off and the solvent removed from the filtrate, first with a rotary evaporator and then with an oil pump, to provide dimethyl phosphorazidate as a colourless liquid (2.1 g, 65%). δ_P (CH_2Cl_2) −0.8 ppm. This azidate can be distilled (bp 90 °C/12 mmHg) (*252*). Its infrared spectrum contains a band at 2170/cm for the azide group and a band at 1270/cm for the phosphoryl group.

▶ *Diethyl phosphorazidate* $(EtO)_2P(O)N_3$ (**169**) (*250*). Diethyl phosphorochloridate (50.0 g, 0.29 mol) was added dropwise over 20 min to a suspension of sodium azide (56.6 g, 0.87 mol) in anhydrous acetone (500 ml) contained in a 3 l three-necked flask equipped with a dropping funnel, a mechanical stirrer, and a reflux condenser. The stirred mixture was heated under reflux for 20 h, cooled, and the salt filtered off with a filter aid. The salt was washed with acetone, the washings were added to the original mother liquor, and the whole was distilled. Vacuum fractionation of the residue gave diethyl phosphorazidate as a colourless liquid (39.5 g, 76%). Bp 101−103 °C/10−11 mmHg. Its infrared spectrum showed a strong band at 2140/cm for the azide group. It is insoluble in water but completely miscible with acetone, ethanol, or ether. *Caution!* Diethyl phosphorazidate is a potent anticholinesterase and must be handled accordingly.

▶ *Bis(2,2,2-trifluoroethyl) phosphorazidate* $(CF_3CH_2O)_2P(O)N_3$ (**170**) (*251*). Finely divided sodium azide (0.93 g, 14.28 mmol) was added in one portion to a stirred solution of *bis*(2,2,2-trifluoroethyl) phosphorochloridate (2.00 g, 7.14 mmol) in acetonitrile (30 ml). The suspension was stirred briskly for 3 h. The solids were removed by filtration and the filtrate concentrated to a liquid that still contained a small amount of solid. Further precipitation of solid was induced by the addition of ether (5 ml). Passage of the resulting solution through a Pasteur pipette containing a small plug of glass wool, and removal of the solvent and drying under high vacuum, gave the title compound as a mobile colourless liquid (1.80 g, 88%). It was shown to be 97% pure by multinuclear NMR and mass spectral analyses. δ_P (202 MHz, $CDCl_3$) −1.3 ppm. The infrared spectrum showed a strong azide stretch at 2182/cm. (*Caution!* Although no safety problems were encountered during work with sodium azide, precautions against possible explosions should be implemented when handling it dry or suspended in solution, and likewise while handling the phosphorazidate product. A plastic spatula is used to weigh out sodium azide; the use of metal spatulas should be avoided.)

4.41 DIALKYL PHOSPHORAMIDATES $(RO)_2P(O)NR_2$ (TODD−ATHERTON REACTION)

Experiments in 1944 by the research team of A. R. Todd on the phosphorylation of nucleosides with dibenzyl *H*-phosphonate led to the discovery of a new method for phosphorylating amines using diesters of phosphorous acid and polyhalogen compounds (*38*,*39*). The method was discovered accidentally by F. R. Atherton when he tried to remove acid impurities from a solution of dibenzyl *H*-phosphonate in carbon tetrachloride by shaking it with ammonia, whereupon the mixture set to a semi-solid mass of dibenzyl phosphoramidate (*209*).

4.41.1 Biography

▶ **Lord Alexander Robertus Todd FRS (1907–1997)**. Alexander Robertus Todd was an organic chemist of great distinction whose influence on the course of education and science in the UK rank him among the great figures of the twentieth century. Born in Glasgow, he attended the university there, graduating in chemistry with first class honours. He joined the laboratory of Walther Borsche in Frankfurt where he studied the structure of bile acids for his PhD. This was followed by 2 years at Oxford University under the tutelage of the 1947 Nobel Laureate for Chemistry, Sir Robert Robinson FRS (*253*), preparing flower pigments. He then moved to Edinburgh University in Scotland where he studied the chemistry of thiamine (vitamin B_1). This work strengthened his interest in substances involved in the metabolism of living cells. His research group devised a simple synthesis of thiamine that was adopted for its commercial manufacture. After 2 years in Edinburgh, Todd and his research group moved to the Lister Institute of Preventative Medicine in London (UK). There, good facilities for animal studies enabled the investigation of the structure of vitamin E, both forms of which the group synthesised, and on the active principle of Indian hemp (*Cannabis indica*). Todd formed a close friendship with the double Nobel Laureate Linus Pauling FRS (*254–256*) during a 6 month sabbatical at the California Institute of Technology. Afterwards, Todd accepted the chair of organic chemistry at the University of Manchester in the UK at the remarkably young age of 31 years. There he broadened his research on vitamins to include their biologically active forms, the coenzymes and related nucleotides. It was in this field that his research team started to develop new preparative methods in organophosphorus chemistry, including the famous Todd–Atherton reaction named after his colleague F. R. Atherton. During World War II, while working at Manchester University, Todd accepted membership and later chairmanship of the Chemical Committee under the British Ministry of Supply responsible for chemical warfare agent research. He visited the Defence Research

Establishment at Porton Down (now the Defence Science and Technology Laboratory, Dstl, at Porton Down) in 1941. His main contribution to defence research was the development of improved synthetic methods to organoarsenic sensory irritants (*257*,*258*).

The chemistry of nucleic acids was not an initial objective of Todd's while he explored organophosphorus chemistry as part of his programme of academic research. In the early 1940s, the importance of the nucleic acids as key components of hereditary material was not fully established and their structure was uncertain. However, several coenzymes were known to contain vitamin and nucleotide components, and Todd considered it vital to resolve the structural details of these nucleotides and to develop unambiguous syntheses of the coenzymes. Todd was appointed to the chair of organic chemistry at Cambridge University in the UK in 1944. There he and his team continued to impress, synthesising adenosine diphosphate (ADP), adenosine triphosphate (ATP), flavin-adenine dinucleotide, nicotinamide-adenine dinucleotide, and uracil diphosphate-glucose, for which Todd was awarded the Nobel Prize for Chemistry in 1957 ('for his work on nucleotides and nucleotide coenzymes') (*259*). By then the importance of nucleic acids was widely recognised and Todd and Brown's demonstration that nucleoside units were connected through 3,5-phosphodiester units helped James Watson and Francis Crick interpret the X-ray data and propose the double helix structure of deoxyribonucleic acid (DNA) (*260*). Todd's team during this era also studied oligonucleotide synthesis, vitamin B_{12}, plant germination factors, and aphid pigments (the latter, it seems, mainly to satisfy their own curiosity) (*261*).

When Todd arrived at the Chemical Laboratories in Cambridge in 1944, the facilities were dishevelled and undistinguished. Within a short time, he transformed them into one of the best research facilities in the world, a reputation that has endured to the current day. Todd's ability to inspire others to reach high standards and his commonsense approach to life meant that he was in high demand outside the laboratory. He contributed significantly to science policy within government, universities and industry. In various periods, he was the president of the Chemical Society, of the British Association, of the International Union of Pure and Applied Chemistry (IUPAC), and of the Royal Society. In addition, he was a master of Christ's College, Cambridge, chairman of the UK Advisory Council on Scientific Policy, and chairman of the British Royal Commission on Medical Education. He was knighted in 1954, made a Life Peer in 1962, and awarded the Order of Merit in 1977.

Alexander Todd is remembered for his outstanding contribution to the interface of chemistry and biology, for his selfless public service and, to his many friends, as a kind and helpful colleague (*262*). Many distinguished chemists were trained in his school (*263*). The photograph shows Alexander Todd in 1941 with his then 18-month-old son, Alexander Henry (Sandy) near their house in Pownall Park in Wilmslow, Cheshire (UK) (*264*). (Sandy Todd trained as a chemist and enjoyed a successful career at I.C.I. (later Zeneca) Pharmaceutical Division at Alderley Park in Cheshire, in the UK. Photograph provided by Sandy Todd and reproduced with his permission.)

4.41.2 Todd–Atherton reaction

The method of phosphorylation of amines by disubstituted *H*-phosphonates in the presence of polyhalogenated compounds – most commonly carbon tetrachloride – is known as the Todd–Atherton reaction, a reaction of wide scope that involves treating a dialkyl or diaryl

H-phosphonate with carbon tetrachloride, ammonia or a primary or secondary amine, and a tertiary amine (if necessary). Thus, dibenzyl *H*-phosphonate (**20**) reacts with carbon tetrachloride in the presence of excess ammonia to give dibenzyl phosphoramidate (**171**), chloroform and ammonium chloride (Fig. 4.41.1) (*38*). The accepted mechanism of the Todd–Atherton reaction is chlorination of the starting ammonium dialkyl phosphite (**172**) by carbon tetrachloride (*265*) to yield the dialkyl phosphorochloridate (**21**), which then phosphorylates the available amine (*266*). The conventional Todd–Atherton reaction with an amine and carbon tetrachloride converts a disubstituted *H*-phosphonate to a disubstituted phosphoramidate with inversion of configuration at the phosphorus atom (*267*). The reaction can be assisted by sonochemical activation (*211*).

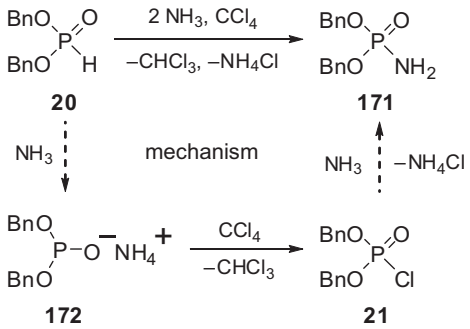


Figure 4.41.1

Instead of carbon tetrachloride, other polyhaloalkanes can be used. These include penta- and hexachloroethane (*209*), bromo- or iodoalkanes (e.g. $CHBr_3$, $CHBrCl_2$, CCl_2BrCCl_2Br, CBr_4, and CHI_3) (*210*), and various chlorofluoroalkanes (*210,268,269*). In general, the reactivity of the haloalkanes is increased by the introduction of bromine or iodine atoms and decreased by the presence of fluorine atoms. Trichlorobromomethane appears to be the reagent of choice for preparative phosphorylation reactions; a mixture of this substance with a dialkyl *H*-phosphonate will phosphorylate even aromatic amines (*210*). Other $RCCl_3$ systems can be used to effect chlorination in related reactions, e.g. 3-methyl-5-trichloromethyl-1,2,4-oxadiazole (*270*).

▶ *Diethyl phosphoramidate $(EtO)_2P(O)NH_2$ (from the Todd–Atherton reaction)* (*271*). Diethyl *H*-phosphonate (138 g, 1 mol) and carbon tetrachloride (154 g, 1 mol) were added to anhydrous benzene (400 g) in a 2 l three-necked flask equipped with a stirrer, a thermometer, and gas inlet and outlet tubes. The outlet tube was connected to a drying tube to prevent ingress of moisture. The flask was cooled to 0–5 °C and ammonia was passed slowly into the stirred contents for 3–4 h at such a rate that the temperature did not exceed 50 °C. The reaction was complete when ammonia escaping through the outlet tube was detectable and heat no longer involved. The ammonia flow was stopped and stirring was continued for an additional 15 min. The reaction mixture was filtered to remove the precipitate of ammonium chloride and the solvent removed from the filtrate. The residue was dried at 80–90 °C under vacuum to provide on cooling a crystalline mass (137.7 g, 90%). Diethyl

phosphoramidate forms colourless needle-like crystals (mp 46–47 °C). It is soluble in water, acetone, ethanol, ether, and carbon tetrachloride, and is insoluble in hexane. It is hygroscopic and liquefies when exposed to moist air.

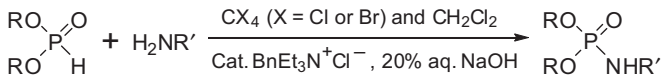
▷ *Di-tert-butyl phosphoramidate (t-BuO)$_2$P(O)NH$_2$* (272). Ammonia gas dried over potassium hydroxide was passed through an efficiently stirred solution of di-*tert*-butyl *H*-phosphonate (87.0 g, 0.45 mol) in carbon tetrachloride (200 ml) at 50–55 °C. After 14 h, the solution was evaporated to dryness and the resulting solid (NH_4Cl and the amidate) extracted continuously with benzene for 10 h. Evaporation of the extract afforded the crude amidate (56.3 g, 60%; mp 134–137 °C). Recrystallisation from light petroleum (bp 60–80 °C) gave an analytically pure sample. Mp 136–137 °C. δ_P ($CHCl_3$) −1.4 ppm.

▷ *Dibenzyl phosphoramidate (BnO)$_2$P(O)NH$_2$* (38). A solution of dibenzyl *H*-phosphonate (6.55 g, 25 mmol) in carbon tetrachloride (125 ml) was cooled to −10 °C and saturated with ammonia. The mixture was left at −10 °C for 5 min, then at room temperature overnight, and the excess of ammonia removed by a stream of nitrogen. The mixture was heated to boiling, filtered, the filter residue extracted with hot carbon tetrachloride, and the combined filtrate and extract concentrated and allowed to cool. Colourless needles separated that after recrystallisation from carbon tetrachloride gave pure dibenzyl phosphoramidate (6.3 g, 91%). Mp 103.5–104.5 °C. The same product was also obtained in slightly lower yield after shaking a carbon tetrachloride solution of dibenzyl phosphorochloridate with aqueous ammonia.

▷ *Dibenzyl N-phenylphosphoramidate (BnO)$_2$P(O)NHPh* (38). Dibenzyl *H*-phosphonate (13.1 g, 50 mmol) in carbon tetrachloride (250 ml) was cooled to −10 °C and aniline (20 ml, 215 mmol) was added with stirring. After 5 min, the mixture was removed from the cooling bath and stored at room temperature overnight. After washing with dilute hydrochloric acid and water, the carbon tetrachloride solution was dried (Na_2SO_4) and evaporated. The thick syrup that remained set to a mass of plates (17.3 g, 98%; mp 80–86 °C). Recrystallisation from hexane–ethylene dichloride and then aqueous ethanol gave dibenzyl *N*-phenylphosphoramidate as colourless plates (mp 91.0–92.5 °C). Using similar methods the following were obtained: dibenzyl *N*-cyclohexylphosphoramidate (BnO)$_2$P(O)NHC$_6$H$_{11}$ (95% yield, colourless needles from hexane, mp 79–80 °C), dibenzyl *N*-benzylphosphoramidate (BnO)$_2$P(O)NHBn (theoretical yield; colourless needles from hexane–benzene or hexane–ethylene dichloride, mp 84–85 °C), dibenzyl *N*-[2-(phenyl)ethyl] phosphoramidate (BnO)$_2$P(O)NHCH(Ph)Me (98% yield; colourless prisms or needles from hexane or cyclohexane, mp 81–82 °C).

The Todd–Atherton reaction is the method of choice for the phosphorylation of ammonia, but has several disadvantages in the case of amines: (a) 1 mol of the 2 mol of amine used for phosphorylation is lost as the hydrochloride, unless it is replaced by 1 mol of a sufficiently strong tertiary base, e.g. triethylamine; (b) separation of the amine salt from the phosphoramidate product is sometimes laborious and difficult; (c) partial monodebenzylation can occur when dibenzyl *H*-phosphonate is used as phosphorylating agent in the presence of a strong tertiary amine (273); (d) when feebly basic amines, e.g. aniline, are phosphorylated in the presence of carbon tetrachloride, addition of a strong base is often necessary to induce reaction; and (e) considerable quantities of brown tarry contaminants are formed when phosphorylation is conducted in the presence of carbon tetrabromide and tertiary amines, e.g. triethylamine.

To avoid such limitations, the phosphorylation of amines can be accomplished conveniently in a two-phase system containing a catalytic amount (~5 mol%) of BTAC and carbon tetrachloride (Method A) (Fig. 4.41.2) (*274*). The use of 50% aqueous sodium hydroxide is inadvisable because of the possibility of formation of dihalocarbene (from the liberated CHX_3) followed by its reaction with the primary or secondary amine. The use of 20–30% aqueous sodium hydroxide causes negligible side reactions and no unwanted hydrolysis of dialkyl *H*-phosphonates providing the temperature is kept low (0–25 °C). The requirement for phase-transfer catalyst was confirmed by experiments in the absence of a catalyst. Attempted phosphorylation of diethyl *H*-phosphonate with aniline failed completely. The same procedure applied to cyclohexylamine gave the corresponding phosphoramidate in low yield (32% versus 89% with catalyst). The use of carbon tetrabromide as the polyhalogen reagent is recommended for phosphorylation of weakly basic aromatic amines (Method B) and is essential when the less reactive, sterically hindered di-*tert*-butyl *H*-phosphonate is used as the phosphorylating agent. Amine hydrochlorides are also phosphorylated using carbon tetrachloride and a slightly altered procedure (Method C).



Dialkyl/diaryl *N*-alkyl or aryl phosphoramidates

R	R′	Method	Yield (%)	Mp (°C) [a]	δ_P (ppm) [b]
Et	Ph	A	77	96–97	3.1
Et	Ph	B	84	96–97	3.1
Et	Ph	C	35	96–97	3.1
Et	*c*-Hex	A	89	75–76	8.8
Et	Bn	A	85	liquid	9.8
t-Bu	Bn	B	92	97–99	−0.3
Bn	Ph	A	40	90–92	3.5
Bn	Ph	B	78	90–92	3.5

a. Recrystallised: 1:1 benzene-hexane. *b.* Measured in CCl_4 (24.3 MHz)

Figure 4.41.2

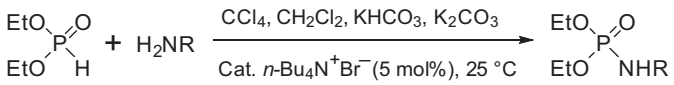
▶ *Dialkyl N-alkylphosphoramidates (RO)$_2$P(O)NHR (Method A)* (*274*). A solution of dialkyl *H*-phosphonate (0.10–0.13 mol) and the corresponding amine (0.10 mol) in dichloromethane (30 ml) was added dropwise to a stirred two-phase system of carbon tetrachloride (30 ml), dichloromethane (30 ml), 20% *w/v* aqueous sodium hydroxide (40 ml) and BTAC (1.0 g, 4.40 mmol). The temperature of the strongly exothermic reaction was maintained at 0–5 °C by external cooling (ice-salt bath). After addition, stirring was continued for 1 h at 0–5 °C and for a further 1 h at room temperature. The mixture was diluted with dichloromethane (25 ml), the organic layer was separated, washed with 5%

w/v hydrochloric acid (50 ml) and water (2 × 50 ml), and dried ($MgSO_4$). Evaporation of solvent followed by heating of the residue (30–40 °C/0.1–0.5 mmHg for 1 h) or its recrystallisation furnished the pure phosphoramidate.

▶ *Dialkyl N-alkylphosphoramidates (RO)$_2$P(O)NHR (Method B)* (*274*). A solution of dialkyl *H*-phosphonate (50 mmol) and the corresponding amine (50 mmol) in dichloromethane (15 ml) was added dropwise to a stirred two-phase system of carbon tetrabromide (8.3 g, 25 mmol), dichloromethane (30 ml), 20% *w/v* aqueous sodium hydroxide (20 ml), and BTAC (0.5 g, 2.2 mmol). Stirring was continued for 3 h at room temperature. Dichloromethane (25 ml) was then added, the organic layer was separated, washed with water (3 × 25 ml), and dried ($MgSO_4$). Evaporation of solvent and one recrystallisation of the residue gave the pure dialkyl phosphoramidate.

▶ *Dialkyl N-alkylphosphoramidates (RO)$_2$P(O)NHR (Method C)* (*274*). A solution of 30% *w/v* aqueous sodium hydroxide (40 ml) was added dropwise to a stirred solution of diethyl *H*-phosphonate (17.25 g, 125 mmol), amine hydrochloride (100 mmol), carbon tetrachloride (40 ml), dichloromethane (40 ml), and BTAC (1.0 g, 4.4 mmol). The resulting two-phase system was stirred at 2 h at room temperature, then diluted with dichloromethane (50 ml) and separated. The organic layer was washed with 5% hydrochloric acid (25 ml) and water (2 × 50 ml), dried ($MgSO_4$) and evaporated. Removal of solvent (30–40 °C/0.1–0.5 mmHg for 1 h) and recrystallisation from an appropriate solvent gave the pure dialkyl phosphoramidate.

Phosphorylation of amines can be accomplished under milder conditions by replacing the catalytic liquid–liquid two-phase system with a solid–liquid variant where potassium bicarbonate and potassium carbonate act as the base (Fig. 4.41.3) (*275*). Tetra-*n*-butylammonium bromide is the



Diethyl *N*-alkyl or *N*-aryl phosphoramidates

R	Method	Yield (%) [a]	Mp (°C)	δ_P (ppm) [b]
Et	E	83	liquid	9.9
n-Bu	D	~100	liquid	10.0
c-Hex	D	~100	72–74	8.8
c-Hex	E	86	72–74	8.8
$(CH_2)_2OH$	D	~100	liquid	10.1
$(CH_2)_3OH$	D	~100	liquid	10.2
Ph	D	~100	94–95	3.0
Ph	E	87	94–95	3.0

a. Yield of crude product. *b.* Measured in CCl_4 and ext. ref. 85% H_3PO_4

Figure 4.41.3

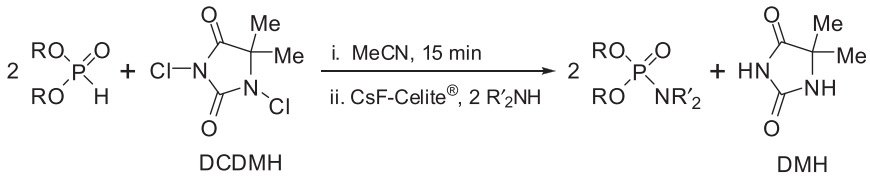
phase-transfer catalyst. The procedure can be applied to amine hydrochlorides or other amine salts where their solubility in the system suffices to secure effective liberation of the free amine at an early stage of the reaction. Phosphorylation can be achieved without the catalyst in the case of strongly basic aliphatic amines, but lower yields of less pure products are often obtained. The phosphorylation of alkanolamines is chemoselective and provides the *N*-phosphorylated derivatives as the sole products.

▶ *Diethyl N-alkylphosphoramidates $(EtO)_2P(O)NHR$ (Method D)* (*275*). A solution of diethyl *H*-phosphonate (6.9 g, 50 mmol) in carbon tetrachloride (10 ml) was added dropwise with occasional external cooling (ice-water bath) to a stirred mixture of the amine (50 mmol), potassium bicarbonate (10.0 g, 100 mmol), potassium carbonate (13.8 g, 100 mmol), dichloromethane (40 ml) and tetra-*n*-butylammonium bromide (0.80 g, 2.5 mmol) at 10–15 °C. Stirring was then continued for 2 h at 15–20 °C and the mixture was left overnight at room temperature. The inorganic salts were filtered off and washed with dichloromethane (2 × 25 ml). The solution combined with the washings was rotary evaporated to give the crude phosphoramidate, which was purified by recrystallisation. Oily specimens after heating to 40–50 °C/0.2 mmHg were contaminated only with a trace of tetra-*n*-butylammonium bromide.

▶ *Diethyl N-alkylphosphoramidates $(EtO)_2P(O)NHR$ (Method E)* (*275*). A mixture of amine hydrochloride (50 mmol), diethyl *H*-phosphonate (6.9 g, 50 mmol), carbon tetrachloride (30 ml), dichloromethane (20 ml), potassium bicarbonate (10.0 g, 100 mmol), potassium carbonate (13.8 g, 100 mol) and tetra-*n*-butylammonium bromide (0.80 g, 2.5 mmol) was stirred for 4 h at 15–20 °C with occasional cooling and then left overnight at room temperature. The work-up described for Method D afforded the pure phosphoramidate contaminated with a small amount of tetra-*n*-butylammonium bromide.

Conversion of dialkyl *H*-phosphonates into dialkyl phosphorochloridates can be effected by 1,3-dichlorodimethylhydantoin (DCDMH). Addition of this reagent, followed by cesium fluoride supported on Celite® (CsF–Celite®) and a dialkylamine, to dialkyl *H*-phosphonates provides dialkyl *N,N*-dialkylphosphoramidates (Fig. 4.41.4) (*276*). Optimal reaction occurs when a 2.0:1.0:4.2 molar ratio of dialkyl *H*-phosphonate–DCDMH–amine is used. The product and by-product 5,5-dimethylhydantoin (DMH) are separated by adding the reaction mixture to ether: the phosphoramidates are soluble, but the DMH is not, and can be removed along with the solid-supported material by filtration. The reaction rate depends on the size of the alkyl groups in the dialkyl *H*-phosphonate and the dialkylamine. The rate decreases in the order Me > Et > *n*-Pr > *i*-Pr, in line with increased steric hindrance as the carbon chain extends. The slowest reaction was observed for diisopropyl *H*-phosphonate and diisopropylamine, which required heating to 60 °C for 90 min for completion.

▶ *Dialkyl N,N-dialkylphosphoramidates $(RO)_2P(O)NR'_2$ (from cesium fluoride and DCDMH)* (*276*). Solid-supported cesium fluoride (CsF–Celite®) was prepared as follows: cesium fluoride (152 g, 1000 mmol) was added to a solution of Celite® 521 (100 g, 1660 mmol) in distilled water (1000 ml). This heterogeneous mixture was stirred for 1 h at room temperature and the water was then removed by rotary evaporation until dry. The solid material was shaken with acetonitrile (3 × 100 ml), filtered and washed with acetonitrile (3 × 25 ml). The CsF–Celite® obtained was dried under vacuum and



Dialkyl *N*,*N*-dialkylphosphoramidates

R	R′	Temp (°C)	Time (min)	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
Me	Me	25	20	89	82–83/6	14.1
Me	Et	35	20	84	98–99/5	13.6
Me	*n*-Pr	35	35	83	92–93/2	13.8
Me	*i*-Pr	40	40	86	95–96/3	11.5
Et	Me	30	25	82	82–83/5	11.5
Et	Et	35	40	80	109–110/1	10.9
Et	*n*-Pr	35	30	88	110–111/2	11.1
Et	*i*-Pr	50	50	83	116–117/1	8.8
n-Pr	Me	30	30	88	92–93/3	11.5
n-Pr	Et	30	30	86	119–120/1	10.3
n-Pr	*n*-Pr	40	40	84	113–114/1	11.2
n-Pr	*i*-Pr	50	65	84	123–124/1	8.9
i-Pr	Me	30	40	82	92/1	9.3
i-Pr	Et	40	50	83	115–116/1	8.2
i-Pr	*n*-Pr	50	50	80	107–108/1	9.1
i-Pr	*i*-Pr	60	90	80	119–120/1	6.9

a. Measured in $CDCl_3$ at 162 MHz with 85% H_3PO_4 as an external standard

Figure 4.41.4

stored in a desiccator before use. Next, the dialkyl *H*-phosphonate (50 mmol) was added to suspension of DCDMH (4.92 g, 25 mmol) in acetonitrile (15 ml). The mixture was stirred for 15 min and the progress of the reaction was monitored by analysing aliquots of the mixture by ^{31}P NMR spectroscopy. A white amorphous precipitate of DMH formed. Once the precipitate stopped increasing, the mixture was cooled to 0 °C, the solvent was removed under reduced pressure at room temperature, and CsF—Celite® (25.32 g, 100 mmol CsF and 160 mmol Celite®) was added. The dialkylamine (50 mmol) was added slowly while shaking the heterogeneous mixture with a vortex shaker. The progress of reaction was further monitored by withdrawing portions of the mixture, extracting them with ether, and analysing the solutions by ^{31}P NMR spectroscopy. Once the reaction was complete

(temperatures and times given in Fig. 4.41.4), the reaction mixture was extracted with ether and the white solid (DMH and solid support) was removed by filtration and washed with acetonitrile (3 × 10 ml). Removal of the solvent from the filtrate and fractionation of the residue under reduced pressure gave the title compounds.

Modern applications of the Todd–Atherton reaction include the synthesis of bisphosphoramidates (*277*), 2-indolylphosphoramidates (*278*), fluorophosphatase substrate analogues (*279*), lipophosphoramidyl cyclodextrins (*280*), and phosphoryl derivatives of the polysaccharide chitosan (**173**), such as **174** (*281*), and derivatives of *O*-trityl chitosan (**175**), such as the anti-HIV drug candidate **176** (*282*) (Fig. 4.41.5).

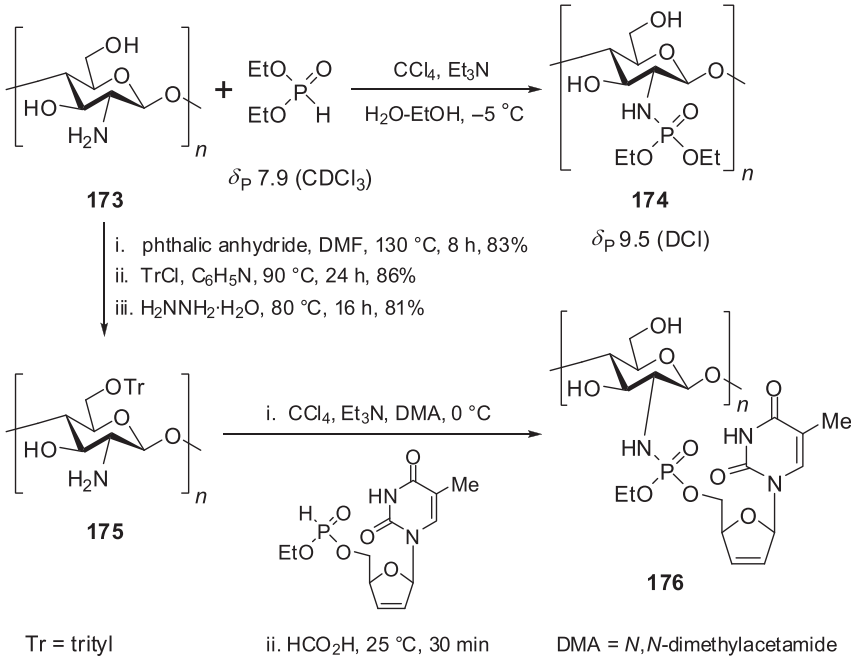


Figure 4.41.5

▶ *Diethylphosphoryl chitosan* (**174**) (*281*). Absolute ethanol (40 ml) followed by triethylamine (15 ml) was added to a stirred solution of chitosan (4 g) in distilled water (80 ml) under nitrogen. This mixture was cooled to −5 °C and treated dropwise over 2 h with a solution of diethyl *H*-phosphonate (6.5 ml) in carbon tetrachloride (16 ml). The mixture was stirred at −5 °C for a further 4 h, then allowed to warm to room temperature, and stirred for 24 h. The mixture was poured into acetone (350 ml) which caused the title compound to precipitate. The precipitate was filtered off and extracted in a Soxhlet apparatus with absolute ethanol for 24 h to remove impurities and then dried in a vacuum at 40 °C for 24 h. The phosphorylated chitosan was less soluble than chitosan in water.

A variant of the Todd–Atherton reaction consists of addition of a dialkyl *H*-phosphonate to iodoform and an amine in chloroform or ether (*163*). The unstable intermediate dialkyl phosphoroiodidate (**177**) reacts with the amine to provide the corresponding phosphoramidate, e.g. diethyl phosphoramidate (**178**) or diethyl *N*-phenylphosphoramidate (**179**) (Fig. 4.41.6).

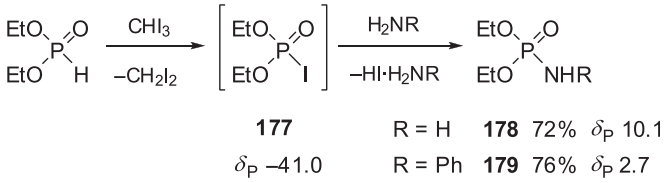


Figure 4.41.6

▶ *Diethyl phosphoramidate $(EtO)_2P(O)NH_2$* (**178**) *(from diethyl H-phosphonate, iodoform and ammonia)* (*163*). Anhydrous ammonia was passed through a stirred solution of diethyl *H*-phosphonate (1.4 g, 10.1 mmol) and iodoform (3.9 g, 10.0 mmol) in anhydrous chloroform (20 ml) until the yellow colour disappeared. Precipitated ammonium iodide was filtered off. The filtrate was concentrated. The solid residue was crystallised from cyclohexane–ether to give a white solid (1.1 g, 72%). Mp 54 °C. δ_P (81 MHz, $CDCl_3$) 10.1 ppm.

▶ *Diethyl N-phenylphosphoramidate $(EtO)_2P(O)NHPh$* (**179**) *(from diethyl H-phosphonate, iodoform and aniline)* (*163*). A solution of diethyl *H*-phosphonate (0.69 g, 5 mmol), aniline (0.93 g, 10 mmol) and iodoform (1.96 g, 5 mmol) in ether (15 ml) was stirred at room temperature for 15 h. The solvent was removed. The residue was dissolved in chloroform (30 ml), washed with water (2 × 10 ml), 0.5% aqueous acetic acid (2 × 15 ml) and again with water (3 × 10 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated, and the crude product was recrystallised from benzene–hexane to give the amidate (0.87 g, 76%). Mp 93 °C. δ_P (81 MHz, $CDCl_3$) 2.7 ppm. Dialkyl *N*-phenylphosphoramidates decompose when heated which often rules out purification by vacuum distillation (*283*).

The traditional method of preparation of dialkyl *N*-alkyl/arylphosphoramidates is to treat dialkyl *N*-alkyl/arylphosphorochloridates with 2 mol equiv. of an amine in an inert solvent (*283–293*). When the amine is precious, 1 mol equiv. can be used with a molar equivalent of triethylamine or pyridine to scavenge the liberated hydrogen chloride. Examples of phosphoramidates easily prepared using such methods are given in Table 4.41.

▶ *Diethyl N-methylphosphoramidate $(EtO)_2P(O)NHMe$* (*165*). Anhydrous methylamine was passed into diethyl phosphorochloridate (20 g, 120 mmol) dissolved in anhydrous ether (200 ml) at 0–5 °C. Methylamine hydrochloride precipitated. When no more solid separated, the methylamine flow was stopped and the mixture filtered. The ether was removed from the filtrate and the residue distilled to provide the amidate (16.3 g, 84%). Bp 130 °C/15 mmHg.

▶ *Diethyl N,N-diethylphosphoramidate $(EtO)_2P(O)NEt_2$* (*294*). Diethyl phosphorochloridate (35 g, 200 mmol) and diethylamine (35 g, 480 mmol) in anhydrous light petroleum (bp 40–60 °C; 250 ml) gave the amidate as a colourless liquid (35 g, 83%). Bp 106–108 °C/20 mmHg.

Table 4.41 Dialkyl/diphenyl *N*-alkyl/phenylphosphoramidates[a] $(RO)_2P(O)X$ made by treating the corresponding dialkyl/diphenyl phosphorochloridates with an appropriate amine in an inert solvent

R	X	Yield (%)	Mp (°C), Bp (°C/mmHg)	Reference/s
Me	NH_2	—	Mp 40—42	(*91*)
Me	NHMe	26	Bp 135/17	(*70*)
Me	NHEt	85	Bp 122—124/10	(*286*)
Me	NHPr-*n*	81	Bp 132—134/11	(*286*)
Me	NHBu-*n*	85	Bp 143—154/9	(*286*)
Me	NHPh	72	Mp 88—88.5	(*70*)
Et	NH_2	—	Mp 55.5	(*165*)
Et	NHMe	84	Bp 130/15	(*165*)
Et	NHEt	80	Bp 79—81/0.03	(*286*)
Et	NHPr-*n*	90	Bp 140/10	(*286*)
Et	NHBu-*n*	85	Bp 101—103/0.035	(*286*)
Et	NHPh	90	Mp 97	(*60,70*)
n-Pr	NH_2	30	Bp 115—116/0.6, mp 39—42	(*148,290*)
n-Pr	NHEt	69	Bp 85—89/0.03	(*286*)
n-Pr	NHPr-*n*	85	Bp 96—98/0.03	(*286*)
n-Pr	NHBu-*n*	91	Bp 105—107/0.03	(*286*)
n-Pr	NHPh	—	Mp 54.5—55.5	(*64*)
i-Pr	NH_2	—	Mp 56—57	(*14*)
i-Pr	NHBu-*i*	63	Bp 103.5—104/1.5	(*288*)
i-Pr	NHBu-*s*	75	Bp 101/2, mp 20—30	(*288*)
i-Pr	NHBu-*t*	83	Bp 107—112/3, mp 60—62	(*288*)
i-Pr	NHPh	76	Mp 120—121.5	(*70*)
n-Bu	NH_2	—	Bp 117/01	(*289*)
n-Bu	NHMe	73	Bp 116—118/0.5—0.6	(*135*)
n-Bu	NHEt	84	98—100/0.03	(*286*)
n-Bu	NHPr-*n*	84	112—113/0.03	(*286*)
n-Bu	NHBu-*n*	88	128—130/0.03	(*286*)
i-Bu	NHEt	92	96—98/0.025	(*286*)
i-Bu	NHPh	—	Mp 43.5—45	(*61*)
t-Bu	NH_2	91	Mp 122—125	(*74*)
t-Bu	NHBn	85	Mp 97—98	(*74*)
$ClCH_2CH_2$	NH_2	85	Mp 77	(*81*)
$ClCH_2CH_2$	NHPh	90	Mp 80.5—83.5	(*135*)
Ph	NH_2	89	Mp 148—149	(*81*)
Ph	NHPr-*n*	69	Bp 208/8, mp 52—54	(*148,290*)
Ph	NHPr-*i*	—	Mp 72—74	(*287*)
Ph	NHPh	—	Mp 129—130	(*291*)
Ph	NHBn	—	Mp 92—94	(*287*)
Bn	NH_2	91	Mp 103.5—104.5	(*38*)
Bn	NHPh	98	Mp 91—92.5	(*38*)
Bn	NHBn	90	Mp 84—85	(*38*)

[a]In compounds having a P—NXMe group, the degree of interaction of the phosphoryl group with the neighbouring nitrogen atom can be inferred from ^{1}H NMR spectroscopic data (*285*). The $^3J_{PNCH}$ values in the system $(MeO)_2P(O)NXMe$ decrease in the order X = Me (10.0 Hz) > Ph (8.0 Hz) > COMe (7.5 Hz). This order indicates a strong resonance interaction of the P and N atoms, which indicates that the P—N bond has some double bond character.

▶ *Diisopropyl N-phenylphosphoramidate (i-PrO)$_2$P(O)NHPh* (*14*). Diisopropyl phosphorochloridate (6.0 g, 30 mmol) was added slowly to aniline (5.6 g, 60 mmol) at 0–5 °C. After standing for 1 h, the product was extracted with boiling benzene and the aniline hydrochloride filtered off. The benzene filtrate was evaporated to give a viscous liquid that solidified. Recrystallisation from ether and petroleum ether (bp 40–60 °C) and then water yielded white needles. Mp 121–121.5 °C. Diethyl *N*-phenylphosphoramidate (mp 96 °C) and diphenyl *N*-phenylphosphoramidate (mp 129–130 °C) were prepared similarly (*294*).

Dialkyl phosphorochloridates react with ethyleneimine in the presence of triethylamine to provide dialkyl *N*-ethylenephosphoramidates (**180**) and (**181**) (Fig. 4.41.7) (*295*). Certain analogues of dimethyl *N*-ethylenephosphoramidate find practical use as chemosterilants (Chapter 1.8). Dialkyl *N*-alkylphosphoramidates derived from α-amino acids for biological studies are synthesised similarly (*296–302*).

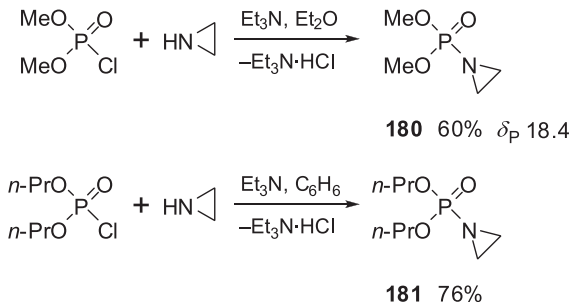


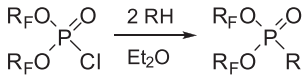
Figure 4.41.7

▶ *Dimethyl N-ethylenephosphoramidate (MeO)$_2$P(O)N(CH$_2$)$_2$* (**180**) (*295*). Ethyleneimine was first prepared: a solution of 2-chloroethylammonium chloride (15.0 g, 130 mmol) and sodium hydroxide (15.6 g, 390 mmol) in water (30 ml) was heated to 50 °C for 2 h under reduced pressure (25 mmHg) and the distillate (bp 30–35 °C) was collected in an ice-cooled receiver. A second distillation of the crude product was carried out at atmospheric pressure, with rigorous exclusion of moisture, and the distillate was collected over solid sodium hydroxide. Ethyleneimine was obtained as a colourless liquid (3.8 g, 70%; bp 55–57 °C; δ_H in D_2O was 1.56 ppm). The amidate was prepared next: a solution of dimethyl phosphorochloridate (5.0 g, 35 mmol) in anhydrous ether (10 ml) was added dropwise to a stirred solution of ethyleneimine (1.5 g, 42 mmol) and triethylamine (3.5 g, 35 mmol) in ether (20 ml) at 10 °C. The cooling bath was removed and stirring was continued for 2 h. Precipitated triethylamine hydrochloride was filtered off and the filtrate concentrated. The crude product was dissolved in ether (30 ml), washed with 10% aqueous potassium carbonate (20 ml), dried ($MgSO_4$), filtered, and the filtrate evaporated. Distillation of the residue yielded the title compound (3.2 g, 60%). Bp 83–84 °C/0.7 mmHg. δ_P ($CDCl_3$) 18.4 ppm.

▶ *Di-n-propyl N-ethylenephosphoramidate (n-PrO)$_2$P(O)N(CH$_2$)$_2$* (**181**) (*303,304*). A solution of di-*n*-propyl phosphorochloridate (31.4 g, 0.157 mol) in anhydrous benzene (50 ml) was added dropwise

over 40 min to a stirred solution of ethyleneimine (6.75 g, 0.157 mol) and triethylamine (15.8 g, 0.157 mol) in anhydrous benzene (50 ml) at between +5 and −5 °C. After addition, the mixture was stirred for 2 h at room temperature and then at 40−50 °C for 1 h. After cooling to room temperature, the triethylamine hydrochloride was filtered off, twice washed with anhydrous benzene, dried and weighed. The benzene filtrate and washings were combined and distilled twice under vacuum to give the pure phosphoramidate (24.7 g, 76%). Bp 127−128 °C/10 mmHg.

Bis(fluoroalkyl) phosphorochloridates react with amines in ether to provide *bis*(fluoroalkyl) phosphoramidates and *N*-alkyl- and *N*,*N*-dialkylphosphoramidates (Fig. 4.41.8) (*5,251*). These compounds are low-melting white solids or liquids that can be distilled without decomposition. Methods for their preparation are general for all dialkyl phosphoramidates. The lower dialkyl phosphorochloridates and *bis*(fluoroalkyl) phosphorochloridates also react with fluorinated primary amines to give phosphoramidates (*305,306*). Sometimes DMAP catalyst needs to be added to accelerate phosphorylation.



Bis(fluoroalkyl) *N*-alkyl- or *N*,*N*-dialkylphosphoramidates

R_F	R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
CF_3CH_2	NH_2	91	Mp 42–43 °C	9.2
CF_3CH_2	NHMe	68	84–86/1	9.4
CF_3CH_2	NMe_2	70	37/0.5	9.7
CF_3CH_2	NHEt	66	96/0.1	8.3
CF_3CH_2	NEt_2	75	62/1	9.0
$C_2F_5CH_2$	NH_2	76	76/0.02	8.7
$C_2F_5CH_2$	NHMe	68	56/0.015	8.7
$C_2F_5CH_2$	NMe_2	74	36/0.015	9.4
$C_2F_5CH_2$	NHEt	81	58/0.1	7.7
$C_2F_5CH_2$	NEt_2	74	39/0.06	8.7

a. Recorded in $CDCl_3$ at 202 MHz

Figure 4.41.8

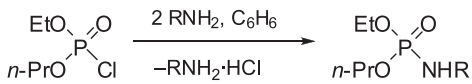
▶ *Reactions of dialkyl phosphorochloridates with ammonia (general procedure)* (*251*). The synthesis of *bis*(2,2,2-trifluoroethyl) phosphoramidate $(CF_3CH_2O)_2P(O)NH_2$ serves as an example. A round-bottomed flask was equipped with a T-adaptor and a dry-ice condenser whose outlet was fitted with a guard tube containing anhydrous calcium chloride. The flask was charged with a solution of *bis*(2,2,2-trifluoroethyl) phosphorochloridate (10 g, 35.7 mmol) in ether (50 ml). The flask and the

condenser were cooled to −78 °C (dry ice—acetone) and ammonia gas was passed through the T-adaptor and allowed to condense into the solution. An instant precipitate of ammonium chloride was observed. Liquefied ammonia was allowed to drop into the reaction mixture until it was clear that more than 2 mol equiv. had been added. The ammonia supply was turned off and the flask was allowed to warm to room temperature (the condenser containing dry ice remained at −78 °C). Once the flask reached room temperature, the dry ice in the cold finger was allowed to evaporate. The reaction mixture was left to stand for 2 h. The precipitate was filtered off and the filtrate concentrated to yield *bis*(2,2,2-trifluoroethyl) phosphoramidate as a white crystalline solid (8.5 g, 91%). Mp 42—43 °C. Multinuclear NMR analysis indicated 99% purity. In other cases, concentration of the filtrate gave a liquid that was purified by bulb-to-bulb distillation under reduced pressure.

▶ *Reactions of dialkyl phosphorochloridates with methylamine and ethylamine (general procedure)* (*251*). These were conducted as described in the previous recipe but on a smaller scale: the dialkyl phosphorochloridate (5 mmol) in ether (20 ml). After filtration, concentration of the filtrate gave solid or liquid products. The solids did not require recrystallisation. The liquids were purified by bulb-to-bulb distillation under reduced pressure.

▶ *Reactions of dialkyl phosphorochloridates with dimethylamine and diethylamine* (*251*). An excess of chilled dimethylamine was pipetted into a stirred solution of the appropriate dialkyl phosphorochloridate (5 mmol) in ether (50 ml) at 0—5 °C. After addition, the mixture was kept at this temperature for a further 30 min, and then allowed to warm to room temperature; the excess of dimethylamine evaporated. After 2 h, the precipitated amine hydrochloride was removed by filtration. Concentration of the filtrate and bulb-to-bulb distillation of the residue under reduced pressure gave the dialkyl *N*,*N*-dimethylphosphoramidates as colourless liquids. Similarly, addition of diethylamine (10 mmol) in ether (10 ml) to the phosphorochloridate (5 mmol) in ether (50 ml), and work-up as before, gave dialkyl *N*,*N*-diethylphosphoramidates as colourless liquids or white solids.

Unsymmetrical dialkyl phosphorochloridates react with primary amines to give dialkyl *N*-alkylphosphoramidates, such as (**182**) and (**183**) (Fig. 4.41.9) (*148*). Unsymmetrical *N*,*N*-dialkylphosphoramidates of structure $(RO)_2P(O)NR'R''$ are also known (*276*,*307*).



R = H **182** 39% bp 119 °C/1 mmHg

R = *n*-Pr **183** 64% bp 85–86 °C/0.2 mmHg

Figure 4.41.9

In a very few cases, dialkyl phosphorobromidates or iodidates can be used instead of the chloridates for amidate formation. An example is the reaction of tris(trimethylsilyl) phosphite with iodine to give the intermediate iodidate (**184**) that reacts with aniline to give the amidate (**185**) (Fig. 4.41.10) (*156*).

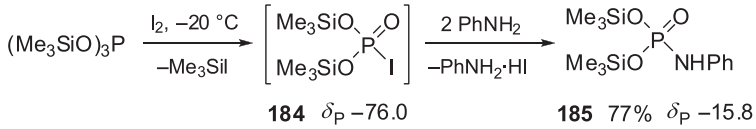


Figure 4.41.10

▶ *Bis(trimethylsilyl) N-phenylphosphoramidate* $(Me_3SiO)_2P(O)NHPh$ (**185**) (*156*). Iodine (7.62 g, 30 mmol) was added to a stirred solution of tris(trimethylsilyl) phosphite (8.93 g, 30 mmol) in ether (60 ml) at −20 °C. After addition, stirring was continued for 30 min. Aniline (8.4 g, 90 mmol) was added dropwise. Afterwards the mixture was allowed to warm to room temperature and the precipitate was filtered off. The ethereal filtrate was evaporated to afford the crude product. Recrystallisation from 1:1 *v/v* benzene—hexane gave the title compound as needles (7.35 g, 77%). Mp 140—142 °C. δ_P −15.8 ppm.

The reaction of alkyl phosphorodichloridates with aminoalcohols can be used to generate cyclic phosphoramidates. Methyl phosphorodichloridate reacts with 2-aminoethanol in chloroform in the presence of triethylamine to afford the corresponding cyclic dialkyl phosphoramidate (**186**) (Fig. 4.41.11) (*295*). To avoid the formation of polymeric products, dilute solutions of the dichloridate and amine reagent are added simultaneously to a stirred solution of triethylamine in chloroform.

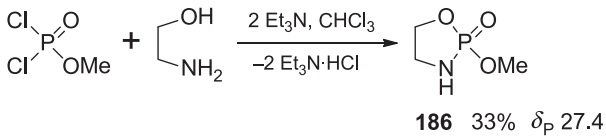


Figure 4.41.11

▶ *2-Methoxy-2-oxo-1,3,2-oxazaphospholidine* (**186**) (*295*). A solution of triethylamine (4.05 g, 40 mmol) in anhydrous chloroform (20 ml) was placed in a three-necked flask equipped with a magnetic stirrer, two dropping funnels, and a drying tube. To this stirred solution was added dropwise simultaneously from the two dropping funnels a solution of methyl phosphorodichloridate (3.0 g, 20 mmol) in chloroform (15 ml) and a solution of 2-aminoethanol (1.22 g, 20 mmol) in chloroform (15 ml) at 0—5 °C. The cooling bath was withdrawn and the stirring was continued for 1 h. The precipitate was filtered off and the solvent was removed from the filtrate. The viscous liquid was treated with anhydrous ether (20 ml) and the residual triethylamine hydrochloride was filtered off. The precipitation process was repeated several times until no further salt precipitated. Removal of the solvent afforded the pure product as colourless crystals (0.90 g, 33%). Mp 197—199 °C. δ_P ($CDCl_3$) 27.4 ppm.

Alkyl azides (**187**) enter into a Staudinger reaction with trialkyl phosphites and yield the dialkyl phosphoramidates (**188**) (Fig. 4.41.12) (*308*). This relatively uncommon route offers some interesting synthetic possibilities.

▶ *2,5-Anhydro-1-[(diethylphosphoryl)ethylamino]-1,4-dideoxy-3-thio-D-threo-pentitol 3-acetate* (**188**) (*308*). Triethyl phosphite (0.85 ml, 4.97 mmol) was added by syringe to a stirred solution of the azide (1.01 g, 4.97 mmol) in anhydrous toluene (5 ml). The mixture was warmed to 45 °C until the

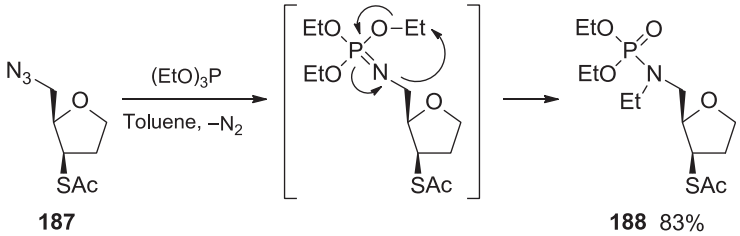


Figure 4.41.12

evolution of nitrogen ceased (after about 2 h). The solvent was removed and the residue chromatographed on silica gel, eluting with 1:1 ethyl acetate—hexane and later with ethyl acetate, to yield a colourless liquid (1.4 g, 83%).

Another little explored reaction is that between *S*-alkyl dialkoxyphosphinylthioformates (Section 4.28) and hydroxylamine in the presence of an excess of pyridine. In the case of *S*-ethyl diisopropoxyphosphinylthioformate, this caused P—C bond cleavage and gave diisopropyl phosphoramidate (**117**) in good yield (Fig. 4.41.13) (*178*).

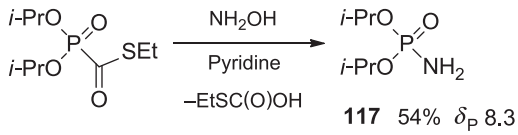


Figure 4.41.13

▶ *Diisopropyl phosphoramidate (i-PrO)$_2$P(O)NH$_2$* (**117**) (*178*). Equimolar amounts of *S*-ethyl diisopropoxyphosphinylthioformate and hydroxylamine hydrochloride were added to an excess of pyridine and stirred for 72 h. The mixture was concentrated and the residue dissolved in ethyl acetate, filtered and chromatographed on silica gel, eluting with ethyl acetate, to provide the phosphoramidate (0.98 g, 54%). Mp 53—54 °C. δ_P ($CDCl_3$) 8.3 ppm.

4.42 DIALKYL *N*-ARYLPHOSPHORAMIDATES (RO)$_2$P(O)NHAr

Routes to such compounds involving the reaction of dialkyl phosphorochloridates with aromatic amines are discussed in the previous section. Less obvious routes start from trivalent phosphorus reagents and include the microwave (MW)-assisted reaction of trialkyl phosphites with a substituted nitrobenzene (e.g. **189**) to yield the phosphoramidate (e.g. **190**) (Fig. 4.42.1) (*309*).

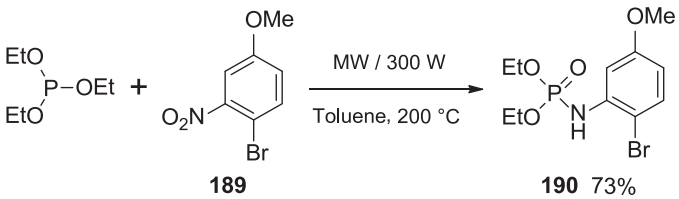


Figure 4.42.1

Another method consists of treating a dialkyl phosphorochloridite with a nitroaromatic system such as 4-nitrobenzaldehyde (**191**). The dialkyl *N*-(4-formylphenyl)phosphoramidate (**192**) is produced in good yield (Fig. 4.42.2) (*310*).

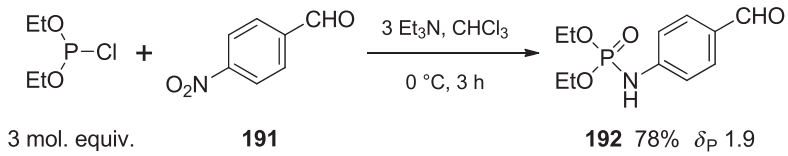


Figure 4.42.2

▷ *Diethyl N-(2-bromo-5-methoxyphenyl) phosphoramidate* (**190**) (*309*). A mixture of triethyl phosphite (995 mg, 6 mmol), 4-bromo-3-nitroanisole (232 mg, 1 mmol) and toluene (3 ml) was sealed in a 10 ml septum reaction vial and irradiated using a CEM Discover™ MW instrument (2450 MHz, 300 W, 200 °C) for 10 min. The mixture was heated to 40–70 °C at 0.1 mmHg to remove volatile matter. The residue was diluted with dichloromethane (30 ml), washed with water (2 × 50 ml) and brine (3 × 20 ml), and dried ($MgSO_4$). After concentration, the residue was chromatographed on silica gel, eluting with 1:2 cyclohexane–ethyl acetate, to give the product (247 mg, 73%). Mp 58 °C.

▷ *Diethyl N-(4-formylphenyl) phosphoramidate* (**192**) (*310*). Diethyl phosphorochloridite (286 µl, 1.99 µmol) and triethylamine (278 µl, 1.99 µmol) were added to a solution of 4-nitrobenzaldehyde (100 mg, 0.66 mmol) in anhydrous chloroform (3 ml) under argon at −10 °C. The mixture was warmed to 0 °C and stirred at this temperature for 3 h. The solvent was removed and the residue chromatographed on silica gel to give the product (131 mg, 78%). δ_P ($CDCl_3$) 1.9 ppm.

4.43 DIARYL PHOSPHORAMIDATES $(ArO)_2P(O)NR_2$

Treatment of *O*-phenyl *O*-(*p*-nitrophenyl) phosphorochloridate (**96**) with an excess of ammonium hydroxide provides the corresponding amidate (**193**) in good yield (Fig. 4.43.1) (*154*). This illustrates the greater reactivity of phosphorochloridates to amino rather than hydroxy nucleophiles.

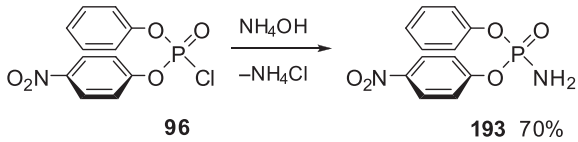


Figure 4.43.1

▷ *Diaryl phosphoramidates $(ArO)_2P(O)NH_2$ (general procedure)* (*81*). Gaseous ammonia was passed into a stirred solution of the diaryl *H*-phosphonate (0.1 mol) in carbon tetrachloride (20.0 g) at 20–30 °C. The passage of ammonia was stopped after the exothermic reaction ceased. The mixture was treated with water (100 ml) to dissolve the by-product ammonium chloride. When the product was a solid insoluble in chloroform, the mixture was filtered and the filter cake was dried. When the

product was soluble in chloroform, the chloroform layer was concentrated and the product isolated as the undistilled residue. The following compound was prepared: diphenyl phosphoramidate $(PhO)_2P(O)NH_2$ (white crystalline solid insoluble in chloroform; 22.0 g, 89%; mp 148–149 °C).

▶ *Phenyl p-nitrophenyl phosphoramidate* $PhO(p\text{-}O_2NC_6H_4O)P(O)NH_2$ (**193**) (*154*). Phenyl *p*-nitrophenyl phosphorochloridate (3.1 g, 10 mmol) was treated with ammonium hydroxide (5 ml). A semisolid mass precipitated which was crystallised by scratching. The product was obtained pure after recrystallisation from ethanol (2.1 g, 70%). Mp 167–168 °C.

4.44 DIALKYL *N*-METHYL-*N*-(PHOSPHORYL)PHOSPHORAMIDATES $(RO)_2P(O)N(Me)P(X)R_2$

Diethyl *N*-methylphosphoramidate (**194**)(*165*) contains an acidic amido proton that can be removed by sodium in ligroin to provide an anion (**195**) that reacts readily with diethyl phosphorochloridite (to give **196**), diethyl phosphorochloridate (to give **197**), diethyl phosphorochloridothionate (to give **198**), *N,N*-dimethyl *O*-ethyl phosphoramidochloridate (to give **199**), or *N,N,N′,N′*-tetramethylphosphorodiamidic chloride (to give **200**) (Fig. 4.44.1) (*311*). The products are obtained pure after repeat fractionation.

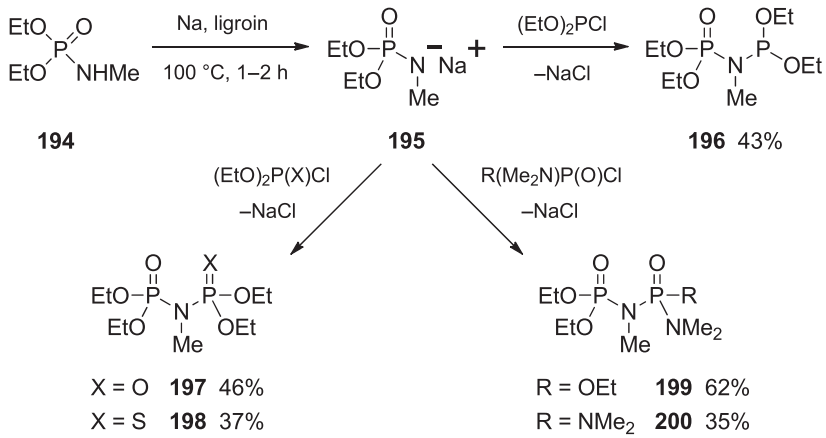


Figure 4.44.1

▶ *O,O-Diethyl N-alkyl-N-sodium phosphoramidates* $(EtO)_2P(O)NR(Na)$ *(where R = Me* **195***, Et, n-Bu, or Ph)* (*311*). A slight excess of the theoretical quantity of sodium was added in small pieces to ligroin (bp 75–125 °C, 6.0–6.5 mol excess over the amidate used) in a three-necked flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser. The amidate was slowly added dropwise. Reaction occurred immediately at room temperature. After addition, the flask was heated to 100 °C for 2 h. Once the reaction was complete, the solution of the sodium phosphoramidate salt was cooled to room temperature, and the excess of sodium removed. The quantity of sodium that reacted was exactly that calculated.

▶ *O,O-Diethyl N-(diethylphosphoryl)-N-methylphosphoramidite* $(EtO)_2P(O)N(Me)P(OEt)_2$ (**196**) (*311*). This was prepared from diethyl phosphorochloridite (14.1 g, 90 mmol), the *O,O*-dialkyl *N*-methylphosphoramidate (15.0 g, 90 mmol) and sodium (2.1 g, 91 mmol) in ligroin. The crude product (22.2 g) was a yellow liquid and was distilled at 3 mmHg to give two fractions: (1) bp 42–110 °C, 2.0 g; and (2) bp 110–117 °C, 17.5 g (residue 2.0 g). Redistillation of fraction 2 gave the title compound as a colourless mobile liquid (11.2 g, 43%). Bp 104–106 °C/1 mmHg. It has a slight phosphite odour and is water soluble.

▶ *O,O-Diethyl N-(diethylphosphoryl)-N-methylphosphoramidate* $(EtO)_2P(O)N(Me)P(O)(OEt)_2$ (**197**) (*311*). Diethyl phosphorochloridate (15.5 g, 90 mmol) was added dropwise over 20 min with cooling and mechanical stirring to a solution of *O,O*-diethyl *N*-methyl-*N*-sodium phosphoramidate prepared from the amidate (15.0 g, 90 mmol) and sodium (2.1 g, 91 mmol) in ligroin. After addition, stirring was continued for some time at room temperature, and finally at 60 °C for 20–30 min. The sodium chloride was removed by centrifugation, the solvent was removed from the supernatant under slight vacuum, and the residual liquid (23.5 g) was distilled. After two distillations, a pure fraction was obtained (12.6 g, 46%). Bp 138–139 °C/3 mmHg. The product is a colourless mobile liquid, soluble in water and ether.

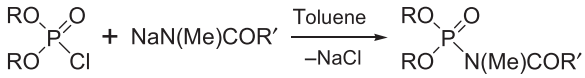
▶ *O,O-Diethyl N-(diethylthiophosphoryl)-N-methylphosphoramidate* $(EtO)_2P(O)N(Me)P(S)(OEt)_2$ (**198**) (*311*). Diethyl phosphorochloridothionate (13.0 g, 69 mmol), *O,O*-diethyl *N*-methylphosphoramidate (11.5 g, 69 mmol) and sodium (1.6 g, 70 mmol) were used. The experiment was conducted under the previously described conditions. The crude product (19 g) was a deep yellow liquid that was distilled at 1.5 mmHg to yield two fractions: (1) bp 64–110 °C, 3.6 g; and (2) bp 110–135 °C, 10.8 g (residue, 3 g). Redistillation of fraction 2 yielded the title compound (8.0 g, 37%). Bp 120 °C/1 mmHg. The product is a mobile yellow liquid, slightly soluble in water, but readily soluble in organic solvents.

▶ *O-Ethyl N-(diethylphosphoryl) N,N′,N′-trimethylphosphorodiamidate* $(EtO)_2P(O)N(Me)P(O)(OEt)NMe_2$ (**199**) (*311*). Prepared from *N,N*-dimethyl *O*-ethyl phosphoramidochloridate (16.1 g, 94 mmol), the *O,O*-diethyl *N*-methylphosphoramidate (15.6 g, 93 mmol) and sodium (2.2 g, 96 mmol) using the previous method. The crude product (24.1 g) after two distillations yielded the title compound (17.5 g, 62%). Bp 139–141 °C/1.5 mmHg. It was a colourless mobile liquid, soluble in water and in ether, but only slightly soluble in ligroin.

▶ *N-(Diethylphosphoryl)pentamethyl phosphoric triamide* $(EtO)_2P(O)N(Me)P(O)(NMe_2)_2$ (**200**) (*311*). This was obtained by the reaction of *N,N,N′,N′*-tetramethylphosphorodiamidic chloride (15.0 g, 88 mmol) with *O,O*-diethyl *N*-methyl-*N*-sodium phosphoramidate prepared from the *O,O*-diethyl *N*-methylphosphoramidate (14.7 g, 88 mmol) and sodium (2.0 g, 88 mmol) in ligroin. Distillation of the crude product (22.2 g) gave three fractions: (1) bp 111–142 °C, 4.0 g; (2) bp 142–144 °C, 1.5 g; and (3) bp 144–148 °C, 13.9 g (residue, 2.0 g). Redistillation of fraction 3 gave the title compound (9.3 g, 35%). Bp 147–149 °C/3 mmHg. The product was a colourless mobile liquid, readily soluble in water and ligroin.

4.45 DIALKYL *N*-METHYL-*N*-ACYLPHOSPHORAMIDATES $(RO)_2P(O)N(Me)COR'$

Dialkyl phosphorochloridates react with the sodium salts of *N*-acetyl-*N*-methyl-acetamide and -benzamide in toluene to provide dialkyl *N*-methyl-*N*-acylphosphoramidates (Fig. 4.45.1) (*285*). Yields are low due to concomitant formation of large amounts of tetraalkyl pyrophosphates.



Dialkyl *N*-methyl-*N*-acylphosphoramidates

R	R′	Yield (%)	Bp (°C/mmHg)
Me	Me	38	68–72/0.15
Et	Me	34	76–79/0.02
Et	Ph	30	not distilled

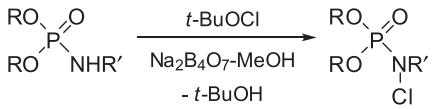
Figure 4.45.1

▶ *Dialkyl N-methyl-N-acylphosphoramidates $(RO)_2P(O)NMeCOR'$* (*285*). A solution of the amide R′C(O)NHMe (0.168 mol) in anhydrous toluene (20 ml) was added dropwise over 30 min to a stirred mixture of finely divided sodium (3.86 g, 0.168 mol) and anhydrous toluene (150 ml). The mixture was heated under reflux under anhydrous conditions until all the sodium had disappeared and produced a suspension of the salt. To the cooled suspension was added dropwise with stirring a solution of the dialkyl phosphorochloridate (0.168 mol) in anhydrous toluene (30 ml) at 5—10 °C. The mixture was slowly warmed to room temperature and stirred overnight. It was filtered and the filtrate was concentrated to give a dark liquid. Chromatography on silica gel, eluting with 1:4 ethyl acetate—chloroform, followed in some cases by distillation, gave the products depicted in Fig. 4.45.1.

4.46 DISUBSTITUTED *N*-ARYL(OR ALKYL)-*N*-CHLOROPHOSPHORAMIDATES $(RO)_2P(O)N(Cl)Ar$

Certain disubstituted *N*-aryl(or alkyl)phosphoramidates undergo *N*-chlorination by *tert*-butyl hypochlorite in a solution of sodium tetraborate (borax) in methanol (Fig. 4.46.1) (*291*). Attempts to prepare these compounds by reaction of *tert*-butyl hypochlorite in the absence of borax, in benzene or ether, gave impure products. The pure disubstituted *N*-aryl(or alkyl)-*N*-chlorophosphoramidates are not appreciably stable. Diethyl *N*-chloro-*N*-phenylphosphoramidate decomposes on storage to a solid from which diethyl *N*-(*p*-chlorophenyl)phosphoramidate $(EtO)_2P(O)NHC_6H_4Cl$-*p* (mp 70 °C) can be isolated; 48% decomposition occurs after 48 h at 25 °C.

▶ *Diphenyl N-chloro-N-phenylphosphoramidate $(PhO)_2P(O)N(Cl)Ph$* (*291*). *Tert*-butyl hypochlorite (5.25 g, 6 ml, 48.3 mmol) (*312*) was added to diphenyl *N*-phenylphosphoramidate (11.0 g, 33.8 mmol) in 4% methanolic borax (200 ml). After 5 min, the mixture was poured into water



Disubstituted *N*-chloro-*N*-aryl(or alkyl)phosphoramidates

R	R′	Yield (%)	Mp (°C)
Et	Ph	92	yellow liquid
Et	*p*-ClC_6H_4	96	yellow liquid
Ph	Ph	74	63.5–64.5
Ph	*p*-MeC_6H_4	95	62–63
Ph	cyclohexyl	98	colourless liquid

Figure 4.46.1

(1000 ml). The oil that separated was extracted with chloroform and the extracts were washed with water and dried ($MgSO_4$). Evaporation at 20 mmHg left a solid whose recrystallisation from light petroleum (bp 40—60 °C) gave the title compound as colourless crystals (9.00 g, 74%). Mp 63.5—64.5 °C. The analogues in Fig. 4.46.1 were prepared similarly.

4.47 DIALKYL *N,N*-DIHALOPHOSPHORAMIDATES $(RO)_2P(O)NX_2$ (X = Cl OR Br)

Diethyl phosphoramidate reacts with gaseous chlorine at 15—20 °C in aqueous acetate buffer (pH 6.3) to provide diethyl *N,N*-dichlorophosphoramidate (**201**) in good yield (Fig. 4.47.1) (*313*). This compound is a yellow mobile liquid (bp 56—57 °C/0.01 mmHg) that cannot be distilled without decomposition; it is stable at room temperature.

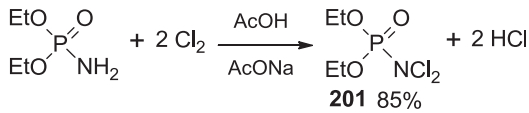
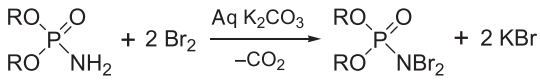


Figure 4.47.1

Dialkyl phosphoramidates react with bromine in aqueous potassium carbonate at 0 °C to give the dialkyl *N,N*-dibromophosphoramidates as liquids or in the case of the di-*tert*-butyl analogue as a low-melting solid (Fig. 4.47.2) (*272*).

Diethyl *N,N*-dichlorophosphoramidate adds to unsaturated hydrocarbons, such as styrene, and forms diethyl *N*-chloro-*N*-(2-chloro-2-phenethyl)phosphoramidate that is reduced by 20% aqueous sodium hydrogen sulfite to the *N*-(2-chloro-2-phenethyl)phosphoramidate (**202**) (Fig. 4.47.3), a pale-yellow viscous liquid (bp 135—136 °C/0.01 mmHg) (*272*). Diethyl *N,N*-dibromophosphoramidate adds to styrene in refluxing dichloromethane and treatment of the corresponding *N*-bromo-(2-bromoalkyl-2-phenethyl)phosphoramidate product with sodium methoxide provides diethyl *N*-(2-phenylaziridinyl) phosphoramidate (**203**), as a colourless liquid (*272*).



O,O-Dialkyl *N,N*-dibromophosphoramidates

R	Yield (%)	Purity (%)	δ_P (ppm)
Et	94	pure	–10.7
n-Pr	94	81	–10.5
i-Pr	94	72	–8.5
n-Bu	94	71	–10.6
t-Bu	78	pure [a]	–0.75

a. mp 88–89 °C

Figure 4.47.2

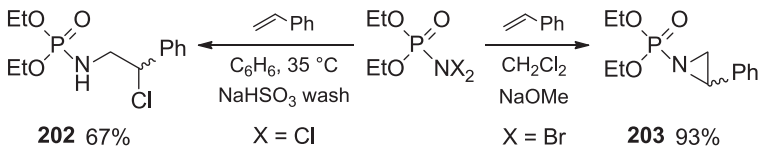


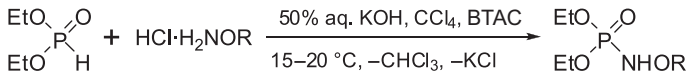
Figure 4.47.3

▶ *Dialkyl N,N-dibromophosphoramidates (RO)$_2$P(O)NBr$_2$ (general procedure)* (272). Bromine (16.0 g, 0.10 mol) was added dropwise to a stirred solution of the dialkyl phosphoramidate (0.05 mol) in water (60 ml) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and finally for 1 h at 20 °C. Dichloromethane (40 ml) was added, the organic layer separated, and the aqueous phase extracted with dichloromethane (3 × 20 ml). The combined extracts were washed with water (2 × 20 ml), dried, and evaporated to provide a liquid from which the residual solvent was removed to give the crude product as an orange-red syrup. The synthesis of di-*tert*-butyl *N,N*-dibromophosphoramidate was carried out for 1 h at 0–5 °C. The yellow precipitate was filtered off, washed with cold water (3 × 15 ml) and dried in the dark in a vacuum desiccator over potassium hydroxide.

▶ *Diethyl N-(2-phenylaziridinyl)phosphoramidate* (**203**) (272). A solution of styrene (5.2 g, 50 mmol) in dichloromethane (15 ml) was added dropwise to a stirred and boiling solution of diethyl *N,N*-dibromophosphoramidate (15.55 g, 50 mmol) in dichloromethane (60 ml). The solution was heated under reflux gently for 30 min, cooled to room temperature and treated with 15% methanolic sodium methoxide (0.1 mol). Stirring was continued for 1 h at room temperature. The precipitated sodium bromide was filtered off and washed with dichloromethane (3 × 50 ml). The solution was washed with water (3 × 30 ml), dried, and evaporated to give crude diethyl *N*-(2-phenylaziridinyl)phosphoramidate (11.9 g, 93%). Distillation under reduced pressure gave the pure title compound as a colourless liquid (9.18 g, 72%). Bp 112–114 °C/0.15 mmHg (bath temperature 145–150 °C).

4.48 DIALKYL *N*-HYDROXY/ALKOXYPHOSPHORAMIDATES $(RO)_2P(O)NHOR$ (R = H OR ALKYL)

Treatment of dialkyl *H*-phosphonates with *O*-alkylhydroxylamine hydrochlorides and potassium hydroxide in water—carbon tetrachloride in the presence of 5 mol% benzyltriethylammonium chloride (BTAC) provides the dialkyl *N*-alkoxyphosphoramidates in acceptable yield (Fig. 4.48.1) (*314*). They are colourless liquids that are stable at ambient temperature. They react with elemental chlorine to provide unstable dialkyl *N*-alkoxy-*N*-chlorophosphoramidates in high yield (not shown).



Dialkyl *N*-alkoxyphosphoramidates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]
Me	78	83–84/0.4	–8.0
Et	47	93–94/0.4	–8.9
n-Bu	45	90/0.2	–8.8
Bn	76	138/0.1	–8.4

a. Neat liquid or solution in CCl_4 measured at 24.3 Hz

Figure 4.48.1

The Todd—Atherton reaction of diisopropyl *H*-phosphonate with hydroxylamine and bromotrichloromethane furnishes diisopropyl *N*-hydroxyphosphoramidate (**204**) (Fig. 4.48.2) (*315*). Similarly, treatment of diphenyl *H*-phosphonate with hydroxylamine or *O*-methylhydroxylamine and carbon tetrachloride provides the *N*-phosphorylated products (**205**) and (**206**).

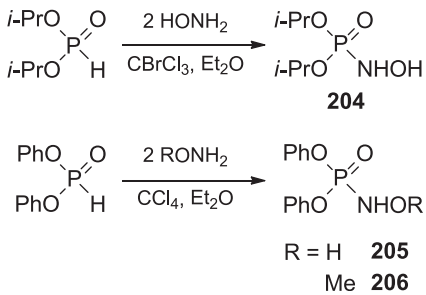


Figure 4.48.2

Treatment of *bis*(2,2,2-trifluoroethyl) phosphorochloridate with aqueous *O*-methylhydroxylamine in chloroform gave a 1:9 mixture of *tris*(2,2,2-trifluoroethyl) phosphate and *bis*(2,2,2-trifluoroethyl) *N*-methoxyphosphoramidate (**207**) (Fig. 4.48.3) (*251*).

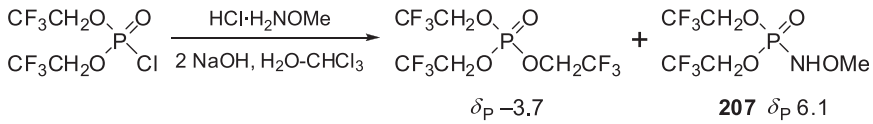


Figure 4.48.3

▶ *Diethyl N-alkoxyphosphoramidates (RO)$_2$P(O)NHOR* (*314*). Fifty percent aqueous potassium hydroxide (22.5 ml, 0.28 mol) was added dropwise to an efficiently stirred mixture of diethyl *H*-phosphonate (17.25 g, 0.125 mol), *O*-alkylhydroxylamine hydrochloride (0.1 mol), carbon tetrachloride (80 ml) and BTAC (1 g, ~5 mol%) at 15–20 °C. Stirring was continued for 2 h at room temperature. The mixture was diluted with dichloromethane (100 ml) and filtered. The layers were separated. The organic layer was dried ($MgSO_4$), concentrated and kept at 30–40 °C/0.1 mmHg for 1–2 h to remove traces of solvent. Analytically pure samples were obtained by distillation under reduced pressure. Compounds prepared using this procedure are shown in Fig. 4.48.1.

▶ *Diisopropyl N-hydroxyphosphoramidate (i-PrO)$_2$P(O)NHOH* (**204**) (*315*). Diisopropyl *H*-phosphonate (1 mol equiv.), hydroxylamine (1 mol equiv.) and bromotrichloromethane (1 mol equiv.) in ether solution were reacted according to the method of Atherton and Todd (*210*). Rotary evaporation of the residue gave a solid. Recrystallisation from light petroleum (bp 30–60 °C) and ether gave the amidate as white crystals (yield not stated). Mp 118–119 °C.

▶ *Diphenyl N-hydroxyphosphoramidate (PhO)$_2$P(O)NHOH* (**205**) (*315*). Diphenyl *H*-phosphonate (1 mol equiv.), hydroxylamine (2 mol equiv.) and carbon tetrachloride (1 mol equiv.) in ether solution were reacted according to the method of Atherton and Todd (*210*). Rotary evaporation of the residue gave a solid. Recrystallisation from ethanol and water gave the amidate as white crystals (yield not stated). Mp 151–152 °C. Diphenyl *N*-methoxyphosphoramidate (PhO)$_2$P(O)NHOMe (**206**) was prepared similarly from *O*-methylhydroxylamine and after recrystallisation from light petroleum (bp 30–60 °C)–ether was obtained as white crystals (yield not stated; mp 57–58 °C).

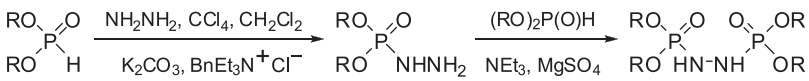
▶ *Bis(2,2,2-trifluoroethyl) N-methoxyphosphoramidate* (**207**) (*251*). A solution of *bis*(2,2,2-trifluoroethyl) phosphorochloridate (2.00 g, 7.14 mmol) in ethanol-free chloroform (10 ml) was added in one portion to a solution of *O*-methylhydroxylamine hydrochloride (0.66 g, 7.85 mmol) and sodium hydroxide (0.63 g, 15.71 mmol) in water (10 ml). The two-phase mixture was stirred vigorously for 3 h. The organic layer was separated, washed with water (2 × 20 ml), dried (Na_2SO_4), filtered and the filtrate concentrated. Bulb-to-bulb distillation of the residue gave a mobile colourless liquid (1.3 g). Multinuclear NMR and mass spectral analyses showed it to comprise a 1:9 mixture of *tris*(2,2,2-trifluoroethyl) phosphate $(CF_3CH_2O)_2P{=}O$ and the title compound. δ_P (202 MHz, $CDCl_3$) 6.1 ppm.

4.49 DIALKYL PHOSPHOROHYDRAZIDATES (RO)$_2$P(O)NH$_2$NH$_2$

The chemistry of phosphorus acid hydrazides has been reviewed (*316*). Few reliable methods of synthesis of dialkyl phosphorohydrazidates are available and for this reason these compounds are poorly

represented in the literature. The formation of diphenyl phosphorohydrazidate from reaction of diphenyl phosphorochloridate and anhydrous hydrazine was reported over 50 years ago (*317*). Attempts to apply classical phosphorylation procedures to the preparation of dialkyl phosphorohydrazidates have generally met with little success. Phase-transfer catalysis using carbon tetrachloride (or this solvent and dichloromethane) and 50% aqueous sodium hydroxide cannot be used for phosphorylation of hydrazine or hydrazine hydrochloride (*318*). Under the usual conditions, in the presence of tetraalkylammonium halide catalyst (5 mol%), the reaction between dialkyl *H*-phosphonates and hydrazine does not take place. This is probably due to the insolubility of the hydrazine free-base in the organic solvent, which diminishes its concentration in the organic phase below the critical level to commence phosphorylation.

To overcome this deficiency, a method involving solid—liquid phase-transfer catalysis is available (*318*). Phosphorylation of hydrazine can be conducted in carbon tetrachloride—dichloromethane containing an excess of K_2CO_3 and BTAC (~1 mol%) as catalyst. The exothermic reaction occurs at room temperature by dropwise addition of the dialkyl *H*-phosphonate to a solution of 80% hydrazine hydrate (Fig. 4.49.1).



208 **209**

	Dialkyl phosphorohydrazidates			Bis(dialkylphosphoryl)hydrazines		
R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm) [a]	Yield (%)	Mp (°C)	δ_P (ppm) [a]
Et	84	100–102/0.5	–10.2	89	96–97	–8.0
n-Pr	90	-	–10.1	95	115–116	–7.1
i-Pr	74	89–90/0.2	–8.1	30	117–118	–5.9
n-Bu	98	-	–10.0	98	103–104	–8.2
t-Bu	41	mp 93–94	0.0	-	-	-

a. Measured in CCl_4 at 24.3 MHz

Figure 4.49.1

Ethyl *n*-propyl phosphorohydrazidate EtO(*n*-PrO)P(O)$NHNH_2$ has been prepared analogously from the unsymmetrical dialkyl *H*-phosphonate (*319*). In all such preparations, only a tiny amount of catalyst is required but its use is essential (*318*). Without it, the yields of crude dialkyl phosphorohydrazidates — almost quantitative in the presence of catalyst — drop below 50%. The crude products are viscous liquids or crystalline solids that are contaminated by the catalyst. Diethyl and diisopropyl phosphorohydrazidates (**208**) can be purified by vacuum fractionation. Other disubstituted phosphorohydrazidates decompose extensively and yield *N,N′-bis*(dialkylphosphoryl)hydrazines (**209**) [i.e. 2 $(RO)_2P(O)NHNH_2 \rightarrow (RO)_2P(O)NHNHP(O)(OR)_2 + NH_2NH_2$]. This appears to be a general property, as diphenyl phosphorohydrazidate also decomposes similarly when heated (*320*). The

identity of the *N,N′-bis*(dialkylphosphoryl)hydrazines was confirmed by their deliberate preparation using a simplified two-step phosphorylation (Fig. 4.49.1): the dialkyl phosphorohydrazidates produced as usual were treated with another molar equivalent of dialkyl *H*-phosphonate in the presence of a stoichiometric amount of triethylamine and an excess of anhydrous magnesium sulfate (dehydrating agent). The *N,N′-bis*(dialkylphosphoryl)hydrazines are colourless crystalline solids that dissolve slightly in hexane and readily in more polar organic solvents.

Dibenzyl phosphorochloridate and diphenyl phosphorochloridate react with hydrazine hydrate in ethanol to provide respectively dibenzyl phosphorohydrazidate (**210**) (*321*) and diphenyl phosphorohydrazidate (**211**) (*320*) in acceptable yield (Fig. 4.49.2).

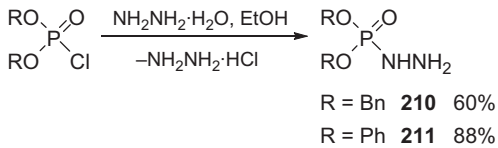


Figure 4.49.2

Dialkyl phosphorohydrazidates, such as $(MeO)_2P(O)NHNH_2$ (mp 73–74 °C), contain a nucleophilic terminal amino group that reacts under acidic conditions with ketones, such as acetone, to give dialkyl phosphorohydrazones, such as $(MeO)_2P(O)NHN{=}CMe_2$ (mp 84–85 °C) (*252*). The P–N bond of dialkyl phosphorohydrazidates is cleaved under acidic conditions to yield dialkyl hydrogen phosphates but is unaffected by alkaline conditions.

▶ *Dialkyl phosphorohydrazidates* $(RO)_2P(O)NH_2NH_2$ (*318*). Eighty percent hydrazine hydrate (12.5 g, 0.2 mol) was added dropwise to a stirred mixture of carbon tetrachloride (120 ml), dichloromethane (200 ml), anhydrous finely powdered potassium carbonate (41.4 g, 0.3 mol) and BTAC (0.4 g, 2 mmol) at room temperature. After addition, stirring was continued for 15 min and a solution of the dialkyl *H*-phosphonate (0.2 mol) in dichloromethane (40 ml) was added with occasional external cooling. After completion of addition, stirring was continued for 4 h at room temperature. The potassium salts were filtered off and washed with dichloromethane. The solvent was removed and the residue kept at 100–110 °C/0.5 mmHg for 2 h to remove traces of volatile impurities. The resulting products were analytically pure (Fig. 4.49.1). Diethyl phosphorohydrazidate and diisopropyl phosphorohydrazidate could be purified by distillation under reduced pressure.

▶ *N,N′-Bis(dialkylphosphoryl)hydrazines* $(RO)_2P(O)NHNHP(O)(OR)_2$ (*318*). The preparation of the corresponding dialkyl phosphorohydrazidate was carried out as described in the previous method, starting with 80% hydrazine hydrate (6.25 g, 0.1 mol), carbon tetrachloride (170 ml), dichloromethane (150 ml), anhydrous potassium carbonate (41.4 g, 0.3 mol), BTAC (0.4 g, 2 mmol) and the dialkyl *H*-phosphonate (0.1 mol). After addition of the latter, the mixture was stirred for 2 h at room temperature and then filtered to remove the potassium salts. Anhydrous magnesium sulfate (20 g) and triethylamine (10.1 g, 0.1 mol) in dichloromethane (20 ml) were added to the filtrate with stirring. A solution of dialkyl *H*-phosphonate (0.1 mol) in dichloromethane (20 ml) was then added dropwise

to the stirred filtrate. After 2 h, the mixture was filtered, evaporated, diluted with benzene (200 ml), and filtered again to remove triethylamine hydrochloride. Removal of the solvent left the crude title compounds as colourless solids that could be purified by crystallisation from 1:1 benzene—hexane. Characterisation details appear in Fig. 4.49.1.

▶ *Dibenzyl phosphorohydrazidate* $(BnO)_2P(O)NHNH_2$ (**210**) (*321*). *N*-Chlorosuccinimide (2.8 g, 21 mmol) was added to a stirred solution of dibenzyl *H*-phosphonate (5.25 g, 20 mmol) in anhydrous benzene (40 ml). The mixture was stirred for 1 h at room temperature. The succinimide was filtered off and the bulk of the benzene evaporated under vacuum. The resulting dibenzyl phosphorochloridate was added to a stirred solution of hydrazine hydrate (10 ml, 50—60% composition) in ethanol (50 ml) at 0—5 °C. After 10 min, water (100 ml) was added and the product extracted into chloroform. The extract was dried, the chloroform removed, and the residue crystallised from a small volume of ether. Recrystallisation gave the title compound as leaflets (3.5 g, 60%). Mp 50—51 °C. A subsequent preparation gave needles of mp 73—74 °C. This is a case of dimorphism as the isopropylidene derivatives from condensation with acetone were identical and had a melting point and mixed melting point of 109 °C.

▶ *Diphenyl phosphorohydrazidate* $(PhO)_2P(O)NHNH_2$ (**211**) (*320*). Diphenyl phosphorochloridate (26 g, 0.103 mol) was added dropwise to a stirred solution of 85% hydrazine hydrate (12 ml, 0.203 mol) in 95% ethanol (48 ml). The heavy oily layer that separated during the course of the extremely vigorous reaction was returned to solution by the addition of distilled water. The product crystallised as a fine white powder when the solution was cooled in an ice bath. Recrystallisation from dilute aqueous ethanol gave pure material (23.3 g, 88%). Mp 116 °C.

4.50 DIALKYL PHOSPHOROISOCYANATIDATES $(RO)_2P(O)NCO$

Dialkyl phosphorochloridates react with silver(I) cyanate in warm acetonitrile to give dialkyl phosphoroisocyanatidates. The cyanate, an ambident nucleophile theoretically able to react through its nitrogen or oxygen atom, prefers to react through the former to produce a P—N bond. Thus, diethyl phosphorochloridate reacts with silver(I) cyanate to give diethyl phosphoroisocyanatidate (**212**) (Fig. 4.50.1) (*322*). Diethyl phosphoramidate, derived from the phosphorochloridate and ammonia, reacts with phosgene at 0 °C in an inert solvent such as benzene or carbon tetrachloride (*323*). However, the isocyanatidates form only in poor yield (and not at all if diaryl phosphoramidates are used). The addition of 2 molar equivalents of a base such as triethylamine or pyridine to the mixture promotes the reaction and in this way it is possible to isolate dialkyl phosphoroisocyanatidates, such as diethyl phosphoroisocyanatidate, as well as diaryl phosphoroisocyanatidates, such as $(PhO)_2P(O)NCO$ (80% yield; bp 140—142 °C/0.1 mmHg). The use of oxalyl chloride as the chlorinating agent, in chlorinated solvents, is often recommended as shown for the synthesis of diethyl phosphoroisocyanatidate (**212**) (*324*) and *bis*(2,2,2-trifluoroethyl) phosphoroisocyanatidate (**213**) (*251*). *Bis*(fluoroalkyl) phosphoramidates by virtue of two electronegative ester groups contain an amino group of greatly reduced nucleophilicity compared to dialkyl phosphoramidates, and therefore react with oxalyl chloride only under harsher conditions, giving phosphoroisocyanatidates containing a carbonyl group of enhanced electrophilicity.

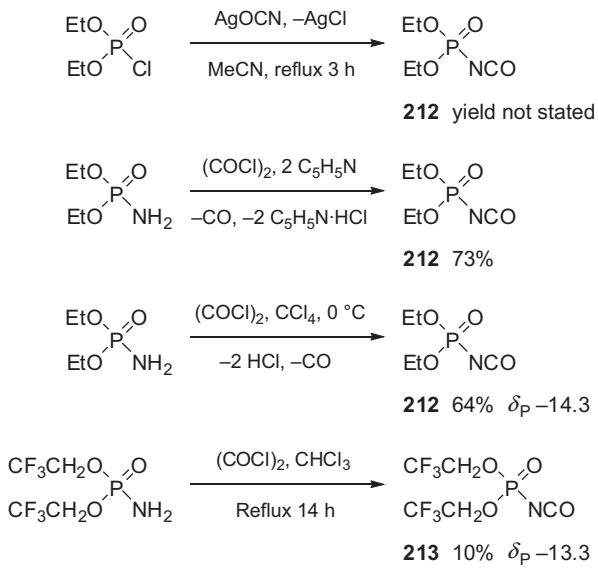


Figure 4.50.1

The lower dialkyl phosphoroisocyanatidates (**214**) are colourless liquids. They are highly reactive and behave similarly to "carbon" isocyanates. In their infrared spectra, the NCO bands occur between 2430 and 2260/cm (*325*). They react very readily with alcohols and phenols to give derivatives (**215**), amines to give derivatives (**216**) and (**217**), and other nucleophiles (Fig. 4.50.2) (*326,327*), and therefore serve as important starting materials for the synthesis of derivatives of dialkyl phosphoramidates.

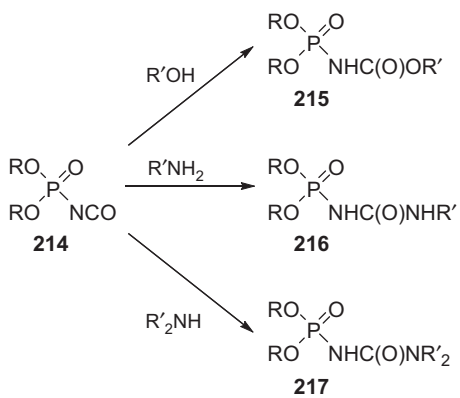


Figure 4.50.2

▶ *Diethyl phosphoroisocyanatidate* $(EtO)_2P(O)NCO$ (**212**) (*322*). A stirred suspension of diethyl phosphorochloridate (11.90 g, 69 mmol), silver(I) cyanate (8.99 g, 60 mmol) and anhydrous acetonitrile (160 ml) was heated under reflux for 3 h. The mixture was cooled and filtered. The solvent was removed from the filtrate and the residue was distilled to give the title compound as a colourless liquid (yield not stated). Bp 60–65 °C/0.3–0.5 mmHg (lit. 91–93 °C/14 mmHg (*323*)). It reacts vigorously with water to evolve carbon dioxide, with methanol to form a methylurethane, and with aniline to form a phenylurea.

▶ *Diethyl phosphoroisocyanatidate* $(EtO)_2P(O)NCO$ (**212**) (*324*). A solution of diethyl phosphoramidate (30.6 g, 0.20 mol) in carbon tetrachloride (50 ml) was added dropwise to a stirred solution of oxalyl chloride (27.9 g, 0.22 mol) in carbon tetrachloride (150 ml) at −5 to 0 °C. After addition, the temperature of the mixture was raised slowly to 50 °C and maintained at 50 °C for 1 h. The mixture was allowed to cool to room temperature. It was filtered and evaporated under vacuum. Fractionation of the liquid residue under reduced pressure gave diethyl phosphoroisocyanatidate (22.9 g, 64%). Bp 85–87 °C/10 mmHg (bath temperature 120–125 °C). δ_P (CCl_4) −14.3 ppm. The compound should be carefully protected from moisture during distillation and storage.

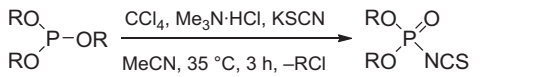
▶ *Bis(2,2,2-trifluoroethyl) phosphoroisocyanatidate* $(CF_3CH_2O)_2P(O)NCO$ (**213**) (*251*). Oxalyl chloride (0.76 g, 6 mmol) in chloroform (25 ml) was added dropwise to a stirred solution of *bis*(2,2,2-trifluoroethyl) phosphoramidate (1.57 g, 6 mmol) in chloroform (30 ml) at 0–5 °C. After addition, the mixture was allowed to warm to room temperature and was left to stand for 14 h. The mixture was heated under reflux for a further 14 h and the progress of reaction was monitored by GC–MS. After this time, it was evident that the reaction would not progress beyond 76% completion. The solvent was removed. Bulb-to-bulb distillation of the residue gave the product as a moisture-sensitive colourless liquid (0.17 g, 10%). Bp 34 °C/0.02 mmHg. δ_P (202 MHz, $CDCl_3$) −13.3 ppm.

▶ *Diethyl N-(t-butoxycarbonyl) phosphoramidate* $(EtO)_2P(O)NHC(O)OBu\text{-}t$ (*324*). A solution of *tert*-butanol (18.50 g, 0.25 mol) in carbon tetrachloride (25 ml) was added dropwise to a stirred solution of freshly distilled diethyl phosphoroisocyanatidate (44.75 g, 0.25 mol) in carbon tetrachloride (50 ml) at room temperature. The mixture was left at room temperature for 1 h and evaporated. The oily residue was kept at 60 °C/1 mmHg for 2 h to remove traces of solvent. The residue crystallised quickly on cooling to give the pure product (63.2 g, ∼100%). Mp 39–40 °C. δ_P (CCl_4) −2.5 ppm.

▶ *Diethyl diethylcarbamoylphosphoramidate* $(EtO)_2P(O)NHC(O)NEt_2$ (*327*). A solution of diethylamine (10.4 g, 0.14 mol) in carbon tetrachloride (15 ml) was added dropwise to a solution of freshly distilled diethyl phosphoroisocyanatidate (25.2 g, 0.14 mol) in carbon tetrachloride (30 ml) at a rate sufficient to maintain the temperature of the mixture below 5 °C. The mixture was then stirred at 50 °C for 45 min, warmed to room temperature, and stirred for an additional 3 h. The solvent was removed under reduced pressure, yielding a liquid that was purified by bulb-to-bulb distillation to give the product (30.0 g, 84%). Bp 150 °C/0.4 mmHg. Pure material crystallised upon standing. Mp 38–42 °C. δ_P ($CDCl_3$) −3.0 ppm.

4.51 DIALKYL PHOSPHOROISOTHIOCYANATIDATES $(RO)_2P(O)NCS$

Trialkyl phosphites react with potassium thiocyanate under modified Todd–Atherton conditions to furnish dialkyl phosphoroisothiocyanatidates (**218**) and (**219**) in moderate yield (Fig. 4.51.1) (*132*).

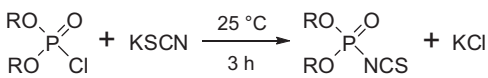


R = Et **218** 40% δ_P –18.8

R = *n*-Bu **219** 40% δ_P –18.9

Figure 4.51.1

Dialkyl phosphorochloridates react with alkali metal thiocyanates neat or in solution to provide dialkyl phosphoroisothiocyanatidates. The thiocyanate, an ambident nucleophile able in theory to react through its nitrogen or sulfur atom, prefers to react through the former to produce a P–N bond. Thus, dialkyl phosphorochloridates react with potassium thiocyanate without solvent (*106*,*165*,*328*) or suspended in benzene (*328*) to give dialkyl phosphoroisothiocyanatidates (Fig. 4.51.2).



Dialkyl phosphoroisothiocyanatidates

R	Solvent	Yield (%)	Bp (°C/mmHg)	Bath temp. (°C)
Et	none	59	80–82/1	not known
Et	benzene	80	64–65/0.6	80
n-Pr	benzene	74	72–73/0.2	105
i-Pr	benzene	77	63–64/0.2	100
n-Bu	benzene	88	86–87/0.12	115

Figure 4.51.2

Heating diethyl phosphorochloridate with trimethylsilyl isothiocyanate to 100–150 °C for several hours provides after distillation diethyl phosphoroisothiocyanatidate (**218**) in modest yield (45%) (Fig. 4.51.3) (*329*). As this product is thermally unstable, an improved procedure using equal moles of (trimethylsilyl)isothiocyanate and *N*-methylmorpholine was shown to proceed at room temperature to give the same phosphoroisothiocyanatidate (**218**) in dramatically improved yield (85%) (*330*).

The lower dialkyl phosphoroisothiocyanatidates are colourless reactive liquids that hydrolyse to give the dialkyl hydrogen phosphates (**221**) (Fig. 4.51.4). Primary amines add to the isothiocyanate carbon atom to yield dialkylphosphoryl thioureas (**222**) (*328*,*330*). The thiocyanate group reacts with chlorine at 0–5 °C to provide dialkylphosphoryl *N*-dichloromethyleneimines (**223**, R = Et; bp 82 °C/1 mmHg) (*36*). The chemistry of phosphorus isothiocyanatidates has been reviewed (*37*).

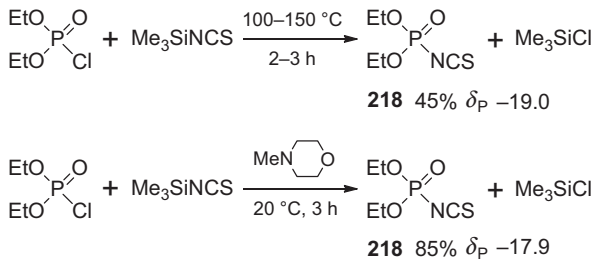


Figure 4.51.3

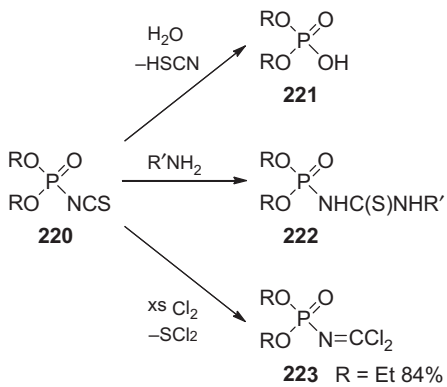


Figure 4.51.4

Dialkyl phosphorothiocyanatidates $(RO)_2P(O)SCN$ are unstable and once formed isomerise at room temperature to the isomeric phosphoroisothiocyanatidates $(RO)_2P(O)NCS$ (*331*). Dineopentyl phosphorothiocyanatidate $(t\text{-}BuCH_2O)_2P(O)SCN$ (δ_P −10.8 ppm), formed from $(t\text{-}BuCH_2O)_2P(O)Cl$ and silver(I) cyanide in dichloromethane, isomerises spontaneously to the isothiocyanatidate (δ_P +17.5 ppm).

▷ *Dialkyl phosphoroisothiocyanatidates $(EtO)_2P(O)NCS$* (**218**) *and $(n\text{-}BuO)_2P(O)NCS$* (**219**) *(from the trialkyl phosphite and potassium thiocyanate under phase-transfer conditions)* (*132*). Carbon tetrachloride (15.4 g, 0.1 mol) was added to a stirred mixture of the trialkyl phosphite (0.1 mol), potassium thiocyanate (14.6 g, 0.15 mol) and trialkylammonium hydrochloride ($Me_3N\cdot HCl$ or $Et_3N\cdot HCl$, 0.15 mol) in acetonitrile (50 ml) warmed to 35 °C while excluding moisture. After 3 h an aliquot of the reaction mixture was analysed by ^{31}P NMR spectroscopy and revealed 60% and 55% conversion to $(EtO)_2P(O)NCS$ and $(n\text{-}BuO)_2P(O)NCS$, respectively. The mixture was filtered; the filtrate was concentrated and the residue was distilled to provide $(EtO)_2P(O)NCS$ (40%, bp 88 °C/1 mmHg; δ_P −18.8 ppm) and $(n\text{-}BuO)_2P(O)NCS$ (40%, bp 104 °C/0.1 mmHg; δ_P −18.9 ppm).

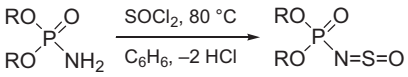
▶ *Diethyl phosphoroisothiocyanatidate* $(EtO)_2P(O)NCS$ (**218**) *(from diethyl phosphorochloridate and potassium thiocyanate)* (*106*). Diethyl phosphorochloridate (10 g, 58 mmol) and anhydrous potassium thiocyanate (7.5 g, 77 mmol) were stirred at room temperature for 3 h, whereupon most of the potassium thiocyanate disappeared and a red solution was obtained. Anhydrous ether was added to precipitate the potassium chloride formed. The solution was filtered and the filtrate distilled to give the title compound as a colourless liquid (6.7 g, 59%). Bp 80–82 °C/1 mmHg, bp 78 °C/0.5 mmHg. It has a characteristic odour and darkens on storage.

▶ *Diethyl phosphoroisothiocyanatidate* $(EtO)_2P(O)NCS$ (**218**) (*330*). A solution of diethyl phosphorochloridate (4.31 g, 25 mmol) in acetonitrile (25 ml) was added dropwise to a stirred solution of (trimethylsilyl)isothiocyanate (3.28 g, 25 mmol) and *N*-methylmorpholine (2.53 g, 25 mmol) in acetonitrile (60 ml). The mixture was stirred at 20 °C for 3 h. Volatile products and solvent were removed at 20 °C (50 mmHg). The residue was diluted with anhydrous benzene and allowed to stand at 0 °C for 12 h. The precipitate was separated, the solvent was evaporated, and the residue was distilled to give diethyl phosphoroisothiocyanatidate (4.14 g, 85%). Bp 86–88 °C/2 mmHg. δ_P (81 MHz, MeCN) −17.9 ppm.

▶ *Diethyl phosphoroisothiocyanatidate* $(EtO)_2P(O)NCS$ (**218**) (*329*). Equimolar amounts of diethyl phosphorochloridate and (trimethylsilyl)isothiocyanate were heated with stirring to 100–150 °C for 2–3 h. The cooled mixture was concentrated on a rotary evaporator to remove the liberated chlorotrimethylsilane (bp 57 °C) and distilled under reduced pressure to yield diethyl phosphoroisothiocyanatidate (45%). Bp 84 °C/0.08 mmHg. δ_P −19.0 ppm.

4.52 DIALKYL PHOSPHORO(THIONYLAMIDATES) $(RO)_2P(O)NSO$

Dialkyl phosphoramidates react with thionyl chloride in hot benzene to provide dialkyl phosphoro(thionylamidates) in good yield (Fig. 4.52.1) (*332*).



Dialkyl phosphoro(thionylamidates)

R	Yield (%)	Bp (°C/mmHg)
Et	78	77/1
n-Pr	70	71/0.05
n-Bu	78	84/0.1

Figure 4.52.1

Dialkyl phosphoro(thionylamidates) (**224**) react readily with water and alcohols to give almost quantitatively the corresponding phosphoramidates (**225**) and sulfur dioxide or dialkyl sulfite, respectively (Fig. 4.52.2) (*332*). Unlike thionylsulphonamides, they do not react with dienes at room temperature. Nevertheless, when dry butadiene is passed through a boiling benzene solution of diethyl

phosphoro(thionylamidate) (**224**, R = Et), the 1,4-cycloadduct (**226**; bp 122 °C/0.05 mmHg) is formed in excellent yield. The chemistry of imides of sulfur dioxide has been reviewed (*333*).

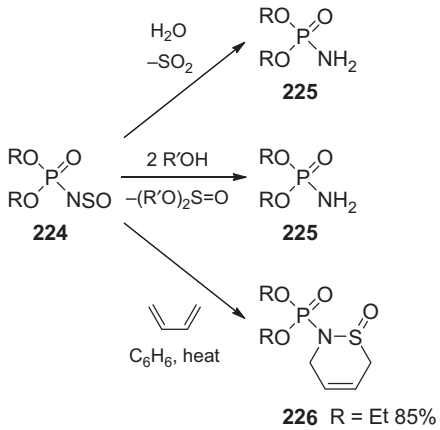


Figure 4.52.2

▶ *Dialkyl phosphoro(thionylamidates) $(RO)_2P(O)NSO$* (*332*). Thionyl chloride (23.8 g, 0.2 mol) was added to a solution of the dialkyl phosphoramidate (0.2 mol) in benzene (100 ml) and the mixture was heated slowly. At 50–55 °C, hydrogen chloride started to evolve and heating was then continued at 80 °C until hydrogen chloride evolution ceased. The solvent was removed and the residue was distilled under reduced pressure to afford the compounds listed in Fig. 4.52.1 as yellowish liquids with a slight odour resembling sulfur dioxide. The infrared spectra of the compounds exhibited a band at 1152/cm characteristic of the —N═S═O group.

4.53 *N,N′-BIS*(DIALKYLPHOSPHORYL)SULFAMIDES $(RO)_2P(O)NHSO_2NHP(O)(OR)_2$

The reaction of diethyl phosphoramidate with sulfuryl chloride in equimolar amounts in dichloromethane presumably provides the reactive *N*-chlorosulfonyl species (**227**) to which the amidate subsequently adds to give the *N,N′-bis*(diethylphosphoryl)sulfamide (**228**) as the major product (Fig. 4.53.1) (*334*).

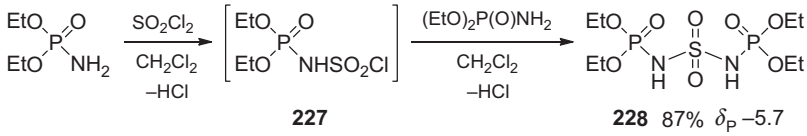


Figure 4.53.1

▶ *N,N′-Bis(diethylphosphoryl)sulfamide $(EtO)_2P(O)NHSO_2NHP(O)(OEt)_2$* (**228**) (*334*). A solution of diethyl phosphoramidate (1.53 g, 10 mmol) in anhydrous dichloromethane (15 ml) was added to a stirred solution of freshly distilled sulfuryl chloride (1.35 g, 10 mmol) in anhydrous dichloromethane

(5 ml) at 0–5 °C. After addition, the temperature was increased to 10 °C and the mixture was stirred for 10 h. Analysis after this time using ^{31}P NMR spectroscopy revealed signals at δ −5.7 (90%), −4.5 (2%), −11.6 (3%), 0.43 (2%) and 10.8 (3%). The volatile components were removed under vacuum. Recrystallisation of the residual solid from chloroform–hexane gave the title compound as colourless needles (1.6 g, 87%). Mp 127 °C. δ_P (81 MHz, $CDCl_3$) −5.7 ppm.

4.54 *N*-(DIALKYLPHOSPHORYL)ALDIMINES $(RO)_2P(O)N{=}CHR$

N-Phosphorylated imines are one of the few types of electron-deficient imines that are sufficiently stable to be isolated. Brief heating of diethyl phosphoramidate with benzaldehyde diethyl acetal at 120–160 °C and removal by distillation of the ethanol formed provides via intermediate (**229**) the pure *N*-(diethylphosphoryl)benzaldimine (**230**) in good yield (Fig. 4.54.1) (*335*).

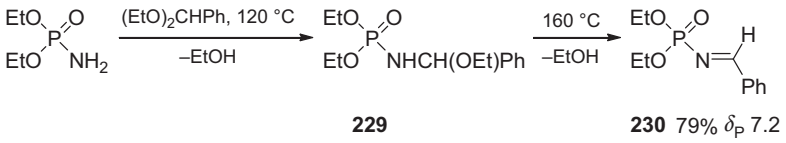


Figure 4.54.1

▶ *N-(Diethylphosphoryl)benzaldimine (EtO)$_2$P(O)N=CHPh* (**230**) (*335*). Diethyl phosphoramidate (3.06 g, 20 mmol) and benzaldehyde diethyl acetal (3.38 g, 20 mmol) were placed in a distillation flask and the mixture was heated gradually from 115 to 160 °C (internal temperature). When about 80% of the stoichiometric amount of ethanol had distilled off (~15 min), the residue was cooled to room temperature, dissolved in benzene (20 ml), and washed with cold water (10 ml) to remove traces of unreacted phosphoramidate. The benzene solution was dried ($MgSO_4$), evaporated, and distilled under reduced pressure to yield a colourless liquid (3.8 g, 79%). Bp 140–141 °C/0.7 mmHg. δ_P (36 MHz, neat) 7.2 ppm.

4.55 *N*-(DIALKYLPHOSPHORYL)GUANIDINES $(RO)_2P(O)N{=}C(NR_2)_2$

N-(Dialkylphosphoryl)guanidines can be prepared by treating dialkyl phosphorochloridates or dialkyl *H*-phosphonates under Todd–Atherton conditions with an appropriate guanidine (or guanidine salt) and a suitable base. Diethyl phosphorochloridate reacts with cyanoguanidine under basic conditions to yield *N*-(diethylphosphoryl)cyanoguanidine (**231**) in modest yield (Fig. 4.55.1) (*336*). Diisopropyl *H*-phosphonate reacts with guanidine hydrochloride in a two-phase system of ethanolic sodium hydroxide and carbon tetrachloride to yield *N*-(diisopropylphosphoryl)guanidine (**232**) in good yield (*337*).

Creatine phosphate is a natural product found in muscle tissue (Chapter 1.4). Its diphenyl ester (**233**) can be prepared by prolonged heating of diphenyl phosphorochloridate with 2 molar equivalents of creatinine in acetone (Fig. 4.55.2) (*338*).

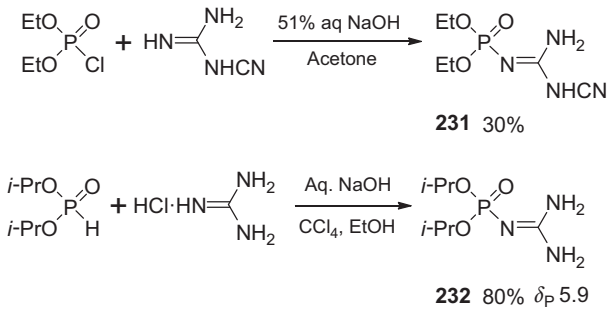


Figure 4.55.1

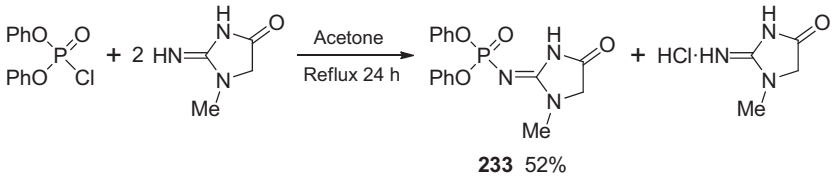


Figure 4.55.2

▶ *N-(Diethylphosphoryl)cyanoguanidine* $(EtO)_2P(O)N{=}C(NH_2)NHCN$ (**231**) (*336*). A solution of diethyl phosphorochloridate (17.29 g, 0.10 mol) in acetone (10 ml) was added dropwise over 37 min to a stirred solution of cyanoguanidine (8.41 g, 0.10 mol) in 51% aqueous sodium hydroxide (15.69 g, 0.20 mol), water (42 ml) and acetone (50 ml). During addition, the temperature increased to 47 °C and the two liquid phases initially present coalesced. The solution was stirred for 30 min longer and poured into water (300 ml). Acidification with 36% acetic acid (17.73 g, 0.11 mol) did not cause the product to separate. The solution was evaporated in a stream of air until crystallisation was observed, then chilled and filtered to give the title compound (6.54 g, 30%). Mp 164–165.5 °C. Recrystallisation gave pure material. Mp 164–165 °C. It was soluble in ethanol, hot water, hot isopropanol, hot acetone, hot acetonitrile, but practically insoluble in chloroform.

▶ *N-(Diisopropylphosphoryl)guanidine* $(i\text{-}PrO)_2P(O)N{=}C(NH_2)_2$ (**232**) (*337*). A solution of guanidine hydrochloride (0.96 g, 10 mmol), sodium hydroxide (0.80 g, 20 mmol), water (5 ml) and ethanol (2 ml) was cooled to 0–5 °C. A solution of diisopropyl *H*-phosphonate (1.66 g, 10 mol) in carbon tetrachloride (5 ml) was added dropwise and the mixture was stirred at 25 °C for 4 h, then diluted with water (3 ml) and extracted with chloroform. The combined organic layers were dried and concentrated. Crystallisation from chloroform gave the title compound (1.78 g, 80%). Mp 126–128 °C. δ_P ($CDCl_3$) 5.9 ppm.

▶ *N-(Diphenylphosphoryl)creatinine* (**233**) (*338*). Diphenyl phosphorochloridate (15 g, 56 mmol) and anhydrous creatinine (13 g, 115 mmol) were heated under reflux in anhydrous acetone for 24 h. The cooled liquid was filtered, the solid was washed with acetone, and stirred with cold water to remove unreacted creatinine and its hydrochloride, and then dried. The yield, including that obtained

from evaporation of the acetone mother-liquor, was 10 g (52%). Recrystallisation thrice from ethanol gave flat prisms. Mp 127–128 °C.

4.56 *O,O*-DIALKYL HYDROGEN PHOSPHOROTHIOATES $(RO)_2P(O)SH$

O,O-Dialkyl hydrogen phosphorothioate groups can be used as biosteric replacements of the phosphate backbones of DNA and RNA for antisense applications to increase the stability of artificial oligo- and polynucleotides towards nucleases (*339*). They can also be used as linkers to carry out efficiently oligonucleotide synthesis on solid supports (*340*). They resist hydrolysis under acidic and basic conditions, are easy to prepare in gram amounts, and are stable at room temperature and in air.

Featuring an SH group bonded to a P═O bond, the reactivity of *O,O*-dialkyl hydrogen phosphorothioates is expected to be between that of a thiol and a thioacid. Their isolation as precisely defined structures is not possible because they exist always as an equilibrium mixture of thiolo and thiono tautomers (Fig. 4.56.1). The thiono form is thermodynamically more stable, but bond energy data suggest that the position of equilibrium depends on the nature of the ester groups (*341*,*342*). The data in Fig. 4.56.1 were measured in 80% ethanol–20% water (*343*). These studies revealed that the equilibrium favours the thiono tautomer (refer to Chapter 5, Section 5.6). Modification of the adenine base of certain nucleotides can affect the pK_a of an adjacent phosphorus thioacid (Fig. 4.56.1).

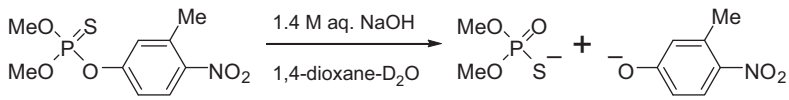
R	pK_a
Me	2.80
Et	2.84
n-Pr	2.93
i-Pr	2.90
n-Bu	3.14
i-Bu	2.94

Compounds	A	B	C	D	E	G	pK_a
Adenosine	N	CH	N	CNH_2	N	OH	3.5
8-Aza-adenosine	N	N	N	CNH_2	N	OH	2.2
Purine riboside	N	CH	N	CH	N	OH	2.1
3-Deaza-adenosine	N	CH	N	CNH_2	CH	OH	7.0
Formycin	C	N	NH	CNH_2	N	OH	4.4
2′-Deoxy-adenosine	N	CH	N	CNH_2	N	CH_2	3.6

Figure 4.56.1

The first synthesis of *O,O*-dialkyl hydrogen phosphorothioates emerged at the start of the twentieth century through the work of P. S. Pistschimuka (*57*,*344*). He described the selective hydrolysis of triethyl phosphorothionate $(EtO)_3P{=}S$ by ethanolic potassium hydroxide heated under reflux for several hours, and obtained *O,O*-diethyl potassium phosphorothioate $(EtO)_2P(O)SK$. The generality

of this method is limited due to the formation of by-products arising from additional P—O bond cleavages. For more selective single P—O bond cleavage, the degradation of *O,O*-dialkyl *O*-aryl phosphonothionates has been recommended, for example, as in the hydrolysis by sodium hydroxide of the insecticide fenitrothion, which provides *O,O*-dimethyl sodium phosphorothioate (**234**) (Fig. 4.56.2) (*345,346*). The hard hydroxide nucleophile reacts at pH >9 with the hard phosphorus centre to cleave the P—OAr bond.

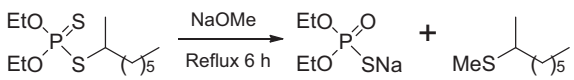


Fenitrothion δ_P 65.2 **234** δ_P 58.1

Figure 4.56.2

▶ *O,O-Dimethyl sodium phosphorothioate* (**234**) (*345,346*). A solution of fenitrothion (9.6×10^{-3} M; δ_P 65.2 ppm) in 5.0:7.5:47.5 *v/v* 1,4-dioxane-D_2O-H_2O in the presence of 1.4 M NaOH was monitored by ^{31}P NMR spectroscopy over 9 days. Formation of *O,O*-dimethyl sodium phosphorothioate (δ_P 58.1 ppm) was observed.

Selective P—S bond cleavage of *O,O,S*-trialkyl phosphorothiolothionates to provide *O,O*-dialkyl hydrogen phosphorothioates has been known since the 1950s. An example is the reaction of *O,O*-diethyl *S*-(2-octyl) phosphorothiolothionate (**235**) with sodium methoxide to give *O,O*-diethyl sodium phosphorothioate (**236**) (Fig. 4.56.3) (*347*). Many such sodium salts are accessible using this procedure; the dialkyl disulfide, a common impurity from aerial oxidation of the liberated thiolate salt, is easily removed.



235 **236** 63%

Figure 4.56.3

▶ *O,O-Diethyl sodium phosphorothioate (EtO)$_2$P(O)SNa* (**236**) (*347*). *O,O*-Diethyl *S*-(2-octyl) phosphorodithioate (149 g, 0.5 mol) was added dropwise over 20 min to sodium methoxide pre-prepared by adding sodium (23 g, 1 mol) to absolute methanol (300 ml). Afterwards, the mixture was heated under reflux for 6 h, cooled to 30 °C, and purged with carbon dioxide for 1 h. The mixture was steam-distilled until only traces of organic material appeared in the distillate (3 l). The residue was evaporated on a steam bath. The resulting salts were extracted with ethyl acetate (400 ml) and insoluble sodium carbonate was removed by filtration. The ethyl acetate solution was evaporated to a volume of 200 ml and cooled in an ice bath. The solution was diluted with petroleum ether (bp 80—100 °C, 1500 ml) and the desired compound precipitated as fine white needles (60 g, 63%). Mp 190—191 °C.

Alkaline hydrolysis of dialkyl phosphorochloridothionates also provides *O,O*-dialkyl hydrogen phosphorothioates. The hydrolysis of diethyl phosphorochloridothionate (**237**) by caustic soda

provides *O,O*-diethyl hydrogen phosphorothioate (**238**) (Fig. 4.56.4) (*348*). Another example is the conversion of *O*-ethyl phosphorodichloridothionate (**239**) to the *O*-ethyl *O*-aryl phosphorochloridothionate (**240**) which reacts with aqueous potassium hydroxide to give, after acidification, the corresponding *O*-ethyl *O*-aryl hydrogen phosphorothioate (**241**) (*349*).

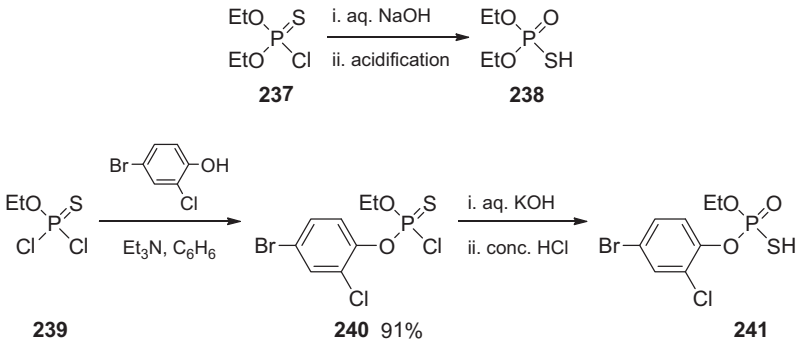


Figure 4.56.4

▶ *O,O-Diethyl hydrogen phosphorothioate* $(EtO)_2P(O)SH$ (**238**) (*348*). Diethyl phosphorochloridothionate and sodium hydroxide (>5 mol equiv.) were diluted in aqueous 1,4-dioxane. The mixture was heated under reflux for 5 h, cooled and washed with ether. The aqueous phase was acidified and extracted with ether. The combined ether layers were dried and worked up in the usual way to give the title acid. Its potassium salt melts at 195–197 °C (*350*).

▶ *O-(4-Bromo-2-chlorophenyl) O-ethyl hydrogen phosphorothioate* $EtO(4\text{-}Br\text{-}2\text{-}ClC_6H_3O)P(O)SH$ (**241**) (*349*). A solution of 4-bromo-2-chlorophenol (10.4 g, 50 mmol) and triethylamine (5.5 g, 54 mmol) in benzene (100 ml) was added dropwise to a stirred solution of *O*-ethyl phosphorodichloridothionate (9.0 g, 50 mmol) in anhydrous benzene (100 ml). The mixture was stirred for 24 h. The precipitated triethylamine hydrochloride was filtered off. The filtrate was washed with water, then with saturated brine, and dried ($MgSO_4$). The solvent was evaporated to leave crude *O*-(4-bromo-2-chlorophenyl) *O*-ethyl phosphorochloridothionate (**240**) as a colourless liquid (16.0 g, 91%; 46 mmol). This material was dissolved in 1,4-dioxane (100 ml) and the resulting solution was added to a solution of potassium hydroxide (4.9 g, 88 mmol) in 1:1 *v/v* dioxane–water (100 ml). The mixture was stirred at room temperature for 24 h and the dioxane was removed under reduced pressure. The alkaline aqueous solution was extracted with benzene and acidified to pH 1 with concentrated hydrochloric acid. The acidic mixture was re-extracted with benzene. The organic layer was dried ($MgSO_4$) and concentrated to give the title compound as a viscous colourless liquid (9.0 g, 59%). Its dicyclohexylammonium salt melts at 170–171 °C.

Dialkyl *H*-thiophosphonates (**242**) can also be used as precursors to *O,O*-dialkyl hydrogen phosphorothioates (**243**) (Fig. 4.56.5) (*351*) and oxidised with 3*H*-2,1-benzoxathiol-3-one 1-oxide (BOTO) in a fast, clean, and stereospecific reaction. Chiral nucleosides containing *O,O*-dialkyl

hydrogen phosphorothioate groups can be prepared similarly for subsequent incorporation into an oligonucleotide chain at a predetermined position.

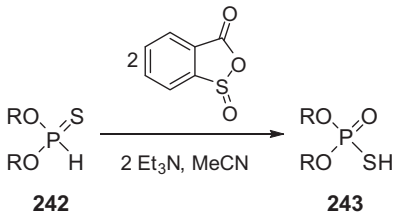


Figure 4.56.5

▶ *O,O-Diaryl hydrogen phosphorothioate (from oxidation of a diaryl H-thiophosphonate with BOTO)* (*351*). A diaryl *H*-thiophosphonate was treated with BOTO (2 mol equiv.) and triethylamine (2 mol equiv.) in acetonitrile. A fast and clean reaction occurred; the first ^{31}P NMR spectrum recorded after about 2 min showed complete conversion to the *O,O*-diaryl hydrogen phosphorothioate.

Trialkyl phosphites can be converted into *O,O*-dialkyl hydrogen phosphorothioates by sulfurisation procedures that use elemental sulfur or sulfur-transfer reagents, e.g. 3*H*-1,2-benzodithiol-3-one 1,1-dioxide (Beaucage reagent) (*352,353*) (refer also to Chapter 5, Section 5.6). Oligonucleotide-based dialkyl *H*-phosphonates and trialkyl phosphites are sulfurised by the Beaucage reagent under mild conditions (*354—356*). Trialkyl phosphite (**244**) reacts with it in pyridine solution to give the phosphorothionate (**245**) whose dealkylation by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provides the phosphorothioate salt (**246**) (Fig. 4.56.6) (*355*). Dialkyl 2-cyanoethyl phosphites (**247**) are sulfurised similarly to give phosphorothionates (**248**) which are dealkylated by sodium methoxide in methanolic THF to give the *O,O*-dialkyl hydrogen phosphorothioates (**243**) (*356*).

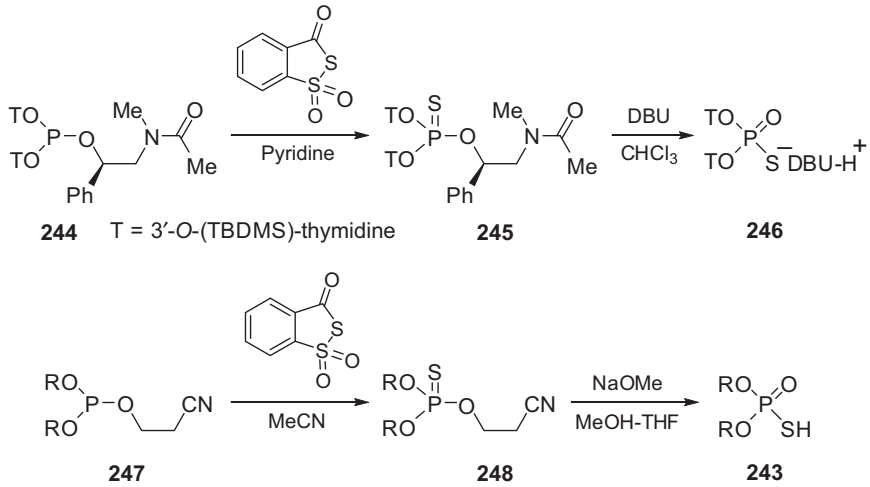


Figure 4.56.6

▶ *1,8-Diazabicyclo[5.4.0]undec-7-enium 5′-O-(tert-butyldiphenylsilyl)thymidin-3′-yl 3′-O-(tert-butyldimethylsilyl)thymidin-5′-yl phosphorothioate* (**246**) (*355*). Beaucage reagent (12 mg, 60 μmol) was added to a solution of trialkyl phosphite **244** (60 μmol) in anhydrous pyridine (43 μl, 500 μmol). DBU (74.6 μl, 500 μmol) was added after 3 min and the resulting mixture heated to 50 °C for 30 min. The mixture was cooled to room temperature, diluted with chloroform (3 ml), and washed with 0.2 M phosphate buffer (pH 7.0, 3 ml). The aqueous layers were back-extracted with chloroform (2 × 3 ml). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by high-performance liquid chromatography, eluting with 99:1:0.5 (2×), and then 96:4:0.5 (2×) dichloromethane—methanol—triethylamine. The product was dissolved in chloroform (3 ml), washed with 0.2 M DBU bicarbonate buffer (3 ml) and back-extracted with chloroform (2 × 3 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford a colourless foam (50.4 mg). δ_P 57.2 ppm.

▶ *O,O-Dialkyl hydrogen phosphorothioates $(RO)_2P(O)SH$* (*356*). A solution of trialkyl phosphite (0.76 mmol) in acetonitrile (1 ml) was treated with Beaucage reagent (152 mg, 0.76 mmol). Flash chromatography of the mixture on silica gel, eluting with 5:1 hexane—ethyl acetate, gave the trialkyl phosphorothionate (75%; δ_P ~70 ppm). This was diluted in 1:2 THF—methanol (3 ml) and treated with 0.4 M sodium methoxide in methanol (0.4 ml, 0.16 mmol). The mixture was stirred for 1.5 h at 23 °C, diluted with THF (3 ml), and neutralised with Amberlite IRC50 (H^+ form). The resin was filtered off and the filtrate evaporated to afford the crude product (95%). δ_P ~60 ppm.

A sulfurisation step features in a synthesis of (*R*) and (*S*)-thymidyl-substituted phosphorothioates (Fig. 4.56.7) (*357,358*). The allyl phosphite **249** reacts with *bis*[3-(triethoxysilyl)propyl] tetrasulfide (TEST) to give the thionate **250**, whose deprotection permits enantiomers of the phosphorothioate **251** to be isolated.

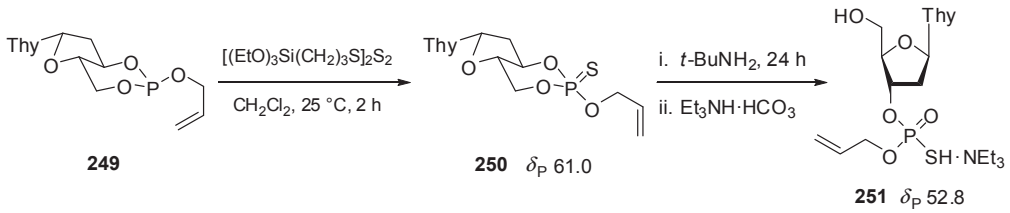


Figure 4.56.7

▶ *Allyl 5′-O-thymidin-3′-yl phosphorothioate triethylammonium salt* (**251**) (*357,358*). TEST (11.8 ml, 13 g, 24 mmol) was added to a stirred mixture of the trialkyl phosphite **249** (24 mmol) and powdered molecular sieves (4 Å) in dichloromethane (25 ml). The mixture was stirred for 2 h, was passed through a Celite™ 545 pad to remove the molecular sieves, and the filtrate was concentrated. The residue was dissolved in ethyl acetate (200 ml) and the resulting solution was washed with aqueous sodium bicarbonate (200 ml). The aqueous layer was extracted with ethyl acetate (2 × 200 ml) and the combined organic phases were washed with brine (300 ml), dried (Na_2SO_4), filtered and concentrated to give a viscous liquid. Flash chromatography of this, eluting with 2:1 hexane—ethyl acetate, gave the pure thionate **250** (5.68 g, 79%, δ_P 61.0 ppm). Some of this material (1.00 g, 1.44 mmol) was dissolved

in *tert*-butylamine (25 ml) and stirred at 35 °C for 24 h. Concentration of the solution gave a yellow liquid that was dissolved in dichloromethane (20 ml). The solution was washed with 0.1 M aqueous triethylammonium bicarbonate (2 × 10 ml), the organic layer was dried ($MgSO_4$), and the crude mixture was chromatographed on silica gel, eluting with 9:1 dichloromethane—methanol. The pure compound obtained was dissolved in dichloromethane (5 ml). The solution was shaken with 0.1 M aqueous triethylammonium bicarbonate (2 × 10 ml) to transform the hydrogen phosphorothioate into its triethylammonium salt. The resulting organic solution was dried ($MgSO_4$) and concentrated. The residue was dissolved in dichloromethane (2 ml) and the solution was poured into petroleum ether (200 ml). The precipitate was collected by filtration and dried (1.04 g, 92%). δ_P 52.8 ppm.

The trialkyl phosphite (**252**) reacts with sulfur with retention of configuration at the phosphorus atom to give the phosphorothionate (**253**) (Fig. 4.56.8) (*359—361*). Deprotection of this compound with acetic acid and demethylation with trimethylamine gives the dialkyl hydrogen phosphorothioate (**254**).

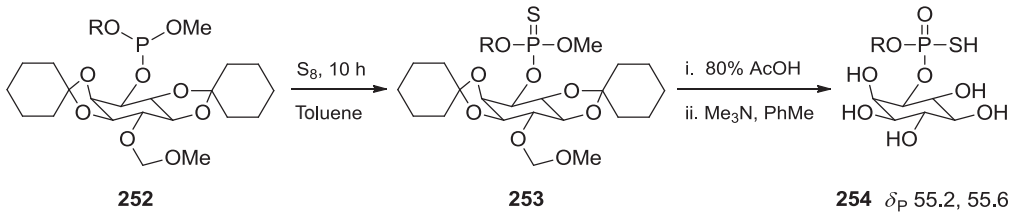
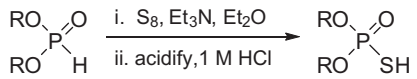


Figure 4.56.8

▶ *O,O-Dialkyl hydrogen phosphorothioate* (**254**) (*359—361*). Sulfur (64 mg, 2.0 mmol) was added to the trialkyl phosphite **252** (1.2 mmol) dissolved in anhydrous toluene (10 ml). The suspension was stirred at room temperature for 10 h. Flash chromatography on silica gel, eluting with 1:1 chloroform—methanol, gave the phosphorothionate (**253**). Treatment of this with 80% acetic acid at 90—100 °C for 2—3 h, and then with anhydrous trimethylamine in toluene (1:1 *v/v*, 5 ml) at 25 °C for 15 h, gave the title compound **254** (73%). δ_P 55.2 and 55.6 ppm.

Dialkyl *H*-phosphonates $(RO)_2P(O)H$ are converted through treatment with a base into their trivalent tautomers $(RO)_2P—OH$ which can add sulfur to give *O,O*-dialkyl phosphorothioate salts of the base. When the dialkyl *H*-phosphonate contains sufficient trivalent tautomer, a base is unnecessary and addition of sulfur can proceed in its absence (*362*). When a base is used, the resulting *O,O*-dialkyl phosphorothioate salt can be converted into the *O,O*-dialkyl hydrogen phosphorothioate upon acidification with a mineral acid (e.g. hydrochloric acid) (*68,363*). This approach has been used to access many *O,O*-dialkyl hydrogen phosphorothioates (Fig. 4.56.9). Examples include the synthesis of a uridine hydrogen 3′-alkylphosphorothioate (*364*), a 5′-(*tert*-butylsilyloxy)thymidine hydrogen phosphorothioate (*339,365,366*) and a 2′,3′-*O,O*-cyclophosphorothioate derivative (not shown) (*340*).

▶ *O,O-Di-n-propyl hydrogen phosphorothioate* $(n\text{-}PrO)_2P(O)SH$ (*68,363*). Triethylamine (9.2 ml, 66 mmol) was added slowly to di-*n*-propyl *H*-phosphonate (10.0 g, 60 mmol) and sulfur (2.1 g, 66 mmol) in ether (45 ml) under argon. After full conversion to product, as indicated by ^{31}P NMR



O,O-Dialkyl hydrogen phosphorothioates

R	Yield (%)	δ_P (ppm)[a]
Et	80	58.0
n-Pr	89	59.1
i-Pr	81	56.3
n-Bu	86	58.4
i-Bu	83	59.2
neopentyl	70	60.1
cyclohexyl	63	57.2
$Cl(CH_2)_2$	62	59.0
$Cl(CH_2)_3$	51	60.1
$Cl(CH_2)_4$	70	59.5
$MeO(CH_2)_2$	18	66.7

a. Recorded at 101.3 MHz

Figure 4.56.9

spectroscopy, the suspension was diluted with ether (100 ml), washed with 1 M hydrochloric acid (100 ml), dried ($MgSO_4$), and concentrated. The resulting suspension was filtered through a cotton plug to yield a yellow liquid (10.6 g, 89%). δ_P 59.1 ppm.

Diethyl *H*-phosphonate reacts with sulfur in the presence of ammonium bicarbonate to give ammonium *O,O*-diethyl phosphorothioate (**255**) which can be selectively alkylated at the sulfur atom upon treatment with alkyl halides (Fig. 4.56.10) (*367*). Diethyl *H*-phosphonate also reacts with sulfur in the presence of sodium ethoxide to give a sodium salt that upon acidification yields *O,O*-diethyl hydrogen phosphorothioate (**238**); this process allows its synthesis on a multigram scale and is general in scope (*368,369*).

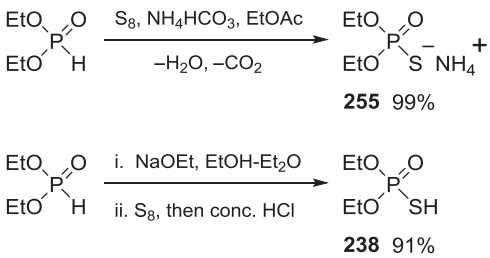
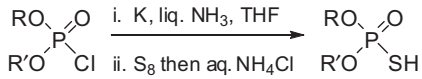


Figure 4.56.10

▶ *Ammonium O,O-diethyl phosphorothioate* $(EtO)_2P(O)S^-NH_4^+$ (**255**) (*363*). Ammonium bicarbonate (7.9 g, 0.1 mol) was added to a mixture of sulfur (3.2 g, 0.1 mol) and diethyl *H*-phosphonate (13.8 g, 0.1 mol) in 1:1 *v*/*v* ethyl acetate—ether (300 ml). The mixture was stirred for 24 h and concentrated to give a solid in quantitative yield that could be recrystallised from ethanol.

▶ *O,O-Diethyl hydrogen phosphorothioate* $(EtO)_2P(O)SH$ (**238**) (*368*,*369*). A solution of diethyl *H*-phosphonate (27.6 g, 0.2 mol) in ether (140 ml) was added to a solution of sodium ethoxide prepared from sodium (4.6 g, 0.2 mol) and absolute ethanol (60 ml). After stirring for 1 h at room temperature, sulfur (6.4—9.6 g, 0.2—0.3 mol) was added in portions over 1 h and the mixture was stirred for 2 h. Any unreacted sulfur was filtered off and the filtrate was evaporated. The residue was dissolved in water (10 ml) and concentrated hydrochloric acid (50 ml, 3 equiv.) was added at 0 °C. The aqueous phase was extracted with ether (3 × 50 ml) and the combined organic phase washed with water (3 × 20 ml). Drying ($MgSO_4$) and solvent removal gave the hydrogen phosphorothioate as light-yellow liquid (31 g, 91%). δ_P 64.4 ppm.

Dialkyl phosphorochloridates react with a mixture of potassium amide and sulfur (Fig. 4.56.11) (*370*). The corresponding *O,O*-dialkyl hydrogen phosphorothioates are isolated after acidification of the reaction mixture with hydrochloric acid. This simple procedure allows the synthesis of many such hydrogen phosphorothioates.



O,O-Dialkyl hydrogen phosphorothioates

R	R′	Yield (%)	δ_P (ppm)
Et	Et	62	64.2
i-Pr	*i*-Pr	82	58.5
Ph	*t*-Bu	95	94.9
$CH_2C(Me)_2CH_2$		78	57.9

Figure 4.56.11

▶ *O,O-Diethyl hydrogen phosphorothioate* $(EtO)_2P(O)SH$ (**238**) (*370*). Potassium (0.39 g, 10 mmol) was added to a stirred mixture of liquid ammonia (25 ml) and THF (25 ml). Once the alkali metal had dissolved completely, the solution was cooled to −78 °C and diethyl phosphorochloridate (0.86 g, 5 mmol) in THF (5 ml) was added dropwise. The blue colour of the solution disappeared a few minutes after the addition of the last drop of the phosphorus electrophile. Sulfur (0.192 g, 6 mmol) was added, the cooling bath was removed, and the mixture was stirred at −33 °C for 30 min. The ammonia was evaporated at 10 mmHg and the residue was poured into a mixture of toluene and aqueous potassium carbonate. The water layer was acidified with hydrochloric acid and was evaporated at 10 mmHg. The residue was extracted with dichloromethane (200 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed to yield the product (0.53 g, 62%). δ_P 64.2 ppm.

Dialkyl *H*-phosphonates are also useful starting materials and can be sulfurised rapidly with a diacyl disulfide. Dimethyl *H*-phosphonate reacts with dibenzoyl disulfide in the presence of *N*,*N*-diisopropylethylamine (DIPEA, Hünig's base) to provide *O*,*O*-dimethyl hydrogen phosphorothioate (**256**) in excellent yield (Fig. 4.56.12) (*371*,*372*).

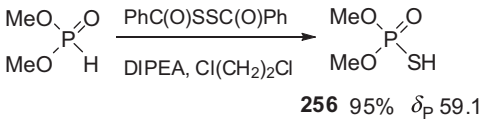


Figure 4.56.12

▶ *O,O-Dimethyl hydrogen phosphorothioate (MeO)$_2$P(O)SH* (**256**) (*371*,*372*). Dibenzoyl disulfide (0.99 g, 3.6 mmol) and DIPEA (0.13 g, 1.0 mmol) were added to a stirred solution of dimethyl *H*-phosphonate (0.13 g, 1.2 mmol) in 1,2-dichloroethane (1.8 ml) at 20 °C. Work-up after 30 min afforded the hydrogen phosphorothioate (0.16 g, 95%). δ_P 59.1 ppm.

Dialkyl *N*-phenylphosphoramidates upon treatment with potassium *tert*-butoxide and then carbon disulfide provide the *O*,*O*-dialkyl hydrogen phosphorothioates, exemplified by the conversion of (**257**) to (**258**) in excellent yield (Fig. 4.56.13) (*373*,*374*).

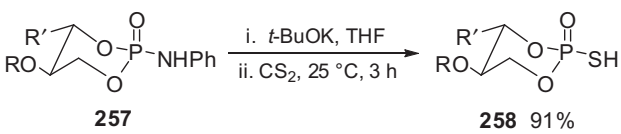


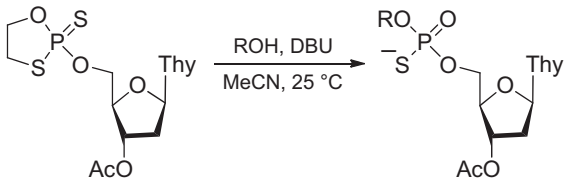
Figure 4.56.13

▶ *O,O-Dialkyl hydrogen phosphorothioate* (**258**) (*373*,*374*). Potassium *tert*-butoxide (3.6 ml of a 1 M solution in THF, 3.6 mmol) was added to a stirred solution of the *N*-phenylphosphoramidate **257** (2.6 mmol) in THF (30 ml). The mixture was stirred for 1 h before carbon disulfide (0.47 ml, 7.8 mmol) was added. The solution was stirred for a further 3 h, its volume was reduced to about 10 ml, and hexane (90 ml) was added. The precipitate was collected by filtration, suspended in water (55 ml), and 1.2 M hydrochloric acid (9 ml) was added. The product was collected by filtration, washed with water, and dried under vacuum to give a solid (91%). δ_P ~58 ppm.

Ring opening of selected oxathiaphospholanes with alcohols in the presence of DBU, functioning as a Lewis base to generate the alkoxide anion which attacks the phosphorus centre, permits the stereocontrolled synthesis of dinucleoside phosphorothioates (Fig. 4.56.14) (*375*). These compounds can be used as building blocks to prepare oligo-deoxyribonucleotides (*376*).

▶ *O-Alkyl O-methyl hydrogen phosphorothioate* (*375*). Methanol (10 mmol) and DBU (75 ml, 5 mmol) were added successively to a stirred solution of the oxathiaphospholane (diastereomeric mixture; 0.21 g, 5 mmol) in acetonitrile (10 ml). When the reaction was complete, as determined by TLC, the solvent was removed. The residue was dissolved in chloroform—5% methanol and this

solution was chromatographed on silica gel, eluting with 4:1 chloroform—methanol, to give the product as a diastereomeric mixture (solid foam, 52%). δ_P 58.1 and 58.0 ppm.



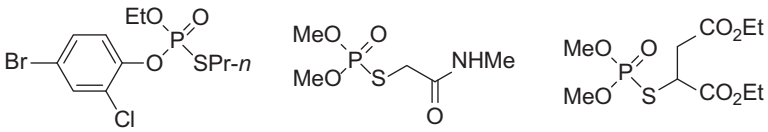
O,O-Dialkyl hydrogen phosphorothioates

R	Yield (%)	δ_P (ppm)
Me	52	58.1, 58.0
n-Bu	72	56.8, 56.6
i-Pr	56	55.6, 55.3
Ph	87	53.2, 52.9
p-$NO_2C_6H_4$	76	51.7, 51.6

Figure 4.56.14

4.57 *O,O,S*-TRIALKYL PHOSPHOROTHIOLATES $(RO)_2P(O)SR$

O,O,S-Trialkyl phosphorothiolates have applications in industrial, agricultural and medicinal chemistry owing to their utility as synthetic intermediates and their biological and physical properties (Fig. 4.57.1). In many cases, they have replaced organochlorine pesticides as they often possess good activity and lower acute toxicity to humans. Profenofos is a potent inhibitor of pyrethroid esterase in mice (*349*) while dimethoxon or malaoxon (*377*) inhibit pest cholinesterases.



Profenofos **Dimethoxon** **Malaoxon**

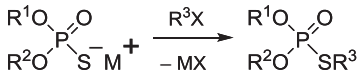
Figure 4.57.1

Oligonucleoside phosphorothiolate antisense drugs have been studied clinically. Some are used to treat viral diseases. To overcome undesired side effects at high concentrations, their incorporation into mixed P—O/P—S oligonucleotides is recommended (*357*,*358*). Phosphorothioate—cAMP analogues are effective immunostimulants for treating HIV and hepatitis B infections (*373*,*374*,*378*).

Although *O,O*-dialkyl hydrogen phosphorothioates exist as an equilibrium mixture of thiono and thiolo tautomers, studies of the reactions of these ambident nucleophiles and their salts with alkyl

halides and tosylates have shown that only *S*-alkylation occurs. The soft sulfur atom is always the reactive centre, rather than the hard oxygen atom, and this permits access to *O,O,S*-trialkyl phosphorothiolates starting from *O,O*-dialkyl phosphorothioate metal salts and the alkyl halide or tosylate. Little variation is observed upon changing the leaving group or solvent. This route is however hampered by the poor availability of the *O,O*-dialkyl hydrogen phosphorothioate starting materials, which usually have to be made beforehand. *S*-Aryl phosphorothioates are inaccessible using this strategy.

Some accessible products appear in Fig. 4.57.2 (*367*,*369*,*370*). MW irradiation shortens the duration of reactions conventional heating takes a long time to complete to a few minutes. Attachment of long alkyl chains to the dithioate is possible starting from the thioate anion and appropriate alkyl halide. Unsymmetrical phosphorothioate salts also undergo *S*-alkylation.



O,O-Dialkyl hydrogen phosphorothiolates

R^1	R^2	R^3	X	Time	Yield (%)	δ_P (ppm)	Ref.
Et	Et	*n*-Bu	Br	2 min [a]	76	27.7	(*367*)
Et	Et	$PhCH_2$	OTs	3 min [a]	67	27.1	(*367*)
Et	Et	$PhCH_2CH_2$	Br	2 min [a]	72	27.9	(*367*)
Et	Et	*o*-$MeC_6H_4CH_2$	Br	3 min [a]	65	26.2	(*367*)
Et	Et	*p*-$ClC_6H_4CH_2$	OTs	2 min [a]	67	26.3	(*367*)
Et	Et	*p*-$NO_2C_6H_4CH_2$	OTs	5 min [a]	83	25.6	(*367*)
Et	Et	$PhC(O)(CH_2)_3$	I	3 h	98	28.9	(*369*)
Et	Et	$MeOC(O)(CH_2)_3$	Cl	3 h	85	28.7	(*369*)
t-Bu	Ph	Me	I	3 h	82	69.4	(*370*)

a. Heated using a microwave (MW) apparatus

Figure 4.57.2

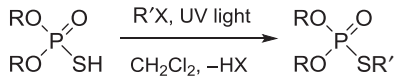
▶ *O,O-Diethyl S-(p-nitrobenzyl) phosphorothiolate* $(EtO)_2P(O)SCH_2C_6H_4NO_2$*-p* (*367*). A mixture of the *O,O*-diethyl phosphorothioate sodium salt (10 mmol) and *p*-nitrobenzyl tosylate (9 mmol) was irradiated by a 720 W kitchen-type MW for 5 min. Chromatography of the product through a plug of silica gel, eluting with 1:9 then 1:1 ethyl acetate—hexane, and evaporation of the solvent gave the phosphorothiolate as colourless liquid (83%). δ_P 25.6 ppm.

▶ *O,O-Diethyl S-(methylbutanoate) phosphorothiolate* $(EtO)_2P(O)S(CH_2)_3CO_2Me$ (*369*). A stirred mixture of methyl 4-chlorobutanoate (0.100 g, 0.732 mmol) and sodium iodide (0.559 g, 3.73 mmol) in acetone (2.9 ml) was heated under reflux for 12 h. The mixture was cooled to room temperature. A solution of *O,O*-diethyl sodium phosphorothioate (0.281 mg, 1.46 mmol) in *N,N*-dimethylformamide (1.2 ml) was added. The mixture was stirred at room temperature for 3 h and the acetone was

removed under reduced pressure. The solution was diluted with ether (50 ml), washed with a 1:1 *v*/*v* water-saturated brine (2 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel, eluting with 1:1 ethyl acetate—hexane, gave a colourless liquid (85% over two steps). δ_P 28.7 ppm.

▶ *O-Phenyl O-(tert-butyl) S-methyl phosphorothiolate PhO(t-BuO)P(O)SMe (370)*. Ammonium *O*-phenyl *O*-(*tert*-butyl)phosphorothioate was diluted with THF (25 ml). Methyl iodide (5 ml) was added and the mixture was stirred for 3 h. Radial chromatography gave the product (0.936 g, 82%). δ_P 69.4 ppm.

O,O-Dialkyl hydrogen phosphorothioates react with linear and cyclic unsaturated alcohols or methyl ethers in the dark or when irradiated with ultraviolet light (Fig. 4.57.3) (*368*). The dialkyl *S*-alkenyl phosphorothioate products are robust under these conditions and do not degrade (*379*,*380*).



O,O-Dialkyl hydrogen phosphorothiolates

R	R′	X	Time	Yield (%)	δ_P (ppm)	Ref.
Et	*c*-CHCH=C(Me)$(CH_2)_3$	OH	2 h	75	27.8	(*368*)
i-Pr	*c*-CHCH=C(Me)$(CH_2)_3$	OH	12 h	93	26.2	(*379*)
Et	*c*-CHCH=C(Ph)$(CH_2)_3$	OH	2 h	87	27.4	(*368*)
Et	*c*-CHCH=C(*i*-Pr)$(CH_2)_3$	OMe	2 h	83	28.0	(*368*)
Et	CHMeCH=CHMe	OMe	48 h	73	27.2	(*368*)
Et	*c*-CHCH=CH$(CH_2)_4$	OMe	48 h	74	27.8	(*368*)

Figure 4.57.3

▶ *Diethyl S-(3-phenylcyclo-2-hexenyl)phosphorothiolate (368)*. A solution of *O,O*-diethyl hydrogen phosphorothioate (357 mg, 0.21 mmol) and 3-phenylcyclo-2-hexen-1-ol (384 mg, 0.20 mmol) in dichloromethane (1.5 ml) was placed in a Rayonet reactor or under a sunlamp ($\lambda > 300$ nm) and irradiated at ambient temperature until the reaction was complete (*ca.* 2 h). The mixture was rotary evaporated. Chromatography of the residue on silica gel, eluting with ethyl acetate—hexane, afforded a pale-yellow liquid (57 mg, 87%). δ_P 27.4 ppm.

Dialkyl *S*-alkyl phosphorothiolates can be prepared by Arbuzov-type reactions of trialkyl phosphites with sulfur-containing electrophiles bearing a good leaving group that once departed dealkylates the phosphonium intermediate $[(RO)_3PSR]^+X^-$. The success of this method depends on the reactivity of the sulfur-containing electrophile and the ease of dealkylation of the alkoxy group. Unsymmetrical trialkyl phosphites offer a choice of groups to dealkylate and can lead to product

mixtures that are difficult to separate. Sulfur-containing reagents that participate in Arbuzov reactions include dialkyl disulfides (RSSR), aliphatic or aromatic sulfenyl chlorides (RSCl), thiophthalimides or thiosuccinimides ($RSNR'_2$), and alkyl thiocyanates (RSCN), and are now discussed in turn.

Triethyl phosphite reacts with diethyl disulfide upon heating to provide *O,O,S*-triethyl phosphorothiolate (**259**) (Fig. 4.57.4) (*381–385*). The sulfur–sulfur bond cleavage is initiated by heating and yields the corresponding phosphonium salt (**260**). Elimination of diethyl sulfide via the dealkylation step of the Arbuzov reaction yields the target compound.

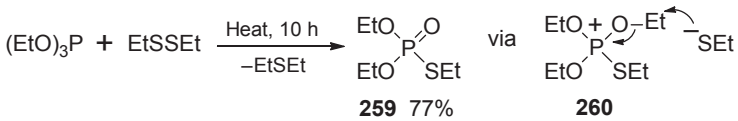
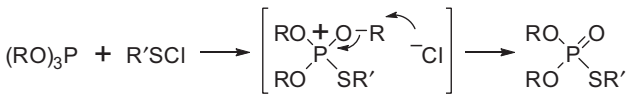


Figure 4.57.4

Trialkyl phosphites react with alkyl and aryl sulfenyl chlorides to give a range of *O,O*-dialkyl *S*-alkyl phosphorothiolates (Fig. 4.57.5) (*386–390*). The usual dealkylation step of the Arbuzov reaction is observed with loss of alkyl chloride.



Dialkyl *S*-alkyl phosphorothiolates

R	R′	Yield (%)	Bp (°C/mmHg)
Et	Me	92	145–150/50
Et	CH_2CH_2Cl	68	147/5
Et	Ph	71	182–186/30
n-Pr	Et	95	141–142/25
n-Bu	Et	89	132/4

Figure 4.57.5

▶ *Di-n-butyl S-ethyl phosphorothiolate (n-BuO)$_2$P(O)SEt* (*386*). A solution of sulfuryl chloride (8.1 ml, 0.1 mol) in toluene (15 ml) was added dropwise to a stirred solution of diethyl disulfide (12.2 g, 0.1 mol) in toluene (50 ml) at −30 °C. The red-orange solution was left for 20 min at −30 °C and then treated dropwise with tri-*n*-butyl phosphite (54.1 ml, 0.2 mol) in toluene (50 ml). The red-orange colour of the sulfenyl chloride was discharged towards the end of the addition. The liquid was warmed to room temperature and extracted with an excess of dilute aqueous sodium carbonate and then with water. The toluene solution was dried (Na_2SO_4) and the solvent was removed. Distillation of the residue under reduced pressure gave the product (45 g, 89%). Bp 132 °C/4 mmHg.

The required alkylsulfenyl chlorides are usually generated by treatment of a dialkyl disulfide with sulfuryl chloride, often in toluene, and are used immediately. A sequence showing the conversion of a dialkyl disulfide (**261**) to the alkylsulfenyl chloride (**262**), then an Arbuzov reaction with dimethyl 2,4-dichlorophenyl phosphite to give a methyl 2,4-dichlorophenyl *S*-functionalised phosphorothiolate (**263**), appears in Fig. 4.57.6 (*391*).

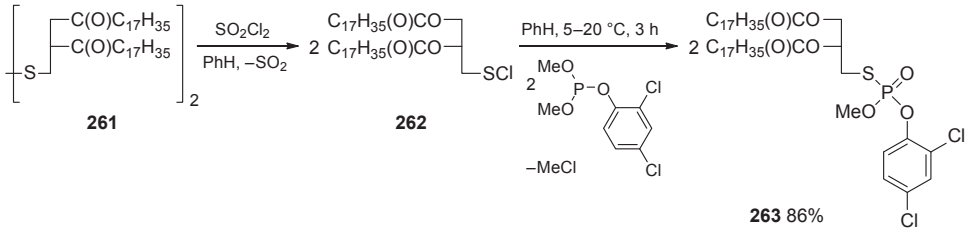


Figure 4.57.6

Similar chemistry can be applied to the transformation of cyclic trialkyl phosphites to ring-opened products (Fig. 4.57.7) (*381–384*). Trialkyl phosphites also react with aromatic sulfonyl chlorides to give dialkyl *S*-aryl phosphorothiolates and trialkyl phosphate by-products.

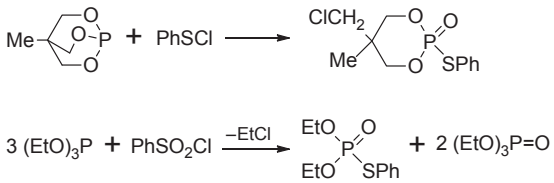
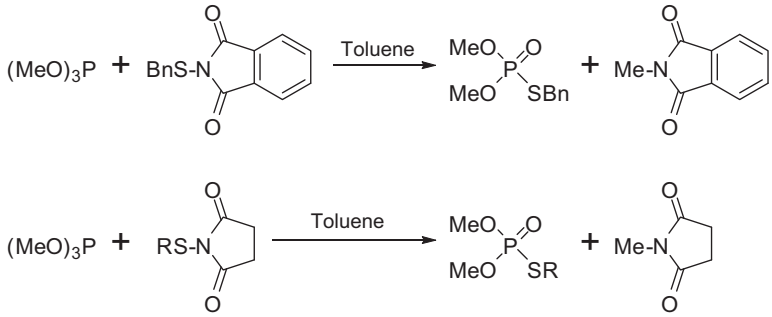


Figure 4.57.7

Trialkyl phosphites react with substituted thiophthalimides or thiosuccinimides in an Arbuzov manner to yield the corresponding *O,O*-dialkyl *S*-alkyl phosphorothiolates (Fig. 4.57.8) (*392*). This strategy to *O,O*-dimethyl *S*-benzyl phosphorothiolate or dialkyl *S*-alkyl phosphorothiolates is accompanied by the formation of neutral by-products (*372,392*).

▶ *O,O-Dimethyl S-benzyl phosphorothiolate* (*392*). Freshly distilled trimethyl phosphite (1.24 g, 10 mmol) in toluene (10 ml) was added slowly to stirred benzyl thiosuccinimide (2.69 g, 10 mmol) in toluene (20 ml) at room temperature. The solvent was removed and the residue distilled to give the product (1.88 g, 81%). Bp 92 °C/0.007 mmHg.

The Arbuzov reaction of trialkyl phosphites with alkyl thiocyanates provides a straightforward method of preparation of *O,O*-dialkyl *S*-alkyl phosphorothiolates. One example is the reaction of triethyl phosphite and methyl thiocyanate to give *O,O*-diethyl *S*-methyl phosphorothiolate (**264**) in excellent yield (Fig. 4.57.9) (*149*).



O,O-Dialkyl *S*-alkyl phosphorothiolates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)
Ph	67	83/0.01	26.4
Bn	81	92/0.007	30.7
n-$C_{18}H_{37}$	77	mp 38 °C	–31.9

Figure 4.57.8

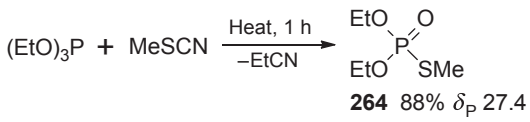
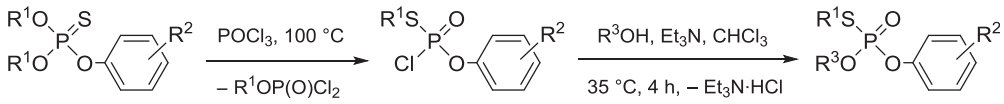


Figure 4.57.9

▶ *O,O-Diethyl S-methyl phosphorothiolate (EtO)$_2$P(O)SMe* (**264**)(*149*). A stirred mixture of triethyl phosphite (166 g, 1 mol) and methyl thiocyanate (73 g, 1 mol) was heated under reflux for 1 h. Analysis by TLC and GC—MS showed excellent conversion to the product. Distillation of the liquid gave the title compound as a 95% pure colourless liquid (162 g, 88%). Bp 90 °C/0.6 mmHg. δ_P ($CDCl_3$) 27.4 ppm.

O,S-Dialkyl (or *O*-aryl *S*-alkyl) *O*-aryl phosphorothiolates can be prepared in a two-step sequence starting from dialkyl aryl phosphorothionates. Heating these with phosphorus oxychloride causes thiono—thiolo isomerisation and replacement of one of the alkoxy groups by a chlorine atom (Fig. 4.57.10) (*393*). The time required for efficient chlorination increases with the number of carbon atoms in the R^1 group, but becomes unfeasible with branched or long alkyl chains. The yield of chlorinated product decreases when the electronegativity of the R^2 group in the aryl substituent increases (e.g. 2,4-di-Cl, 4-NO_2 or 4-MeS) and with other electronegative groups sometimes does not occur at all. When this reaction does proceed, however, the formed *O*-aryl *S*-alkyl phosphorochloridothiolates undergo facile nucleophilic substitution with alcohols in the presence of triethylamine to provide the target phosphorothiolates in generally good yields. This two-step method



O,S-dialkyl (or *O*-aryl *S*-alkyl) *O*-aryl phosphorothiolates

R^1	R^2	R^3	Time (h)	Yield (%)	Bp (°C/mmHg)
n-Pr	H	Me	12	71	126–128/0.2
Et	4-Me	Me	9	74	127–128/0.6
n-Bu	4-Me	Me	13	51	131–134/0.1
n-Pr	4-Cl	Me	38	71	129–131/0.1
Et	2,4-Cl_2	Me	35	50	137–139/0.3
Et	4-Me	2,4,5-$Cl_3C_6H_2$	9	67	dec.
Et	H	4-$O_2NC_6H_4$	9.5	59	dec.
n-Pr	H	4-$MeSC_6H_4$	12	64	dec.

Time = time heated at 100 °C in the first step. dec. = decomposed during distillation (oil bath 150 °C/0.1 mmHg) and thus purified by column chromatography on silica gel

Figure 4.57.10

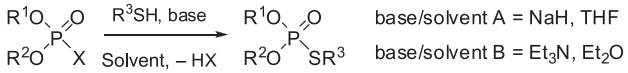
converts achiral dialkyl aryl phosphorothionates into chiral *O,S*-dialkyl (or *O*-aryl *S*-alkyl) *O*-aryl phosphorothiolates.

▶ *O-Methyl O-phenyl S-(n-propyl) phosphorothiolate MeO(PhO)P(O)SPr-n* (*393*). A stirred mixture of *O,O*-di-*n*-propyl *O*-phenyl phosphorothionate (11.0 g, 40 mmol) and phosphorus oxychloride (6.2 g, 40 mmol) was heated to 100 °C for 12 h until TLC, eluting with 1:10 ether—petroleum ether (bp 60—90 °C), revealed maximum consumption of the thionate. The by-product, *n*-propyl phosphorodichloridate *n*-PrOP(O)Cl_2, was distilled off (oil bath 100 °C, 1 mmHg). The residue was dissolved in chloroform (40 ml) and to the resulting solution was added dropwise a mixture of methanol (10 ml) and triethylamine (6.5 g, 64 mmol) at 20 °C. After addition, the mixture was stirred at 35 °C for 4 h, cooled to room temperature, and poured into cold water (50 ml). The organic layer was separated, washed with water (40 ml), and dried ($MgSO_4$). The crude product was distilled under reduced pressure to give the title compound (7.0 g, 71%). Bp 126—128 °C/0.2 mmHg.

Dialkyl phosphorochloridates react with thiols under basic conditions, most usually upon treatment with sodium alkanethiolates, or with the thiol and triethylamine, to provide dialkyl *S*-alkyl phosphorothiolates (Fig. 4.57.11) (*394,395*). The yields are rarely high as the soft thiolate ion is generally capable of dealkylating the soft alkyl group of the chloridate, rather than reacting more selectively with its hard phosphorus atom, which reduces the yield of the desired product.

A small fluoroester group bonded to the phosphorus atom increases its electrophilicity and thus the speed of nucleophilic attack. The mechanism of phosphorylation proceeds via an S_N2P reaction. A trigonal bipyramidal transition state (**265**) is postulated, produced by insertion of a nucleophile which

adopts an apical position, opposite the departing halogen substituent. The tetrahedral product is finally generated by elimination of the departing chlorine atom (Fig. 4.57.12). In some cases, a phosphorane intermediate has been postulated, with the nucleophile and the hydroxy group occupying apical positions. Substituent rearrangement occurs to transfer the chloride leaving substituent to an apical position.

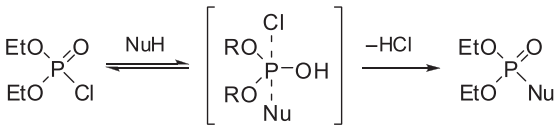


Dialkyl (or alkyl/aryl) *S*-(alkyl or aryl) phosphorothiolates

R^1	R^2	R^3	X	Base/solvent	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)	Ref.
Et	Et	Ph	Cl	A	63	-	22.7	(*394,395*)
i-Pr	*i*-Pr	Ph	Cl	A	92	-	20.1	(*394,395*)
Et	Et	MF [a]	Cl	A	82	-	21.1	(*396–398*)
i-Pr	*i*-Pr	PT [b]	Cl	A	51	-	29.0	(*399*)
Et	2,4-$Cl_2C_6H_3$	*t*-Bu	Cl	A	54	-	-	(*400*)
Et	2-Cl-4-BrC_6H_3	*t*-Bu	Cl	A	40	mp 48–53 °C	-	(*400*)
Et	2,4,5-$Cl_3C_6H_2$	*t*-Bu	Cl	A	44	-	-	(*400*)
Et	2,4,6-$Cl_3C_6H_2$	*t*-Bu	Cl	A	26	-	-	(*400*)
CF_3CH_2	CF_3CH_2	Et	Cl	B	19	44/0.05	30.7	(*149*)
$C_2F_5CH_2$	$C_2F_5CH_2$	Et	Cl	B	13	43/0.03	30.7	(*149*)
$C_3F_7CH_2$	$C_3F_7CH_2$	Et	Cl	B	41	53/0.02	35.3	(*149*)
$(CF_3)_2CH$	$(CF_3)_2CH$	Et	Cl	B	28	35/0.03	35.3	(*149*)
CF_3CH_2	CF_3CH_2	*n*-Pr	Cl	B	19	50/0.04	31.1	(*149*)
$C_2F_5CH_2$	$C_2F_5CH_2$	*n*-Pr	Cl	B	21	53/0.03	31.3	(*149*)
$C_3F_7CH_2$	$C_3F_7CH_2$	*n*-Pr	Cl	B	37	43/0.02	31.1	(*149*)
$(CF_3)_2CH$	$(CF_3)_2CH$	*n*-Pr	Cl	B	21	38/0.03	35.7	(*149*)
CF_3CH_2	CF_3CH_2	Ph	Br	B	43	mp 35–36 °C	25.3	(*149*)
$C_2F_5CH_2$	$C_2F_5CH_2$	Ph	Br	B	46	96/1	25.5	(*149*)

a. MF = Mercaptoferrocene group. *b*. PT = pent-4-yne-1-thio group

Figure 4.57.11



265

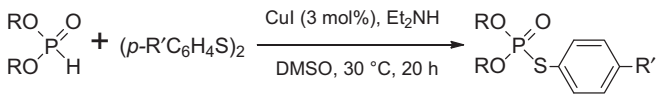
Figure 4.57.12

▶ *O,O-Diisopropyl S-phenyl phosphorothiolate (i-PrO)$_2$P(O)SPh* (*396–401*). Thiophenol (1 ml, 9.7 mmol) was added slowly to a stirred suspension of sodium hydride (500 mg, 60% in mineral oil, 12.5 mmol) in THF (25 ml) under nitrogen. After hydrogen evolution had ceased, a solution of

diisopropyl phosphorochloridate (1.9 g, 9.5 mmol) in THF (5 ml) was added dropwise. The mixture was stirred at room temperature for 20 h. The solvent was removed under reduced pressure, and water (30 ml) and dichloromethane (50 ml) were added to the residue. The organic phase was separated, dried (Na_2SO_4), and the solvent removed to give a yellow liquid (2.6 g). A portion (1 g) was purified by chromatography on silica gel, eluting with 1:4 ether—petroleum ether, to give the title compound (840 mg, 85%). δ_P 20.1 ppm.

▶ *Bis(2,2,3,3,3-pentafluoropropyl) S-phenyl phosphorothiolate* $(C_2F_5CH_2O)_2P(O)SPh$ (*149*). A solution of benzenethiol (0.51 g, 4.64 mmol) and triethylamine (0.65 ml, 4.64 mmol) in ether (10 ml) was added dropwise by cannula to a stirred solution of *bis*(2,2,3,3,3-pentafluoropropyl) phosphorobromidate (1.97 g, 4.64 mmol) in ether (40 ml) at 0—5 °C. An instant precipitate of triethylamine hydrobromide formed. After addition, the mixture was allowed to warm to room temperature and was left for 24 h. The precipitate was removed by filtration and the filtrate, after concentration, gave a liquid that was distilled under reduced pressure using a Kugelrohr apparatus. The title compound was obtained as a colourless liquid (0.98 g, 46%). Bp 96 °C/1 mmHg. δ_P ($CDCl_3$) 25.5 ppm.

Procedures for converting dialkyl *H*-phosphonates to dialkyl *S*-alkyl phosphorothiolates have been devised. Here, P—S bond formation is achieved by reaction with dialkyl disulfides (*402*), alkyl thiosuccinimides (*372,403*), alkylsulfenyl chlorides (*404*) or alkyl thiocyanates (*405*). A new and general method involving the reaction of a dialkyl *H*-phosphonate with symmetrical diaryl disulfides has been reported, employing copper(I) iodide catalyst and diethylamine (in sub-stoichiometric amount) in DMSO (*406*). This method tolerates moisture and air and allows the preparation of various dialkyl *S*-aryl phosphorothiolates in excellent yield (Fig. 4.57.13). The highest yields of thiolate product were obtained when the diaryl disulfide contained an electron-donating group.



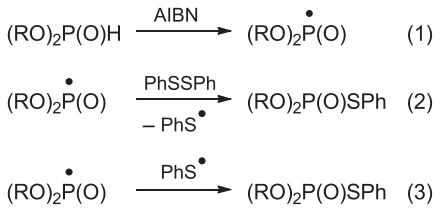
Dialkyl *S*-aryl phosphorothiolates

R	R′	Yield (%)	δ_P (ppm)
Et	H	91	22.7
Et	Me	93	refs. (*359-361*)
Et	Cl	83	-
i-Pr	Me	93	refs. (*359-361*)
n-Bu	H	92	ref. (*362*)
n-Bu	Me	94	24.0
n-Bu	Cl	88	22.8
n-Hexyl	H	92	24.6
n-Hexyl	Me	95	25.1

Figure 4.57.13

▶ *Di-n-hexyl S-(4-tolyl) phosphorothiolate* $(n\text{-}C_6H_{13}O)_2P(O)OC_4H_4Me\text{-}p$ (*406*). Di-*n*-hexyl *H*-phosphonate (0.3 mmol), ditolyl disulfide (0.15 mmol), CuI (3 mol%) and diethylamine (0.06 mmol) were dissolved in DMSO (1 ml) and stirred at 30 °C for 20 h in an atmosphere of air. The mixture was quenched with 0.5 M acetic acid and extracted with ether. The combined organic layers were concentrated under vacuum. Chromatography of the residue on silica gel, eluting with ethyl acetate—petroleum ether, gave the title compound (95%). δ_P 25.1 ppm.

Dialkyl *H*-phosphonates can be coupled to diphenyl disulfide under radical conditions initiated by azobisisobutyronitrile (AIBN) (Fig. 4.57.14) (*407*). The reaction of dialkyl *H*-phosphonates and diphenyl disulfide is slow owing to a slow abstraction rate of the phenylthio group by the dialkylphosphonyl radicals.



Dialkyl *S*-phenyl phosphorothiolates

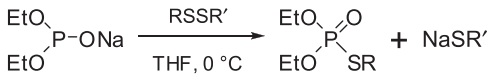
R	Time (h)	Yield (%)	Bp (°C/mmHg)
Me	12	57	70–75/0.05
Et	8	41	84–88/0.02
n-Bu	4	25	118–119/0.005

Figure 4.57.14

▶ *Dimethyl S-phenyl phosphorothiolate* $(MeO)_2P(O)SPh$ (*407*). A mixture of dimethyl *H*-phosphonate (132 mg, 1.2 mmol), diphenyl disulfide (109 mg, 0.5 mmol) and AIBN (82 mg, 50 mol%) in anhydrous benzene (1 ml) was stirred at 60—65 °C under nitrogen in a tubular reactor equipped with a condenser. The mixture was heated for 12 h, the solvent removed under reduced pressure, and the crude product purified by flash chromatography on silica gel, eluting with 2:1 hexane—ethyl acetate, to give a yellow liquid (0.15 g, 57%). Bp 70—75 °C/0.05 mmHg.

The sodium salts of dialkyl *H*-phosphonates react efficiently with dialkyl disulfides at low temperatures (Fig. 4.57.15) (*408*). The reaction of sodium diethyl phosphite with ethyl phenyl disulfide takes place in one direction: the *S*-ethyl group adds to the phosphorus atom to give the *O,O,S*-triethyl phosphorothiolate.

▶ *O,O,S-Triethyl phosphorothiolate* $(EtO)_2P(O)SEt$ (*408*). A solution of sodium diethyl phosphite (17.0 g, 106 mmol) in THF (100 ml) was added over 10 min to a stirred solution of diethyl disulfide (12.9 g, 106 mmol) in THF (100 ml) at 0 °C. As the two solutions mixed, a white precipitate formed



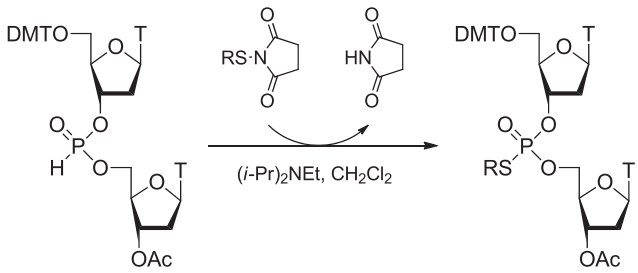
Diethyl *S*-alkyl phosphorothiolates

R	R′	Yield (%)	Bp (°C/mmHg)
Et	Et	74	103–107/7
Et	Ph	71	80/0.5
$(CH_2)_2NHAc$	$(CH_2)_2NHAc$	44	-

Figure 4.57.15

instantly, and after an additional 5 min, the solution was filtered rapidly through a sintered glass funnel under a positive pressure of nitrogen. Distillation of the filtrate gave the title compound (15.5 g, 74%). Bp 103—107 °C/7 mmHg.

Dialkyl *H*-phosphonates react with alkyl thiosuccinimides in the presence of *N,N*-diisopropylethylamine in dichloromethane to provide *O,O*-dialkyl *S*-alkyl phosphorothiolates, enabling a new approach for converting fragile protected nucleotides (e.g. **266**) to oligonucleotides (e.g. **267** and **268**) (Fig. 4.57.16) (*403*). Solution-phase synthesis of oligonucleotides may be possible using this methodology, allowing access to high-molecular-weight bioactive oligonucleotides.



266

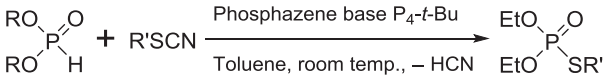
DMT = 4,4'-dimethoxytrityl, T = thymine

R = Ph **267** 92%

R = Bn **268** 95%

Figure 4.57.16

Alkyl thiocyanates are less reactive than the other sulfur-containing reagents already discussed and their addition to dialkyl *H*-phosphonates requires deprotonation of the *H*-phosphonate and a high temperature that can be problematic: the thermal instability of alkyl thiocyanates (RSCN) generally causes isomerisation to the alkyl isothiocyanates (RNCS), and therefore leads to side reactions, or isomerisation of the obtained phosphorothiolate (*405*). Milder conditions are required to improve this synthetic approach. The use of catalytic amounts of a non-nucleophilic base such as phosphazene P_4-*t*-Bu provides a gentle and efficient method for converting dialkyl *H*-phosphonates to the targeted *S*-alkyl phosphorothiolates in high yields through facile departure of the cyanide anion (Fig. 4.57.17).



Diethyl *S*-alkyl phosphorothiolates

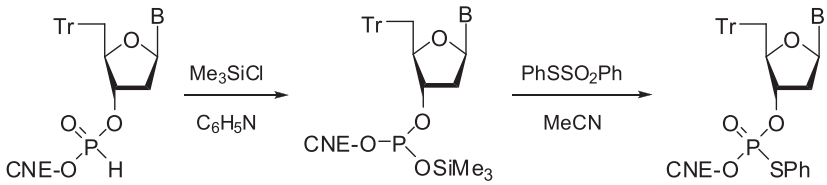
R	R'	Time (h)	Yield (%)	δ_P (ppm)
Et	*c*-C_6H_{11}	3.0	79	28.2
Et	Bn	1.5	86	27.2
Et	$(CH_2)_3OH$	3.0	68	27.4
Et	$(CH_2)_3CN$	3.0	81	27.1
Bn	*c*-C_6H_{11}	3.0	82	29.3
Bn	Bn	1.5	90	28.4
Bn	$(CH_2)_3OH$	18	54	20.4

Figure 4.57.17

▶ *O,O-Diethyl S-cyclohexyl phosphorothiolate* $(EtO)_2P(O)SC_6H_{11}$ (*405*). Phosphazene P_4-*t*-Bu (1.0 M in *n*-hexanes, 0.025 ml) was added to a mixture of diethyl *H*-phosphonate (0.345 g, 2.5 mmol) and cyclohexyl thiocyanate (0.353 g, 2.5 mmol) in toluene (10 ml). To remove hydrogen cyanide, a gentle nitrogen flow to a bubbler containing 1 M aqueous sodium hydroxide solution was used, and the pH of this solution was regularly checked and maintained (pH >12). After 3 h at room temperature, the solvent was removed, and the crude reaction mixture was chromatographed on silica gel, eluting with 1:4 acetone—dichloromethane, to yield the title compound (0.498 g, 79%).

Diethyl *H*-phosphonate reacts with the sulfenyl chloride F_2B(acacSCl) to give the *S*-functionalised phosphorothiolate in 40—45% yield, but it quickly decomposes and must be stored at −10 °C (*404*). Dialkyl trimethylsilyl phosphites are useful alternatives to dialkyl phosphite salts for Arbuzov reactions as the rate-limiting dealkylation step is replaced by a rapid desilylation. Dialkyl trimethylsilyl phosphites are prepared by treating dialkyl *H*-phosphonates with *N,O-bis*(-trimethylsilyl)acetamide (*409*) or chlorotrimethylsilane (*410*). The trimethylsilyl phosphites react with aryl or alkyl thiosulfonates to form *O,O*-dialkyl *S*-aryl or -alkyl phosphorothiolates often in good yield. Conversion of the dialkyl *H*-phosphonate (**269**) to dialkyl trimethylsilyl phosphite (**270**) and subsequent reaction with phenyl phenylthiosulfonate provides the dialkyl *S*-phenyl phosphorothiolate (**271**) (Fig. 4.57.18).

▶ *5′-[4,4′,4″-Tris(tert-butyltrityl)]thymidine 3′-(O-cyanoethyl) S-phenyl phosphorothiolate* (**271**) (*410*). A solution of chlorotrimethylsilane (4.35 g, 20 mmol) in pyridine (20 ml) was added to a stirred solution of the dialkyl *H*-phosphonate **269** (4 mmol) in acetonitrile (10 ml). After 10 min, solid phenyl phenylthiosulfonate (5 mmol) was added. Thiolation was complete in 10 min. The mixture was concentrated to a yellow liquid which was dissolved in ethyl acetate (100 ml) and washed with saturated aqueous sodium bicarbonate and then brine. Flash chromatography of the residue on silica gel and drying under vacuum gave the product (83%). δ_P 24.3 and 24.2 ppm.

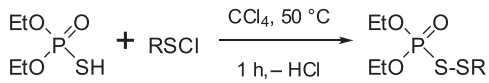


Tr = 4,4',4''-tris-*tert*-butyl trityl, B = thymine, CNE = β-cyanoethyl

Figure 4.57.18

4.58 DIALKYL *S*-(*S*-ALKYL) PHOSPHOROTHIOLATES $(RO)_2P(O)SSR$

Dialkyl *S*-(*S*-alkyl) phosphorothiolates are useful pest control agents that generally have low mammalian toxicity. They also have applications in molecular biology (*411*). They are prepared by reaction of *O,O*-dialkyl hydrogen phosphorothioates with alkylsulfenyl chlorides in carbon tetrachloride (Fig. 4.58.1) (*412,413*). A bridged disulfide widely used to modify groups on RNA was made similarly by coupling an *O,O*-dialkyl hydrogen phosphorothioate of RNA and a 2-thiopyridine-activated substrate (*411*).

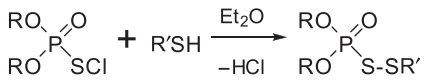


R	Yield (%)
C_6H_5	61
C_6H_4Me	5
C_6H_4Et	7
C_6H_4Cl	62
CCl_3	76

Figure 4.58.1

▶ *Diethyl S-(S-phenyl) phosphorothiolate* $(EtO)_2P(O)SSPh$ (*412,413*). *O,O*-Diethyl hydrogen phosphorothioate (85 g, 0.5 mol) was added in small portions to a stirred solution of phenylsulfenyl chloride (72 g, 0.5 mol) in carbon tetrachloride (200 ml) at 10 °C. The mixture was heated to 50 °C for 1 h and washed with 5% aqueous potassium hydroxide and water. The organic layer was dried ($MgSO_4$) and the solvent was removed. Column chromatography on silica gel, eluting with dichloromethane, gave the title compound (85 g, 61%).

The reverse strategy, involving the reaction between a dialkyl *S*-chloro phosphorothiolate and a thiol, is the most common route to *O,O*-dialkyl *S*-(*S*-alkyl) phosphorothiolates, and permits access to many such compounds (Fig. 4.58.2) (*414–416*).



Dialkyl *S*-(*S*-alkyl) phosphorothiolates

R	R′	Yield (%)
Et	Et	84
Et	*n*-Bu	100
Et	C_6H_5	45
Et	C_6H_4Cl	85
Me	C_6H_4Cl	99
Et	CH_2CO_2Et	85
Me	CH_2CO_2Et	97
Me	$CH(CH_2CO_2Et)CO_2Et$	98

Figure 4.58.2

▶ *Diethyl S-(S-tert-butyl) phosphorothiolate* $(EtO)_2P(O)SS$*-t-Bu* (*414–416*). *Tert*-butanethiol (18.4 g, 0.20 mol) was added over 30 min to a stirred solution of *O,O*-diethyl *S*-chloro phosphorothiolate (31 g, 0.15 mol) in ether (150 ml) at 10 °C. After addition, the mixture was allowed to warm to room temperature and the solvent was removed. The crude product was purified by distillation to remove the hydrogen chloride and to obtain the title compound (38.7 g, 100%). Bp 60 °C/1 mmHg.

Another method involves the reaction of a trialkyl phosphorothionate – preferably trimethyl phosphorothionate (**272**) – with methylsulfenyl chloride. The nucleophilic character of the sulfur atom of the P═S bond allows its attack on the sulfenyl chloride to create a disulfide (**273**) with liberation of the alkyl chloride (Fig. 4.58.3). The chloride anion dealkylates the phosphonium intermediate, as in the Arbuzov reaction, through reaction with an alkyl group – preferably a methyl group – to generate the P═O bond (*417*).

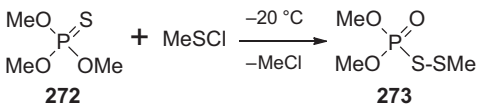


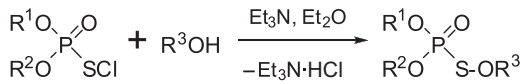
Figure 4.58.3

▶ *Dimethyl S-(S-methyl) phosphorothiolate* $(MeO)_2P(O)SSMe$ (**273**) (*417*). Methylsulfenyl chloride (17.1 g, 0.2 mol) was added slowly to stirred trimethyl phosphorothionate (31.2 g, 0.2 mol) at −20 °C in a three-necked flask fitted with a reflux condenser and an outlet connected to a dry-ice trap. After addition, the mixture was allowed to warm to room temperature. Methyl chloride was recovered in

53% yield after bubbling it through aqueous sodium hydroxide and recondensing it. Chromatography of the residue twice on silica gel, eluting with 1:2 benzene—petroleum ether and then 92:8 benzene—ether, gave the title compound.

4.59 DIALKYL *S*-(*O*-ALKYL) PHOSPHOROTHIOLATES $(RO)_2P(O)SOR$

Dialkyl *S*-(*O*-alkyl) phosphorothiolates have herbicidal and pesticidal activity. Their synthesis proceeds in high yields from *O*,*O*-dialkyl *S*-chloro phosphorothiolates and alcohols. Mild temperatures (<100 °C) and anhydrous conditions are required to avoid reactant decomposition. The fragility of the P—SOR bond requires slow addition rates and low temperatures and the participation of a tertiary amine to scavenge the formed hydrogen chloride to avoid side reactions (*418*,*419*).



Dialkyl *S*-(*O*-alkyl) phosphorothiolates

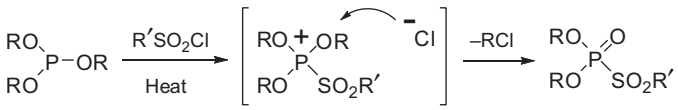
R^1	R^2	R^3	Yield (%)
Et	Et	$CH(CH_2Br)_2$	96
C_8H_{17}	C_8H_{17}	$CH(CH_2Br)_2$	88
Et	C_8H_{17}	$CH(CH_2Br)_2$	100
Et	Et	CH_2CCl_3	95
Et	Et	Bn	99
Et	Et	C_6H_4Cl	98
Et	Et	C_6H_4Ph	99
Et	Et	C_6H_{11}	90
Et	Et	*i*-Pr	98
Et	Et	$C_6H_4OC_6H_4OBu$	98
Et	Et	$CH_2CH(Br)CH_2Br$	95
Et	Et	C_6H_4OMe	98
Et	Et	C_6H_4Me	100
Et	Et	C_6Cl_5	99
C_8H_{17}	C_8H_{17}	C_6Cl_5	88
C_8H_{17}	Et	C_6Cl_5	99
Et	Et	$C_6H_4NO_2$	100
Et	Et	$C_6H_2Br_2NO_2$	100

Figure 4.59.1

▶ *Diethyl S-(O-dibromoisopropyl) phosphorothiolate* $(EtO)_2P(O)SOCH(CH_2Br)_2$ (418,419). *O,O*-Diethyl *S*-chloro phosphorothiolate (30.5 g, 0.15 mol) was added over 30 min at 10 °C to a solution of 1,3-dibromoisopropanol (32.8 g, 0.15 mol) and triethylamine (15.1 g, 0.15 mol) in ether (75 ml). The mixture was stirred for an additional hour at room temperature and then filtered. After removing the solvent under reduced pressure, the product was heated to 50 °C at 1 mmHg pressure, and distilled to yield the product (55.5 g, 96%). Bp 50 °C/1 mmHg.

4.60 DIALKYLPHOSPHORYL ALKYLSULFONATES $(RO)_2P(O)S(O)OR$

Dialkylphosphoryl alkylsulfonates are rarely described in the literature, perhaps because of their low stability. A few examples from the reaction between a trialkyl phosphite and an alkyl or aryl sulfonyl halide have been reported; the process proceeds through an Arbuzov reaction mechanism (420).



Dialkylphosphoryl alkylsulfonates

R	R′	$(RO)_3P$ (mol)	$R'SO_2Cl$ (mol)	Temp. (°C)	Time (h)	Yield (%)	Bp (°C/mmHg)
Et	Me	0.16	0.15	80	2	100	nd
Et	Ph	0.22	0.20	100	1	58	85–91/0.02
Et	*c*-hexyl	0.22	0.20	nd	nd	49	85–90/0.03
Et	$C_6H_4NO_2$	0.11	0.10	80	2	100	nd
i-Pr	Me	0.20	0.25	40	1	92	47–55/0.03

nd = not described

Figure 4.60.1

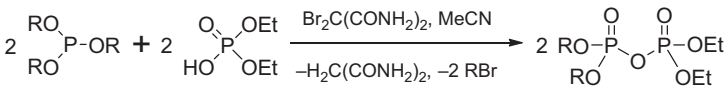
▶ *Diethylphosphoryl phenylsulfonate* $(EtO)_2P(O)SO_2Ph$ (420). Triethyl phosphite (36.5 g, 0.22 mol) was added dropwise to stirred phenylsulfonyl chloride (35.3 g, 0.20 mol). The mixture was stirred at 100 °C for 1 h and then cooled to room temperature. Fractionation under reduced pressure gave the title compound (32 g, 58%). Bp 85—91 °C/0.02 mmHg.

4.61 TETRAALKYL PYROPHOSPHATES $(RO)_2P(O)OP(O)(OR)_2$

Tetraalkyl pyrophosphates are labile compounds of high toxicity. Their toxicity and hydrolysis rate depend on the nature of the alkyl groups: tetraethyl pyrophosphate is the most toxic and tetraisopropyl pyrophosphate the most resistant to hydrolysis (421). Their synthesis has been studied for finding new

phospholipids and for introducing specific genes into cells in cancer research (*422,423*). The P—O—P linkage features in many biologically important molecules (*424*) such as ADP and ATP (Chapter 1.4).

Selective phosphorylation of a trialkyl phosphite by a dialkyl hydrogen phosphate proceeds upon treatment with dibromomalonamide in acetonitrile (*425*) (Fig. 4.61.1). The reaction starts instantly at 0 °C. The intermediate $[(RO)_2P(O)]_2C(CONH_2)_2$, which contains two electrophilic phosphoryl groups and a good leaving group, reacts with the dialkyl hydrogen phosphate to generate the tetraalkyl pyrophosphate and malonamide (*426*).



Dialkyl diethyl pyrophosphates

R	Yield (%)	Bp (°C/mmHg)
Me	68	125–128/0.06
Et	78	126–131/0.55
n-Bu	62	108–114/0.01

Figure 4.61.1

▶ *Diethyl dimethyl pyrophosphate* $(EtO)_2P(O)OP(O)(OMe)_2$ (*426*). A solution of trimethyl phosphite (1.24 g, 10 mmol) in anhydrous acetonitrile (10 ml) was added slowly to a stirred solution of diethyl hydrogen phosphate (1.54 g, 10 mmol) and dibromomalonamide (1.30 g, 5 mmol) in anhydrous acetonitrile (40 ml). The temperature was controlled by cooling with an ice bath. After addition, the mixture was stirred at 0 °C for 4 h and was left overnight at room temperature. The white precipitate of malonamide was removed by filtration and the filtrate was concentrated. The residue was treated with anhydrous ether (50 ml) to remove residual malonamide. After filtering off any remaining malonamide, the filtrate was concentrated and distilled under high vacuum to give diethyl dimethyl pyrophosphate (1.78 g, 68%). Bp 125—128 °C/0.06 mmHg.

Trialkyl phosphites also react with α-bromocyanoacetamide in acetonitrile to give an equilibrium mixture of the enol phosphate (**274a**) and imidoyl phosphate (**274b**) with loss of the alkyl bromide (Fig. 4.61.2) (*426*). Treatment of this mixture with a dialkyl hydrogen phosphate provides the tetraalkyl pyrophosphate (**275**) in addition to cyanoacetamide.

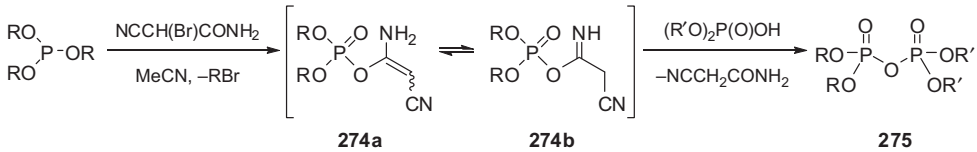
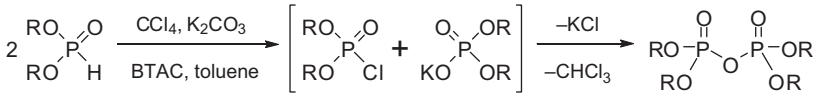


Figure 4.61.2

Tetraalkyl pyrophosphates can be prepared by adding dialkyl *H*-phosphonates in toluene to carbon tetrachloride, anhydrous potassium carbonate, and BTAC. This Todd–Atherton reaction (*212*) provides the dialkyl phosphorochloridate and dialkyl potassium phosphate that react to give the pyrophosphate in good yield (Fig. 4.61.3) (*427, 428*).



Tetraalkyl pyrophosphates

R	Time (h)	Temp. (°C)	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)
Me	1	rt	86	92–94/0.3	–10.5
Et	1	80	82	102–106/0.02	–13.1
i-Pr	3	80	92	99–102/0.05	–15.0
Bn	0.5	60	88	mp 59–61 °C	–13.0
Ph	1	rt	73	165–170/0.05	–25.6

rt = room temperature

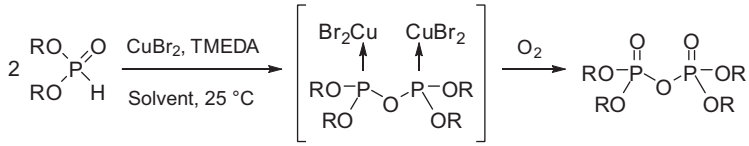
Figure 4.61.3

▶ *Tetraisopropyl pyrophosphate (i-PrO)$_2$P(O)OP(O)(O-i-Pr)$_2$* (*427*). A solution of diisopropyl *H*-phosphonate (3.32 g, 20 mmol) in toluene (10 ml) was added to stirred anhydrous potassium carbonate (5.53 g, 40 mmol), BTAC (0.22 g, 1.0 mmol), carbon tetrachloride (20 ml, 200 mmol) and toluene (20 ml). The mixture was maintained at 80 °C for 3 h. The solid was filtered off and washed with toluene (5 ml). The filtrate was concentrated and the residue was distilled or crystallised to give the product (6.37 g, 92%). Bp 99–102 °C/0.05 mmHg.

A non-classical method to tetraalkyl pyrophosphates starting from dialkyl *H*-phosphonates involves oxidative dehydrogenative coupling in the presence of copper halide catalyst (CuCl or $CuBr_2$) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) (Fig. 4.61.4) (*424*). These conditions, using acetone or THF as solvent, and after aerial oxidation of the intermediate, give the symmetrical pyrophosphates in high yield.

▶ *Tetraisopropyl pyrophosphate (i-PrO)$_2$P(O)OP(O)(O-i-Pr)$_2$* (*424*). TMEDA (11.6 mg, 0.1 mmol) was added to a stirred suspension of $CuBr_2$ (2.2 mg, 10 mmol) in acetone (1 ml). The mixture was stirred for 5 min at room temperature and diisopropyl *H*-phosphonate (166 mg, 1 mmol) was added. The mixture was stirred under anhydrous air for 6 h. Chilled saturated aqueous ammonium chloride was added and the mixture was extracted with chloroform, dried ($MgSO_4$), filtered and concentrated to give the title compound (0.34 g, 99%).

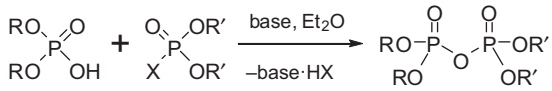
Dialkyl phosphorohalidates react with dialkyl hydrogen phosphates in the presence of pyridine or triethylamine (to neutralise the acid released) to provide tetraalkyl pyrophosphates in good yields (*421*). The method is quite general (Fig. 4.61.5).



Tetraalkyl pyrophosphates

R	$CuBr_2$ (mol%)	TMEDA (mol%)	Solvent	Time (h)	Yield (%)
Et	1	10	acetone	6	99
i-Pr	1	10	acetone	6	99
n-Bu	1	10	acetone	6	99
n-$C_{12}H_{25}$	2	15	THF	8	98
Bn	2	15	THF	15	90
$Me_2CHCH_2CH_2$	2	15	THF	24	96

Figure 4.61.4



Tetraalkyl pyrophosphates

R	R′	X	Base	Yield (%)	Bp (°C/mmHg)
Et	Me	Cl	pyridine	83	100–105/0.003
n-Pr	Me	Cl	pyridine	85	105–110/0.002
i-Pr	Me	Cl	pyridine	51	95–100/0.006–0.008
Et	*n*-Pr	Cl	pyridine	69	118–120/0.005–0.007
Et	*i*-Pr	Cl	pyridine	91	105/0.01–0.006
Et	*n*-Bu	Cl	pyridine	95	115–118/0.007
i-Pr	*n*-Pr	Cl	pyridine	83	110–114/0.003–0.009
i-Pr	*n*-Bu	Cl	NEt_3	87	118–120/0.002
Ph	Ph	I	-	86	ref. (*428*)

Figure 4.61.5

▶ *Diethyl dimethyl pyrophosphate* $(EtO)_2P(O)OP(O)(OMe)_2$ (*424*). A solution of pyridine (24 g, 0.3 mol) in ether (50 ml) was added over 40 min to a stirred mixture of diethyl hydrogen phosphate (46.5 g, 0.3 mol) and dimethyl phosphorochloridate (42.5 g, 0.3 mol) in ether (150 ml). An exothermic reaction caused the temperature to exceed 25 °C; it was maintained at 28–30 °C by

periodic cooling with a water bath. Pyridine hydrochloride precipitated. After addition, which took 40 min, the stirring was continued for 1 h. The mixture was filtered and the residue was washed with ether. The combined filtrate and washings were heated to 55 °C (liquid temperature) at 2 mmHg to remove low-boiling materials. A 32 g portion of the residue obtained was distilled in a Hickman still (bath temperature 100–105 °C/0.003 mmHg, distillation rate: 1 drop/1–2 s) to yield the pyrophosphate (27 g, 83%).

Other methods of pyrophosphate formation through anhydride derivatives that avoid release of a strong acid have been devised, starting from ethyl vinyl ether, diethyl phosphorochloridite, or ketene dimer (Fig. 4.61.6) (*429*). Of these reagents, ketene dimer is of superior efficacy because in the second step of the reaction, acetone and carbon dioxide are produced as by-products, and are readily removed.

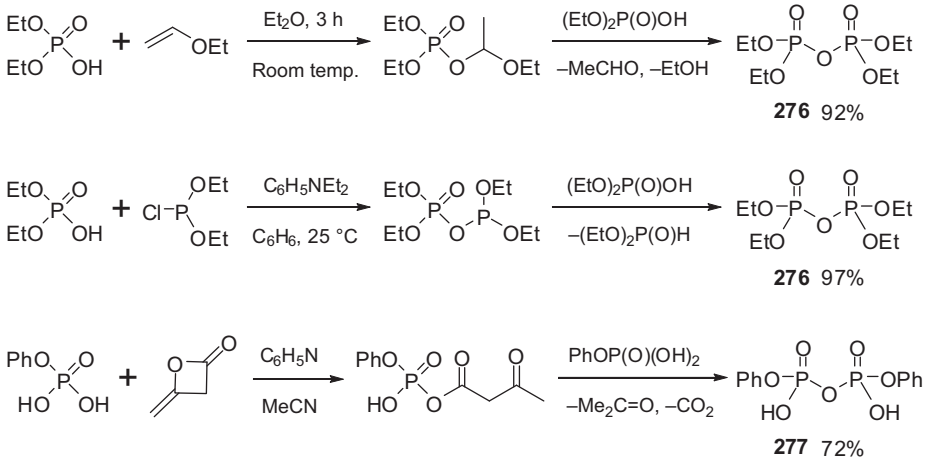


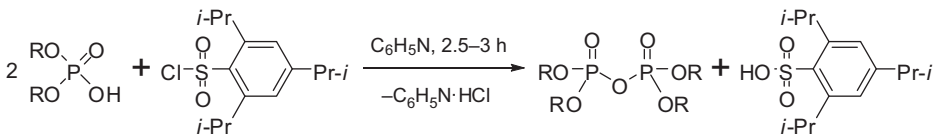
Figure 4.61.6

▶ *Tetraethyl pyrophosphate* $(EtO)_2P(O)OP(O)(OEt)_2$ (**276**) (*429*). A solution of diethyl hydrogen phosphate (5.1 g, 33 mmol) in anhydrous ether (5 ml) was added dropwise to a stirred solution of ethyl vinyl ether (2.4 g, 33 mmol) in anhydrous ether (10 ml). After 3 h at room temperature, the volatile material was evaporated and the residue was fractionated to yield tetraethyl pyrophosphate (4.5 g, 92%). Bp 148–149 °C/1.5 mmHg.

▶ *Tetraethyl pyrophosphate* $(EtO)_2P(O)OP(O)(OEt)_2$ (**276**) (*429*). A solution of diethyl phosphorochloridite (1.6 g, 10 mmol) and *N,N*-diethylaniline (1.5 g, 10 mmol) in anhydrous benzene (10 ml) was added dropwise over 8 min to a stirred solution of diethyl hydrogen phosphate (3.1 g, 20 mmol) in anhydrous benzene (15 ml). After 20 min at room temperature, the mixture was cooled to 0 °C, and the precipitate of *N,N*-diethylanilinium chloride was filtered off. The solvent was removed from the filtrate and the residue fractionated to give diethyl *H*-phosphonate (1.0 g, 72%; bp 72–74 °C/14 mmHg) and tetraethyl pyrophosphate (2.8 g, 97%). Bp 124–130 °C/0.5 mmHg.

▶ *Barium diphenyl pyrophosphate Ba[PhO(⁻O)P(O)OP(O)(O⁻)OPh]* (**277**) (*429*). A solution of ketene dimer (1.0 g, 12 mmol) in acetonitrile (5 ml) was added dropwise over 5 min to a refluxing solution of phenyl dihydrogen phosphate (3.48 g, 20 mmol) and pyridine (1.58 g, 20 mmol) in acetonitrile (5 ml). The mixture was heated under reflux for 1 h and carbon dioxide was evolved. A solution of barium chloride ($BaCl_2 \cdot 2H_2O$, 0.45 g) in water (15 ml) and pyridine (5 ml) was added to the cold reaction mixture. The resulting mixture was allowed to stand in a refrigerator for about 30 min. The white precipitate was washed twice with acetone, dried, and washed with water (50 ml). The undissolved precipitate was filtered and dried under vacuum over phosphorus pentoxide to give the barium salt (3.62 g, 72%). Acidification yielded the free pyrophosphoric acid.

Activation of a dialkyl hydrogen phosphate as a mixed phosphoric—sulfonic anhydride $(RO)_2P(O)OSO_2Ar$ by treatment with an aryl sulfonyl chloride can be used. The anhydride reacts with a second molecule of the dialkyl hydrogen phosphate under basic conditions to give the tetraalkyl pyrophosphate (*422,423*). Activation of dialkyl hydrogen phosphates by addition of 2,4,6-triisopropylbenzenesulfonyl chloride in pyridine produces a mixed anhydride. Dialkyl hydrogen phosphate attacks this at the least hindered site to give the tetraalkyl pyrophosphate in high yield (Fig. 4.61.7). Long-chain pyrophosphates (**278—280**) are purified by chromatography on silica gel to remove 2,4,6-triisopropylbenzenesulfonic acid.



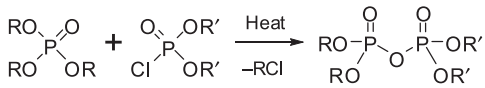
R = $Me(CH_2)_{11}$ **278** 78%
R = $Me(CH_2)_{13}$ **279** 75%
R = $Me(CH_2)_{15}$ **280** 90%

Figure 4.61.7

▶ *Tetralauryl pyrophosphate* $[Me(CH_2)_{11}O]_2P(O)OP(O)[O(CH_2)_{11}Me]_2$ (**278**) (*422,423*). 2,4,6-Triisopropylbenzenesulfonyl chloride (345 mg, 1.15 mmol) was added to a stirred mixture of dilauryl hydrogen phosphate (101 mg, 0.23 mmol) and anhydrous pyridine (0.8 ml) under nitrogen. The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with chloroform, to yield tetralauryl pyrophosphate (77 mg, 78%).

Another strategy to tetraalkyl pyrophosphates involves heating trialkyl phosphates with dialkyl phosphorochloridates. This method is less useful than methods that start with dialkyl hydrogen phosphates because several by-products can form that can lower the yield appreciably. Nevertheless this approach has been used effectively to access unsymmetrical pyrophosphates (Fig. 4.61.8) (*421,430*).

▶ *Diethyl dimethyl pyrophosphate* $(EtO)_2P(O)OP(O)(OMe)_2$ (*430*). Trimethyl phosphate (140 g, 1 mol) was heated with diethyl phosphorochloridate (86.3 g, 0.5 mol). Gaseous methyl chloride



Unsymmetrical tetraalkyl pyrophosphates

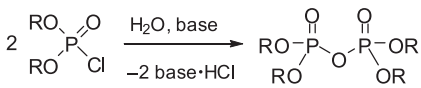
R	R′	Time (h)	Temp. (°C)	Yield (%)	Bp (°C/mmHg)
Me	Et	5.5	115–120	67	100–106/0.01–0.015
Me	*n*-Pr	4.5	120–125	70	103–106/0.02–0.05
Et	*n*-Pr	2.0	138–142	64	nd

nd = not described

Figure 4.61.8

evolved steadily at 110—112 °C. After 3.5 h, evolution of gas slowed down whereupon the temperature of the mixture was raised to 115—120 °C for 2 h, until no further reaction was noticeable. The mixture was cooled to room temperature and had lost 25.6 g in mass (theoretical loss of methyl chloride is 25.3 g). The mixture was distilled under reduced pressure, first to remove the excess trimethyl phosphate, and then to provide the product (87 g, 67%). Bp 100—106 °C/0.01—0.015 mmHg.

Another method for tetraalkyl pyrophosphate synthesis involves the reaction of two molecules of a dialkyl phosphorochloridate with one molecule of water (Fig. 4.61.9). This gives the dialkyl hydrogen phosphate which reacts with the remaining dialkyl phosphorochloridate. The reaction proceeds under reduced pressure or using bases such as pyridine or sodium bicarbonate to neutralise the hydrogen chloride and displace the equilibrium towards the pyrophosphate (*431*).



Tetraalkyl pyrophosphates

R	Base	Time (h)	Temp. (°C)	Yield (%)	Bp (°C/mmHg)
Me	pyridine	1–1.5	0–2	39	114–116/0.5
Et	-	17	25	48	135–138/1
Et	pyridine	0.3	0–35	88	nd
Et	$NaHCO_3$	2	26	41	125–130/0.5
n-Pr	pyridine	0.5	35	73	112–116/0.01
i-Pr	pyridine	-	-	94	92–95/0.01–0.02
n-Bu	pyridine	-	-	85	143–146/0.01

nd = not described

Figure 4.61.9

▶ *Tetraethyl pyrophosphate synthesis under reduced pressure* (*431*). A three-necked 500 ml flask was fitted with three rubber stoppers through which were inserted, respectively, a thermometer and a coarse capillary connected to a dropping funnel, a capillary connected to an anhydrous air source, and a connection to a vacuum distillation system. Diethyl phosphorochloridate (151 g, 0.876 mol) was added to the flask and the pressure was lowered to 8–10 mmHg. Water (7.9 g, 0.438 mol) was introduced slowly below the surface of the liquid through a capillary leading from the dropping funnel. The temperature was maintained at 31–33 °C by periodic cooling. Mixing was effected by introducing anhydrous air through the appropriate capillary. After the addition of water, which took 1–1.5 h, the system was maintained at 8 mmHg at 31–33 °C by periodic cooling, until no further heat of reaction was noted. The product was allowed to stand at room temperature at 5–8 mmHg for 17 h, heated to 60–70 °C at 6 mmHg for 30 min, and then fractionated. The lower boiling fraction was diethyl phosphorochloridate, the higher boiling fraction was the product (61 g, 48%).

▶ *Tetraethyl pyrophosphate synthesis in presence of pyridine* (*431*). A mixture of water (7.14 g, 0.396 mol) and pyridine (62.7 g, 0.794 mol) was added slowly over 1 h to stirred diethyl phosphorochloridate (133.7 g, 0.775 mol) in a 500 ml three-necked flask equipped with a thermometer, a stirrer, and a dropping funnel. The temperature was maintained at 0–2 °C using an ice-salt bath. After addition, the mixture was stirred for 20 min and then heated slowly to 35 °C for 20 min. The mixture was cooled and filtered. The residue was washed with ether. The filtrate and ether washings were combined and fractionated to give the product (99 g, 88%).

▶ *Tetraethyl pyrophosphate synthesis in presence of sodium bicarbonate* (*431*). In a 500 ml three-necked flask equipped with a thermometer, a stirrer and a condenser was placed diethyl phosphorochloridate (86.2 g, 0.50 mol), water (1 ml, 0.06 mol) and finally sodium bicarbonate (43.05 g, 0.51 mol) in one portion. After 28 min, the temperature had reached 35 °C. The mixture was then cooled and maintained at 30 °C. Reaction proceeded with evolution of carbon dioxide. After 2 h, the temperature dropped to 26 °C without external cooling. The reaction product was filtered and the residue washed with benzene. The filtrate and washings were combined, the solvent removed, and the residue distilled under reduced pressure to give tetraethyl pyrophosphate (59.5 g, 41%).

Ozone-mediated oxidation enables the conversion of tetraethyl pyrophosphorothionate (**281**) to tetraethyl pyrophosphate (**276**) cleanly in high yield (Fig. 4.61.10) (*432*). The reaction proceeds at low temperature.

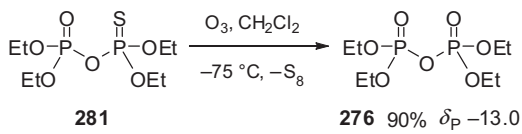


Figure 4.61.10

▶ *Tetraethyl pyrophosphate* $(EtO)_2P(O)OP(O)(OEt)_2$ (*432*). Tetraethyl pyrophosphorothionate (1.53 g, 5 mmol) was dissolved in dichloromethane (25 ml) and the solution was cooled to −75 °C.

A standardised (mol/min) ozone stream was passed through until the solution was slightly blue due to an excess of ozone. The mixture was purged with nitrogen to remove surplus ozone. The sulfur by-product was filtered off. The filtrate was washed with water (4 × 10 ml) and dried ($MgSO_4$). The solvent was removed and distillation of the residue gave the pyrophosphate (1.31 g, 90%). Bp 86 °C/0.05 mmHg. δ_P −13.0 ppm.

4.62 *BIS*(DIALKYLPHOSPHORYL) SULFIDES $(RO)_2P(O)SP(O)(OR)_2$

Bis(dialkylphosphoryl) sulfides (**282**) are toxic and care should be taken to avoid inhalation and skin contact (*433*). Strategies starting from trialkyl phosphites, dialkyl *H*-phosphonates, dialkyl hydrogen phosphates, dialkyl trimethylsilyl phosphites, and dialkyl hydrogen phosphorothioates have been devised to access them (Fig. 4.62.1) (*434*). The key to success is to use soft reagents and mild conditions to avoid the cleavage or isomerisation (to the thiono isomer) of the labile P—S—P bond.

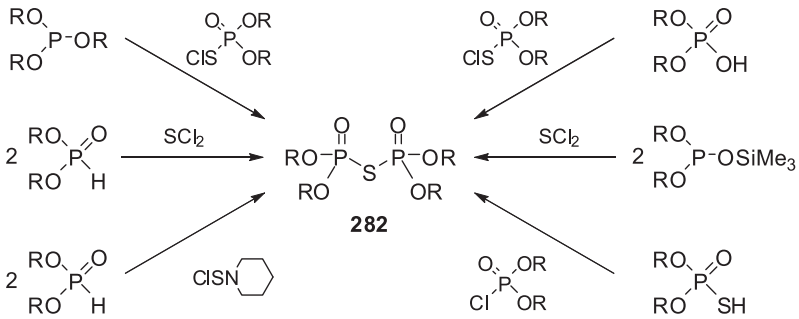
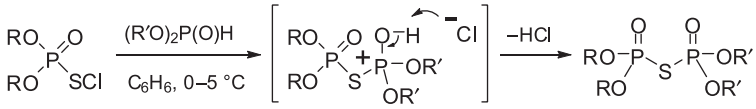


Figure 4.62.1

Dialkyl *S*-chloro phosphorothiolates obtained from trialkyl phosphites (*434*) react readily with dialkyl *H*-phosphonates (in their trivalent form) in anhydrous inert solvents (if moisture is present the sulfide product decomposes through P—S—P bond cleavage) (Fig. 4.62.2). The exothermic reaction must be carried at 5 °C to secure the pure product in high yield. Nucleophilic attack of the trivalent phosphorus atom on the dialkyl *S*-chloro phosphorothiolate sulfur atom occurs and a quasi-phosphonium intermediate forms. Then deprotonation, which is faster than dealkylation or nucleophilic attack of chloride on either the alkyl or phosphoryl group, results in dehydrochlorination and yields the expected *bis*(dialkylphosphoryl) sulfide (*435*).

▶ *Bis(diisopropylphosphoryl) sulfide* $(i\text{-}PrO)_2P(O)SP(O)(O\text{-}i\text{-}Pr)_2$ (*435*). Diisopropyl *S*-chloro phosphorothiolate (11.6 g, 50 mmol) in benzene (30 ml) was added dropwise to a solution of diisopropyl *H*-phosphonate (8.3 g, 50 mmol) in benzene (30 ml) at 0—5 °C. The solvent was evaporated under reduced pressure at below 10 °C and the residue was distilled under vacuum to give the product (18.0 g, 96%). Bp 80—96 °C/0.01 mmHg. δ_P −12.5 ppm.



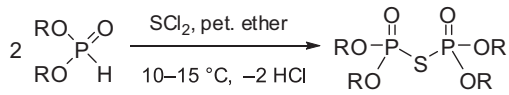
Bis(dialkylphosphoryl) sulfides

R	R′	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)
Et	Et	74	30–60/0.05	–14.3
i-Pr	*i*-Pr	96	80–96/0.01	–12.5
Et	*i*-Pr	90	80–100/0.05	–12.0, –14.3
i-Pr	Et	96	90–95/0.01	nd
Et	*n*-Bu	94	40–80/0.01	–14.5

nd = not determined

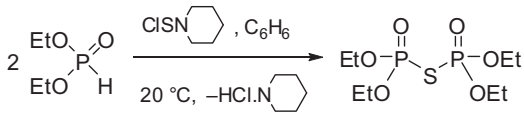
Figure 4.62.2

Treatment of 2 mol equivalents of dialkyl *H*-phosphonates with 1 mol equivalent of sulfur dichloride or piperidinylsulphenyl chloride yields *bis*(dialkylphosphoryl) sulfides in low to high yield, depending on the alkyl substituent (Fig. 4.62.3). *Bis*(dialkylphosphoryl) sulfides obtained by this method exhibit low stability and decompose readily, probably through reaction with residual traces of HCl liberated during their synthesis (*436,437*).



Bis(dialkylphosphoryl) sulfides

R	Yield (%)	Bp (°C/mmHg)
Et	100	138–139/2
n-Pr	39	-
n-Bu	49	-



283 18%

Figure 4.62.3

▶ *Bis(diethylphosphoryl) sulfide* $(EtO)_2P(O)SP(O)(OEt)_2$ (**283**) (*from diethyl H-phosphonate and sulfur dichloride*) (*436,437*). A solution of sulfur dichloride (26 g, 0.25 mol) in petroleum ether (250 ml) was

added to a stirred solution of diethyl *H*-phosphonate (80 g, 0.58 mol) in petroleum ether (250 ml) at 10–15 °C. The mixture was stirred for 1 h and then distilled to give *bis*(diethylphosphoryl) sulfide (76 g, 100%). Bp 138–139 °C/2 mmHg.

▶ *Bis(diethylphosphoryl) sulfide* $(EtO)_2P(O)SP(O)(OEt)_2$ (**283**) *(from diethyl H-phosphonate and piperidinylsulfenyl chloride)* (437). Piperidinylsulfenyl chloride (56 g, 0.37 mol) was added to a solution of diethyl *H*-phosphonate (75 g, 0.54 mol) in benzene (150 ml) at 20 °C. After addition, the solution was stirred at 30–35 °C for 3 h, and the precipitated piperidine hydrochloride was filtered off. Distillation of the filtrate gave the product (30 g, 18%). Bp 140–141 °C/2 mmHg.

Another route comprises the reaction of a dialkyl *S*-chloro phosphorothiolate with a trialkyl phosphite in an inert solvent at low temperature. Formation of a phosphonium intermediate (**284**) by nucleophilic attack on the sulfur atom of the *S*-chloro phosphorothiolate has been suggested, with alkyl chloride elimination occurring to give the pyro product (c.f. the Arbuzov reaction). This strategy, however, is disadvantageous because the *bis*(dialkylphosphoryl) sulfide forms in low yield (*pathway a*) along with related by-products, such as the tetraalkyl pyrophosphorothionate (**285**) (*pathways b and c*) (Fig. 4.62.4) (438). Pathway *c* occurs with triphenyl phosphate because nucleophilic attack by chloride on the phenyl group cannot occur.

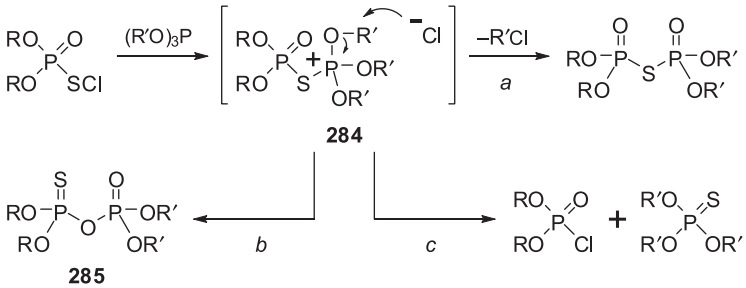
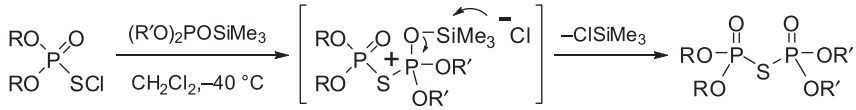


Figure 4.62.4

▶ *Bis(diethylphosphoryl) sulfide* $(EtO)_2P(O)SP(O)(OEt)_2$ (438). A solution of diethyl *S*-chloro phosphorothiolate (30.7 g, 0.15 mol) in benzene (30 ml) was added dropwise to a stirred solution of triethyl phosphite (24.9 g, 0.15 mol) in benzene (100 ml) at 0–5 °C. The temperature of the exothermic reaction was kept at 0–5 °C (ice-salt bath). The solvent was removed and the residue was distilled twice to give the product (6.9 g, 15%). Bp 85–90 °C/0.05 mmHg and subsequent bp 83–84 °C/0.05 mmHg.

▶ *Bis(di-n-propylphosphoryl) sulfide* $(n\text{-}PrO)_2P(O)SP(O)(OPr\text{-}n)_2$ (438). A solution of di-*n*-propyl *S*-chloro phosphorothiolate (23.3 g, 0.1 mol) in benzene (30 ml) was added dropwise to a stirred solution of tri-*n*-propyl phosphite (20.8 g, 0.1 mol) in benzene (100 ml) at 0–5 °C. The temperature of the exothermic reaction was kept at 0–5 °C (ice-salt bath). The volatiles were removed and the residue was distilled twice to give the product (5.8 g, 16%). Bp 87–88 °C/0.01 mmHg.

A straightforward approach to *bis*(dialkylphosphoryl) sulfide synthesis, without side reactions, involves treating dialkyl *S*-chloro phosphorothiolates with dialkyl trimethylsilyl phosphites (Fig. 4.62.5). The desired sulfide is obtained from attack of chloride on the silicon atom of the phosphonium intermediate (taking advantage of its greater leaving character compared to an alkyl group). The reaction is highly exothermic and occurs satisfactorily at −35 to −40 °C with vigorous stirring. The *bis*(dialkylphosphoryl) sulfides obtained are relatively stable, pure, and isolated in almost quantitative yield (*433*,*439*).



Bis(dialkylphosphoryl) sulfides

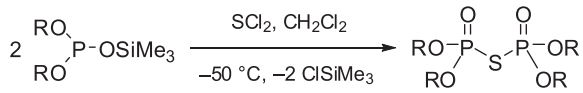
R	R′	Yield (%)	Mp (°C)	δ_P (ppm)
Me	Me	95	-	18.1
Et	Et	95	-	14.7
i-Pr	*i*-Pr	95	-	12.4
t-$BuCH_2$	*t*-$BuCH_2$	96	62–63	15.2
i-$PrCH_2CH_2$	*i*-$PrCH_2CH_2$	95	113–114	5.9
t-$BuCH_2$	*i*-$PrCH_2CH_2$	95	186–187	6.1,14.3

Figure 4.62.5

▶ *Bis(dimethylphosphoryl) sulfide* $(MeO)_2P(O)SP(O)(OMe)_2$ (*439*). A solution of dimethyl trimethylsilyl phosphite (1.82 g, 10 mmol) in dichloromethane (6 ml) was added dropwise to a stirred solution of dimethyl *S*-chloro phosphorothiolate (1.77 g, 10 mmol) in dichloromethane (5 ml) at −40 °C. The mixture was allowed to warm slowly to ambient temperature. The solvent was removed and the liquid product was chromatographed on silica gel by eluting with benzene and chloroform. The solid obtained was recrystallised from 1:1 *v*/*v* benzene—dichloromethane to give the product (2.38 g, 95%). δ_P 18.1 ppm.

Dialkyl *S*-chloro phosphorothiolates can be formed in situ by treating dialkyl trimethylsilyl phosphites (2 mol equiv.) with sulfur dichloride (1 mol equiv.). The formed dialkyl *S*-chloro phosphorothiolate reacts with the residual phosphite to give the *bis*(dialkylphosphoryl) sulfide. The reaction proceeds smoothly at low temperature and in high yield (Fig. 4.62.6) (*440*).

▶ *Bis(dimethylphosphoryl) sulfide* $(MeO)_2P(O)SP(O)(OMe)_2$ (*440*). A solution of sulfur dichloride (1.03 g, 10 mmol) in dichloromethane or ether (10 ml) was added dropwise to a stirred solution of dimethyl trimethylsilyl phosphite (3.64 g, 20 mmol) in dichloromethane or ether (10 ml) at −50 °C. The mixture was stirred until room temperature was reached. Stirring was continued for 15 min and the solvent was removed. Chromatography of the residue on silica gel, eluting with benzene and chloroform, gave the product (2.38 g, 95%). δ_P 17.8 ppm.

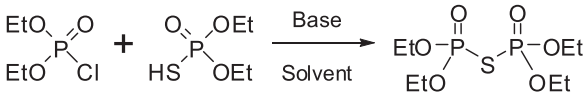


Bis(dialkylphosphoryl) sulfides

R	Yield (%)	δ_P (ppm)
Me	95	17.8
Et	85	16.0
i-Pr	90	13.7
t-Bu	95	6.1
t-BuCH$_2$	82	16.3
i-PrCH$_2$CH$_2$	91	6.7

Figure 4.62.6

A simple method to *bis*(dialkylphosphoryl) sulfides might comprise addition of dialkyl hydrogen phosphorothioates to dialkyl phosphorochloridates (Fig. 4.62.7). However, this is not recommended because of the difficulty accessing the dialkyl hydrogen phosphorothioates and the fragility of the *bis*(dialkylphosphoryl) sulfide in the presence of the released hydrochloric acid. To enhance its nucleophilicity, the dialkyl hydrogen phosphorothioate is deprotonated with sodium hydride to give a thiolate anion that attacks the dialkyl phosphorochloridate (*441*). The hydrochloric acid released is neutralised by the base. This method allows isolation of *bis*(diethylphosphoryl) sulfide (**283**), but only in low yield and purity (*442*).



283 low yield

Figure 4.62.7

4.63 *BIS*(DIALKYLPHOSPHORYL) DISULFIDES (RO)$_2$P(O)SSP(O)(OR)$_2$

One strategy for the synthesis of *bis*(dialkylphosphoryl) disulfides involves the oxidation of, for example, cyclic dialkyl hydrogen phosphorothioate (**286**) by bromine in aqueous potassium bicarbonate and dichloromethane (*443*). Reaction occurs instantaneously at room temperature to give the disulfide (**287**) in excellent yield (Fig. 4.63.1). A cyclic dialkyl hydrogen phosphorothioate is essential to prevent isomerisation to the thiono form; thus, the strategy finds limited application. Another approach involves treating 2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-thione (**288**) with sulfuryl chloride, which also yields disulfide (**287**), but this method is generally lower yielding and the product is difficult to purify (*444*).

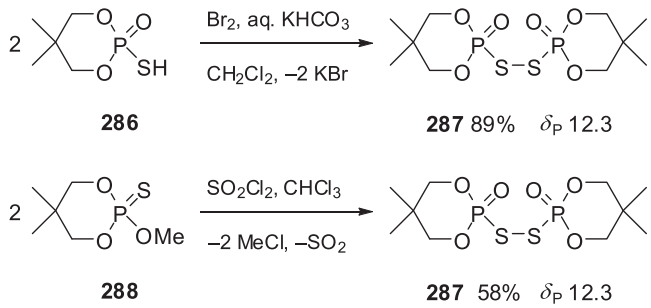


Figure 4.63.1

▷ *Bis(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl) disulfide* (**287**) (*443*). Bromine (1.6 g, 10 mmol) was added slowly to a stirred mixture of 2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-thione (1.82 g, 10 mmol), dichloromethane (20 ml) and 10% aqueous potassium bicarbonate (20 ml) in a flask immersed in a water bath. The bromine colour disappeared quickly during addition. Afterwards, the organic phase was separated, the aqueous phase was extracted with dichloromethane (20 ml), the combined organic layers were dried ($MgSO_4$), and the solvent was evaporated to give the disulfide (1.61 g, 89%). Mp 139—141 °C. δ_P 12.3 ppm.

▷ *Bis(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl) disulfide* (**287**) (*444*). Sulfuryl chloride (2.7 g, 20 mmol) in ethanol-free chloroform (10 ml) was added in portions to a solution of 2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-thione (3.9 g, 20 mmol) in chloroform (25 ml) and the mixture heated under reflux for 3 h. Evaporation of the solution left a liquid that was extracted with ethyl acetate—light petroleum to yield the disulfide (2.1 g, 58%). The potassium salt of 2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-thione (6.3 g, 29 mmol) gave the same disulfide in greater yield (4.7 g, 91%).

Another method of making *bis*(dialkylphosphoryl) disulfides involves treating a dialkyl *S*-chloro phosphorothiolate with triphenylphosphine at −100 °C (Fig. 4.63.2) (*445*). Nucleophilic addition gives a phosphonium salt (**289**) that at −80 °C eliminates dichlorotriphenylphosphorane to give the *bis*(dialkylphosphoryl) disulfide (**290**).

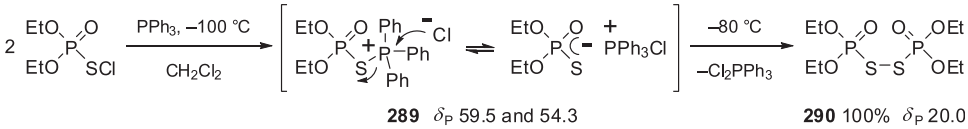


Figure 4.63.2

▷ *Bis(diethylphosphoryl) disulfide* $(EtO)_2P(O)SSP(O)(OEt)_2$ (**290**) (*445*). A solution of triphenylphosphine (5.2 g, 20 mmol) in dichloromethane (25 ml) was added dropwise to a stirred solution of

diethyl *S*-chloro phosphorothiolate (4.1 g, 20 mmol) in dichloromethane (30 ml) at −100 °C under argon. After 1.5 h, NMR spectroscopic analysis showed that the mixture comprised the pure phosphonium salt (δ_P at −80 °C: 59.5 and 54.3 ppm). Stirring was continued at room temperature for 10 min. The solvent was removed and the residue was analysed to prove formation of the title compound (100%). δ_P 20.0 ppm.

4.64 *BIS*(DIALKYLPHOSPHORYL) SULFOXIDES $(RO)_2P(O)S(O)P(O)(OR)_2$

Bis(dialkylphosphoryl) sulfoxides have been scarcely described in the literature: they were first prepared in 1950 as insecticides (*446*). *Bis*(diethylphosphoryl) sulfoxide is more effective insecticidally than analogues with other alkyl groups, but higher alkyl substituted compounds often have a prolonged action. It is desirable to design derivatives with both ethyl and propyl or butyl groups to produce insecticides with a semi-persistent action. Treatment of triethyl phosphite with half a molar equivalent of thionyl chloride provides a postulated phosphorane (**291**) that on heating loses ethyl chloride (c.f. the Arbuzov reaction) to give the *bis*(dialkylphosphoryl) sulfoxide (**292**) (Fig. 4.64.1).

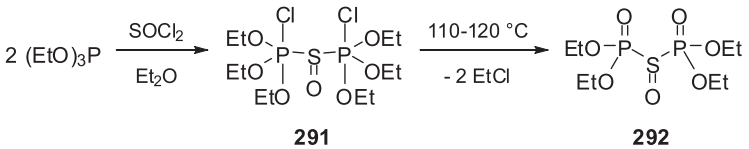


Figure 4.64.1

▶ *Bis(diethylphosphoryl) sulfoxide* $(EtO)_2P(O)S(O)P(O)(OEt)_2$ (**292**) *(from triethyl phosphite and thionyl chloride)* (*446*). Thionyl chloride (17.9 g, 150 mmol) was added dropwise to a stirred solution of triethyl phosphite (8.30 g, 50 mmol) in ether (10 ml) at 0−5 °C. The temperature was maintained below 20 °C. The ether was removed to give the postulated diphosphorane **291**. This was heated to 100−120 °C and held at this temperature for 30 min. After ethyl chloride ceased to be evolved, the heating was stopped, leaving the title compound as a water-insoluble colourless liquid (45.9 g, ∼100%).

Bis(dialkylphosphoryl) sulfoxides can also be made by treating dialkyl sodium phosphites or dialkyl *H*-phosphonates with sulfoxide-containing reagents. Alkali metal salts of dialkyl *H*-phosphonates react with ethoxysulfuryl chloride, and dialkyl *H*-phosphonates react with *N,N*-dimethylaminosulfuryl chloride, to give sulfoxides (**292**) and (**293**) (Fig. 4.64.2) (*447,448*).

▶ *Bis(diethylphosphoryl) sulfoxide* $(EtO)_2P(O)S(O)P(O)(OEt)_2$ (**292**) *(from diethyl sodium phosphite and ethoxysulfuryl chloride)* (*448*). Diethyl *H*-phosphonate (71 g, 0.5 mol) was converted into diethyl sodium phosphite by reaction with powdered sodium (11.5 g, 0.5 mol) in benzene (200 ml). To this was added ethoxysulphuryl chloride (71 g, 0.6 mol). After 1 h at 60 °C, the mixture was cooled to room temperature and sodium chloride was removed. The filtrate was distilled to give the product (40 g, 50%). Bp 66−70 °C/0.01 mmHg.

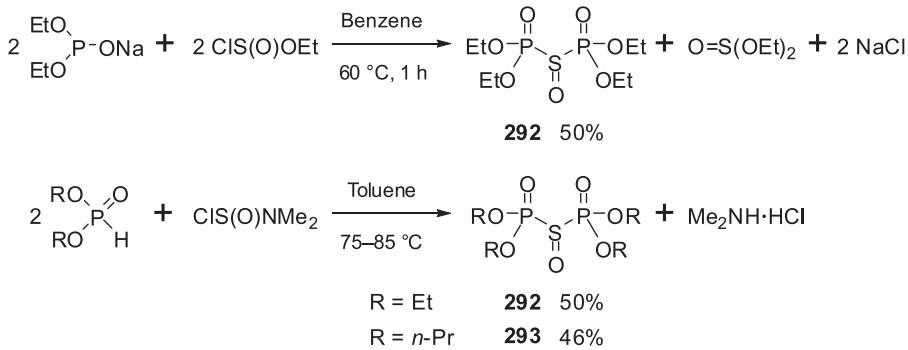


Figure 4.64.2

▶ *Bis(diethylphosphoryl) sulfoxide* $(EtO)_2P(O)S(O)P(O)(OEt)_2$ (**292**) *(from diethyl H-phosphonate and N,N-dimethylaminosulfuryl chloride)* (447). A solution of *N,N*-dimethylaminosulfuryl chloride (64 g, 0.5 mol) in toluene (60 ml) was added to a stirred solution of diethyl *H*-phosphonate (70 g, 0.5 mol) in toluene (100 ml). The mixture was stirred at 85 °C then cooled to room temperature. Dimethylamine hydrochloride was removed and the filtrate was distilled to give the product (40 g, 50%). Bp 65–70 °C/0.01 mmHg.

▶ *Bis(di-n-propylphosphoryl) sulfoxide* $(n\text{-}PrO)_2P(O)S(O)P(O)(OPr\text{-}n)_2$ (**293**) *(from di-n-propyl H-phosphonate and N,N-dimethylaminosulfuryl chloride)* (447). A solution of *N,N*-dimethylaminosulfuryl chloride (64 g, 0.5 mol) in toluene (60 ml) was added to a stirred solution of di-*n*-propyl *H*-phosphonate (83 g, 0.5 mol) in toluene (100 ml). The mixture was stirred at 70 °C for 30 min and then cooled to room temperature. Dimethylamine hydrochloride was removed and the filtrate was distilled to give the sulfoxide (86 g, 46%). Bp 90–95 °C/0.01 mmHg.

4.65 *N*-ALKYLPHOSPHORAMIDIC DICHLORIDES $RNHP(O)Cl_2$

Treating phosphorus oxychloride with 2 mol of an amine, or in the case of an expensive amine, 1 mol of it and 1 mol of triethylamine, provides *N*-alkylphosphoramidic dichlorides (e.g. **294**) generally in acceptable yields (Fig. 4.65.1) (*306*). Bases other than triethylamine, e.g. pyridine or *N,N*-diethylaniline, can be employed. The *N*-alkylphosphoramidic dichlorides can be used to prepare diamido or triamido derivatives with similar or different groups. Some *N*-alkylphosphoramidic dichlorides with non-fluorinated alkyl groups, e.g. $MeNHP(O)Cl_2$, are unstable during distillation and difficult to obtain pure (*449*).

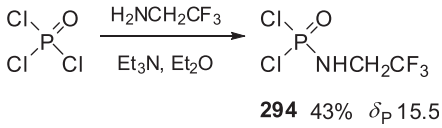
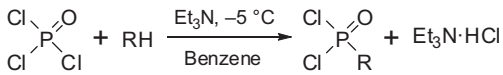


Figure 4.65.1

▶ *N-(2,2,2-Trifluoroethyl)phosphoramidic dichloride* $CF_3CH_2NHP(O)Cl_2$ (**294**) (*306*). A solution of 2,2,2-trifluoroethylamine (5.9 g, 60 mmol) and triethylamine (8.4 ml, 60 mmol) in ether (50 ml) was added dropwise to a stirred solution of phosphorus oxychloride (9.1 g, 60 mmol) in ether (50 ml) at 0–5 °C. After addition, the mixture was allowed to warm to room temperature and was left for 14 h. The precipitated triethylamine hydrochloride was filtered off and the filtrate was concentrated to reveal a liquid. Kugelrohr distillation gave a colourless liquid (5.6 g, 43%). Bp 62 °C/0.02 mmHg. δ_P (202 MHz, $CDCl_3$) 15.5 ppm.

4.66 *N,N*-DIALKYLPHOSPHORAMIDIC DICHLORIDES $R_2NP(O)Cl_2$

These compounds are commonly prepared by adding 2 mol of a secondary amine, or 1 mol each of the reacting amine and a tertiary amine (e.g. triethylamine), to 1 mol of phosphorus oxychloride in an inert solvent at temperatures between 0 and 5 °C or lower (Fig. 4.66.1) (*16,188,450–453*). In this way, it is easy to obtain *N,N*-dialkylphosphoramidic dichlorides from symmetrical and unsymmetrical secondary amines (*453*).



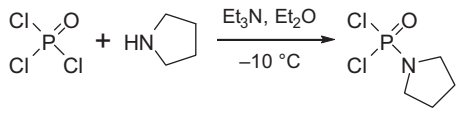
N,N-Dialkylphosphoramidic dichlorides

R	Bp (°C/mmHg) [a]
NMe_2	90/21
NEt_2	76/2
N(*n*-Pr)$_2$	89/1
N(*i*-Pr)$_2$	86/1
NMeEt	82/1.5
NMe(*n*-Pr)	78/2
NMe(*i*-Pr)	88/1.5
NEt(*n*-Pr)	80/1
NEt(*i*-Pr)	92/1
N(*n*-Pr)*i*-Pr	82/1

a. Yields not stated but expected to be high

Figure 4.66.1

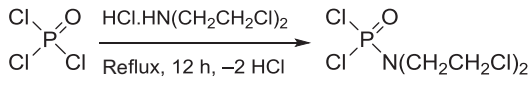
Phosphorus oxychloride also reacts with cyclic amines in the presence of triethylamine in ether to afford dichlorides with cyclic amide groups, e.g. *N*-pyrrolidinylphosphoramidic dichloride (**295**) (Fig. 4.66.2) (*454*).



295 90%

Figure 4.66.2

Another method of *N,N*-dialkylphosphoramidic dichloride formation involves heating under reflux a secondary amine hydrochloride with an excess of phosphorus oxychloride for a protracted time. *N,N*-Dimethylphosphoramidic dichloride $Me_2NP(O)Cl_2$ can be prepared by refluxing pure dimethylamine hydrochloride with an excess of phosphorus oxychloride until evolution of hydrogen chloride ceases. Fractionation of the residue under reduced pressure provides the target dichloride (*449*). To ensure good yields, the dimethylamine hydrochloride used must be dry. *N,N*-Di(2-chloroethyl)phosphoramidic dichloride (**296**), a precursor to the anticancer drug cyclophosphamide (Chapter 1; Section 1.8), is prepared similarly (Fig. 4.66.3) (*455*).

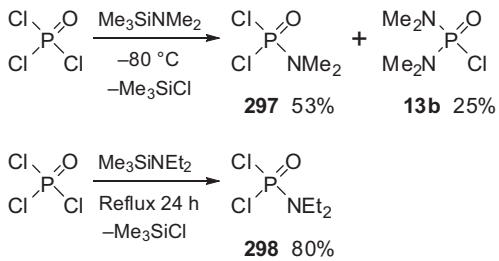


excess

296 80%

Figure 4.66.3

N,N-Dialkylphosphoramidic dichlorides can also be prepared from phosphorus oxychloride and dialkylaminotrimethylsilanes (Fig. 4.66.4) (*456*). Dimethylaminotrimethylsilane at −80 °C provides a 2:1 mixture of *N,N*-dimethylphosphoramidic dichloride (**297**) and *N,N,N′,N′*-tetramethylphosphorodiamidic chloride (**13b**) separable by distillation. Diethylaminotrimethylsilane is less reactive and requires heating under reflux to give *N,N*-diethylphosphoramidic dichloride (**298**) more selectively, partly as a result of the larger size of the diethylamino group.



297 53% **13b** 25%

298 80%

Figure 4.66.4

▷ *N,N-Dimethylphosphoramidic dichloride $Me_2NP(O)Cl_2$ (from phosphorus oxychloride and dimethylamine hydrochloride)* (*58*). Dimethylamine hydrochloride (8.2 g, 0.1 mol) was refluxed with phosphorus oxychloride (38.4 g, 0.25 mol) for 18–24 h until hydrogen chloride evolution slowed. The product was fractionated under reduced pressure to yield unreacted phosphorus oxychloride and the title compound (14.6 g, 90%). Bp 48 °C/1 mmHg.

▷ *N,N-Dialkylphosphoramidic dichlorides $R_2NP(O)Cl_2$ (from phosphorus oxychloride and the dialkylamine)* (*453*). A solution of phosphorus oxychloride (0.1 mol) in anhydrous benzene was added over 1 h to a stirred solution of the dialkylamine (0.1 mol) and triethylamine (0.1 mol) in anhydrous benzene at −5 °C. The mixture was stirred at room temperature for 4 h. Triethylamine hydrochloride was filtered off and the solvent was removed. Distillation under reduced pressure gave the products listed in Fig. 4.66.1.

▷ *N,N-Dimethylphosphoramidic dichloride $Me_2NP(O)Cl_2$ (from phosphorus oxychloride and dimethylaminotrimethylsilane)* (*456*). Dimethylaminotrimethylsilane (15.22 g, 0.13 mol) was added dropwise to phosphorus oxychloride (19.96 g, 0.13 mol) at −80 °C. After a vigorous reaction, distillation gave chlorotrimethylsilane (90%) and subsequent vacuum fractionation of the residue gave the title compound (11.20 g, 53%; bp 76 °C/10 mmHg) and crude *N,N,N′,N′*-tetramethylphosphorodiamidic chloride (5.30 g, 25% based on the aminosilane). *N,N*-Dimethylphosphoramidic dichloride is a colourless liquid with a fruity odour. It is soluble in ether, benzene, ethanol and chlorinated solvents, and slightly soluble in water.

▷ *N,N-Diethylphosphoramidic dichloride $Et_2NP(O)Cl_2$ (from phosphorus oxychloride and diethylamine)* (*16*). A solution of diethylamine (73 g, 1 mol) in ether (300 ml) was added dropwise with stirring to phosphorus oxychloride (77 g, 0.5 mol) at 0–5 °C. After addition, the reaction mixture was allowed to warm to room temperature, and was stirred for a further 2.5 h. The ether was removed and more phosphorus oxychloride (240 g, 1.57 mol) was added. The stirred mixture was boiled for 6 h. Excess phosphorus oxychloride was removed by distillation (bp 106 °C) and the residue distilled under reduced pressure, yielding the title compound as a colourless liquid with a pungent aromatic odour (72 g, 76%). Bp 94–105 °C/14 mmHg (lit. bp 104 °C/12 mmHg (*451*)). These homologues were prepared similarly: *n*-$Pr_2NP(O)Cl_2$ (bp 127 °C/14 mmHg) and *n*-$Bu_2NP(O)Cl_2$ (bp 78 °C/0.06 mmHg) (*451*).

▷ *N-Pyrrolidinylphosphoramidic dichloride $(CH_2)_4NP(O)Cl_2$* (**295**) *(from phosphorus oxychloride and the amine)* (*454*). A solution of pyrrolidine (7.1 g, 0.1 mol) and triethylamine (10.1 g, 0.1 mol) in ether (150 ml) was added dropwise to a stirred solution of phosphorus oxychloride (15.4 g, 0.1 mol) in ether (50 ml) at −10 °C. After 5 h at room temperature, the triethylamine hydrochloride was filtered off and the filtrate was concentrated. Distillation of the residue gave a pale-yellow liquid (17.0 g, 90%). Bp 63–65 °C/0.2 mmHg.

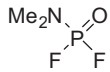
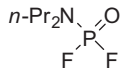
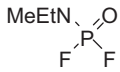
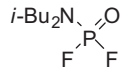
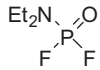
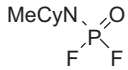
▷ *N,N-Di(2-chloroethyl)phosphoramidic dichloride $(ClCH_2CH_2)_2NP(O)Cl_2$* (**296**) *(from phosphorus oxychloride and the amine hydrochloride)* (*455*). A suspension of *bis*(2-chloroethyl)amine hydrochloride (50 g, 0.28 mol) in distilled phosphorus oxychloride (130 ml, 1.39 mol) was heated under reflux for 12 h until complete dissolution resulted. The excess phosphorus oxychloride was removed by

distillation (bp 106 °C) and the residue was distilled under reduced pressure. The fraction boiling between 123 and 125 °C/0.6 mmHg was collected as a colourless liquid that crystallised on cooling to give a solid (58 g, 80%). Recrystallisation from acetone—petroleum ether gave, after standing in the cold, large prisms. Mp 54—56 °C.

4.67 *N,N*-DIALKYLPHOSPHORAMIDIC DIFLUORIDES $R_2NP(O)F_2$

Schrader showed that the interaction of *N,N*-dimethylphosphoramidic difluoride $Me_2NP(O)F_2$ with water or alcohols results in displacement of dimethylamine and the formation of products of structure $ROP(O)F_2$, where R is H or alkyl (*58*,*449*). This was confirmed by British (*457*) and Russian chemists (*458*). Some difluorides prepared by Schrader (*58*) and others (*451*) are shown in Fig. 4.67.1. The dichloride is stirred for 24 h with 2 mol equivalents of sodium fluoride in benzene at 20—30 °C prior to fractionation. Triethylamine hydrofluoride in ether can also be used to effect the same transformation (*5*).

N,N-dialkylphosphoramidic difluorides prepared by Schrader (*58*)

Compound	Bp (°C/mmHg)	Compound	Bp (°C/mmHg)
	28/10		84/21
	35/10		98/17
	46/9		103/13

Cy = cyclohexyl

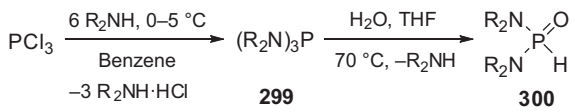
Figure 4.67.1

▶ *N,N-Dimethylphosphoramidic difluoride $Me_2NP(O)F_2$* (*5*). Triethylamine (4.04 g, 40 mmol) was added to a solution of triethylamine trihydrofluoride (3.22 g, 20 mmol) in ether (250 ml) in a 250 ml three-necked flask. The reaction was exothermic and triethylamine hydrofluoride precipitated as a solid. It was broken up with a glass rod to give a fine suspension upon stirring. The centre neck was fitted with a pressure-equalising dropping funnel with a gas bubbler. The outer necks were fitted with septa, one of which was pierced by an argon entry needle. To the funnel, *N,N*-dimethylphosphoramidic dichloride (4.86 g, 30 mmol) in ether (75 ml) was added. The flask was cooled to 0 °C and the dichloride added dropwise with stirring over 40 min. Stirring was continued for 1 h at 0 °C and for a further 2 h at room temperature. The mixture was left under argon for 12 h. The clear liquid was

decanted from the mixture through a thin layer of Celite® in a sinter funnel. Ether (80 ml) was added to the residue, which was shaken, and the liquid (and some solid) was decanted into the filter and this procedure was repeated about five times until all the solid was in the funnel. The precipitate was rinsed with more ether and the filtrate was concentrated on a rotary evaporator (2.4 g crude product). The procedure was repeated and the crude products were combined and distilled at reduced pressure in a microdistillation apparatus with a single receiver flask cooled in a dry-ice acetone-slush bath. The title compound was isolated as a colourless mobile liquid (3.28 g, 42%). Bp 23 °C/20 mmHg (oil pump with an adjustable air bleed). δ_P (121.5 MHz, $CDCl_3$) −4.5 ppm (t, $^1J_{PF}$ 999 Hz). δ_F (282 MHz, $CDCl_3$) −79.7 ppm (d, $^1J_{PF}$ 999 Hz).

4.68 *N,N,N′,N′*-TETRAALKYL PHOSPHORODIAMIDITES $(R_2N)_2P(O)H$

Interest in the synthesis and chemistry of $R_2N{-}P$ compounds arises from the versatility of their chemical transformations, enabled by the many ways of causing N−P bond rupture. Key starting materials include tris(dialkylamino)phosphines (**299**). These are prepared from phosphorus trichloride and 6 M equivalents of a dialkylamine in an inert solvent (Fig. 4.68.1) (*459,460*). Treatment of the tris(dialkylamino)phosphines with a mole of water in THF displaces a mole of dialkylamine and gives the *N,N,N′,N′*-tetraalkyl phosphorodiamidites (**300**). Hydrolysis occurs rapidly and exothermically at 70 °C. This route offers a simple and attractive way of preparing the desired products, which are purified by distillation at low pressure.



Tris(dialkylamino)phosphines			Tetraalkyl phosphorodiamidites	
R	Yield (%)	Bp (°C/mmHg)	Yield (%)	Bp (°C/mmHg)
Me	60	62–63/20	60	56–57/1.3
Et	80	72–74/0.6	60	54–55/0.03
n-Pr	82	83–84/0.02	95	100–105 [a]
n-Bu	68	104–105/0.005	94	100–105 [a]

a. Bath temperature for short-path distillation apparatus at 0.001 mmHg

Figure 4.68.1

Another route to *N,N,N′,N′*-tetraalkyl phosphorodiamidites involves heating a 2:1 mol ratio of tris(dialkylamino)phosphines and phosphorus trichloride (Fig. 4.68.2) (*460*). Tris(diethylamino) phosphine furnishes *N,N,N′,N′*-tetraethyl phosphorodiamidochloridite (**301**) which on careful hydrolysis provides *N,N,N′,N′*-tetraethyl phosphorodiamidite (**302**). The two-step procedure is

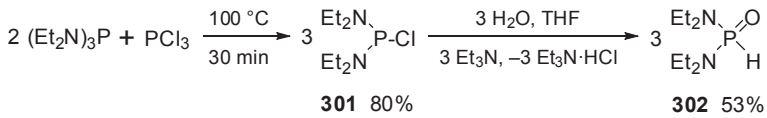


Figure 4.68.2

however of limited interest due to a low overall yield (40%) and contamination of the final product with triethylamine hydrochloride.

Alternative methods of synthesis of *N,N,N′,N′*-tetraethyl phosphorodiamidite (**302**) include the reaction of tris(diethylamino)phosphine with phosphorous acid (*460*) or that of diethyl *H*-phosphonate with a molar equivalent of titanium tetrakis(diethylamide) (Fig. 4.68.3) (*461*). The latter process requires aqueous work-up and extraction with dichloromethane prior to distillation.

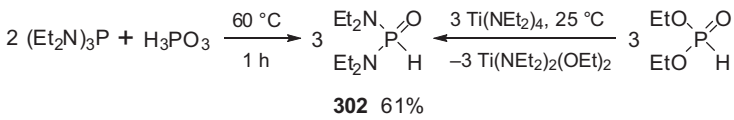


Figure 4.68.3

N,N,N′,N′-Tetraalkyl phosphorodiamidites are colourless high-boiling liquids that are readily soluble in water and organic solvents (*460*). The diamidites are thermally unstable and acquire an orange-brown colour at room temperature, especially when impure. When heated to 130–150 °C, they decompose rapidly and extensively, depositing copious yellowish-brown precipitate. In the pure state, they can be stored at 0–5 °C for indefinite periods of time without appreciable change. Like dialkyl *H*-phosphonates (Section 4.18), they exist predominantly in the *H*-phosphonate form. Their infrared spectra contain a band at 1200–1220/cm for the P═O group and a sharp band of medium intensity at 2320/cm for the P–H stretching vibrations. Further evidence for the $(R_2N)_2P(O)H$ structure is provided by the reactions of *N,N,N′,N′*-tetraalkyl phosphorodiamidites with *N*-chlorosuccinimide which yield *N,N,N′,N′*-tetraalkyl phosphorodiamidochloridates $(R_2N)_2P(O)Cl$ (Section 4.69).

▶ *Tris(dialkylamino)phosphines* $(R_2N)_3P$ (**299**) (*460*). Phosphorus trichloride (68.8 g, 0.5 mol) in benzene (150 ml) was added dropwise to an efficiently stirred solution of the appropriate dialkylamine (3.3 mol) in benzene (1000 ml) at 0–5 °C. With dimethylamine, the addition was conducted at −5 °C. The reaction mixture was then stirred at 30–40 °C for 2 h, and the dialkylamine hydrochloride was filtered off under suction, and washed with benzene (2 × 200 ml). The solvent was removed from the filtrate and the residue was distilled under reduced pressure to give the pure tris(dialkylamino)phosphine as a pale-yellow or colourless liquid: $(Me_2N)_3P$ (60%; bp 62–63 °C/20 mmHg), $(Et_2N)_3P$ (80%; bp 72–74 °C/0.6 mmHg; bath temp. 110–115 °C); $(n\text{-}Pr_2N)_3P$ (82%; bp 83–84 °C/0.02 mmHg; bath temp. 125 °C), and $(n\text{-}Bu_2N)_3P$ (68%; bp 104–105 °C/0.005 mmHg; bath temp. 165–170 °C).

▶ *N,N,N′,N′-Tetraalkyl phosphorodiamidites* $(R_2N)_2P(O)H$ *(from tris(dialkylamino)phosphines and water)* (460). A solution of the tris(dialkylamino)phosphine (50 mmol) in THF (15 ml) was added to a three-necked flask fitted with a dropping funnel, a mechanical stirrer and a reflux condenser. The stirred solution was heated to about 70 °C (gentle reflux). The external heating bath was then removed and a solution of water (0.9 ml, 50 mmol) in THF (5 ml) was added at a sufficient rate to maintain a gentle reflux of the reaction mixture. After addition, stirring was continued for 5 min, and the solvent was removed under reduced pressure. The residue was distilled under high vacuum in a short-path distillation apparatus (bath temperature < 100–105 °C) to give the product.

▶ *N,N,N′,N′-Tetraethyl phosphorodiamidochloridite* $(Et_2N)_2PCl$ (**301**) *(from tris(diethylamino)phosphine and phosphorus trichloride)* (460). Phosphorus trichloride (17.2 g, 125 mmol) was added dropwise over 15 min to stirred tris(diethylamino)phosphine (61.8 g, 250 mmol). Once the strongly exothermic reaction ceased, the mixture was kept at 100 °C for 30 min and distilled to give a colourless mobile liquid (62.5 g, 80%). Bp 63–64 °C/0.6 mmHg (bath temperature 100 °C). *Caution!* This compound ignites spontaneously and explodes if added to water.

▶ *N,N,N′,N′-Tetraethyl phosphorodiamidite* $(Et_2N)_2P(O)H$ (**302**) *(from controlled hydrolysis of N,N,N′,N′-tetraethyl phosphorodiamidochloridite)* (460). A solution of water (1.8 g, 0.1 mol) in THF (10 ml) was added dropwise to a stirred solution of *N,N,N′,N′*-tetraethyl phosphorodiamidochloridite (21.1 g, 0.1 mol) and triethylamine (10.1 g, 0.1 mol) in benzene (100 ml) at 30–40 °C. The mixture was kept at this temperature for 2 h, filtered, and the filtrate distilled under vacuum to yield a colourless liquid (10.1 g, 53%). Bp 59–60 °C/0.08 mmHg (bath temperature 85–95 °C). The product deposited some crystals of triethylamine hydrochloride on standing.

▶ *N,N,N′,N′-Tetraethyl phosphorodiamidite* $(Et_2N)_2P(O)H$ (***302***) *(from tris(diethylamino)phosphine and phosphorous acid)* (460). Tris(diethylamino)phosphine (14.6 g, 60 mmol) was mixed with anhydrous phosphorous acid (2.46 g, 30 mmol), stirred for 1 h at 60 °C, and then left at room temperature for 12 h. Distillation of the resulting yellow-brown solution gave a colourless liquid (10.5 g, 61%). Bp 55–56 °C/0.05 mmHg (bath temp. 95–100 °C).

4.69 *N,N,N′,N′*-TETRAALKYL PHOSPHORODIAMIDOCHLORIDATES $(R_2N)_2P(O)Cl$

Phosphorus oxychloride reacts with 4 mol of a primary amine to produce *N,N′*-dialkyl(or diaryl) phosphorodiamidic dichlorides such as **303** or **304** (Fig. 4.69.1) (*106,462*).

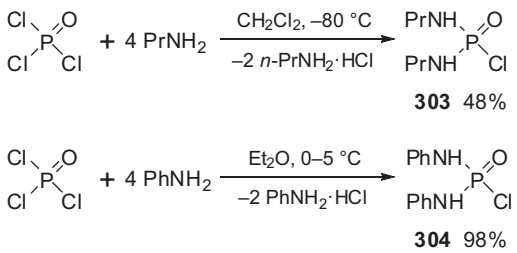


Figure 4.69.1

Treatment of phosphorus oxychloride with 4 mol of dimethylamine provides *N,N,N′,N′*-tetramethylphosphorodiamidic chloride (**13b**) (Fig. 4.69.2) (*106*). Alternatively, *N,N*-dimethylphosphoramidic dichloride, the intermediate in the last reaction, can be treated with 2 mol of dimethylamine to give the same product (*463*). In both cases, the yields are high. It is also possible to use 2 mol each of a secondary amine and triethylamine in diethyl ether, as in the synthesis of *N,N′*-di(pyrrolidinyl)phosphorodiamidic chloride (**305**) (*454*). Bulky amines can react slowly and heating in a high boiling solvent may be necessary to drive the reaction to completion.

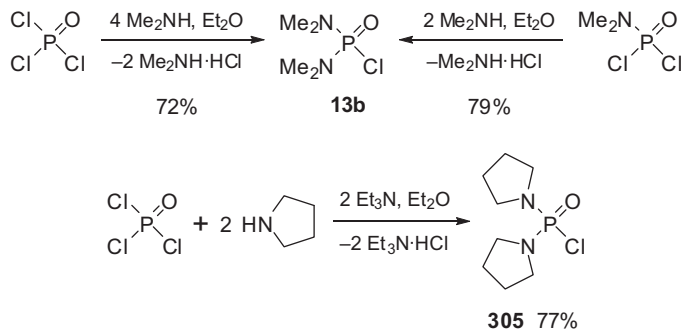


Figure 4.69.2

Transferring dialkylamino groups to phosphoryl chlorides can be achieved with dialkylaminotrimethylsilanes. Phosphorus oxychloride and diethylaminotrimethylsilane react at room temperature to give *N,N,N′,N′*-tetraethylphosphorodiamidic chloride (**306**) and chlorotrimethylsilane (Fig. 4.69.3) (*456*).

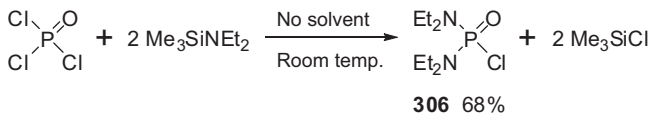


Figure 4.69.3

N,N,N′,N′-Tetraethyl phosphorodiamidite (**302**) reacts with *N*-chlorosuccinimide in warm carbon tetrachloride to yield *N,N,N′,N′*-tetraethyl phosphorodiamidochloridate (**306**) in acceptable yield (Fig. 4.69.4) (*460*). The choice of chlorinating reagent to effect such a transformation is crucial as those that produce hydrogen chloride are likely to cleave the P—N bonds of the starting material and

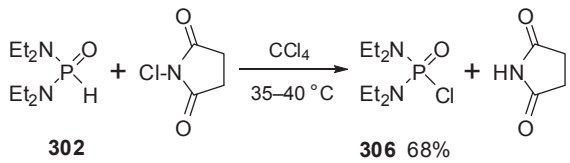


Figure 4.69.4

product. *N*-Chlorosuccinimide produces neutral succinimide that does not degrade the other components of the reaction mixture.

▶ *N,N′-Di-n-propylphosphorodiamidic dichloride (n-PrNH)$_2$P(O)Cl* (**303**) (*462*). A solution of *n*-propylamine (47.6 ml, 0.6 mol) in dichloromethane (100 ml) was added dropwise over 2 h to a stirred solution of phosphorus oxychloride (18.2 ml, 0.2 mol) in dichloromethane (300 ml) at −80 °C. After several hours at −80 °C, the solution was allowed to warm to room temperature, then cooled to 0 °C, and extracted twice with ice water. More dichloromethane was added as required to keep the products in solution. The dichloromethane phase was separated and dried ($MgSO_4$). Addition of ether and cooling to −80 °C under nitrogen caused crystallisation. The crude product was recrystallised under nitrogen from dichloromethane—ether to yield fluffy white crystals (16.6 g, 48%). Mp 104.2—104.8 °C.

▶ *N,N′-Diphenylphosphorodiamidic chloride (PhNH)$_2$P(O)Cl* (**304**) (*106*). A solution of aniline (37.2 g, 0.4 mol) in ether (50 ml) was added slowly to phosphorus oxychloride (15.3 g, 0.1 mol) in ether (50 ml) at 0—5 °C. After addition, the mixture was allowed to warm to room temperature and was left for 12 h. Aniline hydrochloride was filtered off and the filtrate was washed with water. The usual work-up and recrystallisation from ethanol gave the product (26.1 g, 98%). Mp 167 °C.

▶ *N,N,N′,N′-Tetramethylphosphorodiamidic chloride (Me$_2$N)$_2$P(O)Cl* (**13b**) *(from phosphorus oxychloride)* (*106*). A solution of phosphorus oxychloride (15.4 g, 0.1 mol) in ether (60 ml) was added dropwise over 1 h to a stirred solution of anhydrous dimethylamine (18.0 g, 0.4 mol) in ether (60 ml) cooled using a solid carbon dioxide-methylated spirit bath. A vigorous reaction occurred. After addition, the mixture was left at room temperature for 12 h and the dimethylamine hydrochloride precipitate was filtered off. The ether was removed and the residue was fractionated to give the title compound (12.3 g, 72%). Bp 79—82 °C/0.6 mmHg. δ_P −30 ppm (*249*). *N,N,N′,N′*-Tetraethylphosphorodiamidic chloride (Et$_2$N)$_2$P(O)Cl (bp 142—144 °C/12 mmHg, lit. bp 101 °C/0.3 mmHg (*451*)) was prepared similarly in approximately the same yield. Other analogues were likewise prepared: [(*n*-Pr)$_2$N]$_2$P(O)Cl (bp 118 °C/0.2 mmHg) and [(*n*-Bu)$_2$N]$_2$P(O)Cl (bp 144 °C/0.4 mmHg) (*451*).

▶ *N,N,N′,N′-Tetramethylphosphorodiamidic chloride (Me$_2$N)$_2$P(O)Cl* (**13b**) *(from phosphorus oxychloride)* (*16*). A solution of *N,N*-dimethylphosphoramidic dichloride (162 g, 1 mol) in anhydrous ether (100 ml) was added dropwise to a stirred solution of dimethylamine (90 g, 2 mol) in anhydrous ether (450 ml) at 0—5 °C. After addition the mixture was left at room temperature for 12 h. Dimethylamine hydrochloride was removed by filtration and washed with ether. The filtrate and washings were combined and concentrated. Vacuum distillation of the residue gave a colourless liquid (135 g, 79%). Bp 96—102 °C/6—7 mmHg. It is soluble in water and most organic solvents.

▶ *N,N′-Di(pyrrolidinyl)phosphorodiamidic chloride [(CH$_2$)$_4$N]$_2$P(O)Cl* (**305**) (*454*). A solution of pyrrolidine (7.73 g, 0.11 mol) and triethylamine (11.00 g, 0.11 mol) in ether (150 ml) was added dropwise to a stirred solution of phosphorus oxychloride (8.36 g, 0.055 mol) in ether (50 ml) at 0 °C. After 20 h at room temperature, triethylamine hydrochloride was filtered off and the filtrate was concentrated. Recrystallisation of the residue from petroleum ether (bp 40—60 °C) gave the product (9.3 g, 77%). Mp 32—35 °C.

▶ *N,N,N′,N′-Tetraethylphosphorodiamidic chloride* $(Et_2N)_2P(O)Cl$ (**306**) *(diethylaminotrimethylsilane method)* (*456*). Diethylaminotrimethylsilane (11.66 g, 80.41 mmol) was added slowly to stirred phosphorus oxychloride (4.12 g, 26.84 mmol) at room temperature. Slight warming occurred on standing. After 24 h, distillation gave chlorotrimethylsilane (60%). Vacuum fractionation of the residue gave the title compound (4.20 g, 68%). Bp 79 °C/0.03 mmHg.

▶ *N,N,N′,N′-Tetraethylphosphorodiamidic chloride* $(Et_2N)_2P(O)Cl$ (**306**) *(from N,N,N′,N′-tetraethyl phosphorodiamidite and N-chlorosuccinimide)* (*460*). Finely powdered *N*-chlorosuccinimide (6.7 g, 50 mmol) was added in portions to a stirred solution of *N,N,N′,N′*-tetraethyl phosphorodiamidite (9.6 g, 50 mmol) in carbon tetrachloride (50 ml). The temperature of the exothermic reaction was maintained at 35–40 °C. The mixture was then stirred for 1 h at room temperature and refrigerated overnight. Succinimide was filtered off and the filtrate was distilled under vacuum to give a colourless liquid (7.7 g, 68%). Bp 69–70 °C/0.02 mmHg (bath temp. 110–115 °C).

4.70 *BIS*(*N*-ALKYL) OR *N,N,N′,N′*-TETRAALKYL PHOSPHORODIAMIDOFLUORIDATES $(R_2N)_2P(O)F$

These compounds, typified by the pesticides mipafox $(i\text{-PrNH})_2P(O)F$ and dimefox $(Me_2N)_2P(O)F$, can cause delayed neurotoxicity (Chapter 1.10.2.3) (*463*) and should be handled with care. Synthetic routes to dimefox and analogues first discovered by Schrader (*58*) include reactions of *N,N*-dialkylphosphoramidic difluorides with aliphatic amines, *N,N*-dialkylphosphoramidic dichlorides with aliphatic amines and sodium fluoride, and *N,N,N′,N′*-tetraalkyl phosphorodiamidochloridates with sodium fluoride in an organic solvent or aqueous potassium fluoride (Fig. 4.70.1) (*463–465*). Aqueous fluorination is tolerated as *N,N,N′,N′*-tetraalkyl phosphorodiamidochloridates and the fluoridate products resist hydrolysis under neutral conditions (*466,467*). Dimefox is also produced in 67% yield by treating phosphorus oxydichlorofluoride ($POCl_2F$) with an excess of dimethylamine in ether (*468*), on a small scale by treating *N,N,N′,N′*-tetramethylphosphorodiamidic chloride with Amberlyst® A-26 fluoride resin in THF (*120*), and as a by-product from the reaction of hexamethylphosphoramide (HMPA) with hexafluorobenzene (*469*) or schradan with potassium bifluoride (*58*). ^{32}P-Dimefox (*470*) and its ^{18}F homologue (*471*) have been prepared as radiotracers for use in biological systems. Some symmetrical and unsymmetrical dimefox analogues reported by Schrader appear in Fig. 4.70.2 (*58*). Other examples of unsymmetrical variants have also been reported (*470*).

Dimefox and related analogues are generally poor inhibitors of acetylcholinesterase (*472*) compared to dialkyl phosphorofluoridates, e.g. $(i\text{-PrO})_2P(O)F$ (*225,226*), and are thought to undergo *N*-oxidation to more active AChE inhibitors through metabolism in vivo.

▶ *N,N,N′,N′-Tetramethyl phosphorodiamidofluoridate (dimefox, from N,N-dimethylphosphoramidic difluoride)* (*58*). Dimethylamine (45 g, 1 mol) was added dropwise to a stirred solution of *N,N*-dimethylphosphoramidic difluoride (66 g, 0.5 mol) in benzene (50 ml) while the temperature was maintained at 7–10 °C. After addition, stirring was continued at room temperature for 12 h. Filtering and fractionating gave dimefox (48 g, 62%). Bp 67 °C/4 mmHg. δ_F −82.8 ppm and δ_P 18.3 ppm ($^1J_{PF}$ 945 Hz) (*120*).

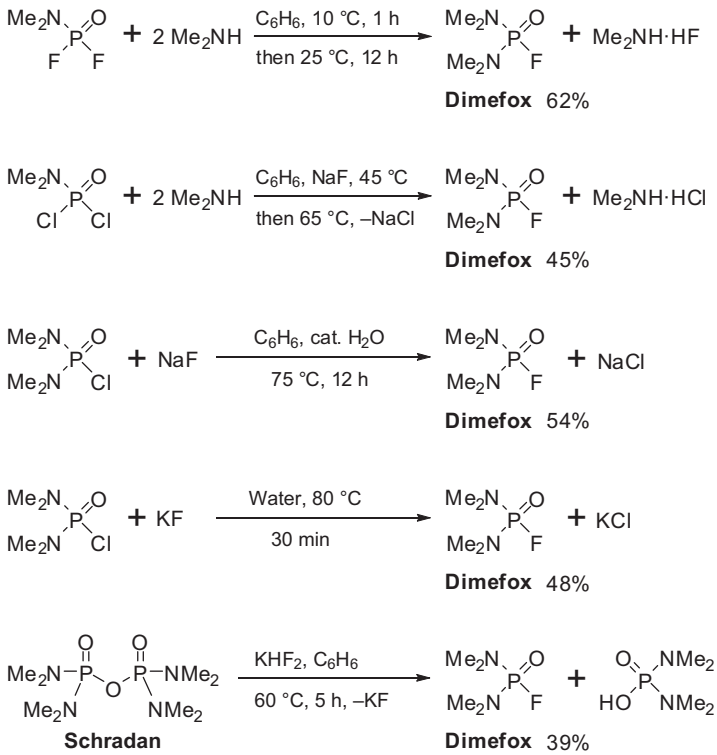


Figure 4.70.1

Dimefox and related analogues prepared by Schrader (*58*)

Compound	Bp (°C/mmHg)	Compound	Bp (°C/mmHg)
Me2N O P Me2N F *a*	67/4	Et2N O P Et2N F	113/8
Me2N O P MeEtN F	90/11	Me2N O P MeHN F	110/3
MeEtN O P MeEtN F	105/9	Me2N O P MeCyN F	77/6
Me2N O P Et2N F	102/10	Me2N O P CyEtN F	100–115/4

a. Dimefox. Cy = cyclohexyl

Figure 4.70.2

▶ *N,N,N′,N′-Tetramethyl phosphorodiamidofluoridate (dimefox, from N,N-dimethylphosphoramidic dichloride)* (*58*). A solution of dimethylamine (45 g, 1 mol) in benzene (200 ml) was added slowly to a stirred mixture of *N,N*-dimethylphosphoramidic dichloride (81 g, 0.5 mol) and finely powdered sodium fluoride (90 g, 2.1 mol) in benzene (15 ml) while the temperature was maintained at 40–45 °C. After the reaction had subsided, the mixture was heated for a further 4 h at 60–65 °C. The usual work-up gave dimefox (35 g, 45%). Bp 96 °C/17 mmHg.

▶ *N,N,N′,N′-Tetramethyl phosphorodiamidofluoridate (dimefox, from N,N,N′,N′-tetramethyl phosphorodiamidochloridate and sodium fluoride in benzene)* (*58*). *N,N,N′,N′*-Tetramethyl phosphorodiamidochloridate (bp 95 °C/3 mmHg; 100 g, 0.6 mol) was added to a stirred mixture of sodium fluoride (100 g, 2.4 mol) and distilled water (0.3 g) in benzene (300 ml), the stirring being continued after completion of the addition for 12 h at 75 °C. The usual work-up gave dimefox (50 g, 54%). Bp 69–70 °C/5 mmHg.

▶ *N,N,N′,N′-Tetramethyl phosphorodiamidofluoridate (dimefox, from N,N,N′,N′-tetramethyl phosphorodiamidochloridate and potassium fluoride in water)* (*58*). *N,N,N′,N′*-Tetramethyl phosphorodiamidochloridate (85 g, 0.5 mol) was added to a stirred solution of potassium fluoride (105 g, 1.8 mol) in water (90 ml). The temperature rose to about 75 °C. After addition, the mixture was heated for 30 min to 80 °C and was then cooled. Water (*ca.* 90 ml) was added and the product was extracted with ether. Solvent removal and fractionation of the residue gave dimefox (37 g, 48%). Bp 86 °C/10 mmHg.

▶ *N,N,N′,N′-Tetramethyl phosphorodiamidofluoridate (dimefox, from schradan and aqueous KHF_2 in benzene)* (*58*). Schradan (72 g, 0.25 mol; *Caution!* Toxic) was stirred with potassium hydrogenfluoride (100 g, 1.28 mol) and benzene (300 ml) for 5 h at 80 °C. The standard work-up gave dimefox (15 g, 39%). Bp 65–67 °C/3 mmHg.

4.71 *N,N,N′,N′*-TETRAALKYL PHOSPHORODIAMIDOAZIDATES $(R_2N)_2P(O)N_3$

The reaction of *N,N,N′,N′*-tetramethyl phosphorodiamidochloridate with an excess of sodium azide in acetonitrile (*249*) or water (*470,473*) at room temperature yields the corresponding phosphorazidate, the pesticide mazidox (Fig. 4.71.1).

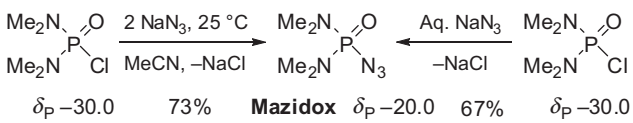


Figure 4.71.1

Likewise treatment of *N,N′*-di(pyrrolidinyl)phosphorodiamidic chloride (**305**) with sodium azide in aqueous acetone provides the azidate (**307**) which undergoes transformations typical of phosphoryl azides, such as the Staudinger reaction with triphenylphosphine to yield the phosphinimine (**308**) (Fig. 4.71.2) (*454*).

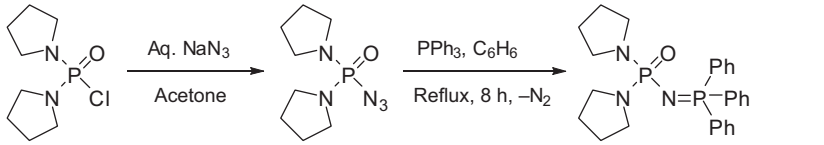


Figure 4.71.2

▶ *N,N,N′,N′-Tetramethyl phosphorodiamidoazidate $(Me_2N)_2P(O)N_3$ (mazidox, from sodium azide in acetonitrile)* (*249*). A solution of *N,N,N′,N′*-tetramethyl phosphorodiamidochloridate (3.41 g, 20 mmol) in acetonitrile (30 ml) was added dropwise to a stirred suspension of sodium azide (2.60 g, 40 mmol) in acetonitrile (25 ml) and the mixture was stirred for 36 h at room temperature. The inorganic salts were filtered off and the solvent removed from the filtrate, first with a rotary evaporator then with an oil pump, to provide a colourless liquid (2.6 g, 73%). δ_P (CH_2Cl_2) −20.0 ppm. The compound can be distilled (bp 93−94 °C/2 mmHg) (*474*). The infrared spectrum shows a band for the azide group at 2146/cm.

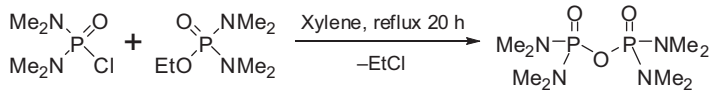
▶ *N,N,N′,N′-Tetramethyl phosphorodiamidoazidate $(Me_2N)_2P(O)N_3$ (mazidox, from sodium azide in water)* (*473*). *N,N,N′,N′*-Tetramethyl phosphorodiamidochloridate (10 g, 59 mmol) was added over 30 min to a stirred solution of sodium azide (5 g, 77 mmol) in water (25 ml) at 0−5 °C. The mixture was stirred at 15 °C for 1 h and then extracted with chloroform (2 × 25 ml) to obtain the product free from sodium chloride. The combined organic extracts were dried ($MgSO_4$) and the solvent was removed from the filtrate to give the title compound as a colourless mobile liquid (7 g, 67%).

▶ *N,N′-Di(pyrrolidinyl) phosphorodiamidoazidate $[(CH_2)_4N]_2P(O)N_3$* (**307**) (*454*). A solution of *N,N′*-di(pyrrolidinyl) phosphorodiamidic chloride (2.2 g, 10.0 mmol) in acetone (30 ml) was added to a stirred solution of sodium azide (1.3 g, 20.0 mmol) in water (10 ml) at 40−50 °C. After being stirred at room temperature for 10 h, the mixture was concentrated and extracted with ether (150 ml). The extract was washed with water (3 × 100 ml), dried ($MgSO_4$), and evaporated under reduced pressure to provide a pale yellow liquid (1.48 g, 64%). ν_{max} 2140 (N_3) and 1260 (P═O)/cm.

▶ *N,N′-Di(pyrrolidinyl) phosphorotriphenylphosphinimine $[(CH_2)_4N]_2P(O)N{=}PPh_3$* (**308**) (*454*). A mixture of *N,N′*-di(pyrrolidinyl) phosphorodiamidoazidate (0.30 g, 1.3 mmol) and triphenylphosphine (0.34 g, 1.3 mmol) in benzene (30 ml) was heated under reflux for 8 h. The solvent was removed and the residue was recrystallised from 2:1 petroleum ether (bp 60−80 °C)−THF to give the product (0.28 g, 46%). Mp 125−129 °C. ν_{max} 1205 (P═O)/cm. δ_P (36.4 MHz, $CDCl_3$) 6.2 (P═O) and 7.8 (N═PPh_3) ppm.

4.72 *BIS*(*N,N*-DIALKYL) PYROPHOSPHORODIAMIDATES $(R_2N)_2P(O)OP(O)(NR_2)_2$

This class of compounds is typified by schradan, first prepared by Schrader (*58,475*), and one of the first systemic insecticides (absorbed by plants through the roots or leaves, rendering the sap toxic to feeding insects) (*476*). The route of Schrader involves prolonged heating of equimolar amounts of



13b **309** **Schradan** 81%

Figure 4.72.1

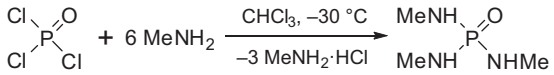
N,N,N′,N′-tetramethylphosphorodiamidic chloride (**13b**) and *O*-ethyl *bis*(*N,N*-dimethyl)phosphorodiamidate (**309**) in boiling xylene, with loss of ethyl chloride and formation of schradan. ^{32}P-labelled schradan for studying transport in plants has been synthesised similarly (*477*) and various analogues of schradan have been prepared (*478*).

Schradan is a colourless viscous liquid that is miscible with water and most organic solvents. It is hydrolysed under acid conditions, but is stable in water and alkali. The acute oral LD_{50} to male and female rats is 13.5 and 35.5 mg/kg, respectively (*479*). Schradan itself has no anticholinesterase activity in vitro, but is metabolised in vivo to a potent inhibitor of cholinesterases (*480,481*).

▶ *Schradan* $(Me_2N)_2P(O)OP(O)(NMe_2)_2$ (*476*). Pure starting materials were employed and the intermediates were all fractionated one or more times through a 60 cm column packed with glass helices and with a variable take-off stillhead. The procedure was based on that of Schrader (*58*): dimethylamine hydrochloride and an excess of phosphorus oxychloride were heated under reflux for 20 h and fractionated to give $Me_2NP(O)Cl_2$ (94%, bp 88 °C/18 mmHg). Treatment of this (1 mol) with dimethylamine (2 mol) in ether at room temperature yielded $(Me_2N)_2P(O)Cl$ **13b** (84%, bp 102 °C/6 mmHg). Reaction of this with an equimolar amount of sodium ethoxide in ethanol gave $(Me_2N)_2P(O)OEt$ **309** (88%, bp 93.5 °C/8 mmHg). Heating equimolar amounts of **13b** and **309** in boiling xylene for 20 h resulted in evolution of ethyl chloride and yielded schradan after fractionation as a colourless liquid (81%; *Caution!* Neurotoxic). Bp 106 °C/0.004 mmHg, 102 °C/0.003 mmHg, and 98 °C/0.002 mmHg.

4.73 TRI- AND HEXAALKYLPHOSPHORAMIDES $(RNH)_3P{=}O$ AND $(R_2N)_3P{=}O$

Phosphorus oxychloride reacts with 6 mol of a primary amine in an inert solvent at low temperature to give *N,N′,N″*-trimethylphosphoramides (e.g. **310**) (Fig. 4.73.1) (*482*).



310 66%

Figure 4.73.1

The use of 6 mol of a secondary amine yields the corresponding hexaalkylphosphoramide. The lowest member, hexamethylphosphoramide (HMPA), is a colourless liquid (bp 68–70 °C/1 mmHg, mp 7 °C) (*483*) that is soluble in water and polar and non-polar solvents (*484*). It resists alkaline and

dilute acid hydrolysis; P—N cleavage occurs in strongly acidic conditions. HMPA was used as a chemosterilant for flies but was discontinued once it was realised that it was a potent carcinogen in animals and a suspected human carcinogen (*485*). Homologues are prepared analogously: $(Et_2N)_3P{=}O$ (bp 111 °C/1.3 mmHg) and $[(n\text{-}Pr)_2N]_3P{=}O$ (bp 125 °C/0.2 mmHg) (*451*). Proton NMR data for hexaalkylphosphoramides and related compounds have been compiled (*486*).

N,N′,N″-Trimethylphosphoramide $(MeNH)_3P{=}O$ (**310**) (*482*). Phosphorus oxychloride (153.5 g, 1 mol) was added dropwise to a stirred solution of methylamine (186.0 g, 6 mol) in anhydrous chloroform (1400 ml) at −40 to −20 °C. The mixture was left overnight at room temperature and the methylamine hydrochloride (162.1 g, 80%) was filtered off. The filtrate was concentrated under reduced pressure and the residue was dissolved in methanol. The remainder of the methylamine hydrochloride was neutralised with an amount of potassium hydroxide in methanol equivalent to the unprecipitated hydrochloride. The potassium chloride formed was filtered off and the filtrate concentrated. The liquid residue was dissolved in boiling benzene and boiled until the remaining methanol was removed. The solution was filtered hot and on cooling deposited the title compound (90.4 g, 66%). Mp 102—103 °C.

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CHAPTER 5

Thiophosphoryl Compounds

Christopher M. Timperley and Nicholas Cooper
Detection Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK

5.1 INTRODUCTION

This chapter describes the synthesis of phosphorothionate and phosphorodithioate derivatives containing one or two sulfur atoms, respectively, with one of the sulfur atoms doubly bonded to phosphorus (nomenclature: thiono for P═S and thiolo for P—S). Phosphorothionate esters are usually less toxic and more stable than the corresponding phosphate esters, and comprise one of the most important classes of organophosphorus pesticides (*1—4*). Over 30 compounds of this class were used as insecticides globally at least up to the 1970s, after which human toxicity and environmental concerns reduced their practical application. Their general structures include dialkyl aryl/heteroaryl phosphorothionates (**A**) which encompass the majority of pesticides, and dialkyl β-(alkylthio)ethyl phosphorothionates (**B**) (Fig. 5.1.1) (*5*). Esters of thiophosphorylated oximes (**C**) were developed later. The discovery of the low-toxicity insecticide malathion in the 1950s prompted the growth of phosphorodithioates as one of the most important classes of pesticide, having insecticidal, fungicidal or herbicidal activity, although here aryl ester derivatives are not as important as they are in the phosphorothionate series. Many phosphorodithioate pesticides contain a heteroatom bonded to the α- or β-carbon atom of an *S*-aliphatic group to construct carboxy (**D**), sulfoxide (**E**), or amide (**F**) derivatives.

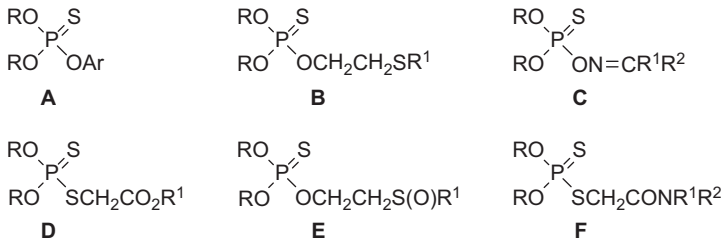

Figure 5.1.1 Some thiophosphoryl pesticide classes.

Phosphorothionates often convert into the *S*-alkyl phosphorothiolates upon heating to 150 °C or above (*3,4*) or upon reaction with alkylating agents (Pistschimuka reaction) (*6—8*) (Fig. 5.1.2). The thermal reaction involves self-alkylation (isomerisation) through intermolecular attack of the P═S sulfur atom on the alkoxy carbon atom. To obtain intermolecular C—O cleavage, a high

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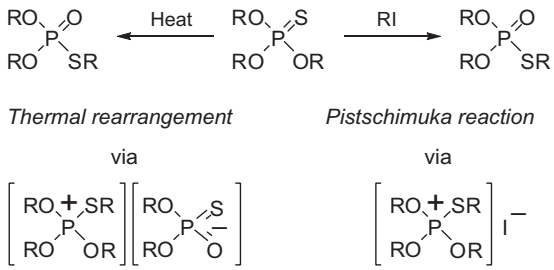


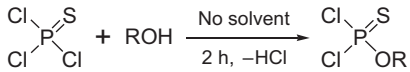
Figure 5.1.2

temperature and a long reaction time are usually required: these conditions are readily achievable in laboratory syntheses. Once the reaction commences the resulting intermediate phosphonium salt is a powerful alkylating agent and accelerates the conversion of the phosphorothionate to the phosporothiolate. Thiono—thiolo rearrangement often occurs more efficiently through the action of alkyl halides (reactivity order: RI > RBr > RCl > RF) and proceeds also through a phosphonium intermediate. The use of high-boiling polar solvents, such as nitromethane (bp 101 °C) or *N*,*N*-dimethylformamide (DMF) (bp 153 °C) heated under reflux assists the rearrangement. Combinations of methyl-substituted phosphorothionates $(RO)_2P(S)OMe$ and iodomethane are among the most useful, giving often cleanly the corresponding phosphorothiolate $(RO)_2P(O)SMe$. No reaction or incomplete conversion can occur when the starting phosphorothionate contains a P—OEt or a higher alkoxy group, as these are more hindered and less easily dealkylated.

Owing to possible self-alkylation, preparations of phosphorothionates (P═S) are sometimes contaminated with isomeric phosphorothiolates (P—S). The thiolate isomers are frequently more toxic to mammals (*9*) and caution must be observed during manipulation of such preparations. The pure thiono isomer is often obtainable by careful fractionation under reduced pressure or by column chromatography on silica gel. The latter is preferred for purifying phosphorothiolates for biological work and usually provides material of >98% purity.

5.2 ALKYL PHOSPHORODICHLORIDOTHIONATES $ROP(S)Cl_2$

Mixing equimolar proportions of thiophosphoryl chloride and aliphatic alcohols (ROH where R is Me, Et, *n*- or *i*-Pr) in the absence of solvent, followed by double vacuum fractionation, provides alkyl phosphorodichloridothionates in acceptable yield (Fig. 5.2.1) (*10*,*11*). A temperature of 100—120 °C is recommended for formation of *n*-butyl phosphorodichloridothionate (*12*). Pyridine as base and 1,2-dichloroethane as solvent have been used to prepare 2-chloroethyl phosphorodichloridothionate and 2-ethoxyethyl phosphorodichloridothionate (*13*). Alkyl phosphorodichloridothionates are corrosive liquids that react slowly with moisture and alcohols. They are less reactive than the corresponding alkyl phosphorodichloridates towards these nucleophiles.



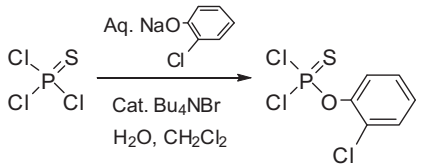
Alkyl phosphorodichloridothionates

R	Yield (%)	Bp (°C/mmHg)
Me	52	50–54/10
Et	65	60–63/10
n-Pr	58	78–81/22
i-Pr	61	59–60/10
n-Bu	31	81–82/10
$ClCH_2CH_2$	44 [a]	104–108/14
$EtOCH_2CH_2$	32 [a]	108–114/23

a. Pyridine (1 mol) and solvent ($ClCH_2CH_2Cl$).

Figure 5.2.1

Aryl phosphorodichloridothionates can be prepared in excellent yields by treating thiophosphoryl chloride with the sodium salts of aromatic alcohols under two-phase conditions in the presence of a phase-transfer catalyst (PTC) such as tetra-*n*-butylammonium bromide (*14*). The method for 2-chlorophenyl phosphorodichloridothionate (**1**), a useful reagent for oligonucleotide synthesis, is a typical example (Fig. 5.2.2).



1 89–94% δ_P 54.4

Figure 5.2.2

▶ *Ethyl phosphorodichloridothionate EtOP(S)Cl$_2$* (*15*). Absolute ethanol (58 ml, 1.0 mol) was added via a dropping funnel at a rate of 0.5 ml/min to stirred thiophosphoryl chloride (104 ml, 1.0 mol) at 0—5 °C in a 500-ml three-necked flask equipped with a sealed mechanical stirrer and a water-cooled condenser (capped by a drying tube containing anhydrous calcium chloride). The ice bath was removed after the ethanol had been added and stirring was continued until the mixture reached room temperature. The apparatus attached to the three necks of the reactor was replaced by two stoppers and a Vigreux fractionating column adapted for vacuum distillation. The pressure within the system was reduced slowly to 25 mmHg. After the unreacted ethanol and dissolved hydrogen chloride had evaporated, the contents of the flask were heated slowly. A fraction boiling between 20 and 45 °C (mainly unreacted thiophosphoryl chloride) was collected first. A later fraction comprising a colourless liquid was pure ethyl phosphorodichloridothionate (70 g, 39%). Bp 57 °C/25 mmHg,

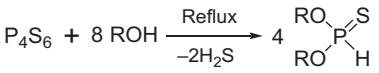
52 °C/20 mmHg. The compound does not hydrolyse appreciably in air or water at ambient temperature. It reacts slowly with aqueous sodium hydroxide and is soluble in acetone, carbon tetrachloride, ethanol, and ether. It is unstable at temperatures above 90 °C.

▶ *n-Butyl phosphorodichloridothionate n-BuOP(S)Cl$_2$ (12)*. *n*-Butanol (296 g, 4 mol) was added dropwise with stirring to thiophosphoryl chloride (678 g, 4 mol) at 80 °C. After addition the temperature was raised to 100–120 °C and maintained for 5 h. Unreacted thiophosphoryl chloride and liberated hydrogen chloride were removed and the product was distilled to provide the title compound (298 g, 31%). Bp 81–82 °C/10 mmHg.

▶ *2-Chlorophenyl phosphorodichloridothionate 2-ClC$_6$H$_4$OP(S)Cl$_2$* (**1**) *(14)*. A 2-l three-necked round-bottomed flask fitted with a 250-ml addition funnel, glass stoppers, and a magnetic stirrer bar was charged with thiophosphoryl chloride (271 g, 1.60 mol), tetra-*n*-butylammonium bromide (3.2 g, 0.01 mol) and dichloromethane (400 ml), and cooled to 0–5 °C. 2-Chlorophenol (51.4 g, 0.40 mol) was added to stirred 25% *w/w* aqueous sodium hydroxide (350 ml) in a 500-ml glass flask cooled to 0–5 °C. This solution was transferred to the addition funnel and added slowly over 30 min to the stirred contents of the 2-l flask. The resulting two-phase mixture was stirred for 8 h while being allowed to warm to room temperature. The aqueous layer was separated and extracted with dichloromethane (100 ml). The organic layer was combined, washed with brine (100 ml), dried ($MgSO_4$) and filtered. The filtrate was concentrated and the residue was distilled under reduced pressure through a short-path still head (two traps cooled with liquid nitrogen were connected between the distillation apparatus and the vacuum pump to trap excess $PSCl_3$). The title compound was collected as a colourless liquid (93.2–98.4 g, 89–94%). Bp 90–93 °C/0.2 mmHg. δ_P (202 MHz, $CDCl_3$) 54.4 ppm.

5.3 DIALKYL *H*-THIOPHOSPHONATES (RO)$_2$P(S)H

Phosphorus hexasulfide (P_4S_6) reacts with alcohols when heated to generate dialkyl *H*-thiophosphonates (Fig. 5.3.1) *(16)*. A ten-fold molar excess of the alcohol is employed and the yields are generally around 20% regardless of the alcohol. The lower dialkyl *H*-thiophosphonates are colourless liquids that when treated with water do not dissolve or decompose, and in this way dialkyl *H*-phosphonate impurities, which are soluble in water, can be removed.



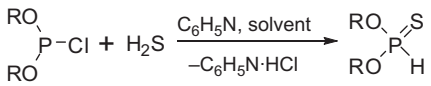
Dialkyl *H*-thiophosphonates

R	Reflux (h)	Yield (%)	Bp (°C/mmHg)
Me	20	20	69–70/30
Et	12–15	20	87/26
n-Pr	10	20	112/30
i-Pr	10	20	95/26
n-Bu	9	20	148/32

Figure 5.3.1

The infrared spectrum of thiophosphoryl chloride ($Cl_3P{=}S$) contains bands at 754/cm and between 535 and 745/cm. Similar bands appear in the infrared spectra of dimethyl, diethyl and di-*n*-propyl *H*-thiophosphonates. These spectra lack the S—H stretching vibration (2550—2600/cm) but show bands for the P—H group (2400/cm) and P—O—C vibration (~1000/cm) (*16*). The structure of dialkyl *H*-thiophosphonates therefore compares to that of dialkyl *H*-phosphonates. A tautomeric equilibrium between $(RO)_2P(S)H$ and $(RO)_2P{-}SH$ favouring the thiono form exists. Accordingly, dialkyl *H*-thiophosphonates possess only weak nucleophilic activity, although their alkali metal salts are strongly nucleophilic and exhibit the character of trivalent phosphorus compounds: they add sulfur and selenium readily, undergo alkylation, and add to activated double bonds (e.g. the carbonyl group of chloral (*16*)). The predominant $(RO)_2P(S)H$ configuration is confirmed by treatment with sulfuryl chloride (*17*) which yields dialkyl phosphorochloridothionates $(RO)_2P(S)Cl$ (Section 5.4).

Another method of preparing disubstituted *H*-thiophosphonates involves treating a dialkyl or diaryl phosphorochloridite with hydrogen sulfide in an inert solvent (e.g. light petroleum or benzene) in the presence of a suitable base (e.g. *N*,*N*-diethylaniline, pyridine, triethylamine) (Fig. 5.3.2) (*16*,*17*). The yields obtained are far superior to those from the reactions of phosphorus hexasulfide with alcohols. Diphenyl *H*-thiophosphonate is a high-boiling liquid that is purified by distillation at very low pressure. Anhydrous conditions are necessary for good yields of the pure *H*-thiophosphonates: water reacts with dialkyl phosphorochloridites even in the absence of tertiary amines, yielding dialkyl *H*-phosphonates. Removal of the latter, which can contaminate the products if moisture has not been excluded, can be difficult due to the close proximity of the boiling points of the *H*-thiophosphonates and *H*-phosphonates.



Dialkyl *H*-thiophosphonates

R	Solvent	Yield (%)	Bp (°C/mmHg)
Et	A	81	87/26
n-Pr	A	73	112/30
i-Pr	A	34	95/26
n-Bu	A	83	148/32
Ph	B	70	70/0.001–0.005

Solvent : (A) light petroleum, (B) benzene

Figure 5.3.2

The same methodology can be used to obtain cyclic dialkyl *H*-thiophosphonates (Fig. 5.3.3) (*17*). Good conversions of ethylene phosphorochloridite (**2**) to the five-membered *H*-thiophosphonate (**3**) and trimethylene phosphorochloridite (**4**) to the six-membered *H*-thiophosphonate (**5**) are

possible. However the cyclic products are less stable than the acyclic *H*-thiophosphonates. Ethylene *H*-thiophosphonate (**3**) decomposes violently at 100 °C and when impure at lower temperatures, but it can be purified successfully by careful distillation at about 60 °C/1 mmHg. Trimethylene *H*-thiophosphonate (**5**) is more stable and can be distilled under reduced pressure, and the pure material is crystalline (mp 34 °C).

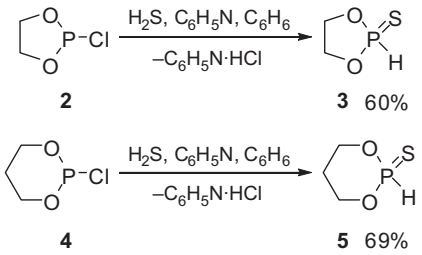


Figure 5.3.3

The use of pure starting esters is not always necessary. Somtimes, the crude phosphorochloridite (**6**), obtained by alcoholysis of phosphorus trichloride in the presence of a tertiary amine, can be treated with hydrogen sulfide to give the product in adequate yield (Fig. 5.3.4). Saturating a mixture of phosphorus trichloride (1 mol), 4-bromo- or 4-nitrobenzyl alcohol (2 mol) and *N*,*N*-diethylaniline (3 mol) with hydrogen sulfide gives the *H*-thiophosphonates (**7a—b**) in modest yields (*17*).

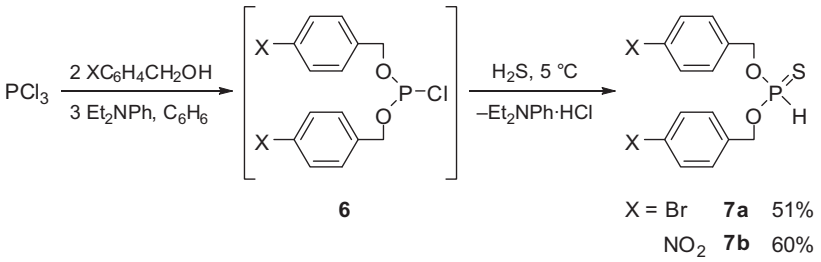


Figure 5.3.4

▶ *Dialkyl H-thiophosphonates (RO)₂P(S)H (from phosphorus hexasulfide and an alcohol)* (*16*). Phosphorus hexasulfide (1 mol) was heated under reflux with the alcohol (10 mol) for varying periods: methanol 20 h, ethanol 12—15 h, *n*-propanol 10 h, isopropanol 10 h, and *n*-butanol 9 h. The products listed in Fig. 5.3.1 were isolated by distillation.

▶ *Dialkyl H-thiophosphonates (RO)₂P(S)H (from the dialkyl phosphorochloridite and hydrogen sulfide, method A)* (Fig. 5.3.2) (*16*). Illustrated for the synthesis of diethyl *H*-thiophosphonate: diethyl phosphorochloridite (72.0 g, 0.46 mol), pyridine (37.0 g, 0.47 mol) and light petroleum (450 ml) were introduced into a nitrogen-filled flask. Hydrogen sulfide was passed slowly into the stirred mixture so that the gas was absorbed completely. After the exothermic reaction subsided and the gas was no longer

absorbed, the pyridinium chloride formed was filtered off. Distillation of the filtrate gave diethyl *H*-thiophosphonate (57.5 g, 81%). Bp 87 °C/26 mmHg.

▶ *Dialkyl H-thiophosphonates $(RO)_2P(S)H$ (from the dialkyl phosphorochloridite and hydrogen sulfide, method B)* (Fig. 5.3.2) (*17*). Hydrogen sulfide (dried over phosphorus pentoxide) was passed over 3 h into a stirred solution of the dialkyl phosphorochloridite (0.1 mol) and pyridine (or *N,N*-diethylaniline; 0.1 mol) in benzene (75 ml). The reaction was exothermic. The temperature was kept at 5 °C. The amine hydrochloride precipitate was filtered off and the filtrate was washed with ice water (2 × 25 ml), dried ($MgSO_4$) and concentrated. Distillation of the residue under reduced pressure gave the dialkyl *H*-thiophosphonates listed in Fig. 5.3.2 as colourless liquids.

▶ *Ethylene H-thiophosphonate* (**3**) (*17*). Ethylene phosphorochloridite (20.1 g, 159 mmol) and pyridine (12.5 g, 158 mmol) in benzene (120 ml) were stirred and hydrogen sulfide was introduced slowly for 2.5 h at 5 °C. The pyridine hydrochloride was filtered off. The filtrate was washed with ice water (2 × 25 ml) and dried ($MgSO_4$). The solvent was removed at 55–65 °C/0.7 mmHg to give ethylene *H*-thiophosphonate (12.0 g, 60%).

▶ *Trimethylene H-thiophosphonate* (**5**) (*17*). As in the previous experiment, hydrogen sulfide was bubbled into trimethylene phosphorochloridite (12.5 g, 89 mmol) and pyridine (10.0 g, 127 mmol) in benzene (60 ml). The same work-up and fractionation under vacuum gave trimethylene *H*-phosphonate (8.5 g, 69%). Bp 60 °C/0.02 mmHg.

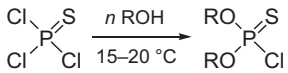
▶ *Bis(4-bromobenzyl) H-thiophosphonate $(4\text{-}BrC_6H_4O)_2P(S)H$* (**7a**) (*17*). A solution of 4-bromobenzyl alcohol (15.0 g, 80 mmol) and *N,N*-diethylaniline (17.9 g, 120 mmol) in benzene (75 ml) was added to a stirred solution of phosphorus trichloride (5.5 g, 40 mmol) in benzene (25 ml) at 5 °C. After addition the mixture was stirred for 15 min and then saturated with hydrogen sulfide for 5 h at 5 °C. The precipitated *N,N*-diethylaniline hydrochloride was filtered off and the filtrate was concentrated to 50 ml, and the anilinium hydrochloride was filtered off again. The filtrate was treated with light petroleum (150 ml) and the layers were separated. The petroleum layer was removed and the oily layer was extracted with hot benzene (2 × 25 ml). The combined extracts were evaporated under reduced pressure to dryness. Crystallisation of the residue from light petroleum–benzene gave colourless plates (9.0 g, 51%). Mp 84 °C.

▶ *Bis(4-nitrobenzyl) H-thiophosphonate $(4\text{-}O_2NC_6H_4O)_2P(S)H$* (**7b**) (*17*). A solution of 4-nitrobenzyl alcohol (10.0 g, 65 mmol) and *N,N*-diethylaniline (15.0 g, 101 mmol) in benzene (80 ml) and ether (20 ml) was added dropwise to a stirred solution of phosphorus trichloride (4.5 g, 33 mmol) in ether (20 ml) at 5 °C. After addition the mixture was stirred for 1 h and then saturated with hydrogen sulfide for 3.5 h at 5 °C. The precipitated *N,N*-diethylaniline hydrochloride was filtered off. The filtrate was concentrated to dryness and the residue was crystallised from benzene to give yellow needles (7.3 g, 60%). Mp 135 °C.

5.4 DIALKYL PHOSPHOROCHLORIDOTHIONATES $(RO)_2P(S)Cl$

Treatment of thiophosphoryl chloride with a 10- to 60-fold molar excess of an alcohol at room temperature allows dialkyl phosphorochloridothionates to be isolated in adequate yield (Fig. 5.4.1) (*18*). Dilution using the alcohol as a reactant and a solvent is necessary to suppress the side reaction

between the alcohol and liberated hydrogen chloride: ROH + HCl → RCl + H_2O. The water produced can hydrolyse the intermediate chloridate, $ROP(S)Cl_2$ + 2 H_2O → $ROP(S)(OH)_2$ + 2 HCl, and product chloridate, $(RO)_2P(S)Cl$ + H_2O → $(RO)_2P(S)OH$ + HCl, producing more hydrogen chloride and lowering the yield of the target dialkyl phosphorochloridothionate.



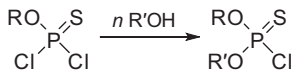
Dialkyl phosphorochloridothionates

R	*n* [a]	Time (h)	Yield (%)	Bp (°C/mmHg)
Me	10	3	53	65–66/16
Et	60	24	34	96–97/25
n-Pr	60	27	46	110/17
n-Bu	60	29	48	128/10

a. Number moles of ROH per mole of $PSCl_3$.

Figure 5.4.1

Better yields of dialkyl phosphorochloridothionates are obtained by carefully controlled reactions of alkyl phosphorodichloridothionates with alcohols, since the concentration of hydrogen chloride in solution is lower; consequently processes that furnish unwanted by-products occur to a lesser extent. The highest yields of the target compounds are obtained by methanolysis of alkyl phosphorochloridothionates. Symmetrical and unsymmetrical dialkyl phosphorochloridothionates can be prepared using this tactic (Fig. 5.4.2).



Dialkyl phosphorochloridothionates

R	R′	*n* [a]	Temp. (°C)	Time (h)	Yield (%)	Bp (°C/mmHg)
Me	Me	10	5–10	6	71	56–57/10
Et	Et	40	20–30	24	61	95/20
n-Pr	*n*-Pr	40	20–30	24	63	109–111/17
n-Bu	*n*-Bu	40	25	25	60	140–142/15
Et	Me	15	20–25	4	81	80–81/17
n-Pr	Me	10	30–35	1.5	65	107–110/25
n-Bu	Me	11	30	1.5	77	45–47/0.3
i-Bu	Me	12	30–35	2	90	110–114/22

a. Number moles of ROH per mole of $PSCl_3$

Figure 5.4.2

The use of an amine base such as pyridine to effect the reaction between an alkyl phosphorodichloridothionate usually offers no advantage and often reduces the yield of the dialkyl phosphorochloridothionate (*12*,*13*). A convenient hydrogen chloride acceptor is anhydrous potassium carbonate. Treatment of methyl phosphorodichloridothionate with 3-methyl-(4-methylthio)phenol in the presence of this base in acetonitrile affords chloridothionate (**8**) (*19*), a precursor handy for accessing analogues of the pesticide fenthion (Fig. 5.4.3).

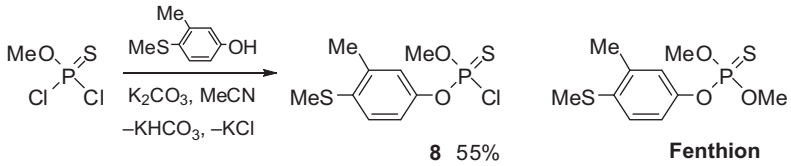
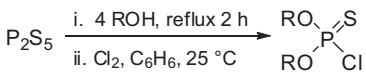


Figure 5.4.3

Phosphorus pentasulfide suspended in benzene reacts with 4 mol of certain aliphatic alcohols and chlorination of the *O*,*O*-dialkyl hydrogen phosphorodithioate products provides dialkyl phosphorochloridothionates (Fig. 5.4.4) (*20*). These are quite stable in aqueous solution at ordinary temperatures over a considerable pH range. Adding the reaction mixture after chlorination to water at 20—40 °C produces a crude product whose distillation with no special attention to fractionation provides a high-quality chloridothionate.



Dialkyl phosphorochloridothionates

R	Yield (%)	Bp (°C/mmHg)
Me	53	70–72/20
Et	59	94–96/20
n-Pr	58	70–75/1
i-Pr	55	56–59/1
n-Bu	64	95–98/0.7
i-Bu	62	76–82/0.5

Figure 5.4.4

Phosphorus pentasulfide reacts with 4 molar equivalents of phenol upon warming to provide a good yield of *O*,*O*-diphenyl hydrogen phosphorodithioate (**9**) (Fig. 5.4.5) (*20*). Its chlorination proceeds readily and produces *O*,*O*-diphenyl phosphorochloridothionate (**10**). This two-step approach offers a general method for the preparation of *O*,*O*-diaryl phosphorochloridothionates.

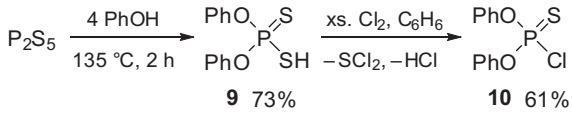


Figure 5.4.5

Dialkyl or diaryl *H*-thiophosphonates react with sulfuryl chloride in benzene to provide the corresponding phosphorochloridothionates (Fig. 5.4.6) (*17*). The method is illustrated for diphenyl phosphorochloridothionate (**10**) and di-*n*-propyl phosphorochloridothionate (**11**).

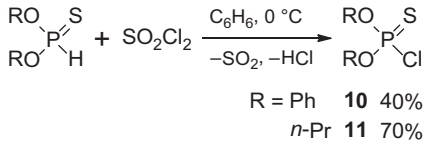
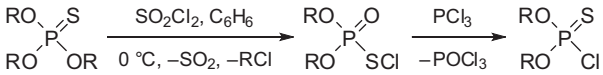


Figure 5.4.6

Trialkyl phosphorothionates react with sulfuryl chloride to yield dialkyl *S*-chloro phosphorothiolates (Fig. 5.4.7) (*21*). The by-products are sulfur dioxide and the alkyl chloride. Addition of phosphorus trichloride to the reaction mixture converts the dialkyl *S*-chloro phosphorothiolate into the chloridothionate. This one-pot process is of general utility and one of the highest yielding methods available for the synthesis of the desired chloridothionates.



Dialkyl phosphorochloridothionates

R	Yield (%)	Bp (°C/mmHg)	δ_P (ppm)
Me	85	68/12	–71.7
Et	71	65–67/12	–67.5
n-Pr	83	68–69/1.5	–68.2
i-Pr	57	53–55/1	–65.0
n-Bu	76	88/1	–68.2

Figure 5.4.7

▶ *Dialkyl phosphorochloridothionates $(RO)_2P(S)Cl$ (from trialkyl phosphorothionates and sulfuryl chloride)* (Fig. 5.4.7) (*21*). Sulfuryl chloride (5.5 g, 40.7 mmol) was added dropwise to a stirred solution of trimethyl phosphorothionate (6.3 g, 40.3 mmol) in benzene (20 ml) at 0—5 °C. The mixture was stirred at room temperature for 1 h and degassed under vacuum. The resulting solution of dimethyl

S-chloro phosphorothiolate was added to a solution of phosphorus trichloride (7.0 g, 51 mmol) in benzene (15 ml) at 0–5 °C. The mixture was left for 12 h at room temperature, the solvent was removed, and the residue was fractionated to give dimethyl phosphorochloridothionate (5.6 g, 85%). Bp 68 °C/12 mmHg. To remove small amounts of dialkyl phosphorochloridate impurities (0–3%) it is advantageous to dissolve the crude product in benzene and wash the resulting solution with 10% *w/w* aqueous sodium carbonate and subsequently water. Drying, solvent removal, and then distillation provide the pure dialkyl phosphorochloridothionate.

▶ *Symmetrical dialkyl phosphorochloridothionates $(RO)_2P(S)Cl$ (from thiophosphoryl chloride)* (Fig. 5.4.1) (*18*). The appropriate alcohol (10 or 60 mol equiv.) was added gradually with vigorous stirring and cooling (15–20 °C) to thiophosphoryl chloride (1 mol equiv.) in a flask fitted with a reflux condenser and a mechanical stirrer. After the required amount of alcohol had been added, the reaction mixture was left for a certain period of time. The alcohol was then washed out with water (in the case of water-soluble alcohols) or removed in vacuum. The residual crude dialkyl phosphorochloridothionate was obtained pure after fractionation under reduced pressure. Compounds obtained this way and conditions for their preparation appear in Fig. 5.4.1. Small deviations from the given conditions resulted in considerable changes in yield.

▶ *Unsymmetrical dialkyl phosphorochloridothionates $RO(R'O)P(S)Cl$ (from the alkyl phosphorodichloridothionate)* (Fig. 5.4.2) (*18*). Under the conditions given in Fig. 5.4.2, the alkyl phosphorodichloridothionate was mixed with the appropriate alcohol in the stated molar ratio and kept at the given temperature for a set time. Afterwards the mixture was cooled and washed with water. The products were then fractionated under reduced pressure.

▶ *Methyl 3-methyl-4-(methylthio)phenyl phosphorochloridothionate* (**8**) (Fig. 5.4.3) (*19*). A solution of 3-methyl-4-(methylthio)phenol (6.46 g, 42.1 mmol) in acetonitrile (20 ml) was added dropwise to a stirred solution of methyl phosphorodichloridothionate (7.64 g, 46.3 mmol) in acetonitrile (30 ml) containing finely ground anhydrous potassium carbonate (6.34 g, 46.3 mmol). After stirring for 1 h at room temperature, the mixture was filtered through Celite™ and the solvent was removed from the filtrate under reduced pressure. Column chromatography of the residue on silica gel eluting with 1:1 benzene–hexane gave a colourless syrup (6.47 g, 55%). R_f 0.68.

▶ *Dialkyl phosphorochloridothionates $(RO)_2P(S)Cl$ (from phosphorus pentasulfide)* (Fig. 5.4.4) (*20*). The appropriate alcohol (2 mol) was added over 1.5–2.5 h to phosphorus pentasulfide (0.5 mol) suspended in benzene (150 ml) at 65–80 °C. Sufficient heat was provided to maintain the mixture at reflux. Refluxing was continued for 2 h and the temperature of the mixture rose to 90–100 °C. The mixture was cooled to room temperature and chlorine (91 g, 1.28 mol) was passed below the surface of the liquid for 75–90 min. The temperature was kept at 25–30 °C by controlling the rate of introduction of chlorine and by occasional application of an ice bath. The mixture was stirred for 15–20 min to complete the reaction; the mixture was then added over 30–45 min to water (350 ml) to destroy the sulfur chlorides. During this time, good stirring was essential and ice was added if necessary to keep the hydrolysis mixture at 25–35 °C. Sulfur separated sometimes as a curd-like solid or a sticky ball. After stirring for a short time to ensure complete hydrolysis, the mixture was filtered through Celite™ and

dried ($CaCl_2$). Filtering and distillation of the filtrate gave the dialkyl phosphorochloridothionates listed in Fig. 5.4.4.

▶ *Diphenyl phosphorochloridothionate $(PhO)_2P(S)Cl$* (**10**) *(from phosphorus pentasulfide)* (Fig. 5.4.5) (*20*). A mixture of phenol (376 g, 4.00 mol) and powdered phosphorus pentasulfide (222 g, 1.00 mol) was stirred and heated at 130–140 °C for 2 h. The dark-coloured mixture was cooled and crystallised from 1:1 *v/v* benzene–hexane (500 ml) to give *O,O*-diphenyl hydrogen phosphorodithioate **9** (410 g, 73%). Mp 58–62 °C (a small portion was recrystallised from the same solvent giving white crystals, mp 62.5–63.5 °C). Chlorine (110 g, 1.55 mol) was passed over 2 h into a stirred solution of the phosphorodithioate (282 g, 1.00 mol) in benzene (500 ml) at 15–25 °C (periodic cooling with an ice bath). After all the chlorine had been added, the mixture was stirred for a few minutes, and added slowly with efficient stirring to water (500 ml). The temperature of the hydrolysis mixture was kept at 25–35 °C by adding ice. The organic layer was separated, filtered, and the solvent removed from the filtrate. Crystallisation of the crude product from acetone gave the title compound (175 g, 61%). Mp 68–71 °C.

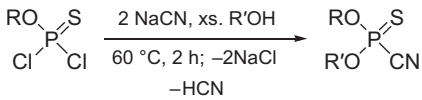
▶ *Diphenyl phosphorochloridothionate $(PhO)_2P(S)Cl$* (**10**) *(from the diaryl H-thiophosphonate and sulfuryl chloride)* (Fig. 5.4.6) (*17*). A solution of sulfuryl chloride (8.2 g, 61 mmol) in benzene (10 ml) was added dropwise to a stirred solution of diphenyl *H*-thiophosphonate (13.5 g, 54 mmol) in benzene (50 ml) at 0 °C and the whole stirred for 1 h. The volatiles were removed and the residue was crystallised from hot ethanol to give the product (6.1 g, 40%). Mp 67 °C.

▶ *Di-n-propyl phosphorochloridothionate $(n\text{-}PrO)_2P(S)Cl$* (**11**) *(from the dialkyl H-thiophosphonate and sulfuryl chloride)* (Fig. 5.4.6) (*17*). A solution of sulfuryl chloride (4.5 g, 33 mmol) in benzene (10 ml) was added dropwise to a stirred solution of di-*n*-propyl *H*-thiophosphonate (6.0 g, 33 mmol) in benzene (30 ml) at 5 °C and the whole stirred for 1 h. The solvent was removed and the residue distilled to provide the product (5.0 g, 70%). Bp 113–114 °C/14 mmHg.

5.5 DIALKYL PHOSPHOROCYANIDOTHIONATES $(RO)_2P(S)CN$

Schrader prepared the first examples of these compounds by treating alkyl phosphorodichloridothionates with sodium cyanide and an alcohol (Fig. 5.5.1) (*22*). These substances are relatively nontoxic and are insoluble in water and not as easily hydrolysed as the corresponding dialkyl phosphorocyanidates $(RO)_2P(O)CN$. The stability of dialkyl phosphorochloridothionates to hydrolysis permits their cyanidation under two-phase conditions. Thus, treatment of solutions of dimethyl and diethyl phosphorochloridothionates in dichloromethane with aqueous potassium cyanide in the presence of a PTC gives dialkyl phosphorocyanidothionates (**12**) and (**13**) in modest yields (Fig. 5.5.2) (*23*).

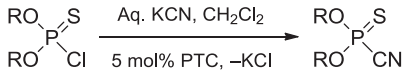
▶ *Dimethyl phosphorocyanidothionate $(MeO)_2P(S)CN$* (**12**) (*23*). A solution of dimethyl phosphorochloridothionate (8.03 g, 0.05 mol) in dichloromethane (25 ml) was added to a stirred mixture of aqueous potassium cyanide (6.50 g, 0.10 mol in 40 ml of water), dichloromethane (125 ml) and cetyltrimethylammonium bromide (5 mol%) at room temperature. After stirring for 15 h, the organic layer was separated, washed with water (2 × 25 ml) and dried ($MgSO_4$). Evaporation of the solvent



Dialkyl phosphorocyanidothionates

R	R′	Bp (°C/mmHg)
Me	Me	68/13
Me	Et	86/12
Et	Et	88/13
Et	*n*-Pr	98/12
Et	*i*-Pr	97/12
Et	$MeOCH_2CH_2$	125/12
n-Pr	*n*-Pr	115/12

Figure 5.5.1



PTC = cetyltrimethyl–ammonium bromide

R = Me **12** 52%
R = Et **13** 72%

Figure 5.5.2

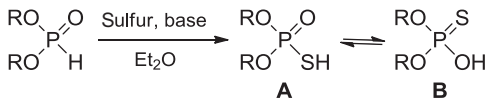
revealed a reddish brown liquid. Fractionation under reduced pressure using a spinning band column gave the title compound (3.93 g, 52%). Diethyl phosphorocyanidothionate (bp 104–105 °C/19 mmHg) can be prepared similarly in 72% yield starting from diethyl phosphorochloridothionate.

▷ *Diethyl phosphorocyanidothionate* $(EtO)_2P(S)CN$ (**13**) (*22*). Ethyl phosphorodichloridothionate (54 g, 0.3 mol) was added dropwise to a stirred suspension of sodium cyanide (45 g, 0.9 mol) in absolute ethanol (300 ml, 5.1 mol) at 55–60 °C. After addition the mixture was heated to 60 °C for 2 h. Standard work-up gave diethyl phosphorocyanidothionate (40 g, 74%). Bp 88 °C/13 mmHg. The use of other alcohols in place of ethanol gave the unsymmetrical products listed in Fig. 5.5.1.

5.6 *O,O*-DIALKYL HYDROGEN PHOSPHOROTHIOATES $(RO)_2P(S)OH$

These compounds exist in equilibrium with their oxo tautomers $(RO)_2P(O)SH$ (**A**) and for this reason are also discussed in Chapter 4. However the major tautomer present in solution, sometimes almost exclusively, tends to be the thiono tautomer $(RO)_2P(S)OH$ (**B**) (Fig. 5.6.1) (*24*). A useful general method for the synthesis of *O,O*-dialkyl hydrogen phosphorothioates is the reaction of dialkyl *H*-phosphonates, some of which are commercially available or easily synthesised from

phosphorus trichloride and an alcohol, with sulfur in the presence of a base such as triethylamine (*25–31*). A solvent such as ether is usually used, and acidic work-up followed by distillation of the product gives the hydrogen phosphorothioate in typically good to excellent yields.



Disubstituted hydrogen phosphorothioates

R	Yield (%)	Reference
Me	98	25
Et	68	26
n-Pr	89	27
i-Pr	81	27
n-Bu	86	27
t-$BuCH_2$	83	27
$ClCH_2CH_2$	62	27
$Cl(CH_2)_2CH_2$	62	27
$Cl(CH_2)_3CH_2$	69	27
$MeOCH_2CH_2$	18	27
2-Ethylhexyl	79	28
C_8H_{18}	70	29
Cyclohexyl	67	27
Adamantyl	95	30
Ph	not stated	31

Figure 5.6.1

Acidic work-up can be detrimental if the dialkyl hydrogen phosphorothioate product has acid-labile alkyl groups; the hydrogen phosphorothioate derived from $[(MeO)_2CHCH_2O]_2P(O)H$ was isolated in only 18% yield due to presumed hydrolysis of the acetal side chain during work-up (*25*). For certain applications, notably the synthesis of oligonucleotide *O,O*-dialkyl hydrogen phosphorothioates, the low solubility of sulfur in organic solvents can be problematic. More soluble sulfurising reagents to circumvent the dependency on elemental sulfur have been developed. For isolation of *O,O*-dialkyl phosphorothioate ammonium salts, liquid ammonia is a useful solvent; it avoids an acidic work-up and tolerates acid-sensitive *H*-phosphonate starting materials (*32*).

Oligodeoxyribonucleotide phosphorothioates (*S*-oligos **14**) find application as antisense molecules and effort has been expended in the search for efficient methods to produce them from the corresponding dialkyl *H*-phosphonates (Fig. 5.6.2). The sulfur atom in *S*-oligos renders the phosphorus group less reactive to enzymatic hydrolysis and increases the potential for these compounds to cross

lipid bilayers. The use of sulfur to accomplish this reaction is hindered by its low solubility in organic media. Carbon disulfide as a solvent to help dissolve the sulfur has been suggested, but it has associated toxicity and flammability problems. The rate of reaction of oligodinucleotide dialkyl *H*-phosphonates with sulfur is slow, making the synthesis of large amounts of product inefficient.

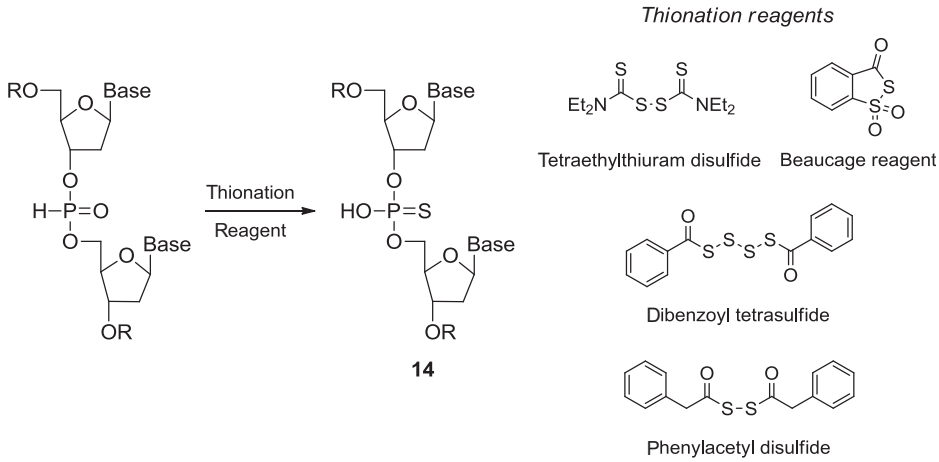


Figure 5.6.2

Reagents that can be used instead of sulfur include tetraethylthiuram disulfide (TETD) (*33*), 3*H*-1,2-benzodithiol-3-one 1,1-dioxide (Beaucage reagent) (*34*) and 2,4-*bis*(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson reagent) (*35*). Low concentrations (0.05—0.2 M) of Beaucage reagent in acetonitrile convert dinucleoside phosphite triesters to the phosphorothionates in >99% yield in 30 s at room temperature (Beaucage reagent also thionates dialkyl *H*-phosphonates). Dibenzoyl tetrasulfide effects rapid thionation and has acceptable solubility properties for solid-phase synthesis of nucleotides. A solution of this reagent in tetrahydrofuran (0.4 M) gave nearly quantitative yields of thionated product in 1 min. Phenylacetyl disulfide and TETD react with trialkyl phosphites more slowly than the Beaucage reagent (*36*). *Bis*[3-(triethoxysilyl)propyl] tetrasulfide, a liquid sulfurising agent used in solution-phase synthesis, has been suggested for the solid-phase synthesis of *S*-oligos (*37*).

▶ *O,O-Diisopropyl hydrogen phosphorothioate (i-PrO)$_2$P(S)OH (from diisopropyl H-phosphonate, sodium isopropoxide and sulfur)* (*27*). A solution of diisopropyl *H*-phosphonate (2.16 g, 13 mmol) in ether (4 ml) was added to a stirred solution of sodium isopropoxide made from sodium (0.29 g, 13 mmol) and isopropanol (4 ml). After stirring for 1 h at room temperature, sulfur (0.40—0.60 g, 13—19 mmol) was added in portions over 1 h, and the mixture was stirred for 48 h more. Excess sulfur was filtered off and the filtrate was concentrated. The residue was dissolved in ethyl acetate (20 ml), washed with saturated aqueous sodium bicarbonate (3 × 10 ml) and the aqueous extracts combined. The combined extracts were acidified with 12 M HCl at 0 °C and extracted with ethyl acetate (3 × 20 ml). The combined

organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to give a pale yellow liquid (2.00 g, 80%). δ_P (121.5 MHz, $CDCl_3$) 56.3 ppm.

▶ *O,O-Diisopropyl hydrogen phosphorothioate (i-PrO)$_2$P(S)OH (from diisopropyl H-phosphonate, liquid ammonia and sulfur)* (*32*). A flask containing a magnetically stirred suspension of powdered sulfur (0.32–0.38 g, 10–12 mmol) in anhydrous liquid ammonia (15–25 ml) was cooled to −35 °C (dry-ice bath). The suspension was stirred for 20 min, and freshly prepared diisopropyl *H*-phosphonate (1.66 g, 10 mmol) dissolved in anhydrous ether (0.5 ml) was added. Stirring was continued for 6–8 h at −33 to −35 °C. The cooling bath was removed and the mixture was stirred until the ammonia had evaporated. The crude product was dissolved in anhydrous chloroform (10–15 ml) and the solution was filtered through Celite™. Evaporation of the solvent and drying of the solid residue for 2 h at room temperature at 0.01–1.00 mmHg gave practically analytically pure product (90%). Mp 143–144 °C. δ_P 55.3 ppm.

▶ *O,O-Diisobutyl hydrogen phosphorothioate (i-BuO)$_2$P(S)OH* (*27*). Triethylamine (8.0 ml, 58 mmol) was added slowly to a mixture of diisobutyl *H*-phosphonate (10.00 g, 51 mmol) and sulfur (1.82 g, 56 mmol) in ether (40 ml) under argon. Upon full conversion to the product, as indicated by ^{31}P NMR spectroscopy, the suspension was diluted with ether to a volume of 100 ml and washed with aqueous 1 M HCl (100 ml), dried ($MgSO_4$), concentrated under reduced pressure and dried under high vacuum. The resulting suspension was filtered through a small cotton plug to provide a yellow liquid (10.15 g, 87%). δ_P (121.5 MHz, $CDCl_3$) 59.2 ppm.

Treatment of dialkyl phosphorochloridothionates (**15**) with aqueous sodium hydroxide followed by acidification with hydrochloric acid gives the corresponding *O,O*-dialkyl hydrogen phosphorothionate (**16**) which is converted to the sodium salt (**17**) by passage through an ion exchange resin (Fig. 5.6.3) (*38,39*). Hydrolysis of the unsymmetrical phosphorochloridothionate (**18**) also occurs similarly to provide the hydrogen phosphorothioate (**19**) (*39*).

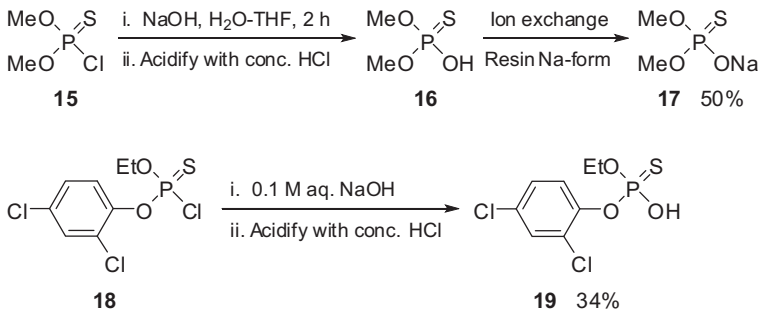


Figure 5.6.3

▶ *O,O-Dimethyl sodium phosphorothioate (MeO)$_2$P(S)ONa* (**17**) (*38*). Dimethyl phosphorochloridothionate (3.2 g, 20 mmol) was added dropwise to a stirred mixture of tetrahydrofuran (20 ml), sodium hydroxide (1.7 g, 42 mmol) and water (10 ml). The mixture was stirred for 2 h and the volatile material was removed under reduced pressure. The aqueous solution was washed with dichloromethane (2 × 50 ml) and acidified with 6 M hydrochloric acid. The acidic aqueous solution

was extracted with dichloromethane (4 × 25 ml) to collect *O,O*-dimethyl hydrogen phosphorothioate **16**. The organic layer was concentrated, dissolved in water (10 ml), and passed through an ion exchange column (Na^+ form) to give the title compound (50% yield).

▶ *O-(2,4-Dichlorophenyl) O-ethyl hydrogen phosphorothioate* (**19**) (*39*). A solution of 2,4-dichlorophenol (0.81 g, 5 mmol) and triethylamine (1.4 ml, 10 mmol) in anhydrous benzene (10 ml) was added dropwise over 10 min to a stirred solution of thiophosphoryl chloride (0.51 ml, 5 mmol) in anhydrous benzene (10 ml) at 5–10 °C. Stirring was continued for 4 h, followed by the dropwise addition of ethanol (0.29 ml, 5 mmol) in anhydrous benzene (5 ml). The mixture was stirred at room temperature for 18 h and filtered. The residue was dissolved in 0.1 M NaOH (50 ml). After extraction with ether (60 ml), the aqueous phase was acidified to pH 1 with a few drops of concentrated hydrochloric acid, and extracted again with ether (60 ml). The combined ether extracts were dried (Na_2SO_4), filtered and concentrated to give a colourless liquid. Chromatography on silica gel, eluting with 9.5:0.5 hexane–ether, gave a pure sample (0.48 g, 34%).

Phosphorus pentasulfide reacts with 2 molar equivalents of pyridine to give a product (**20**) that on treatment with ethanol provides *O,O*-diethyl pyridinium phosphorothioate (**21**) in quantitative yield (Fig. 5.6.4) (*40*).

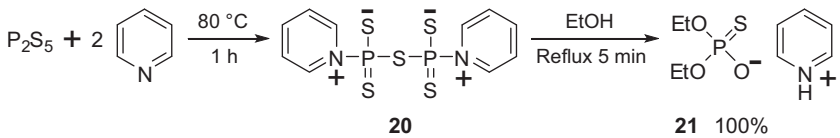


Figure 5.6.4

▶ *O,O-Diethyl pyridinium phosphorothioate* $(EtO)_2P(S)OH \cdot C_6H_5N$ (**21**) (*40*). Phosphorus pentasulfide (44.5 g, 0.2 mol) was added in portions to stirred anhydrous pyridine (560 ml) at 80 °C. After heating under reflux for 1 h, a clear yellow solution was obtained that deposited light-yellow crystals upon cooling. After 2 h the crystals were collected, washed with anhydrous acetonitrile, and transferred to a desiccator (containing a beaker filled with concentrated sulfuric acid to remove traces of pyridine). Yield 62.3 g (84%). Mp 167–169 °C. This material (1.0 g) in ethanol (5 ml) was heated under reflux for 5 min and the clear solution obtained was evaporated to give the title compound as a liquid that solidified (100%). ^{1}H NMR (300 MHz, DMSO-d_6) 1.08 (t, $J = 7$ Hz, 6 H), 3.79 (m, 4H), 8.09 (m, 2 H), 8.62 (m, 1 H), 8.97 (m, 2 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 16.1 (q, $^3J_{PC}$ 9 Hz), 59.8 (t, $^2J_{PC}$ 7 Hz), 127.2 (d), 142.5 (d), 146.0 (d).

Treatment of trialkyl phosphites and dialkyl *H*-phosphonates with dibenzoyl disulfide or phenacetyl disulfide in the presence of *N,N*-diisopropylethylamine (Hűnig's base) gives, respectively, trialkyl phosphorothionates $(RO)_3P{=}S$ and *O,O*-dialkyl hydrogen phosphorothioates $(RO)_2P(S)OH$. Treatment of triethyl phosphite with phenacetyl disulfide in 1,2-dichloroethane at 20 °C gives within 5 min triethyl phosphorothionate in 70% yield after distillation. The analogous reaction with dimethyl *H*-phosphonate gives a highly coloured mixture, although the use of benzoyl disulfide

gives *O,O*-dimethyl hydrogen phosphorothioate in 95% yield (*41*). The reaction of trialkyl phosphites with hydrogen sulfide in the presence of pyridine gives the corresponding trialkyl phosphorothionates in good yield. The amine base influences the course and rate of the reaction: out of triethylamine, diethylamine, *N,N*-diethylaniline, and pyridine, the latter, in conjunction with an alkali alkoxide catalyst, gave the highest yield of product (**22**) (Fig. 5.6.5) (*42*).

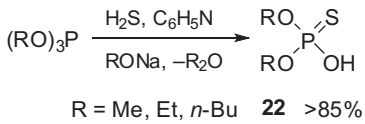


Figure 5.6.5

Selective demethylation of phosphorothioic *O*-methyl esters with lithium chloride generates the corresponding thioacids. One example is the demethylation of *O,O*-dimethyl *O*-(2-chloro-4-nitrophenyl) phosphorothionate (**23**) with lithium chloride and 18-crown-6 in acetone to provide *O*-(2-chloro-4-nitrophenyl) *O*-methyl hydrogen phosphorothioate (**24**) (Fig. 5.6.6) (*43*). The success of such reactions hinges on the greater propensity of a methyl ester group to dealkylate compared to higher alkyl ester groups (which dealkylate more slowly) or aryl ester groups (which do not cleave).

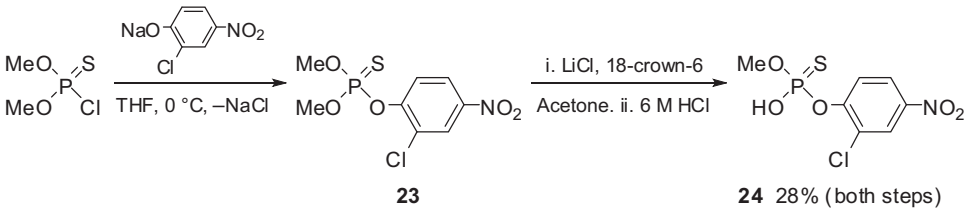


Figure 5.6.6

▶ *O-(2-Chloro-4-nitrophenyl) O-methyl phosphorothioate* (**24**) (*43*). Sodium hydride (60% dispersion in mineral oil; 440 mg, 11 mmol) was added to stirred 2-chloro-4-nitrophenol (1.74 g, 10 mmol) in anhydrous tetrahydrofuran (30 ml) at 0 °C. The mixture was warmed to room temperature and dimethyl phosphorochloridothionate (720 mg, 4.5 mmol) was added dropwise. After 24 h the volatiles were removed under reduced pressure. The crude material was dissolved in ether (50 ml), washed with saturated aqueous potassium carbonate (3 × 10 ml), then brine (10 ml), dried ($MgSO_4$) and the solvent removed. The residue was dissolved in acetone (20 ml) and to this solution was added lithium chloride (420 mg, 10 mmol) and 18-crown-6 (26 mg, 0.1 mmol). The mixture was stirred for 48 h and concentrated. The white solid residue was dissolved in water and washed with dichloromethane (2 × 10 ml). The aqueous layer was acidified to pH ~1 and washed with more dichloromethane (2 × 10 ml). Next the aqueous layer was acidified to 6 M HCl and extracted with dichloromethane until the organic fraction no longer showed a spot by thin layer chomatography observable under ultraviolet light. The organic fractions were combined and the solvent removed to give the title compound (0.35 g, 28%).

5.7 TRIALKYL (OR DIALKYL ARYL) PHOSPHOROTHIONATES $(RO)_2P(S)OR'$

This substructure describes a large number of pesticides including chlorpyrifos, parathion, diazinon, fenitrothion, fenthion and coumaphos (Fig. 5.7.1) (*3–5*). The reaction of thiophosphoryl chloride, alkyl phosphorodichloridothionates, and dialkyl phosphorochloridothionates with a range of alcohols or alkoxides is convenient for preparing trisubstituted phosphorothionates (Table 5.7.1).

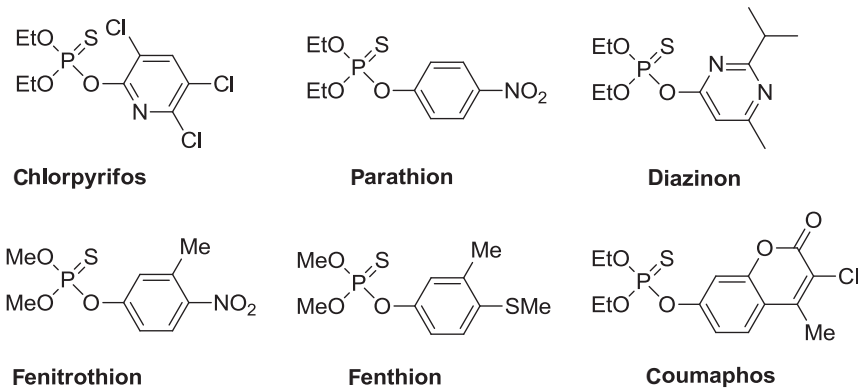


Figure 5.7.1 Some phosphorothionate pesticides.

The reaction of dialkyl phosphorochloridothionates with alkoxides is exemplified by the synthesis of the insecticide chlorpyrifos from diethyl phosphorochloridothionate (**25**) and 3,5,6-trichloropyridin-2-ol. The main production route for chlorpyrifos uses the sodium salt of the pyridinol. Phase-transfer catalysis and single- or two-phase solvent systems can be used. A biphase system of dichloromethane and water in conjunction with a tertiary amine and PTC gives chlorpyrifos in high purity and avoids the formation of sulfotep $[(EtO)_2P(S)]_2O$ from unwanted hydrolysis of diethyl phosphorochloridothionate. Phase-transfer catalysis has been reinvestigated and the reaction optimised on a 0.3 mol scale: the best conditions are water–dichloromethane, 4-(dimethylamino)pyridine (DMAP, 0.5 mol%) and benzyltriethylammonium chloride (BTEAC, 0.5 mol%) at 40 °C for 2 h (Fig. 5.7.2) (*53*). These gave a high yield of chloropyrifos free from sulfotep.

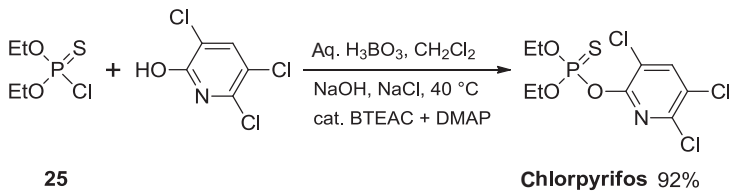


Figure 5.7.2

Table 5.7.1 Reactions of thiophosphoryl chlorides with alkoxides to give phosphorothionates

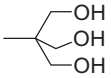
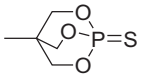
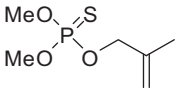
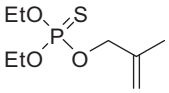
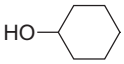
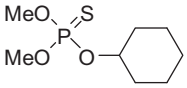
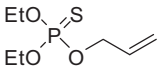
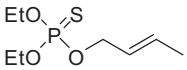
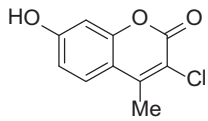
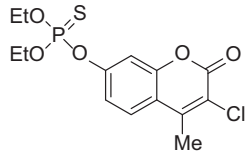
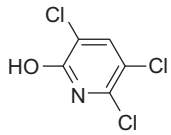
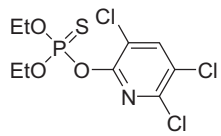
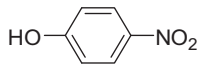
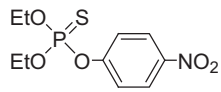
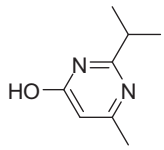
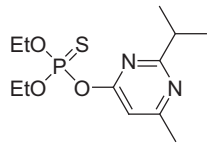
Thiophosphoryl reactant	Alcohol or alkoxide	Product	Yield (%)	Ref.
$PSCl_3$	3 MeOH	$(MeO)_3P{=}S$	56	18
$PSCl_3$			29	44
$MeC({=}CH_2)CH_2OP(S)Cl_2$	2 MeOH		74	45
$MeC({=}CH_2)CH_2OP(S)Cl_2$	2 EtOH		77	45
$(MeO)_2P(S)Cl$	EtOH	$(MeO)_2P(S)OEt$	46	18
$(MeO)_2P(S)Cl$	*n*-PrOH	$(MeO)_2P(S)O$-*n*-Pr	73	18
$(MeO)_2P(S)Cl$	*n*-BuOH	$(MeO)_2P(S)O$-*n*-Bu	30	18
$(MeO)_2P(S)Cl$			-	46
$(EtO)_2P(S)Cl$	$NaOCH_2CH{=}CH_2$		85	47
$(EtO)_2P(S)Cl$	$NaOCH_2CH{=}CHMe$-(*E*)		99	48

Table 5.7.1 Reactions of thiophosphoryl chlorides with alkoxides to give phosphorothionates—cont'd

Thiophosphoryl reactant	Alcohol or alkoxide	Product	Yield (%)	Ref.
$(EtO)_2P(S)Cl$		 **Coumaphos**	58	49
$(EtO)_2P(S)Cl$		 **Chlorpyrifos**	97	50
$(EtO)_2P(S)Cl$		 **Parathion**	94	51
$(EtO)_2P(S)Cl$		 **Diazinon**	97	52

▶ *Chlorpyrifos* (*53*). A solution of boric acid (3.48 g, 57.0 mmol), sodium chloride (1.59 g, 27.0 mmol), sodium hydroxide (1.89 g, 48.0 mmol) and benzyltriethylammonium chloride (0.34 g, 1.5 mmol) in water (375 ml) was added to 3,5,6-trichloropyridin-2-ol sodium salt (73.20 g, 0.33 mol) in a 1-l three-necked reactor. A solution of 4-(dimethylamino)pyridine (0.183 g, 1.5 mmol) in dichloromethane (150 ml) was added and the mixture stirred at 30 °C. A solution of diethyl phosphorochloridothionate (56.10 g, 0.30 mol) in dichloromethane (105 ml) was added over 15 min and the mixture stirred at 40 °C for 2 h. The layers were separated and the organic layer was washed with water (2 × 50 ml) and dried ($CaCl_2$). The solution was filtered and concentrated under reduced pressure to give the product (96.74 g, 92%). δ_P 61.0 ppm.

Thiophosphoryl chlorides are less reactive than the corresponding phosphoryl chlorides to nucleophilic attack which often enables thiophosphorylation to be conducted in water. Treatment

of thiophosphoryl chloride with 2 molar equivalents of sodium ethoxide, followed by aqueous work-up, provides diethyl phosphorochloridothionate (**25**) and its reaction with 4-nitrophenol, sodium hydroxide and powdered copper in water gives parathion in high yield (Fig. 5.7.3) (*54*). Copper (*55*,*56*) or mercury (*57*) catalysts have been used to accelerate parathion and diazinon synthesis.

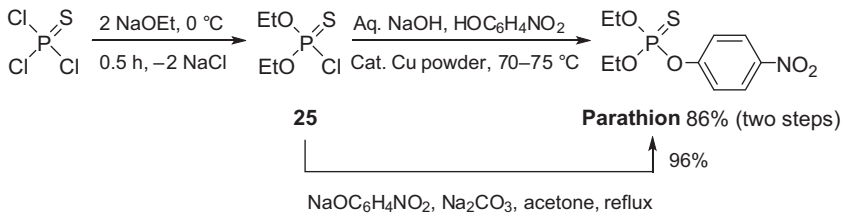


Figure 5.7.3

▶ *Parathion $(EtO)_2P(S)OC_6H_4NO_2$-p (from diethyl phosphorochloridothionate and 4-nitrophenoxide in the presence of copper powder)* (Fig. 5.7.3) (*54*). Sodium ethoxide made from sodium (23.4 g, 1.02 mol) and anhydrous ethanol (310 ml) was added over 30 min to stirred thiophosphoryl chloride (84.7 g, 0.50 mol) at −6 °C, the mixture kept at 0 °C for 30 min, and the resulting solution added to water (1300 ml). The diethyl phosphorochloridothionate layer was separated and added over 1 h to a mixure of *p*-nitrophenol (73 g, 0.52 mol), sodium hydroxide (21.2 g, 0.53 mol), powdered copper (2 g, 0.03 mol) and water (300 ml) at 70−75 °C. The mixure was treated with sodium carbonate (5 g), kept at 70−75 °C for 1 h, filtered and the filtrate evaporated to yield parathion (125.1 g, 86%).

▶ *Parathion $(EtO)_2P(S)OC_6H_4NO_2$-p (from diethyl phosphorochloridothionate and 4-nitrophenoxide in the presence of sodium carbonate)* (Fig. 5.7.3) (*20*). A stirred mixture of equimolar amounts (e.g. 0.2 mol) of diethyl phosphorochloridothionate, 4-nitrophenol, and anhydrous sodium carbonate in acetone or methyl ethyl ketone (500−1000 ml/mol) was heated under reflux for 3−5 h. The mixture was cooled to room temperature and filtered (to separate sodium chloride and sodium bicarbonate) and the solvent was removed from the filtrate under vacuum. Parathion of good quality (purity ∼95%) was obtained by dissolving the residue in benzene, washing with dilute sodium carbonate and then water, drying, and concentrating again under reduced pressure. Heating (oil bath: 110 °C) at 1 mmHg removed traces of unreacted diethyl phosphorochloridothionate. Parathion analogues having different ester groups were prepared analogously from the appropriate dialkyl phosphorochloridothionate.

Addition of sulfur to 4-nitrophenyl phosphorodichloridite (**26**) gives 4-nitrophenyl phosphorodichloridothionate (**27**) that reacts with 2 mol of ethanol and pyridine to produce parathion (Fig. 5.7.4) (*58*).

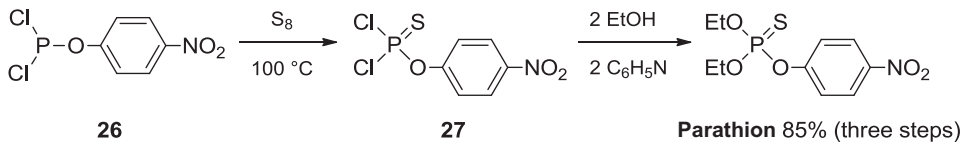


Figure 5.7.4

▶ *Parathion $(EtO)_2P(S)OC_6H_4NO_2$-p (from 4-nitrophenyl phosphorodichloridite, sulfur and ethanol)* (*58*). 4-Nitrophenol (135 g, 0.97 mol) was stirred over 15 min into a solution of phosphorus trichloride (135 g, 0.99 mol) in carbon tetrachloride (150 ml) at about 60 °C. The mixture was heated to evaporate part of the carbon tetrachloride and the residue was added to sulfur (34 g, 1.06 mol). The mixture was heated under reflux until most of the sulfur dissolved. The temperature of the mixture was about 100 °C at the beginning of the refluxing period, but rose during the 24 h of reflux. The mixture was cooled and filtered through glass wool to remove unreacted sulfur. The crude product was added to a mixture of anhydrous ethanol (100 ml, 1.71 mol) and pyridine (158 g, 2.00 mol) while maintaining the temperature of the mixture at about 60 °C. A rapid reaction occurred: the mixture was held at 60 °C for 30 min after the addition was complete and then cooled and stirred slowly into water (700 ml). The two layers were separated and the lower layer was washed with dilute hydrochloric acid. The oily layer was distilled to give parathion (240 g, 85%).

Diethyl phosphorochloridothionate (**25**) reacts with the sodium salt of 2-isopropyl-4-methyl-6-hydroxypyrimidine in benzene in the presence of copper(II) chloride to give diazinon in high yield (Fig. 5.7.5) (*56*).

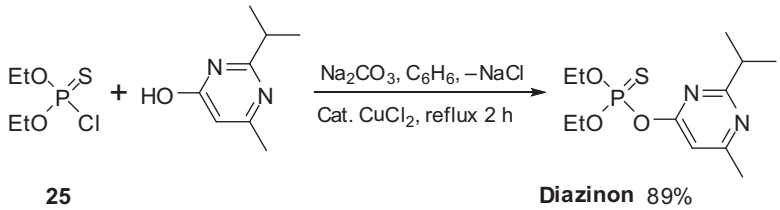


Figure 5.7.5

Diazinon (*56*). A mixture of 2-isopropyl-4-methyl-6-hydroxypyrimidine (210 g, 1.38 mol), sodium carbonate (139 g, 1.31 mol) and benzene (500 ml) was heated under reflux for 2 h with azeotropic removal of water. At 70 °C, diethyl phosphorochloridothionate (247 g, 1.31 mol) was added. The mixture was refluxed for 145 min with addition at 10 min intervals of aliquots (0.3 ml) of a solution (1.66 ml) of copper(II) chloride dihydrate (1.68 g, 9.85 mmol) in water (5 ml) to yield diazinon (354 g, 89%). Diazinon of 99% purity (a colourless liquid, R_f 0.2) can be obtained by column chromatography on silica gel, eluting with 12:1 hexane—acetone (*59*).

Trialkyl phosphites react with sulfur exothermically to produce trialkyl phosphorothionates (Fig. 5.7.6) (*60*). Lawesson reagent can be used instead of sulfur. Tri-*n*-propyl phosphite and this reagent heated in refluxing benzene gave tri-*n*-propyl phosphorothionate in 47% yield (*61*).

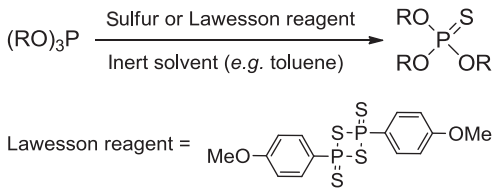
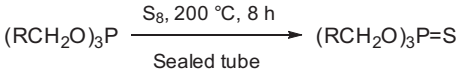


Figure 5.7.6

▶ *Triethyl phosphorothionate (EtO)$_3$P═S* (*60*). Powdered sulfur (3.5 g, 0.11 mol) was added in portions to a stirred solution of triethyl phosphite (16.6 g, 0.10 mol) in toluene (60 ml). An exothermic reaction caused the sulfur to dissolve. The mixture was heated under reflux for 3 h. Progress of reaction was monitored by ^{31}P NMR spectroscopy (disappearance of the signal at δ_P 138.3 ppm for triethyl phosphite). The mixture was filtered, the solid residue discarded, and the filtrate evaporated and dried to obtain the product (19.8 g, 100%). Bp 91–92 °C/10 mmHg. δ_P −68.3 ppm.

Trialkyl phosphites bearing polyfluorinated alkyl groups have a phosphorus atom of low nucleophilicity and add sulfur only under forcing conditions. Tris(polyfluoroalkyl) phosphites (**28a–c**) need to be heated with sulfur in a sealed tube to 200 °C for 8 h (Fig. 5.7.7) (*62*). Although conversion to the product does not exceed 50%, the thionates (**29a–c**) are easily isolated in a pure state after column chromatography on silica gel.



28a	R = CF_3	**29a**	30%	δ_P −68.5
28b	R = C_2F_5	**29b**	34%	δ_P −68.0
28c	R = C_3F_7	**29c**	31%	δ_P −68.1

Figure 5.7.7

▶ *Tris(polyfluoroalkyl) phosphorothionates* (**29a–c**) (*62*). The appropriate tris(polyfluoroalkyl) phosphite (20 mmol) was placed in a borosilicate tube (Pierce vacuum hydrolysis tube, Rockford, IL, USA) and finely divided sulfur (2.56 g, 80 mmol) was added. The tube was sealed by tightening the Teflon® screw valve and heated to 200 °C for 8 h in an aluminium block (Reacti-Therm™ heating module, Rockford, IL, USA). The mixture was cooled to room temperature and an aliquot withdrawn. Analysis of this by gas chromatography–mass spectrometry showed not more than 50% conversion to product. Excess sulfur was removed from the mixture by filtration and the filtrate concentrated by rotary evaporation. Chromatography of the residue over silica gel, eluting with 20:1 hexane–acetone, gave the title compounds as yellow liquids. Yields and ^{31}P NMR spectroscopic data measured in $CDCl_3$ appear in Fig. 5.7.7.

5.8 DIALKYL ENOL PHOSPHOROTHIONATES $(RO)_2P(S)OCR{=}CR'_2$

Dialkyl enol phosphorothionates are relatively rare and are prepared by thiophosphorylation of enolates. For example, α-acetyl-γ-butyrolactone (**30**) and lithium *N,N*-diisopropylamide (LDA) provide enolate (**31**) which reacts with dialkyl phosphorochloridothionates to give dialkyl enol phosphorothionates (**32**) (Fig. 5.8.1) (*63*). Six-membered α-carboethoxy lactones (**33**) produce enolates (**34**) that add to dialkyl phosphorochloridothionates to give mainly enol phosphorothionates (**35**) with the *E*-configuration of the alkene double bond.

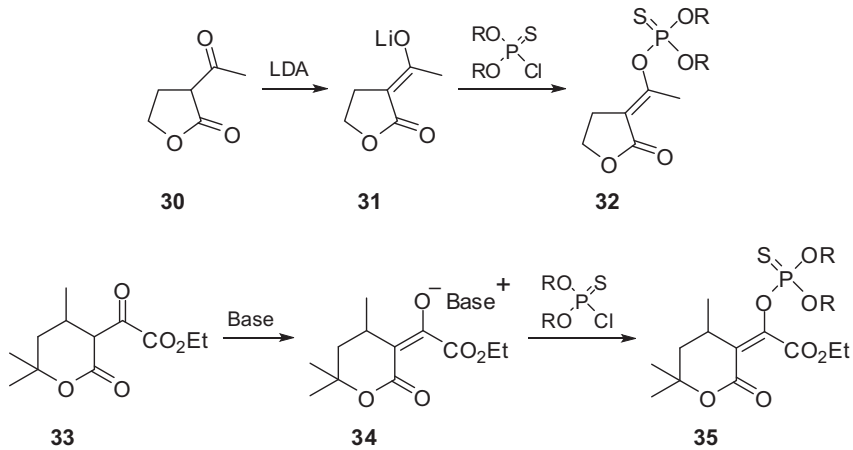


Figure 5.8.1

The phase-transfer catalysed thiophosphorylation of pentane-2,4-dione and ethyl acetoacetate has a specific stereochemical outcome (Fig. 5.8.2) (*64*). Thiophosphorylation of pentane-2,4-dione (**36a**) gives a 71% conversion to essentially equal amounts of *E*- and *Z*-alkenes. In contrast, thiophosphorylation of ethyl acetoacetate (**36b**) results in 45% conversion to the *E*-isomer only. Conversion using sodium hydride of 2,2′,5′-trichloroacetophenone (**37**) to its enolate and addition of this to diethyl phosphorochloridothionate gives product (**38**) (*65*). The reaction of dimethyl 2-(diethyl phosphorothiolothionyl)malonate (**39**) with methyl iodide proceeds with 1,4-*S* to *O* migration of the thiophosphoryl group to yield the corresponding diethyl enol phosphorothionate (**40**) (*66*).

▶ *Diethyl enol phosphorothionates* $(EtO)_2P(S)OC(Me){=}CHCOR$ *(R = Me, OEt)* (**36a**,**b**) (*64*). The β-dicarbonyl compound (10 mmol) in dichloromethane (25 ml) was added to stirred tetrabutylammonium hydrogensulfate (2 mmol) in 2 M aqueous sodium hydroxide (10 ml). Diethyl phosphorochloridothionate (1.89 g, 10 mmol) was added dropwise over 5 min and stirring was continued for another 30 min. The aqueous layer was separated, washed with dichloromethane (10 ml), the organic layers combined, washed with water (2 × 10 ml), dried ($MgSO_4$), filtered and concentrated. Residual ammonium salts were precipitated by addition of ether (25 ml) and the mixture was filtered. Evaporation of the solvent from the filtrate gave the title compounds.

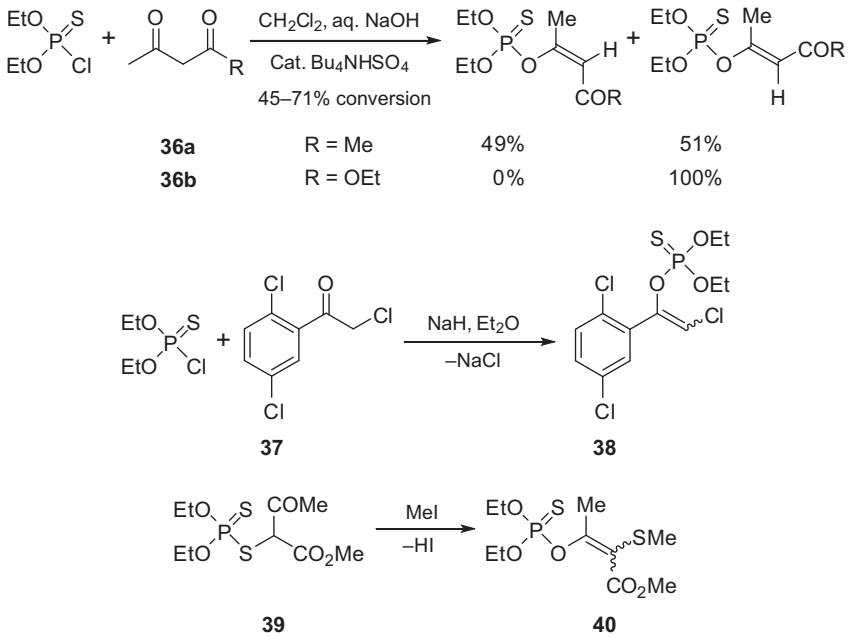


Figure 5.8.2

▶ *Diethyl 2-chloro-1-(2,5-dichlorophenyl)vinyl phosphorothionate* (**38**) (*65*). Diethyl phosphorochloridothionate (46.6 g, 0.25 mol) was added over 15 min to a stirred suspension of sodium hydride (50% dispersion in mineral oil; 4.95 g, 0.10 mol) in ether (100 ml). A solution of 2,2′,5′-trichloroacetophenone (46 g, 0.21 mol) in ether (200 ml) was added and the mixture was stirred for 5.5 h. After heating under reflux for another 1.5 h, the mixture was filtered, concentrated, and extracted with pentane to give the crystalline product. Mp 27.5–28.5 °C.

5.9 *O,O*-DIALKYL *O*-OXIMINO PHOSPHOROTHIONATES $(RO)_2P(S)ON{=}CR'_2$

The insecticide phoxim is a mixture of *E*- and *Z*-thiophosphoryl oximes and is synthesised by treating diethyl phosphorochloridothionate with the sodium salt of phenyl glyoxylonitrile oxime (Fig. 5.9.1) (*67*). Large-scale production of phoxim in China was accomplished in 95% yield by adding benzyl cyanide, ethyl nitrite, and sodium hydroxide to a continuous reactor, to generate NaON=C(CN)Ph, which was then treated with diethyl phosphorochloridothionate. The use of the oxime, an amine (e.g. triethylamine) and a PTC (e.g. benzyltriethylammonium chloride or 18-crown-6) also provides phoxim in acceptable yield.

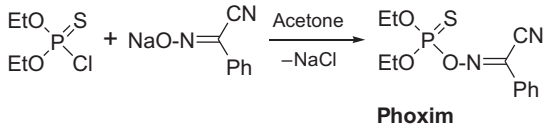


Figure 5.9.1

▶ *O,O-Diethyl O-(α-cyanobenzylideneamino) phosphorothionate (phoxim)* (*68*). Diethyl phosphorochloridothionate (5.7 g, 30 mmol) was added dropwise to sodium phenyl glyoxylonitrile oxime (6.1 g, 36 mmol) suspended in anhydrous acetone (20 ml). The mixture was stirred for 1 h, poured into water, and extracted with benzene. The benzene extracts were dried over molecular sieves, decanted, and the solvent was removed to give the pesticide.

Many *O,O*-dialkyl *O*-oximino phosphorothionates have been made as potential pesticides by two methods (*69*). The first comprises the reaction of dialkyl *H*-thiophosphonates (**41**) with carbon tetrachloride to generate a dialkyl phosphorochloridothionate (**42**) that combines with the oxime to give the product (**43**) (Fig. 5.9.2). The dialkyl *H*-thiophosphonates and carbon tetrachloride are believed to enter into an Arbuzov reaction involving nucleophilic attack of the dialkyl *H*-thiophosphite tautomer $(RO)_2P{-}SH$ on carbon tetrachloride to produce the intermediate dialkyl phosphorochloridothionate (*70*). The second method comprises the reaction of dialkyl *H*-thiophosphonates with nitroso chlorides $ClON{=}CR_2$ in the presence of a base (not shown).

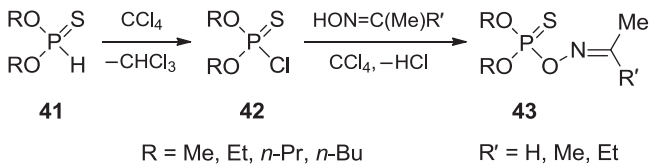


Figure 5.9.2

An unusual rearrangement reaction between disubstituted phosphorochloridothionates and oximes sometimes occurs. For example, diphenyl phosphorochloridothionate (**10**) reacts with *N*-phenylacetamidoxime to give an unstable intermediate (**44**) which loses sulfur to give a phosphorylated amidine (**45**) (Fig. 5.9.3) (*71*).

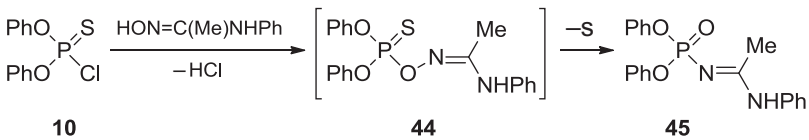
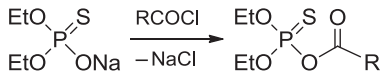


Figure 5.9.3

5.10 *O,O*-DIALKYL *O*-ACYL PHOSPHOROTHIONATES $(RO)_2P(S)OC(O)R'$

O,O-Diethyl phosphorothioate sodium salts react with acetyl chloride, methyl chloroformate, and ethyl chloroformate when heated on a steam bath, yielding the *O,O*-diethyl *O*-acyl phosphorothionates (Fig. 5.10.1) (*72*).

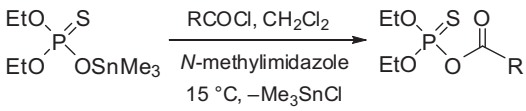


O,O-Diethyl *O*-acyl phosphorothionates

R	Yield (%)	Bp (°C/mmHg)
Me	71	89–90/4
OMe	43	115–117/4
OEt	21	72–74/2.5

Figure 5.10.1

Similarly, *O,O*-diethyl *O*-(trimethylstannyl) phosphorothionates react with acetyl chloride or trifluoroacetic anhydride to give *O,O*-diethyl *O*-acyl phosphorothionates (**46a**,**b**) in quantitative yield (Fig. 5.10.2) (*73*).

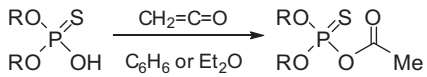


R = CH_3 **46a** 100% δ_P 58.0
R = CF_3 **46b** 100% δ_P 56.0

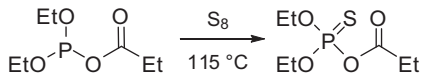
Figure 5.10.2

▶ *O,O-Diethyl O-acetyl/trifluoroacetyl phosphorothionates* $(EtO)_2P(S)OC(O)CH_3/CF_3$ (**46a**/**46b**) (*73*). A solution of *N*-methylimidazole (82 mg, 1 mmol) in anhydrous dichloromethane (5 ml) was added to a stirred solution of acetyl chloride (0.79 g, 10 mmol) or trifluoroacetic anhydride (2.1 g, 10 mmol) in anhydrous dichloromethane (20 ml) at 15 °C. To this mixture was added a solution of *O,O*-diethyl *O*-(trimethylstannyl) phosphorothionate (3.3 g, 10 mmol) in anhydrous dichloromethane (20 ml). The mixture was stirred for 1 h at room temperature and volatile material was removed under vacuum (30 °C/0.01 mmHg) to give the pure title compounds.

O,O-Dialkyl hydrogen phosphorothioates add to ketene to yield *O,O*-dialkyl *O*-acetyl phosphorothionates (**46a**, **47a**,**b**) (Fig. 5.10.3) (*74*). A trivalent approach is also feasible: diethyl proprionyl phosphite (**48**) and sulfur when heated together give *O,O*-diethyl *O*-proprionyl phosphorothionate (**49**) (*75*).



R = Et **46a** 79%
R = *i*-Pr **47a** 70%
R = *n*-Bu **47b** 84%



48 **49**

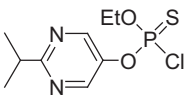
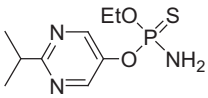
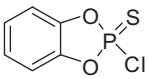
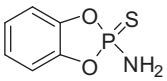
Figure 5.10.3

▶ *O,O-Diethyl O-proprionyl phosphorothionate* $(EtO)_2P(S)OC(O)C_2H_5$ (**49**) (*75*). Sulfur (1.28 g, 40 mmol) was added with stirring to diethyl proprionyl phosphite (8.86 g, 45 mmol). The mixture was heated at 115 °C until the sulfur had dissolved. The crude product was purified by distillation (yield not stated). Bp 72–74 °C/8.5 mmHg.

5.11 DIALKYL PHOSPHORAMIDOTHIONATES $(RO)_2P(S)NH_2$

Dialkyl phosphoramidothionates are used to make the pesticides methamidophos, acephate and isocarbophos, and are prepared from dialkyl phosphorochloridothionates and aqueous or anhydrous ammonia (Table 5.11.1) (*76–87*).

Table 5.11.1 Dialkyl phosphoramidothionates made from dialkyl phosphorochloridothionates and ammonia

P–Cl compound	Product	Yield (%)	Ref.
$(MeO)_2P(S)Cl$	$(MeO)_2P(S)NH_2$	99	76
$(EtO)_2P(S)Cl$	$(EtO)_2P(S)NH_2$	67	77
$(n\text{-}PrO)_2P(S)Cl$	$(n\text{-}PrO)_2P(S)NH_2$	–	78
$(i\text{-}PrO)_2P(S)Cl$	$(i\text{-}PrO)_2P(S)NH_2$	–	78
$(n\text{-}BuO)_2P(S)Cl$	$(n\text{-}BuO)_2P(S)NH_2$	–	78
$(C_{10}H_{21}O)_2P(S)Cl$	$(C_{10}H_{21}O)_2P(S)NH_2$	–	79
$MeO(PhO)P(S)Cl$	$MeO(PhO)P(S)NH_2$	95	80
$MeO[2\text{-}(i\text{-}PrO_2C)C_6H_4O]P(S)Cl$	$MeO[2\text{-}(i\text{-}PrO_2C)C_6H_4O]P(S)NH_2$[a]	76	81
$MeO(2,4,6\text{-}Cl_3C_6H_2O)_2P(S)Cl$	$MeO(2,4,6\text{-}Cl_3C_6H_2O)_2P(S)NH_2$	89	82
$i\text{-}BuO(CH_2{=}CHCH_2O)P(S)Cl$	$i\text{-}BuO(CH_2{=}CHCH_2O)P(S)NH_2$	92	83
$(PhO)_2P(S)Cl$	$(PhO)_2P(S)NH_2$	–	84
		60	85
		68	86

[a]Isocarbophos.

▶ *Dimethyl phosphoramidothionate* $(MeO)_2P(S)NH_2$ (*76*). Ammonium hydroxide (28% in H_2O, 8.68 g, 69.4 mmol) was added dropwise to a stirred solution of dimethyl phosphorochloridothionate (4.82 g, 30.0 mmol) in dichloromethane (10 ml) at 0 °C. The mixture was heated under reflux and then cooled to room temperature. It was stirred for an additional 35 min to form two phases. The organic phase was washed with water (3 ml) and the aqueous phase with dichloromethane (2 × 5 ml). The aqueous phase was discarded, the organic phase was dried

(Na_2SO_4), and the solvent was evaporated to obtain a colourless liquid (4.19 g, 99%). δ_P ($CDCl_3$) 76.2 ppm.

▶ *Diethyl phosphoramidothionate* $(EtO)_2P(S)NH_2$ (*87*). Gaseous ammonia (15.3 g, 0.9 mol) was passed into a solution of diethyl phosphorochloridothionate (75.4 g, 0.4 mol) in benzene (500 ml) at 15–20 °C. Ammonium chloride precipitated. The mixture was filtered after 12 h. The filtrate was washed with water, dried ($MgSO_4$), and the solvent removed to yield the product (45.3 g, 67%).

▶ *Methyl phenyl phosphoramidothionate* $MeO(PhO)P(S)NH_2$ (*80*). Gaseous ammonia was bubbled into a solution of methyl phenyl phosphorochloridothionate (5.8 g, 26 mmol) in benzene (50 ml) until no further reaction occurred. The mixture was washed with water, dried ($MgSO_4$), filtered, and concentrated to give a liquid (5.2 g, 95%).

▶ *Methyl 2-(isopropoxycarbonyl)phenyl phosphoramidothionate (isocarbophos)* $MeO(2\text{-}i\text{-}PrO_2CC_6H_4O)P(S)NH_2$ (*81*). A mixture of isopropyl 2-hydroxybenzoate (144 g, 0.8 mol), sodium hydroxide (24 g, 0.6 mol) and water (220 ml, 12.2 mol) was added to methyl phosphorodichloridothionate (182 g, 1.1 mol) at 40–50 °C, stirred for 4 h, dissolved in benzene (400 ml) and fractionated to give methyl 2-(isopropoxycarbonyl)phenyl phosphorochloridothionate (155 g, 46%). Bp 120 °C at 0.01 mmHg. A portion (166 g, 0.5 mol) of this was added to 15% *w/w* aqueous ammonia (90 ml), stirred for 24 h, and extracted with benzene to give isocarbophos (110 g, 76%).

Ethyl 2-isopropyl-5-pyrimidinyl phosphoramidothionate $EtO(2\text{-}i\text{-}PrC_4H_2N_2O)P(S)NH_2$ (*85*). Ethyl phosphorodichloridothionate (15.5 g, 87 mmol) was added to a stirred mixture of 2-isopropyl-5-pyrimidinol (12.0 g, 87 mmol), potassium carbonate (12 g, 87 mmol) and acetonitrile (100 ml). The mixture was stirred at room temperature for 12 h. An excess of gaseous ammonia was introduced at 0 °C and the mixture was stirred overnight. The salts were filtered off and the solvent was removed from the filtrate. High-performance liquid chromatography of the residue gave a pale amber liquid (13.4 g, 60%).

5.12 *S,S*-DIALKYL PHOSPHORAMIDODITHIOLOTHIONATES $(RS)_2P(S)NHR'$

Treatment of *N,S*-dialkyl phosphoramidochloridothiolothionates (**50**) with thiols and a suitable base gives *S,S*-dialkyl phosphoramidodithiolothionates (**51**) (Fig. 5.12.1) (*88*). *N*-Alkyl- or *N,N*-dialkyl phosphoramidodichloridothionates (**52**) react similarly with 2 molar equivalents of a sodium thiolate, or a thiol and amine base, to provide the phosphoramidodithiolothionates (**53**) in modest yields (*89*). Reaction of *S,S′*-ethylene phosphorochloridodithiolite (**54**) with esters of phenylalanine or tryptophan in the presence of pyridine, followed by treatment with sulfur, gives a product (**55**) useful for derivatising the antiviral drug azidothymidine (Fig. 5.12.2) (*90*). Another method for accessing *S,S′*-dialkyl phosphoramidodithiolothionates consists of alkylating suitable P–SH precursors with alkyl halides in the presence of triethylamine (e.g. the conversion of **56** to **57**) (*91*).

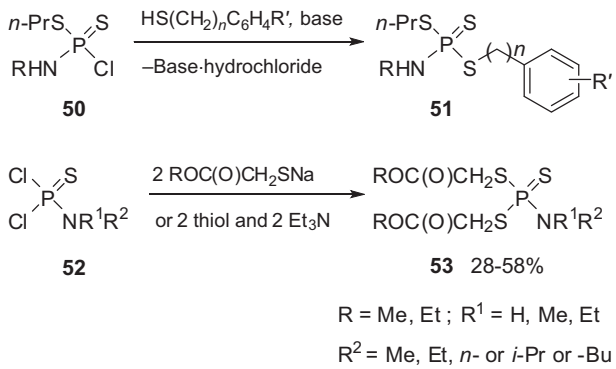


Figure 5.12.1

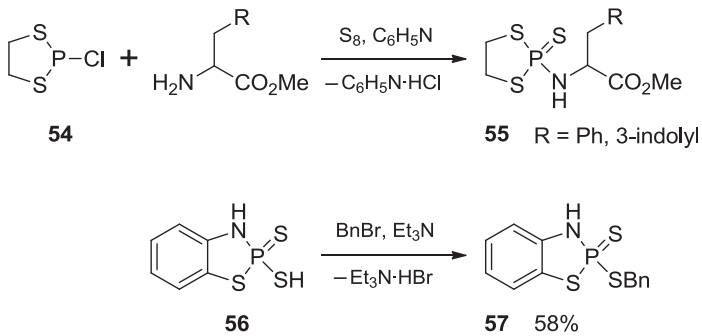


Figure 5.12.2

5.13 TRIS(*N,N*-DIALKYLAMINO)PHOSPHOROTHIONATES $(R_2N)_3P{=}S$

The reaction of thiophosphoryl chloride with amines, in the presence of a base such as triethylamine (or another molar equivalent of the amine), gives mono-, di- or tri-substituted products depending on the stoichiometry. The addition of an amino group usually renders the phosphorus atom less reactive to nucleophilic attack, so selective addition of one or two molecules of an amine is often possible. Tris(1-aziridinyl)phosphorothionate (thiotepa) has been assessed as a potential anticancer drug and chemosterilant and several routes to it are available. The most obvious involves the addition of an excess of aziridine to thiophosphoryl chloride in a suitable solvent (e.g. ether, benzene, or water) (Fig. 5.13.1) (*92*). Addition of the first molecule of aziridine to thiophosphoryl chloride provides the dichloridophosphorothionate, which is sufficiently reactive due to poor overlap of the nitrogen lone pair with the P═S bond, to react with another two molecules of the amine. Many amines, including aniline, can be added to thiophosphoryl chloride to produce trisubstituted products (e.g. **58**). Thiotepa has also been prepared from phosphorus trichloride and 6 molar equivalents of aziridine: the trivalent

triamide formed reacts with sulfur in benzene. Similarly, treatment of phosphorus trichloride with 6 mol of dimethylamine in ether provides tris(dimethylamino)phosphine (**59**) that adds to sulfur to provide the thionate (**60**) in one pot (*93*).

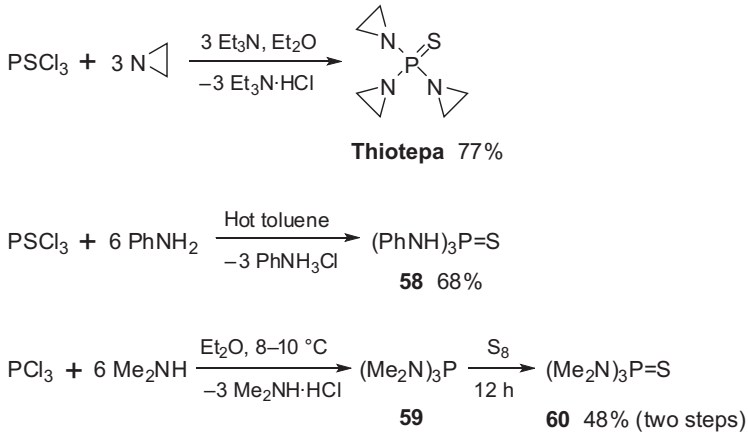


Figure 5.13.1

▶ *Tris(1-aziridinyl)phosphorothionate (thiotepa)* (*92*). A solution of thiophosphoryl chloride (50.7 g, 0.30 mol) in ether (270 ml) was added to a stirred solution of aziridine (40.3 g, 0.94 mol), triethylamine (91 g, 0.90 mol) and ether (540 ml) at −5 °C and stirring was continued for 6 h. The mixture was cooled to −50 °C for 2−3 h. The crystalline product was filtered off and dried under vacuum at a temperature <30 °C to yield thiotepa (31.0 g). More thiotepa was obtained from the mother liquor (12.4 g; total yield 43.4 g, 77%). Mp 52−57 °C.

▶ *Tris(phenylamino)phosphorothionate* $(PhNH)_3P{=}S$ (**58**) (*93*). A stirred mixture of thiophosphoryl chloride (40 mmol) and aniline (250 mmol) in toluene (2 ml per g of aniline) was heated under reflux for 48 h. After cooling, the mixture was washed with water, 1 M hydrochloric acid, and again with water. The organic layer was dried ($MgSO_4$), filtered, and the filtrate evaporated. Two recrystallisations from carbon tetrachloride gave the product as white crystals (9.2 g, 68%). Mp 152−153 °C.

▶ *Tris(dimethylamino)phosphorothionate* $(Me_2N)_3P{=}S$ (**60**) (*93*) Dimethylamine (11.25 g, 250 mmol) was bubbled slowly into a solution of phosphorus trichloride (5.36 g, 39 mmol) in anhydrous ether (75 ml) at 8−10 °C. The mixture was stirred overnight at room temperature, filtered and concentrated to a volume of 50 ml. Sulfur (1.28 g, 40 mmol) was added over 5 min (to prevent a vigorous exothermic reaction). After 30 min, additional sulfur (1.60 g, 50 mmol) was added. The mixture was stirred at room temperature overnight and concentrated under reduced pressure to give a viscous red liquid. Column chromatography on silica gel, eluting with 1:4 ethyl acetate−hexane, gave a reddish solid (3.65 g, 48%). Mp 24−26 °C. Attempts to purify this product by distillation were unsuccessful.

The reaction of 2-(diethylamino)-1,3-dimethyl-1,3,2-diazaphosphinan-4-one (**61**) with sulfur produces the thionated product (**62**) in good yield (Fig. 5.13.2) (*94*).

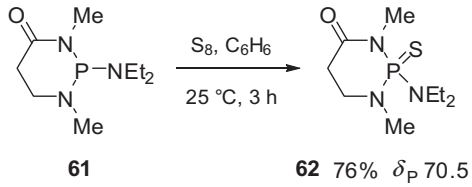


Figure 5.13.2

▷ *2-(Diethylamino)-1,3-dimethyl-1,3,2-diazaphosphinan-4-one 2-sulfide* (**62**) (*94*). A mixture of 2-(diethylamino)-1,3-dimethyl-1,3,2-diazaphosphinan-4-one (2.17 g, 10 mmol) and sulfur (0.32 g, 10 mmol) in benzene (15 ml) was stirred for 3 h at room temperature. The solvent was removed and the residue was distilled under reduced pressure to give the product (1.89 g, 76%). Bp 90—95 °C/0.001 mmHg. Mp 43—44 °C. δ_P 70.5 ppm.

5.14 DISUBSTITUTED *N*-(ALKOXY)PHOSPHORAMIDOTHIONATES $(RO)_2P(S)NHOR'$

Disubstituted phosphorochloridothionates (**63**) react with *O*-alkylhydroxylamines to give disubstituted *N*-(alkoxy)phosphoramidothionates (**64**) that have been assessed as potential insecticides (Fig. 5.14.1) (*95*).

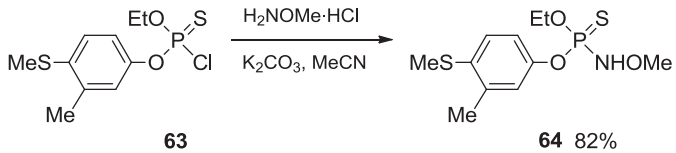


Figure 5.14.1

▷ *Ethyl 3-methyl-4-(methylthio)phenyl N-(O-methoxy)phosphoramidothionate EtO(3-Me-4-MeSC$_6$H$_3$O)P(S)NHOMe* (**64**) (*95*). *O*-Methylhydroxylamine hydrochloride (1 mol equiv.) and potassium carbonate (1 or 2 mol equiv.) were added to stirred ethyl 3-methyl-4-(methylthio)phenyl phosphorochloridothionate (1 mol equiv.) in acetonitrile. The mixture was heated to 40 °C for 4 h, filtered, and concentrated to give the title compound (82%).

5.15 DIALKYL PHOSPHOROHYDRAZIDOTHIONATES $(RO)_2P(S)NR'NR'_2$

Alkyl phosphorodichloridothionates $ROP(S)Cl_2$ and dialkyl phosphorochloridothionates $(RO)_2P(S)Cl$ react with hydrazine monohydrate and anhydrous hydrazine to produce bis- and mono-hydrazidates $ROP(S)(NHNH_2)_2$ and $(RO)_2P(S)NHNH_2$, respectively (*96*). Diphenyl phosphorochloridothionate (**10**) reacts with 2 molar equivalents of hydrazine hydrate in benzene to provide diphenyl phosphorohydrazidothionate (**65**) in excellent yield (Fig. 5.15.1). An excess of

hydrazine is incompatible with dialkyl phosphorochloridothionates having easily dealkylated ester groups as it can effect *O*-dealkylation.

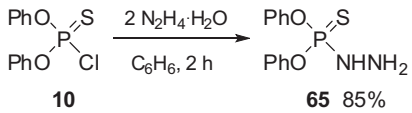


Figure 5.15.1

▶ *Diphenyl phosphorohydrazidothionate* $(PhO)_2P(S)NHNH_2$ (**65**) (*96*). Hydrazine monohydrate (50.0 g, 1 mol) was added dropwise over 2 h to a solution of diphenyl phosphorochloridothionate (142.3 g, 0.5 mol) in benzene (900 ml). Several hours after addition, water (250 ml) was added with stirring, and the benzene layer was separated and evaporated to give the product (120.0 g, 85%).

Dialkyl phosphorochloridites such as cyclic species (**66**) react with *N*,*N*′,*N*′-trialkylhydrazines to give dialkyl phosphorohydrazidites (**67**) that add sulfur to provide the dialkyl phosphorohydrazidothionates (**68**) (Fig. 5.15.2) (*97*).

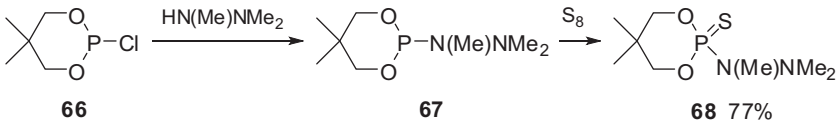


Figure 5.15.2

5.16 DIALKYL PHOSPHOROISOCYANATIDOTHIONATES $(RO)_2P(S)NCO$

Treatment of dialkyl phosphoramidothionates with phosgene or oxalyl chloride can often convert the $-NH_2$ group to the $-NCO$ group (Fig. 5.16.1) (*98*,*99*). Dimethyl phosphoramidothionate (**69**) reacts with phosgene to give as the major product the hydrochloride salt (**70**) and as the minor product the isocyanatidate (**71**) (*98*). Diethyl phosphoramidothionate (**72**) reacts exothermically with oxalyl chloride to give the corresponding isocyanatidate (**73**) in acceptable yield. Diaryl phosphoramidothionates contain a less nucleophilic amino group because of electron withdrawal by the electronegative aryl substituents and require heating for 2–3 h for complete reaction (*100*). Unsymmetrical phosphoroisocyanatidothionates can also be accessed using the same methodology (*101*,*102*).

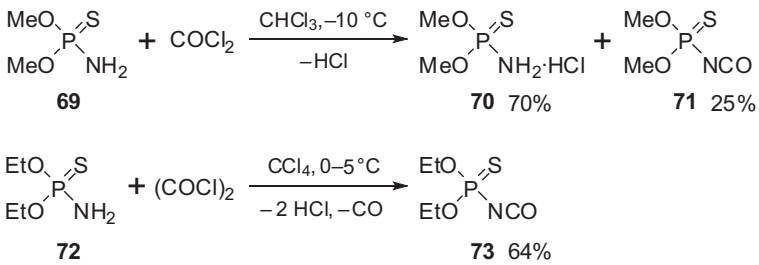


Figure 5.16.1

▶ *Dimethyl phosphoroisocyanatidothionate* $(MeO)_2P(S)NCO$ (**71**) (*98*). Dimethyl phosphoramidothionate (14.1 g, 0.10 mol) was added to a solution of phosgene (10.9 g, 0.11 mol) in chloroform (250 ml) at −10 °C and stirred at that temperature for 1 h. The mixture was warmed to room temperature and stirred for 1 h. The solvent was removed to give 70% $(MeO)_2P(S)NH_2 \cdot HCl$ (mp ~50 °C) and 25% $(MeO)_2P(S)NCO$ (bp 59–60 °C/10 mmHg).

▶ *Diethyl phosphoroisocyanatidothionate* $(EtO)_2P(S)NCO$ (**73**) (*100*). A solution of phosgene (5.5 g, 55 mmol) in carbon tetrachloride (100 ml) was added to a stirred solution of diethyl phosphoramidothionate (8.5 g, 50 mmol) in carbon tetrachloride (100 ml) at 0 °C (exothermic). After addition, warming to 50 °C followed by filtration and distillation gave the product (6.2 g, 64%). Bp 78–79 °C/20 mmHg (lit. 84–85 °C/10 mmHg (*99*)). A similar experiment with diphenyl phosphoramidothionate required refluxing for 2–3 h and gave $(PhO)_2P(S)NCO$ (bp 128 °C/0.08 mmHg; mp 50–52 °C). Filtration of reaction mixtures through Celite™ lowers product yields (*99*).

Disubstituted phosphoroisocyanidite (**74**) and thiophosphoryl chloride react when heated to give the phosphoroisocyanatidothionate (**75**) and phosphorus trichloride (Fig. 5.16.2) (*103*,*104*). These products have different boiling points and are easily separated by fractionation.

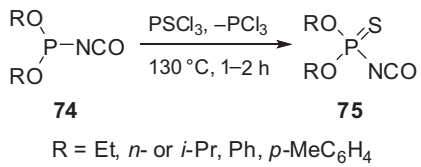


Figure 5.16.2

▶ *Diethyl phosphoroisocyanatidothionate* $(EtO)_2P(S)NCO$ (*103*). An equimolar mixture of a disubstituted phosphoroisocyanatidite and thiophosphoryl chloride heated to 120–140 °C for 1–2 h gave PCl_3 (80–95%) and $(EtO)_2P(S)NCO$ (69%, bp 87–89 °C/25 mmHg) or $(PhO)_2P(S)NCO$ (62%, bp 127–129 °C/0.05 mmHg; mp 51–52 °C).

5.17 DIALKYL PHOSPHOROISOTHIOCYANATIDOTHIONATES $(RO)_2P(S)NCS$

Dialkyl phosphoroisothiocyanatidothionates can be prepared from appropriate P–Cl species and potassium thiocyanate. Reaction occurs selectively at the thiocyanate nitrogen atom rather than at the sulfur atom and is enabled in acetonitrile or acetone. The use of *N*-methylimidazole as a catalyst sometimes gives a higher yield of product (*105*). The phosphoroisothiocyanatidothionates decompose in aqueous solution with P–N bond cleavage. A one-pot method for converting ethyl phosphorodichloridothionate (**76**) to *O*-ethyl *O*-(2,4-dichlorophenyl) phosphorochloridothionate (**77**) and then to isothiocyanatidothionate (**78**) is advantageous (Fig. 5.17.1).

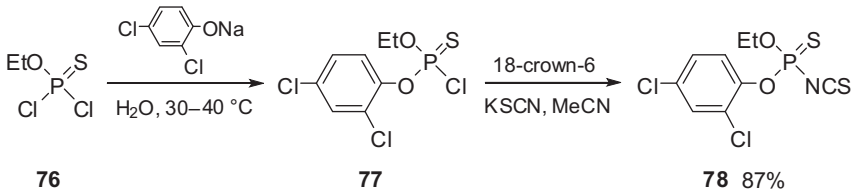


Figure 5.17.1

▶ *O-Ethyl O-(2,4-dichlorophenyl) phosphoroisothiocyanatidothionate EtO(2,4-$Cl_2C_6H_3O$)P(S)NCS* (**78**) (*105*). Ethyl phosphorodichloridothionate (3.60 g, 20 mmol) and a catalytic amount of 18-crown-6 was added to 2,4-dichlorophenol (3.26 g, 20 mmol) and sodium hydroxide (0.8 g, 20 mmol) in water (5 ml). The mixture was stirred at 30–40 °C for 2 h, left for 12 h, and extracted with benzene (100 ml). The organic phase was washed with water (20 ml), dried ($MgSO_4$) and concentrated to give crude *O*-ethyl *O*-(2,4-dichlorophenyl) phosphorochloridothionate **77**. This was added to a suspension of potassium thiocyanate (1.94 g, 20 mmol) in acetonitrile (20 ml). The mixture was stirred at room temperature for 4–5 h, diluted with ether (20 ml) and filtered. Column chromatography of the concentrated filtrate on silica gel gave the title species (5.71 g, 87%).

Diethyl phosphorochloridothionate (**25**) reacts with potassium thiocyanate in warm acetonitrile to provide *O,O*-diethyl phosphoroisothiocyanatidothionate (**79**) in low yield (Fig. 5.17.2) (*106*). A better yield is obtained when *N*-methylimidazole catalyst is employed.

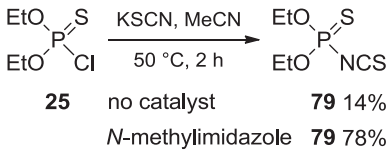


Figure 5.17.2

▶ *O,O-Diethyl phosphoroisothiocyanatidothionate $(EtO)_2P(S)NCS$* (**79**) *(from diethyl phosphorochloridothionate and potassium thiocyanate)* (*106*). Diethyl phosphorochloridothionate (188.5 g, 1.0 mol) was added dropwise to a slurry of potassium thiocyanate (145.5 g, 1.5 mol) in anhydrous acetonitrile (700 ml) at 50 °C. The resulting mixture was stirred for 2 h and left overnight. The slurry was filtered and the solvent was removed from the filtrate at 30–40 °C under reduced pressure. Residual solid was removed by filtration. Distillation of the filtrate gave the product (30 g, 14%). Bp 61–63 °C/0.1–0.2 mmHg.

▶ *O,O-Diethyl phosphoroisocyanatidothionate $(EtO)_2P(S)NCS$* (**79**) *(from diethyl phosphorochloridothionate, potassium thiocyanate and N-methylimidazole)* (*106*). Diethyl phosphorochloridothionate (377.0 g, 2.0 mol) in acetonitrile (90 ml) was added over 1 min to a stirred mixture of dried potassium thiocyanate (291.0 g, 3.0 mol) and *N*-methylimidazole (0.2 g, 2 mmol) in anhydrous acetonitrile (700 ml). The orange–red mixture was stirred for 6 h and left overnight. Removal of the solvent at 30 °C under reduced pressure gave an oil from which residual solid was filtered. Distillation of the filtrate gave the title compound (295.0 g, 78%). Bp 61–63 °C/0.1–0.2 mmHg.

The sodium and ammonium salts of *O,O*-dialkyl hydrogen phosphorodithioates (**80**) react with $ClSN{=}CCl_2$ in acetone to give disulfides (**81**) and isothiocyanatidothionates (**82**) (Fig. 5.17.3) (*107*). The latter can be separated by fractional distillation in yields of around 70%.

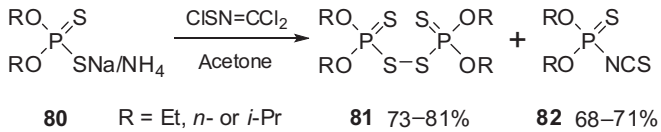


Figure 5.17.3

Schrader reported in the 1950s that *O,O*-dialkyl hydrogen phosphorodithioates react with cyanogen bromide or cyanogen chloride in the presence of triethylamine to produce dialkyl phosphoroisothiocyanatidothionates efficiently (*108*). An example is the conversion of *O,O*-diethyl hydrogen phosphorodithioate (**83**) to *O,O*-diethyl phosphoroisothiocyanatidothionate (**84**) which proceeds in good yield (Fig. 5.17.4). The initial P—SCN product presumably isomerises to the P—NCS isomer.

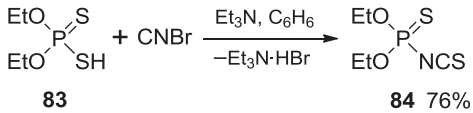


Figure 5.17.4

▶ *O,O-Diethyl phosphoroisothiocyanatidothionate* $(EtO)_2P(S)NCS$ (**84**) (*108*). A solution of cyanogen bromide (33 g, 0.31 mol) and triethylamine (32 g, 0.31 mol) in benzene (100 ml) was added to a stirred solution of *O,O*-diethyl hydrogen phosphorodithioate (55.8 g, 0.30 mol) in benzene (100 ml). The mixture was stirred for 1 h, filtered, the solvent removed from the filtrate, and the residue purified by fractionation to give the title compound (48 g, 76%). Bp 82—83 °C/2 mmHg.

5.18 DIALKYL PHOSPHORAZIDOTHIONATES $(RO)_2P(S)N_3$

Nucleophilic attack of azide ion on phosphorochloridothionates is facilitated by mercury(II) compounds presumably through their coordination to the sulfur atom of the P═S group. Treatment of methyl phosphorodichloridothionate in acetone with sodium 3-methyl-4-(methylthio)phenoxide gives the chloridothionate (**8**) which in contact with sodium azide and mercury(II) chloride gives the azidothionate (**85**) in high yield (a precursor to fenthion) (Fig. 5.18.1) (*109*). Useful solvents for the last step include acetone, DMF, methyl ethyl ketone, and methyl propyl ketone, because they dissolve small quantities of sodium azide.

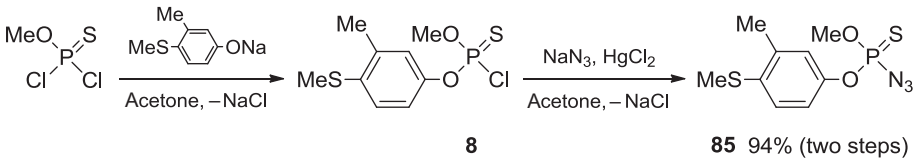


Figure 5.18.1

Attempts to prepare pure [*o*-(OHC)C_6H_4O]$_2$P(S)Cl from thiophosphoryl chloride and the corresponding phenoxide gave a mixture of products which could not be purified successfully by column chromatography. However, the crude chloridate could be transformed into the azidate [*o*-(OHC)C_6H_4O]$_2$P(S)N_3 which could be purified chromatographically. This conversion is useful for the synthesis of 'chloridate substitutes' (as azidates react similarly with nucleophiles with loss of azide rather than chloride). A stirred suspension of sodium azide in DMF converts disubstituted phosphorochloridothionates (**86**) into the phosphorazidothionates (**87**) (Fig. 5.18.2). The same transformation can be effected by triethylamine hydrogen azide (e.g. **25** → **88**) and this approach is often effective if the metal azide method fails (*110*,*111*). Details for the synthesis of dimethyl phosphorazidothionate (*112*) and catechol phosphorazidothionate (*109*) are provided.

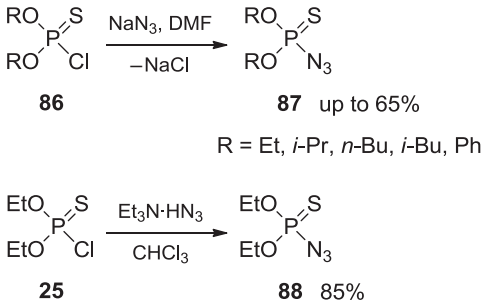


Figure 5.18.2

▶ *Dimethyl phosphorazidothionate (MeO)$_2$P(S)N_3 (112)*. Dimethyl phosphorochloridothionate (33 g, 0.21 mol) was added to a stirred suspension of sodium azide (40 g, 0.62 mol) in anhydrous acetone (200 ml). The mixture was heated under reflux for 20 h. The inorganic salts were filtered off and washed with acetone. The filtrate was concentrated and the residue distilled under reduced pressure to give the azidothionate (16 g, 47%). Bp 38–39 °C/0.5 mmHg.

▶ *Catechol phosphorazidothionate ($C_6H_4O_2$)P(S)N_3 (109)*. A solution of 1,2-dihydroxybenzene (0.36 g, 3.25 mmol) and triethylamine (1 ml, 7.20 mmol) in tetrahydrofuran (20 ml) was added dropwise to a solution of thiophosphoryl chloride (0.33 ml, 3.25 mmol) in tetrahydrofuran (30 ml). After stirring for 24 h, the solution was filtered and concentrated. Acetone (20 ml) and sodium azide (0.23 g, 3.5 mmol) were added, and the resulting mixture was stirred for 3 days, concentrated and centrifuged. The solution was evaporated to yield a maroon liquid (0.56 g, 88%).

Disubstituted phosphorazidothionates are usually more stable to hydrolysis than the corresponding phosphorochloridothionates, although the former in very rare instances can be explosive if heated, so precautions should be adopted when preparing phosphorus azides (i.e. small scale with apparatus positioned behind a reinforced screen and minimal distillation operations; column chromatography on silica gel is the preferred and safest method of purification). Phosphorazidothionates are useful reagents for the Staudinger reaction with trialkyl phosphites to produce phosphazenes, as discussed next. The synthesis, chemical and physical properties, and physiological activity, of phosphorus acid azides have been reviewed (*113*).

5.19 DIALKYL *N*-(PHOSPHINIMIDO)PHOSPHOROTHIONATES $(RO)_2P(S)N{=}PR^1_3$

Treatment of disubstituted phosphoramidothionates (**89**) with phosphorus pentachloride and triethylamine (2 mol) in a suitable solvent provides dialkyl *N*-(trichlorophosphinimido)phosphorothionates (**90**) with loss of hydrogen chloride (2 mol) (Fig. 5.19.1) (*114*). An equimolar mixture of diphenyl phosphoramidothionate and phosphorus pentachloride stirred at room temperature for 5–6 h, and then at 50–60 °C for 30 min, gives in quantitative yield the iminophosphazene $(PhO)_2P(S)N{=}PCl_3$. Treatment of this with a sodium alkoxide causes triple substitution with loss of chloride: sodium phenolate and sodium 4-nitrophenolate give $(PhO)_2P(O)N{=}P(OPh)_3$ and $(PhO)_2P(O)N{=}P(OC_6H_4NO_2\text{-}p)_3$ in 69% and 70% yield, respectively. Amines react similarly. Exposure of $(PhO)_2P(S)N{=}PCl_3$ to water does not give $(PhO)_2P(S)N{=}P(OH)_3$, but instead yields $(PhO)_2P(S)NH_2$ and H_3PO_4 (*42*,*115*). The phosphoramidothionates (**89**) react with triphenylphosphine dichloride (Cl_2PPh_3 generated from triphenylphosphine and carbon tetrachloride) to provide the species (**91**) (*116*).

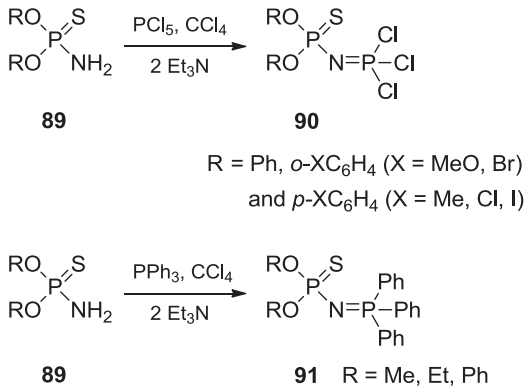


Figure 5.19.1

Disubstituted phosphorazidothionates enter into the Staudinger reaction when treated with trisubstituted phosphines or phosphites with or without solvent. The by-product is nitrogen which usually escapes through gentle effervescence from the reaction mixture. Equimolar quantities of the phosphorazidothionates (**92**) and *bis*(diphenylphosphino)methane give products (**93a**,**b**) (Fig. 5.19.2) (*117*). The Staudinger reaction with trialkyl phosphites normally proceeds readily. Disubstituted phosphorazidothionates (**92**) combine with trisubstituted phosphites to give the iminophosphazenes (**94**) in good yields (*42*). The temperature used varies from room temperature to around 100 °C (*110*).

Disubstituted N-[diphenyl(diphenylphosphinomethylene)phosphinimido]phosphorothionates $(RO)_2P(S)N{=}P(Ph)_2CH_2PPh_2$ (**93a**,**b**) (*117*). The phosphorazidothionate (5.2 mmol) was added to a stirred solution of *bis*(diphenylphosphino)methane (2 g, 5.2 mmol) in tetrahydrofuran (80 ml) at −78 °C. The mixture was warmed slowly to room temperature and the solvent removed to give a colourless liquid. Slow diffusion of *n*-pentane into a saturated solution of this liquid in dichloromethane at room temperature gave a white solid (R = Et, 94%; R = Ph, 89%).

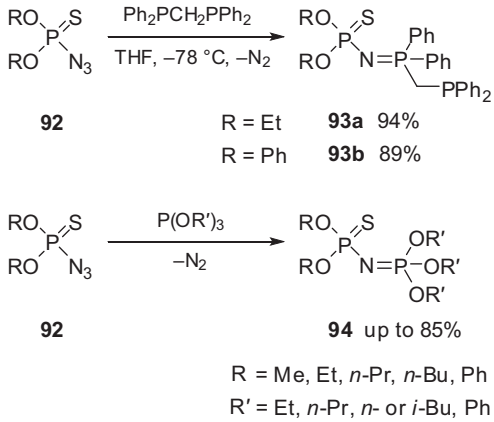


Figure 5.19.2

5.20 *O,O*-DIALKYL *S*-(DIALKYLAMINO) PHOSPHOROTHIOLOTHIONATES $(RO)_2P(S)SNR'_2$

Treatment of *bis*(*O,O*-dialkylthiophosphoryl) disulfides (**81**) with ammonia or amines gives *O,O*-dialkyl *S*-(*N,N*-dialkylamino) phosphorothiolothionates (**95**) (Fig. 5.20.1) (*118*) and the *O,O*-dialkyl phosphorothioate ammonium salt as a by-product.

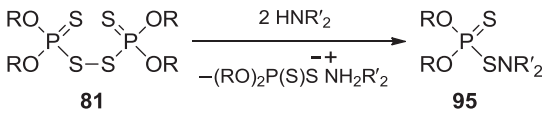


Figure 5.20.1

O,O-Diethyl phosphorodithioate potassium salt (**96**) reacts with *N*-chloro-*N*-methylacetamide in benzene to provide the potential insecticide *O,O*-diethyl *S*-(*N*-methylacetamido) phosphorothiolothionate (**97**) (Fig. 5.20.2) (*119*). *O,O*-Diethyl phosphorodithioate sodium salt (**98**) reacts with *N*-chloroamines such as *N*-chlorocyclohexylamine in aqueous acetone to give S—N derivatives (**99a**,**b**) (*120*).

▶ *O,O-Diethyl S-(N-methylacetamido) phosphorothiolothionate* $(EtO_2)P(S)SN(Me)C(O)Me$ (**97**) (*119*). *N*-Chloro-*N*-methylacetamide (162 g, 1.51 mol) was added to a suspension of potassium *O,O*-diethyl phosphorodithioate (312 g, 1.39 mol) in benzene (1500 ml). The mixture was stirred for 3 h, filtered, the filtrate concentrated, and the residue fractionated to provide a colourless liquid (235 g, 66%). Bp 87—95 °C/0.25 mmHg.

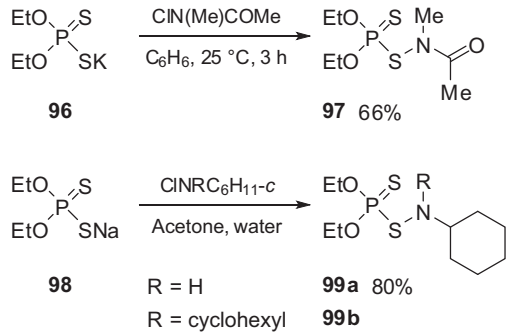


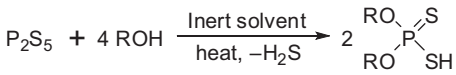
Figure 5.20.2

O,O-Diethyl S-(N-cyclohexylamino) phosphorothiolothionate $(EtO)_2P(S)SNHC_6H_{11}$ (**99a**) (*120*) A solution of *O,O*-diethyl phosphorodithioate sodium salt (104 g, 0.5 mol) in water (200 ml) was added dropwise to a stirred solution of *N*-chlorocyclohexylamine (66.8 g, 0.5 mol) in acetone (100 ml) and water (100 ml). A mildly exothermic reaction occurred and the mixture separated into two layers. After 1 h, the aqueous layer was discarded, the organic layer was dissolved in ether (150 ml), washed with water (200 ml) and dried ($MgSO_4$). The ether was removed to give the title compound (113 g, 80%).

O,O-Diethyl S-(N,N-dicyclohexylamino) phosphorothiolothionate $(EtO)_2P(S)SN(C_6H_{11})_2$ (**99b**) (*120*). *O,O*-Diethyl phosphorodithioate sodium salt (104 g, 0.5 mol) in water (200 ml) was added dropwise to a stirred solution of *N*-chlorodicyclohexylamine (108 g, 0.5 mol) in acetone (200 ml). A mildly exothermic reaction occurred and the mixture separated into two layers; the temperature was kept between 15 and 30 °C using a water bath. After stirring for another hour, the aqueous layer was separated and discarded. The organic phase was dissolved in ether (250 ml), filtered under suction from precipitated material, washed with water (250 ml), dried (Na_2SO_4) and filtered. The solvent was removed from the filtrate and the brownish yellow liquid residue was crystallised from hot ethanol to give a white solid (yield not given). Mp 70–71 °C.

5.21 *O,O*-DIALKYL HYDROGEN PHOSPHORODITHIOATES $(RO)_2P(S)SH$

O,O-Dialkyl hydrogen phosphorodithioates are readily synthesised by the alcoholysis of phosphorus pentasulfide (Fig. 5.21.1). *O,O*-Dimethyl hydrogen phosphorodithioate is a precursor for the insecticide malathion and is produced on a large scale. Toluene is generally used as the solvent and any unreacted phosphorus pentasulfide is removed by filtration at the end of the experiment. Since the reaction generates toxic and foul-smelling hydrogen sulfide gas, an efficient bleach or alkali scrubber is recommended. Microwave irradiation is useful for accelerating the reaction (*128*). Phosphorus pentasulfide does not react with *tert*-butanol at 80–85 °C for 5–6 h: a large amount of butylene is produced. *O,O*-Di(*tert*-butyl) hydrogen phosphorodithioate is isolated by heating the same reagents at 45 °C for 4–5 h, but is unstable; it is isolated as the lead salt (*125*).

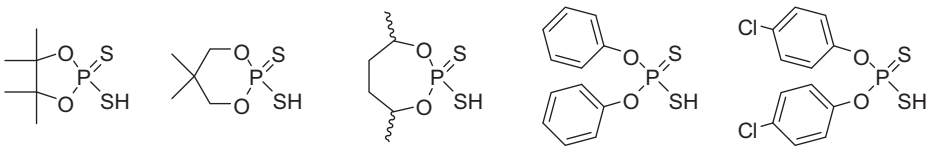


O,O-Dialkyl hydrogen phosphorodithioates

R	Yield (%)	Ref.
Me	85	121
Et	85	26
n-Pr	89	122
i-Pr	100	123
n-Bu	94	124
i-Bu	100	123
t-Bu	71	125
2-ethylhexyl	97	126
2-$ClCH_2CH_2$	49	127
Bn	83	125

Figure 5.21.1

O,O-Cycloalkyl phosphorodithioates (**100**–**102**) and *O,O*-diaryl phosphorodithioates (**103**,**104**) are prepared by heating the respective diol (1 mol) or aryl alcohol (4 mol) with phosphorus pentasulfide (1 mol) in benzene or toluene (Fig. 5.21.2).



100 *(129)* **101** (80%) *(130)* **102** (79%) *(131)* **103** (100%) *(132)* **104** (87%) *(133)*

Figure 5.21.2

▶ *O,O-Dimethyl hydrogen phosphorodithioate* $(MeO)_2P(S)SH$ *(121)*. Methanol (150 g, 4.7 mol) at 25–35 °C was added over 90–120 min to a 1-l four-necked flask equipped with a mechanical stirrer, thermometer, and pressure-equalising funnel, containing phosphorus pentasulfide (222 g, 1.0 mol) and toluene (150 ml) under nitrogen (an alkali scrubber was used to trap the released hydrogen sulfide). Once addition was complete the temperature of the mixture was raised to 50 °C and maintained at 50–55 °C for 5 h. Evolution of hydrogen sulfide was confirmed by checking with lead acetate paper. The mixture was cooled to 25–28 °C. Nitrogen was bubbled through it for 20–30 min to expel traces of hydrogen sulfide. The mixture was filtered through a high-flow bed to remove unreacted

phosphorus pentasulfide and washed with toluene (150 ml). The layers were separated to remove a small amount of lower layer and retain the upper toluene layer. The latter was concentrated under vacuum at 45–50 °C until high-performance liquid chromatography showed a toluene content <5%, leaving behind the title compound (260–270 g, 82–85%).

▶ *O,O-Diethyl hydrogen phosphorodithioate* $(EtO)_2P(S)SH$ (*26*). Phosphorus pentasulfide (4.44 g, 20 mmol) was added in one portion to ethanol (3.22 g, 70 mmol) in a 25-ml vessel equipped with a thermometer, condenser and stirrer. The mixture reached 59 °C and the gases liberated were scrubbed with bleach. The mixture was heated to 70 °C for 3 h, cooled, and filtered to afford a pale-yellow liquid (6.3 g, 85%).

▶ *O,O-Di-n-pentyl potassium phosphorodithioate* $(n\text{-}C_5H_{11}O)_2P(S)SK$ (*122*). 1-Pentanol (7.05 g, 80 mmol) was added gradually to a stirred suspension of phosphorus pentasulfide (4.44 g, 20 mmol) in toluene (100 ml). The mixture was stirred at 80–100 °C for 3 h. The suspension was filtered to remove unreacted phosphorus pentasulfide. 50% Aqueous potassium hydroxide (2.24 g, 40 mmol) was added to the filtrate with stirring. Toluene and water were removed and the crude product was dried and washed with hexane to provide the potassium salt (9.24 g, 75%). δ_P (EtOH) 112.8 ppm.

▶ *5,5-Dimethyl-2-mercapto-2-thiono-1,3,2-dioxaphospholane* (**101**) (*130*). 2,2-Dimethyl-1,3-propanediol (41.6 g, 0.4 mol) was added to a suspension of phosphorus pentasulfide (44.8 g, 0.2 mol) in anhydrous benzene (260 ml). The mixture was stirred at 50–55 °C for 15 h under nitrogen. Unreacted phosphorus pentsulfide was filtered off, the filtrate was evaporated, and the residue was kept under vacuum at room temperature for 30 min. The obtained sticky solid was distilled under vacuum to give the title compound (63.4 g, 80%). Bp 120–125 °C/1 mmHg. (*Caution!* A pressure below 1.5 mmHg is recommended, otherwise the contents of the flask can decompose violently during heating.) Mp 81–82 °C. δ_P ($CDCl_3$) 77.7 ppm.

The reaction of white phosphorus, sulfur, an alcohol and an amine base provides *O,O*-dialkyl phosphorodithioate ammonium salts (**105**) with evolution of hydrogen (Fig. 5.21.3) (*123*).

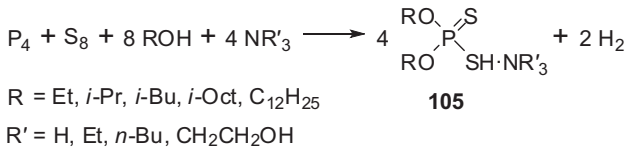


Figure 5.21.3

Dialkyl *H*-thiophosphonates react with sulfur in the presence of a tertiary amine to give *O,O*-dialkyl phosphorodithioates (Fig. 5.21.4) (*134*). The reactive species is thought to be the thiolo tautomer $(RO)_3P{-}SH{\cdot}NR'_3$ which, unlike the thiono tautomer, contains a nucleophilic phosphorus atom capable of reacting with electrophiles. This reaction has been used to convert dinucleoside *H*-thiophosphonates (**106**) to hydrogen phosphorodithioates (**107**) (*135*) and simpler dialkyl *H*-thiophosphonates (**108**) to analogous products (**109**) (*134*).

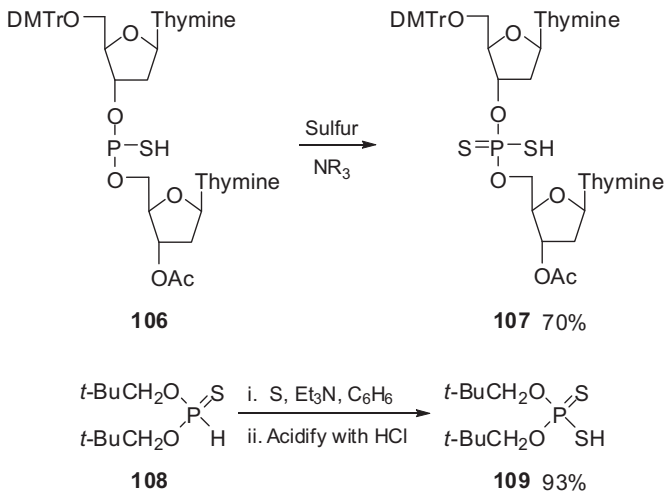


Figure 5.21.4

▶ *O,O-Dineopentyl phosphorodithioate (t-BuCH$_2$O)$_2$P(S)SH* (**109**) (*134*). Sulfur (1 g, 31 mmol) was added to a stirred solution of dineopentyl *H*-thiophosphonate (6 g, 25 mmol) in benzene (25 ml). Then triethylamine (2.6 g, 26 mmol) was added dropwise. After 2 h, the solvent was removed and the residue was recrystallised from hexane to give the triethylammonium salt of the acid (8.5 g, 93%). This was dissolved in water and acidified with dilute hydrochloric acid. The acid was extracted with ether, the organic layer was dried ($MgSO_4$), filtered and concentrated to give the product as a low-melting solid (6.3 g, 93%). δ_P ($CDCl_3$) 85 ppm.

5.22 *O,O*-DIALKYL *S*-ALKYL PHOSPHOROTHIOLOTHIONATES (RO)$_2$P(S)SR'

These comprise a large family of pesticides and many compounds of this type have been assessed for biological activity. *S*-Alkylation of *O,O*-dialkyl phosphorodithioates is the main method of synthesis. Thionation of *O,O,S*-trialkyl phosphorothiolates (RO)$_2$P(O)SR′ with Lawesson reagent, phosphorus pentasulfide, or boron trisulfide also gives *O,O*-dialkyl *S*-alkyl phosphorothiolothionates. With Lawesson reagent, the P═O precursor (**110** or **111**) is heated under reflux in toluene or acetonitrile, and the P═S product (**112** or **113**) purified by column chromatography (thionation proceeds with retention of configuration at phosphorus) (Fig. 5.22.1) (*136,137*).

▶ *O,S-Dimethyl O-(p-nitrophenyl) phosphorothiolothionate MeO(MeS)P(S)OC$_6$H$_4$NO$_2$-p* (**112**) (*136*). A mixture of (−)-*O,S*-dimethyl *O*-(*p*-nitrophenyl) phosphorothiolate (60 mg, 0.22 mmol, 94% ee) and Lawesson reagent (53 mg, 0.12 mmol) in anhydrous toluene (6 ml) was stirred at 90 °C for 12 h. The solvent was removed and the residue chromatographed on silica gel, eluting with chloroform, to give a pale-yellow liquid (49 mg, 77%; 94% ee).

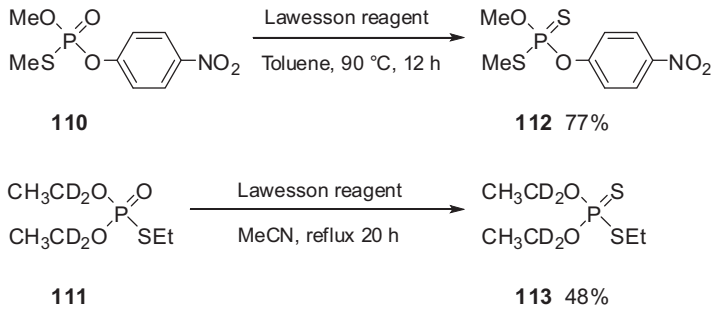


Figure 5.22.1

▶ *O,O-Bis(ethyl-1,1-d$_2$) S-ethyl phosphorothiolothionate* (**113**) (*137*). Lawesson reagent (0.99 g, 2.4 mmol) was added in one portion to a stirred solution of *bis*(ethyl-1,1-d_2) *S*-ethyl phosphorothiolate (0.9 g, 4.4 mmol) in anhydrous acetonitrile (20 ml). The mixture was heated under reflux and monitored periodically by gas chromatography-mass spectrometry. After 20 h of reflux, 60% conversion to the product had occurred. The solvent was removed and the residue was chromatographed on silica gel, eluting with 40:1 hexane—acetone, to give a colourless liquid (0.46 g, 48%). δ_P ($CDCl_3$) 95.6 ppm.

Addition of *O,O*-dialkyl hydrogen phosphorodithioates (**114**) to alkyl halides provides *O,O,S*-trialkyl phosphorothiolothionates (**115**) generally in good yields (Fig. 5.22.2). Similarly, addition of *O,O*-diethyl hydrogen phosphorodithioate to methyl thiocyanate (*138*) or diazomethane (*139*) provides *O,O*-diethyl *S*-methyl phosphorothiolothionate $(EtO)_2P(S)SMe$ (in the latter case in 93% yield). *O,O*-Dialkyl hydrogen phosphorodithioates also react with aromatic diazonium salts to yield products of structure $(RO)_2P(S)SAr$ (*140*).

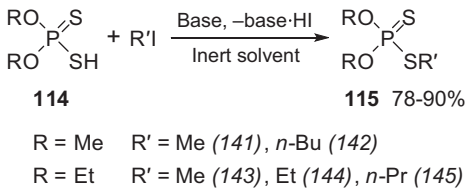


Figure 5.22.2

Addition of *O,O*-cycloalkyl hydrogen phosphorodithioates to alkyl halides also provides *O,O*-cycloalkyl *S*-alkyl phosphorothiolothionates (**116—118**) (Fig. 5.22.3). A solvent-free microwave method using alumina as a solid support is also available (*146*).

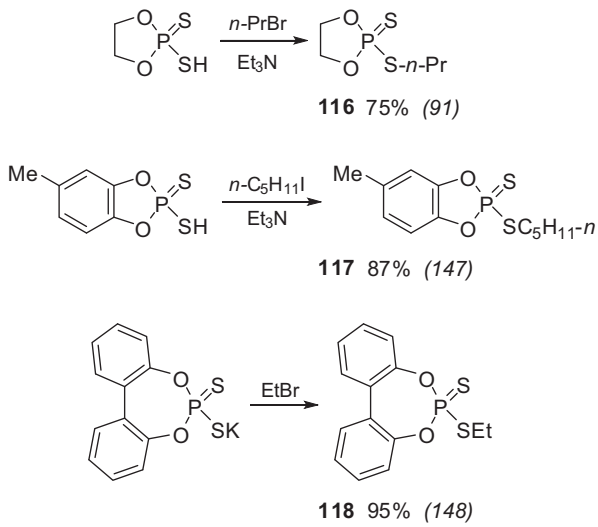


Figure 5.22.3

▶ *O,O,S-Trialkyl phosphorothiolothionates (microwave method)* (*146*). Alumina (2.5 g) and ammonium acetate (0.8 g, 10 mmol) were ground together for 5—10 min until a fine homogeneous powder was obtained. Phosphorus pentasulfide (2.2 g, 10 mmol) and ethanol (5 ml) were stirred together for 1 h and the alumina-supported ammonium acetate was added. This mixture was irradiated in a microwave oven (720 W) for 1 min. The alkyl halide (9 mmol) was added and the mixture was irradiated again for 2—4 min. Chromatography through a plug of silica gel, eluting with 9:1 hexane—ethyl acetate, gave the products in 75—93% yield.

Alkylation of *O,O*-diisopropyl phosphorodithioate ammonium salt (**119**) in boiling benzene with 2,3-dichloropropanoic acid occurs at the primary halide site and gives a monochlorinated analogue (**120**) (Fig. 5.22.4) (*149*). The reaction of *O,O*-dialkyl hydrogen phosphorothioates with chloroacetic acid in benzene is slow (8 h of heating under reflux) presumably because of the high acidity of the acid; the reaction with trichloroacetic acid is even slower (20—22 h in refluxing benzene). Treatment of *O,O*-dimethyl phosphorodithioate potassium salt (**121**) with 2-chloro-*N*-methylacetamide under two-phase conditions provides the pesticide dimethoate (*150*).

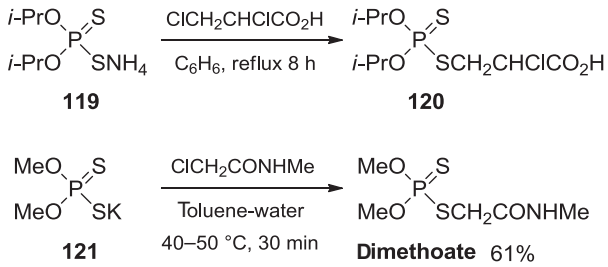
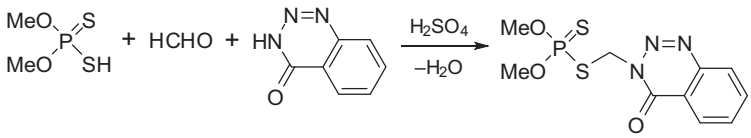


Figure 5.22.4

▶ *O,O-Dimethyl S-[2-(methylamino)-2-oxoethyl] phosphorothiolothionate (dimethoate) $(MeO)_2P(S)SCH_2CONHMe$ (150)*. A solution of *O,O*-dimethyl hydrogen phosphorodithioate (158 g, 1.0 mol) and 85% potassium hydroxide (66 g, 1.2 mol) in water (200 ml) was added over 30 min to a mixture of 2-chloro-*N*-methylacetamide (129 g, 1.2 mol), toluene (200 ml) and water (100 ml) at 40–50 °C and the mixture heated under reflux. The aqueous layer was extracted with toluene (2 × 200 ml). The combined organic layers were washed with saturated sodium bicarbonate and with water, concentrated to half the volume, and cooled to give dimethoate (140 g, 61%). Mp 52–53 °C.

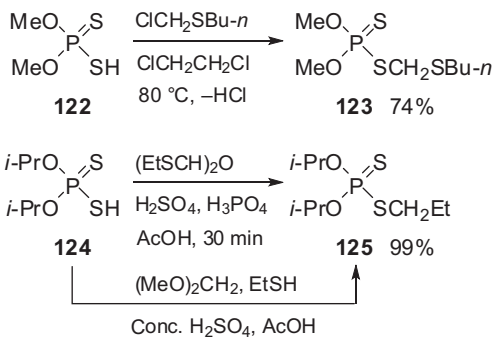
O,O-Dimethyl hydrogen phosphorodithioate (**122**) reacts with formaldehyde and 1,2,3-benzotriazin-4(3*H*)-one in the presence of sulfuric acid as a dehydrating agent to produce the pesticide azinphos-methyl (Fig. 5.22.5) (*151,152*).



122 **Azinphos-methyl**

Figure 5.22.5

Treatment of *O,O*-dimethyl hydrogen phosphorodithioate (**122**) with *n*-butyl chloromethyl sulfide in warm 1,2-dichloroethane provides *O,O*-dimethyl *S*-(*n*-butylthiomethyl) phosphorothiolothionate (**123**) in good yield (Fig. 5.22.6) (*153*). *O,O*-Diethyl hydrogen phosphorothioate reacts with 2-chloromethyl ethyl sulfide in the presence of a base (*154*) and with formaldehyde (or an equivalent such as bismethoxymethane) and ethanethiol (*155*) to provide the pesticide phorate $(EtO)_2P(S)SCH_2SEt$. Many phorate analogues have been prepared (*156–158*). *O,O*-Diisopropyl hydrogen phosphorodithioate (**124**) reacts with *bis*(ethylthiomethyl) ether in a mixture of sulfuric, phosphoric and acetic acids, or with bismethoxymethane and ethanethiol in a concentrated sulfuric acid–acetic acid mixture to give *O,O*-diisopropyl *S*-(ethylthiomethyl) phosphorothiolothionate (**125**) in excellent yield.



122 **123** 74% **124** **125** 99%

Figure 5.22.6

▶ *O,O-Dimethyl S-(n-butylthiomethyl) phosphorothiolothionate* $(MeO)_2P(S)SCH_2SBu$*-n* (**123**) *(from the dialkyl hydrogen phosphorodithioate and n-butyl chloromethyl sulfide)* (*153*). *n*-Butyl chloromethyl sulfide (42 g, 0.30 mol) was added dropwise to a stirred solution of *O,O*-dimethyl hydrogen phosphorodithioate (48 g, 0.30 mol) in 1,2-dichloroethane (50 ml) at 70 °C. Hydrogen chloride was evolved. The mixture was maintained at 80 °C for 5 min and then fractionated to provide the title compound as a colourless liquid (58 g, 74%). Bp 93 °C/0.01 mmHg.

▶ *O,O-Diisopropyl S-(ethylthiomethyl) phosphorothiolothionate* $(i\text{-}PrO)_2P(S)SCH_2SEt$ (**125**) *(from the dialkyl hydrogen phosphorodithioate and bis(ethylthiomethyl) ether)* (*156*). A mixture of *O,O*-diisopropyl hydrogen phosphorodithioate (228 g, 1.06 mol) and *bis*(ethylthiomethyl) ether (83 g, 0.50 mol) was added dropwise over 30 min to a mixture of sulfuric acid (50 g), phosphoric acid (85% wt in water; 75 g) and acetic acid (25 g). The mixture was kept at room temperature for 1 h and extracted with benzene to give the product.

▶ *O,O-Diisopropyl S-(ethylthiomethyl) phosphorothiolothionate* $(i\text{-}PrO)_2P(S)SCH_2SEt$ (**125**) *(from the dialkyl hydrogen phosphorodithioate, bismethoxymethane and ethanethiol)* (*157*). *O,O*-Diisopropyl hydrogen phosphorodithioate (21.6 g, 0.10 mol), bismethoxymethane (9.9 g, 0.13 mol) and ethanethiol (6.5 g, 0.10 mol) was added over 10 min to a stirred mixture of concentrated sulfuric acid (30 g), acetic acid (8 g) and water (6 g). The mixture was heated at 40 °C for 30 min and extracted with benzene (50 ml) to give the title compound (28.7 g, 99%).

The pesticide disulfoton has been synthesised by several routes starting from *O,O*-diethyl hydrogen phosphorodithioate (**83**), its ammonium salt (**126**) or *O,O*-diethyl phosphorothiolite sodium salt (**127**) and *bis*(2-ethylthioethyl) disulfide (Fig. 5.22.7) (*159–163*).

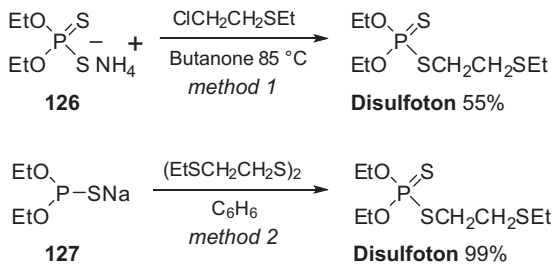


Figure 5.22.7

▶ *O,O-Diethyl S-(2-ethylthioethyl) phosphorothiolothionate* $(EtO)_2P(S)SCH_2CH_2SEt$ *(disulfoton). Method 1* (*160*). 2-Chloroethyl ethyl sulfide (40 g, 0.23 mol) was added dropwise to a stirred solution of *O,O*-diethyl phosphorodithioate ammonium salt (38 g, 0.20 mol) in butanone (120 ml). After warming to 85 °C for 2 h, the mixture was cooled to room temperature, the salts were separated by filtration, and the residue was dissolved in chloroform, washed with ice water, dried, and distilled to give disulfoton (30 g, 55%). *Method 2* (*161*). Sodium methoxide (0.30 mol) was added slowly to a stirred solution of diethyl *H*-thiophosphonate (48 g, 0.31 mol) and *bis*(2-ethylthioethyl) disulfide

(73 g, 0.30 mol) in benzene (200 ml). The mixture was stirred briefly, washed to neutral pH with water, separated, dried (Na_2SO_4), and the solvent removed to give a colourless liquid (82 g, 99%). Bp 87 °C/0.01 mmHg.

Michael addition of *O,O*-dialkyl hydrogen phosphorodithioates to alkenes yields *O,O,S*-trialkyl phosphorothiolothionates. The regiochemistry of addition depends on whether the alkene possesses electron-donating groups (e.g. vinyl ethers and asymmetric olefins; Markovnikov addition) or electron-withdrawing groups (e.g. acrylonitrile and alkenyl acylates; anti-Markovnikov addition). Additions of *O,O*-dialkyl hydrogen phosphorodithioates to non-activated alkenes are slow in the absence of catalysts and give low yields of products. Ultrasound or Lewis acid catalysts increase the rate of reaction. Zinc(II) chloride (1 wt%) is particularly useful: the uncatalysed reaction of *O,O*-diethyl hydrogen phosphorodithioate with hexadec-1-ene to give Markovnikov and anti-Markovnikov products takes 50 days at room temperature, but only 1 day when $ZnCl_2$ is added (*164*). Radical initiators such as organic peroxides promote anti-Markovnikov addition to unactivated alkenes by a radical mechanism: *O,O*-diethyl hydrogen phosphorodithioate adds to oct-1-ene in the presence of cumene hydroperoxide to give the anti-Markovnikov product. Note that unpurified *O,O*-dialkyl hydrogen phosphorodithioates often contain a small amount of phosphorus pentasulfide that acts as a radical inhibitor and encourages Markovnikov addition.

The insecticide malathion is produced on a large scale by reaction of phosphorus pentasulfide with 4 molar equivalents of methanol to give *O,O*-dimethyl hydrogen phosphorodithioate (**122**) which is then treated with maleic anhydride and ethanol. Azeotropic removal of water provides the pesticide in high yield (Fig. 5.22.8) (*165*).

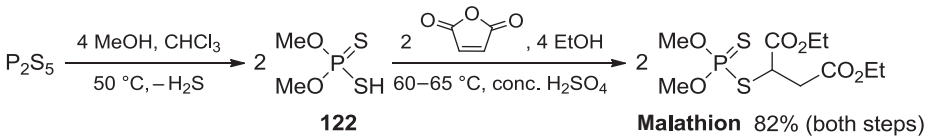


Figure 5.22.8

▶ *O,O-Dimethyl S-(1,2-dicarbethoxyethyl) phosphorothiolothionate (malathion)* (*165*). Methanol (128 g, 4 mol) was added dropwise to a stirred mixture of phosphorus pentasulfide (222 g, 1 mol) and chloroform (200 ml) at 50 °C. Stirring was continued until all the hydrogen sulfide departed. The mixture was cooled and filtered. The filtrate containing *O,O*-dimethyl hydrogen phosphorodithioate (1.5–1.6 mol) in chloroform (200 ml) was added dropwise to maleic anhydride (138 g, 1.4 mol) and ethanol (193 g, 4.2 mol) at 60–65 °C. The mixture was boiled and concentrated sulfuric acid (2 ml) was added in portions. The condensing vapours were collected as a distillate that separated into layers. The upper layer containing water was discarded and the bottom layer was recycled continuously; in this way, all the water was removed from the mixture in 4 h. The residue was cooled, neutralised with 10% *w/w* aqueous sodium carbonate (300 ml) and the mixture separated. The organic layer was washed with water (300 ml) and dried (Na_2SO_4). The solvent was removed to leave the product (520 g

containing 70% malathion; yield 82%). Hydroquinone can be added as an antioxidant during malathion synthesis (*166*). Pure malathion boils at 156–157 °C/0.7 mmHg and melts at 3 °C.

O,S-Disubstituted phosphorochloridothiolothionates RO(RS)P(S)Cl are useful reagents that react with nucleophiles (NuH) to give species of structure RO(RS)P(S)Nu. Their high reactivity to alcohols has been utilised in a one-pot conversion of thiophosphoryl chloride to [^{14}C]-labelled prothiofos (*38*). Treatment of thiophosphoryl chloride (1 mol) with 2,4-dichlorophenol (1 mol) then *n*-propanethiol (1 mol) in benzene in the presence of triethylamine (3 mol) provides *O*-(2,4-dichlorophenyl) *S*-propyl phosphorochloridothiolothionate (**128**) (Fig. 5.22.9). Addition of ethanol (1 mol) to the reaction mixture provides prothiofos in good yield.

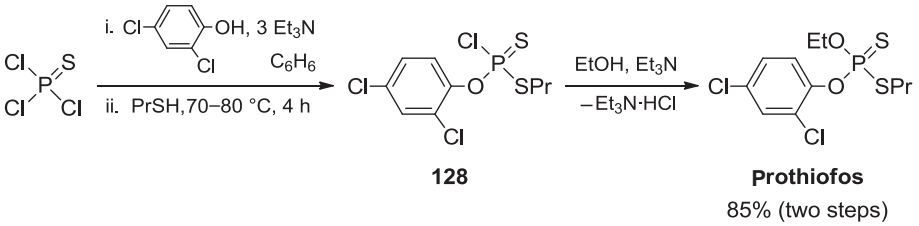


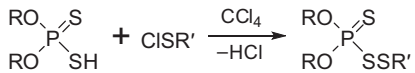
Figure 5.22.9

▶ *O-Ethyl O-(2,4-dichlorophenyl) S-propyl phosphorothiolothionate (prothiofos)* EtO(2,4-$Cl_2C_6H_3O$)P(S)SPr-*n* (*38*). A mixture of 2,4-dichlorophenol (1.62 g, 10 mmol) and triethylamine (4.2 ml, 30 mmol) in anhydrous benzene (20 ml) was added dropwise over 20 min to thiophosphoryl chloride (1.0 ml, 10 mmol) in anhydrous benzene (20 ml) at 5–10 °C, and after addition, stirring was continued for 4 h. A solution of propanethiol (0.9 ml, 10 mmol) in anhydrous benzene (5 ml) was added dropwise to this mixture at 5–10 °C. Afterwards the temperature was raised to 70–80 °C for 4 h and then ethanol (0.6 ml, 10 mmol) in anhydrous benzene (5 ml) was added dropwise. The mixture was stirred at room temperature overnight, filtered and the solvent removed. Chromatography of the residue on silica gel, eluting with 19:1 hexane–ether, gave a colourless liquid (2.93 g, 85%).

5.23 *O,O*-DIALKYL *S*-(ALKYL/ARYL-THIO) PHOSPHORODITHIOATES $(RO)_2P(S)SSR'$

The reaction of *O,O*-dialkyl hydrogen phosphorodithioates with sulfenyl chlorides provides a convenient method of accessing *O,O*-dialkyl *S*-(alkyl/arylthio) phosphorodithioates (Fig. 5.23.1) (*167*).

▶ *O,O-Dimethyl S-(ethylthio) phosphorodithioate* $(MeO)_2P(S)SSEt$ (*167*). A solution of ethylsulfenyl chloride (0.2 mol) in carbon tetrachloride (300 ml) was added over 30 min to a stirred solution of *O,O*-dimethyl hydrogen phosphorothioate (37.6 g, 0.2 mol) in ether (75 ml) at 10 °C. After addition, the solvent was removed and the residue was distilled to give the product (40.2 g, 92%). Bp 95 °C/1 mmHg.

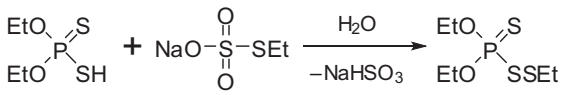


O,O-Dialkyl *S*-(alkyl/arylthio) phosphorodithioates

R	R′	Yield (%)
Me	CCl_3	90
Me	*n*-Bu	98
Me	*t*-Bu	100
Me	$CH(COEt)CH_2CO_2Et$	99
Me	Ph	66
Me	C_6H_4Cl-*p*	85
Et	Me	35
Et	Et	96
Et	*n*-Bu	98
Et	CH_2CO_2Et	88
Et	$CH(COEt)CH_2CO_2Et$	92
Et	Ph	78
Et	C_6H_4Cl-*p*	84

Figure 5.23.1

Salts of thiosulfuric monoesters, e.g. $NaOSO_2SR$, can be used instead of sulfenyl chlorides (*168*). For example, *O,O*-diethyl hydrogen phosphorodithioate (**83**) reacts with aqueous sodium *S*-ethyl sulfothioate to provide *O,O*-diethyl *S*-(ethylthio) phosphorodithioate (**129**) (Fig. 5.23.2).



83 **129** 79%

Figure 5.23.2

▶ *O,O-Diethyl S-(ethylthio) phosphorodithioate* $(EtO)_2P(S)SSEt$ (**129**) (*168*). *O,O*-Diethyl hydrogen phosphorodithioate (58 g, 0.31 mol) was added dropwise to a stirred solution of sodium *S*-ethyl sulfothioate (66 g, 0.40 mol) in water (150 ml). The mixture was stirred overnight and the oil extracted with petroleum ether. The organic layer was neutralised with aqueous sodium bicarbonate, washed with water (50 ml), dried ($MgSO_4$) and distilled to give the product (60 g, 79%). Bp 62 °C/0.01 mmHg.

Phosphorus sulfenyl halides contain an electrophilic sulfur atom that reacts with nucleophiles with loss of halide. Reactions with thiols (HSR) proceed to give P-SSR groups. For example, *O,O*-diethyl *S*-chloro phosphorodithioate (**130**) combines with *tert*-butanethiol to provide the corresponding *S*-(*tert*-butylthio) phosphorodithioate (**131**) in acceptable yield (Fig. 5.23.3) (*167*).

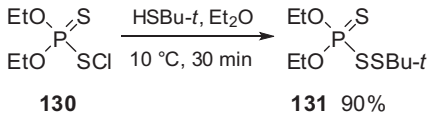


Figure 5.23.3

▶ *O,O-Diethyl S-(tert-butylthio) phosphorodithioate* $(EtO)_2P(S)SSBu\text{-}t$ (**131**) (*167*). *Tert*-butanethiol (18 g, 0.20 mol) was added over 30 min to a stirred solution of *O,O*-diethyl *S*-chloro phosphorodithioate (31 g, 0.14 mol) in ether (150 ml) at 10 °C. The ether was later removed under reduced pressure to give the product (34.5 g, 90%).

5.24 *O,O*-DIALKYL *S*-(DIALKYLAMINOTHIO) PHOSPHORODITHIOATES $(RO)_2P(S)SSNR^1_2$

O,O-Diethyl sodium phosphorodithioate (**98**) reacts with *N,N*-dialkylaminosulfenyl chlorides to provide *O,O*-dialkyl *S*-(*N,N*-dialkylaminothio) phosphorodithioates (**132a–c**) with loss of sodium chloride (Fig. 5.24.1) (*120*). *O,O*-Dicyclohexyl hydrogen phosphorothioate (**133**) reacts with phthalimidosulfenyl chloride in the presence of a base to give the disulfide (**134**) (*169*).

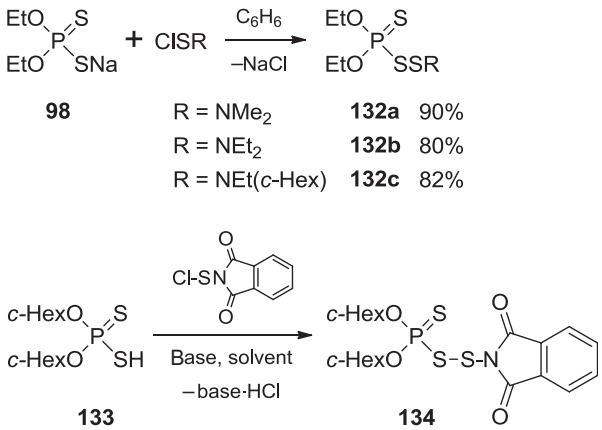


Figure 5.24.1

▷ *O,O-Diethyl S-(N-cyclohexyl-N-ethylaminothio) phosphorodithioate (EtO)$_2$P(S)SSNEt(c-Hex)* (**132c**) (*120*). A suspension of *O,O*-diethyl sodium phosphorodithioate (52 g, 0.25 mol) in benzene (250 ml) was added dropwise to a stirred solution of *N*-cyclohexyl-*N*-ethylaminosulfenyl chloride (48.4 g, 0.30 mol) in benzene (200 ml). The temperature rose slightly and the mixture was stirred for 1 h. It was washed with water (2 × 100 ml), dried (Na_2SO_4), filtered and concentrated to give a brown liquid (70 g, 82%).

5.25 *O,O*-DIALKYL *S*-(ALKOXY) PHOSPHORODITHIOATES (RO)$_2$P(S)SOR'

O,O-Dialkyl *S*-halogeno phosphorodithioates (**135**) react with alcohols in the presence of 2,6-lutidine to give *O,O*-dialkyl *S*-(alkoxy) phosphorodithioates (**136a–c**) (Fig. 5.25.1) (*170*). The use of *S*-bromo phosphorodithioates (RO)$_2$P(S)SBr is preferred over *S*-chloro phosphorodithioates as they are more stable and more easily prepared (by mixing the disulfides (RO)$_2$P(S)SSP(S)(OR)$_2$ with an equimolar amount of bromine).

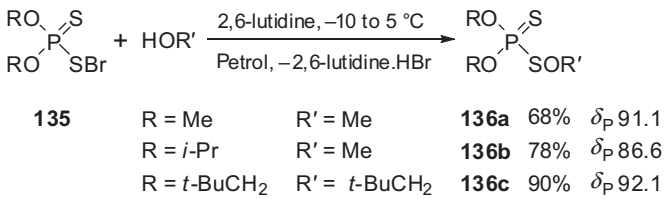


Figure 5.25.1

▷ *O,O-Dialkyl S-(alkoxy) phosphorodithioates (RO)$_2$P(S)SOR′* (**136a–c**) (*170*). A solution of the alcohol (30 mmol) and anhydrous 2,6-lutidine (30 mmol) was added dropwise to a stirred solution of the *O,O*-dialkyl *S*-bromo phosphorodithioate (30 mmol) in petroleum ether (40 ml) at −10 to +5 °C. The precipitated 2,6-lutidine hydrobromide was filtered off and the sulfenyl esters isolated by distillation: dimethoxy (68%; bp 78 °C/0.03 mmHg), diisopropoxy (78%, bp 65 °C/0.01 mmHg), and dineopentoxy (90%, bp 70–72 °C/0.01 mmHg).

O,O-Dimethyl *S*-chloro phosphorodithioate (**137**) reacts with acetophenoxime (**138**) in the presence of triethylamine to provide *O,O*-dimethyl *S*-(acetophenoximo) phosphorodithioate (**139**) in quantitative yield (Fig. 5.25.2) (*167*). This compound and relatives have been studied as potential insecticides.

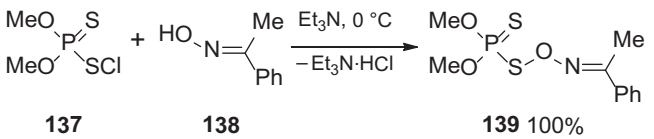
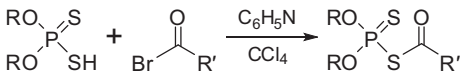


Figure 5.25.2

▶ *O,O-Dimethyl S-(acetophenoximo) phosphorodithioate* $(MeO)_2P(S)SON{=}C(Me)Ph$ (**139**) (*167*). Triethylamine (11.2 g, 0.11 mol) was added over 30 min to a stirred solution of *O,O*-dimethyl *S*-chloro phosphorodithioate (19.3 g, 0.10 mol) and acetophenoxime (13.5 g, 0.10 mol) at 0 °C. The mixture was allowed to warm to room temperature over 1 h, filtered, and the filtrate concentrated under reduced pressure. Further concentration at 50 °C and 1 mmHg gave the solid product (29.1 g, 100%).

5.26 *O,O*-DIALKYL *S*-ACYL PHOSPHORODITHIOATES $(RO)_2P(S)SC(O)R'$

O,O-Dialkyl hydrogen phosphorodithioates react with acyl chlorides (*127*) or acyl bromides in the presence of a base to give a range of *S*-acyl derivatives (Fig. 5.26.1) (*171*). Symmetrical *O,O*-dialkyl hydrogen phosphorodithioates with $ROCH_2CH_2O$ groups (R = Me, Et, Ph) react with acetyl chloride and benzoyl chloride to give *S*-acyl products (*172*).



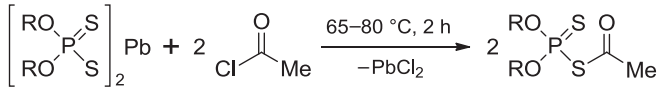
O,O-Dialkyl *S*-acyl phosphorodithioates

R	R′	Yield (%)
Ph	Me	93
Bn	Me	89
Me	Et	91
i-Pr	Et	89
MeCH=CH	Et	87
p-$(NO_2)C_6H_4$	Et	93
Me	CH_2Cl	90
p-ClC_6H_4	CH_2CH_2Cl	85

Figure 5.26.1

▶ *O,O-Dimethyl S-(chloroacetyl) phosphorodithioate* $(MeO)_2P(S)SC(O)CH_2Cl$ (*171*). *O,O*-Dimethyl phosphorodithioate (190 g, 1.2 mol) and chloroacetyl bromide (189 g, 1.2 mol) in carbon tetrachloride (200 ml) was slowly neutralised with pyridine (100 g, 1.3 mol) at 40 °C and stirred for 4 h. The mixture was washed with 3% hydrochloric acid and water, and the usual work-up followed, to give a colourless liquid (253 g, 90%).

O,O-Dialkyl phosphorodithioate lead salts (**140**) react with acyl chlorides to give the *S*-acyl phosphorodithioates (**141a–c**) in high yield (Fig. 5.26.2) (*173*). The formed lead(II) chloride is easily separated by filtration and the *S*-acyl compounds are purified by distillation.



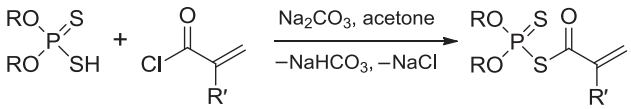
140

R = Et **141a** 85%
R = *i*-Pr **141b** 67%
R = *i*-Bu **141c** 70%

Figure 5.26.2

▶ *O,O-Diethyl S-acetyl phosphorodithioate* $(EtO)_2P(S)SC(O)Me$ (**141a**) (*173*). Acetyl chloride (7.8 g, 10 mmol) was added to the *O,O*-diethyl phosphorodithioate lead(II) salt (2.8 g, 5 mmol) and the mixture heated to 65–80 °C for 2 h. The cooled mixture was filtered to remove the lead(II) chloride (1.2 g) and the filtrate distilled to give the title compound (1.9 g, 85%). Bp 98 °C/2 mmHg.

O,O-Dialkyl hydrogen phosphorodithioates react with acryloyl or 2-methylacryloyl chloride in acetone in the presence of sodium carbonate to give *O,O*-dialkyl *S*-acylated monomers (**142a–c**) in high yield (Fig. 5.26.3) (*174*).

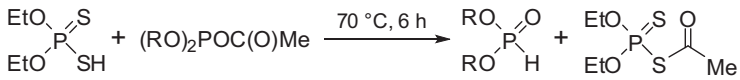


R = Et R′ = H **142a** 78% δ_P 79.7
R = Et R′ = Me **142b** 76% δ_P 79.8
R = *i*-Pr R′ = Me **142c** 86% δ_P 76.1

Figure 5.26.3

▶ *O,O-Dialkyl S-(acryloyl/methacryloyl) phosphorodithioates* $(RO)_2P(S)SC(O)C(H/Me){=}CH_2$ (**142a–c**) (*174*). The *O,O*-dialkyl hydrogen phosphorodithioate (10 mmol) was added to a stirred supension of sodium carbonate (2.44 g, 23 mmol) in anhydrous acetone (20 ml). After addition the mixture was stirred for 15 min. It was cooled to 15 °C and either acryloyl chloride or 2-methylacryloyl chloride (10 mmol) was added. The mixture was stirred at room temperature for 15 h, filtered and concentrated to give a yellow liquid that was purified by column chromatography on silica gel eluting with 1:1 ether–hexane. Yields and phosphorus chemical shifts appear in Fig. 5.26.3.

An equimolar mixture of *O,O*-diethyl hydrogen phosphorodithioate (**83**) and acetyl dialkyl phosphite on heating provides the dialkyl *H*-phosphonate (**143a**,**b**) and *O,O*-diethyl *S*-acetyl phosphorodithioate (**141a**) (Fig. 5.26.4) (*175*). These products can be separated by vacuum fractionation as the difference in boiling points between the two is large.



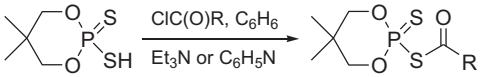
83

R = Et **143a** 63% **141a** 62%
R = *n*-Pr **143b** 62% **141a** 60%

Figure 5.26.4

▶ *O,O-Diethyl S-acetyl phosphorodithioate* $(EtO)_2P(S)SC(O)Me$ (**141a**) (*175*). *O,O*-Diethyl hydrogen phosphorodithioate (9.3 g, 50 mmol) was added to acetyl diethyl phosphite (9.0 g, 50 mmol) (slight exotherm) and the mixture was then heated for 6 h at 70 °C. Fractional distillation of the mixture gave diethyl *H*-phosphonate (63%, bp 73–74 °C/13 mmHg) and the title compound (7.1 g, 62%; bp 65–67 °C/0.5 mmHg).

Treatment of *O,O*-dialkyl hydrogen phosphorodithioates with acyl chlorides and triethylamine or pyridine immediately yields *S*-acyl derivatives (Fig. 5.26.5) (*176*). To obtain these pure the reaction mixture is cooled with ice and worked up as quickly as possible, with subsequent evaporation of the solvent at room temperature.



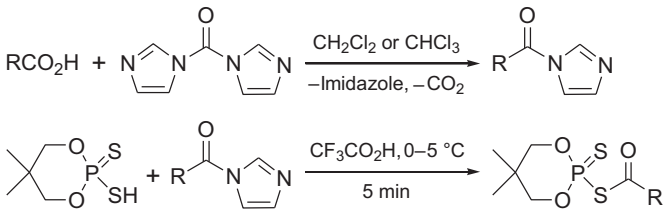
O,O-(Cycloalkyl) *S*-acyl phosphorodithioates

R	Yield (%)	δ_P (ppm)
Me	89	69.1
n-Pr	92	70.1
i-Pr	98	70.6
t-Bu	96	70.8
n-hexyl	93	71.0
CH_2Ph	90	68.9
$CHPh_2$	94	69.4
CH_2OPh	90	67.9
$(CH_2)_4CO_2Me$	100	69.2
CH=CHPh-(*E*)	93	69.7
Ph	98	69.1
C_6H_4OMe-*p*	85	70.3
$C_6H_4NO_2$-*p*	85	65.9
1-naphthyl	100	69.6

Figure 5.26.5

▶ *O,O-Dialkyl S-acyl phosphorodithioates* $(RO)_2P(S)SC(O)R'$ *(general method)* (*176*). An acyl chloride (3 mmol) was added to a solution of the *O,O*-dialkyl hydrogen phosphorodithioate (3 mmol) in benzene (10 ml) at 0–5 °C. Triethylamine (0.30 g, 3 mmol) or pyridine (0.24 g, 3 mmol) was then added dropwise. Triethylamine hydrochloride or pyridininium chloride precipitated immediately. After 15 min, the reaction mixture was filtered through a short pad of silica gel. Evaporation of the solvent gave the pure product (Fig. 5.26.5).

O,O-Dialkyl *S*-acyl phosphorodithioates can be prepared from carboxylic acids activated by treatment with 1,1′-carbonyldiimidazole (Fig. 5.26.6) (*176*). *O,O*-Dialkyl hydrogen phosphorodithioates react with the 1-acylimidazoles produced to provide the *S*-acyl phosphorodithioates and imidazole. The process requires the use of 3 molar equivalents of the *O,O*-dialkyl hydrogen phosphorodithioate, so it is inefficient if an expensive acid is used. A modification that includes trifluoroacetic acid allows the amount of starting phosphorodithioate required to be lowered to 1 molar equivalent. The yield of *S*-acyl product thus obtained is sometimes higher and imidazole trifluoroacetate forms as the by-product.



O,O-(Cycloalkyl) *S*-acyl phosphorodithioates

R	Yield (%)	δ_P (ppm)
Me	95 [a]	69.1
n-Pr	98 [a]	70.1
t-Bu	84, 99 [a]	70.8
$(CH_2)_4CO_2Me$	99 [a]	69.2
CH_2NPhth	81	65.7
CH_2CH_2Phth	93	67.7
Ph	94	69.1
1-naphthyl	81	69.6

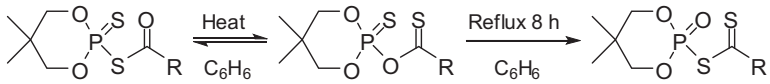
a. With CF_3CO_2H. Phth = phthalimide group

Figure 5.26.6

▶ *O,O-Dialkyl S-acyl phosphorodithioates (general method)* (*176*). A solution of 1,1′-carbonyldiimidazole (0.32 g, 2 mmol) in dichloromethane or chloroform (3 ml) was added dropwise to a solution or suspension of the carboxylic acid (2 mmol) in dichloromethane or chloroform (1 ml). After evolution of carbon dioxide ceased (15—30 min), a solution of the *O,O*-dialkyl hydrogen phosphorodithioate (2 mmol) was added while cooling the mixture with ice water. Then trifluoroacetic acid (0.46 g, 4 mmol) was added dropwise. After 15 min of stirring at ambient temperature, imidazole trifluoroacetate precipitated. The reaction mixture was filtered through a short pad of silica gel and the solvent evaporated to give the pure product.

On prolonged standing or heating, some *O,O*-dialkyl *S*-acyl phosphorodithioates (**144**) convert from the P(S)SC═O to the P(S)OC═S isomer (**145**) and then sometimes to the phosphoryl P(O)

SC═S isomer (**146**) (Fig. 5.26.7) (*176*). The R group influences the product distribution: in refluxing benzene for 8 h, the CH_2OPh compound gives isomer (**145**) in 15% yield and the 1-naphthyl compound gives 99% of isomer (**146**).

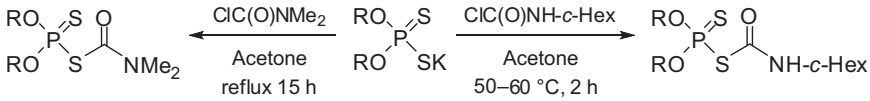


144	**145**	**146**
R = CH_2OPh	15%	0%
R = 1-naphthyl	0%	99%

Figure 5.26.7

5.27 *O,O*-DIALKYL *S*-(*N*-ALKYLCARBAMOYL) PHOSPHORODITHIOATES $(RO)_2P(S)SC(O)NR^1_2$

O,O-Dialkyl potassium phosphorodithioates react with *N*-alkyl- or *N,N*-dialkylcarbamoyl chlorides in refluxing acetone to give *O,O*-dialkyl *S*-(*N*- or *N,N*-di-alkylcarbamoyl) phosphorodithioates such as (**147**) and (**148**) (Fig. 5.27.1) (*177,178*). The method is of general utility.



147 69% R = *i*-Pr R = Et **148** 72%

Figure 5.27.1

▶ *O,O-Diisopropyl S-(N,N-dimethylcarbamoyl) phosphorodithioate* (**147**) (*177*). Dimethylcarbamoyl chloride (75.3 g, 0.70 mol) was added rapidly to *O,O*-diisopropyl potassium phosphorodithioate (189 g, 0.75 mol) in anhydrous acetone (800 ml) at room temperature The mixture was heated under reflux for 15 h, filtered, and the filtrate concentrated to yield the product (137 g, 69%).

▶ *O,O-Diethyl S-(N-cyclohexylcarbamoyl) phosphorodithioate* (**148**) (*178*). Cyclohexylcarbamoyl chloride (82 g, 0.51 mol) was added to *O,O*-diethyl potassium phosphorodithioate (115 g, 0.51 mol) in acetonitrile (300 ml). The temperature rose to 50 °C. The solution was then held at 60 °C for an additional 2 h. The cooled mixture was diluted with benzene (600 ml), washed with water (100 ml), the organic layer separated and dried (Na_2SO_4), and the solved removed to yield a liquid (115 g, 72%).

5.28 TETRA-ALKYL PYROPHOSPHORODITHIONATES $(RO)_2P(S)OP(S)(OR)_2$

The main synthetic routes to these compounds involve the thionation of trivalent diphosphorus compounds with sulfur or the controlled hydrolysis of dialkyl phosphorochloridothionates in the

presence of a base. Diethyl phosphorochloridite combines with diethyl *H*-phosphonate in the presence of pyridine in hot toluene to provide the symmetrical phosphite (**149**) that readily adds sulfur to provide tetraethyl pyrophosphorodithionate (**150**) in good overall yield (Fig. 5.28.1) (*179*).

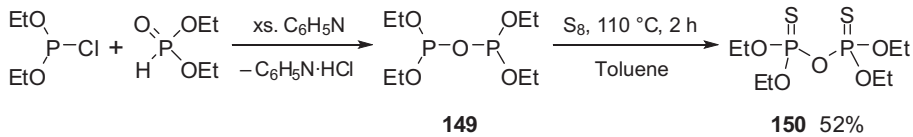


Figure 5.28.1

▶ *Tetraethyl pyrophosphorodithionate* $(EtO)_2P(S)OP(S)(OEt)_2$ (**150**) (*179*). Diethyl phosphorochloridite (79 g, 0.5 mol) was added dropwise to a stirred solution of diethyl *H*-phosphonate (69 g, 0.5 mol) in pyridine (40 g, 0.5 mol) and toluene (200 ml). Sulfur (32 g, 1.0 mol) was added over 1 h and the temperature kept below 50 °C by cooling. Then the mixture was heated for 2 h at 110 °C and the pyridine hydrochloride dissolved by the addition of water (100 ml). The aqueous layer was removed and the organic layer worked-up as usual. Fractionation of the residue gave the product (85 g, 52%). Bp 140–141 °C/3 mmHg.

Dialkyl phosphorochloridothionates and water (2:1 molar ratio) react in the presence of suitable inorganic or organic bases to provide the symmetrical tetra-alkyl pyrophosphorodithionates (Fig. 5.28.2) (*180,181*). Methods for the lower members of the series (**150–151**) are provided. Side reactions involving decomposition lower yields and can be minimised by controlling the temperature, sequence and rate of addition of the reactants. Inorganic bases are excellent substitutes for tertiary amines as long as a sterically unhindered amine catalyst is added.

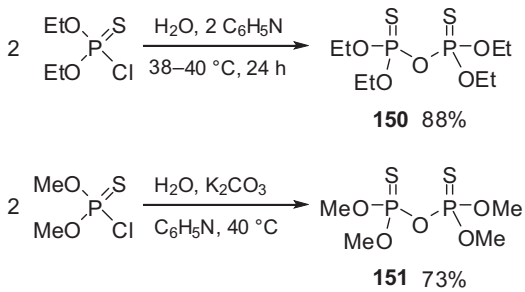


Figure 5.28.2

▶ *Tetraethyl pyrophosphorodithionate* $(EtO)_2P(S)OP(S)(OEt)_2$ (**150**) (*180*). Diethyl phosphorochloridothionate (188.5 g, 1.0 mol) was treated over 40 min with pyridine (86 g, 1.1 mol) and water (10 g) (the temperature was kept at 38–40 °C by periodic cooling). Cooling was continued for 25 min and the mixture was stirred for 2 h at room temperature, followed by heating to 38–40 °C overnight. The paste was washed with water (100 ml). The organic layer was washed with water (3 × 100 ml),

separated and dried ($MgSO_4$). Volatile material was removed from the filtrate and the residue distilled to give the product (142 g, 88%). Bp 110–113 °C/0.2 mmHg.

▶ *Tetramethyl pyrophosphorodithionate* $(MeO)_2P(S)OP(S)(OMe)_2$ (**151**) (*181*). Pyridine (5 ml) was added gradually to a mixture of dimethyl phosphorochloridothionate (175 g, 1.1 mol), powdered potassium carbonate (75 g, 0.5 mol) and water (80 ml) at 40 °C. The mixture was stirred at this temperature overnight, cooled to room temperature and washed with 5% hydrochloric acid, and then 5% aqueous sodium carbonate. The organic product was dried (Na_2CO_3) and distilled to yield the product (97 g, 73%). Bp 118–120 °C/2 mmHg.

2,2-Dimethyl-1,3-propanediol reacts with thiophosphoryl chloride in the presence of excess 3-methylpyridine to give the cyclic phosphorochloridothionate (**152**) whose hydrolysis provides the pyrophosphorodithionate (**153**) (Fig. 5.28.3) (*182*).

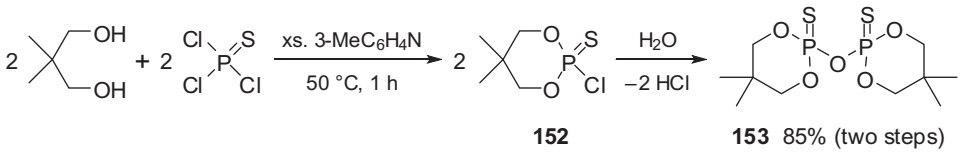


Figure 5.28.3

▶ *2,2′-Oxy-bis(5,5-dimethyl-1,3,2-dioxaphosphorinane)-2,2′-disulfide* (**153**) (*182*). Thiophosphoryl chloride (169.5 g, 1.00 mol) was added over 3 h to a 1-l stirred reactor charged with 2,2-dimethyl-1,3-propanediol (104.0 g, 1.0 mol) and 3-methylpyridine (595.0 g, 6.4 mol) at 50 °C. One hour after the introduction of thiophosphoryl chloride started, continuous addition of water (9.0 g, 0.5 mol) over 5.5 h was commenced, and after completion of the thiophosphoryl chloride addition the temperature was increased to 60 °C within 1 h. After completion of the water addition, stirring was continued for approximately 16 h at 60 °C. Water (180 g) was then added over 2 min to dissolve the 3-methylpyridinium chloride formed. The product was isolated by filtration and washed with the filtrate (147 g, 85%).

5.29 TETRA-ALKYL PYROPHOSPHOROTHIONATES $(RO)_2P(S)OP(O)(OR)_2$

Routes to these products include the reaction of dialkyl phosphorochloridothionates with dialkyl phosphate ammonium or alkali metal salts or the reaction of *O,O*-dialkyl hydrogen phosphorothioates with dialkyl phosphorochloridates (Fig. 5.29.1) (*183,184*). Both routes permit the preparation of symmetrical tetra-alkyl pyrophosphorothionates (**154–155**) or unsymmetrical products depending on the choice of starting materials.

Tetramethyl pyrophosphorothionate $(MeO)_2P(S)OP(O)(OMe)_2$ (**154**) (*183*). Dimethyl phosphorochloridothionate (3.95 g, 24.7 mmol) was added dropwise to a solution of *O,O*-dimethyl tetra-*n*-butylammonium phosphate (9.8 g, 26.7 mmol) in acetonitrile (7 ml) at −35 °C. The mixture was stirred at this temperature for 30 min, immediately loaded onto a silica gel column (250 ml) and eluted

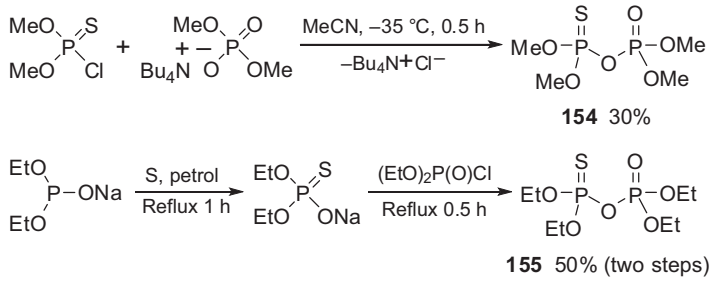


Figure 5.29.1

with dichloromethane. Removal of solvent from the combined product fractions gave the title compound as a yellow liquid (1.85 g, 30%). δ_H ($CDCl_3$) 3.86 (6 H, d, J_{HP} 0.7 Hz), 3.9 (6 H, d, J_{HP} 0.9 Hz). δ_C ($CDCl_3$) 55.1 (d, J_{CP} 6 Hz), 55.4 (d, J_{CP} 5.5 Hz). δ_P ($CDCl_3$) −13.8 and 55.6 ppm (each d, J_{PP} 20 Hz, P═O and P═S respectively).

▶ *Tetraethyl pyrophosphorothionate* $(EtO)_2P(S)OP(O)(OEt)_2$ (**155**) (*184*). Sulfur (116 g, 3.6 mol) was added to a stirred solution of diethyl sodium phosphite (3.6 mol) [pre-prepared from diethyl *H*-phosphonate (497 g, 3.6 mol) and sodium metal (82.8 g, 3.6 mol)] in petroleum ether (2500 ml). The mixture was heated under reflux for 1 h and the resulting solution of *O,O*-diethyl sodium phosphorothioate was cooled and treated with diethyl phosphorochloridate (690 g, 4.0 mol). After addition, the mixture was refluxed for 0.5 h, treated with ice water, and the organic layer dried and concentrated. Distillation of the residue (911 g) gave the product (550 g, 50%). Bp 135−136 °C/1 mmHg.

Partial desulfurisation and simultaneous rearrangement of *bis*(dialkylthiophosphoryl) disulfides by alkali metal cyanides provides the pyrophosphorothionate (**156** → **154**) as does the reaction of ammonium *O,O*-dialkyl phosphorothioates with phosgene or thiophosgene (**157** → **155**) (Fig. 5.29.2) (*185,186*). The mechanisms of these rather obscure reactions do not seem to have been determined.

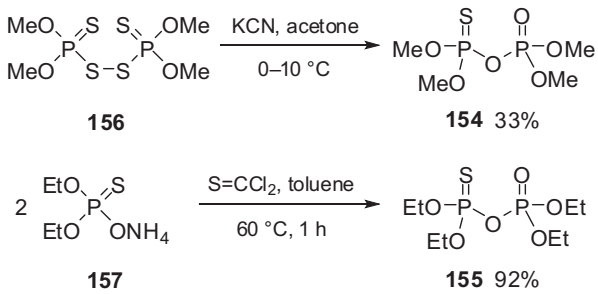


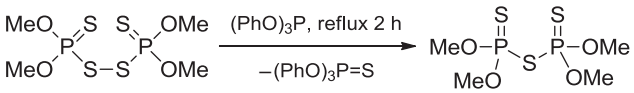
Figure 5.29.2

▶ *Tetramethyl pyrophosphorothionate* $(MeO)_2P(S)OP(O)(OMe)_2$ (**154**) (*185*). A solution of *bis*(dimethylthiophosphoryl) disulfide (27 g, 85 mmol) in acetone (30 ml) was added to a stirred suspension of potassium cyanide (6 g, 90 mmol) in acetone (20 ml) at 0–10 °C. The mixture was warmed to room temperature and the acetone removed. The residue was dissolved in benzene, filtered, and fractionated to give the product (7 g, 33%). Bp 65 °C/0.01 mmHg.

▶ *Tetraethyl pyrophosphorothionate* $(EtO)_2P(S)OP(O)(OEt)_2$ (**155**) (*186*). A solution of thiophosgene (12 g, 0.1 mol) in toluene (12 ml) was added to stirred ammonium *O,O*-diethyl phosphorothioate (37 g, 0.2 mol) in toluene (200 ml) at 60 °C. After 1 h the mixture was cooled, filtered, and the filtrate fractionated to give the product (28 g, 92%). Bp 90 °C/0.05 mmHg. It can also be made using phosgene in toluene at 20 °C.

5.30 TETRA-ALKYL THIOPYROPHOSPHORODITHIONATES $(RO)_2P(S)S(S)P(OR)_2$

These can be obtained by treating *O,O*-dialkyl phosphorodithioate salts with dialkyl phosphorochloridothionates (*187*) or by desulfurising *bis*(dialkylthiophosphoryl) disulfides with triaryl phosphites; the latter are converted into the corresponding triaryl phosphorothionates (Fig. 5.30.1). The nature of the phosphite used affects the yield, for example tris(4-chlorophenyl) phosphite gives lower yields of the target dithionate than triphenyl phosphite (*188*,*189*). This is because it is less nucleophilic and therefore less able to accept a sulfur atom.

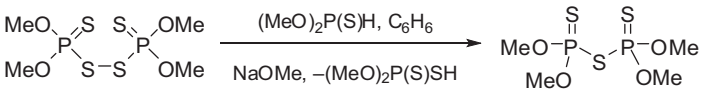


158 78%

Figure 5.30.1

▶ *Tetramethyl thiopyrophosphorodithionate* $(MeO)_2P(S)SP(S)(OMe)_2$ (**158**) (*188*). Triphenyl phosphite (7.75 g, 25 mmol) was added to a stirred solution of *bis*(dimethylphosphoryl) disulfide (7.85 g, 25 mmol) in ligroin (25 ml) in a flask equipped with a reflux condenser. The mixture was heated under reflux for 2 h. The solvent was removed and the residue was fractionated under high vacuum to yield the title compound (5.50 g, 78%). Bp 109–111 °C/0.075 mmHg. Mp 33–34 °C. The by-product $(PhO)_3P{=}S$ (mp 45–51 °C) was obtained in 74% yield. Analogous results were obtained when the experiment was conducted without a solvent.

Bis(dialkylthiophosphoryl) disulfides also react with dialkyl *H*-thiophosphonates $(RO)_2P(S)H$ or dialkyl *H*-phosphonates $(RO)_2P(O)H$ in inert solvents at room temperature in the presence of bases (alkoxides or tertiary amines) to yield tetra-alkyl thiopyrophosphorodithionates (**158**) (Fig. 5.30.2) (*190*).



158 53%

Figure 5.30.2

▶ *Tetramethyl thiopyrophosphorodithionate* $(MeO)_2P(S)SP(S)(OMe)_2$ (**158**) (*190*). To a solution of *bis*(dimethylphosphoryl) disulfide (94 g, 0.3 mol) and dimethyl *H*-thiophosphonate (38 g, 0.3 mol) in benzene (200 ml), the equivalent amount of sodium methoxide was added at room temperature, and the mixture kept at room temperature for 15 min. The mixture was washed with water (50 ml), dried ($MgSO_4$) and evaporated. The residue was cooled to −10 °C and triturated with ice-cold petroleum ether to give the target compound (45 g, 53%). Mp 40−41 °C.

Tetra-alkyl thiopyrophosphorodithionates are formed by the reaction of dialkyl *H*-thiophosphonates with *N,N*-dialkylaminosulfenyl chlorides or alkali metal salts of *O,O*-dialkyl hydrogen phosphorodithioates with sulfur dichloride (Fig. 5.30.3) (*192,193*). They are also obtainable from the reaction of *O,O*-dialkyl potassium phosphorodithioates with dialkyl phosphorochloridothionates (*187*) or *O,O*-dialkyl *S*-chloro phosphorothiolothionates with dialkyl *H*-thiophosphonates (*193*).

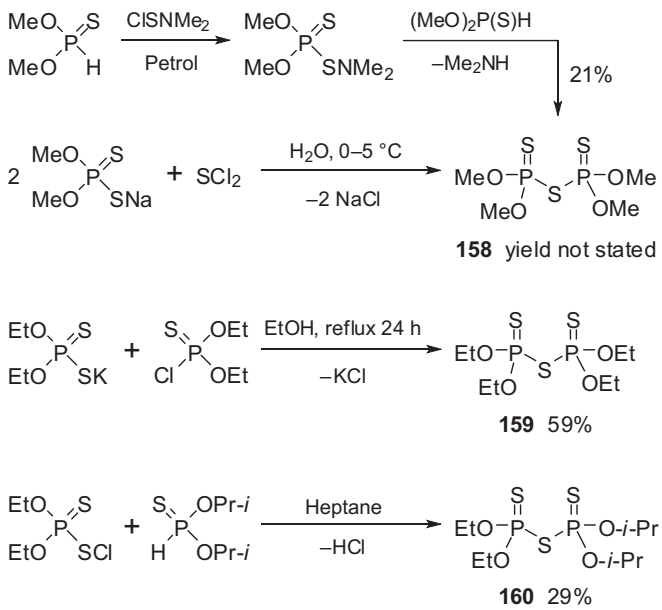


Figure 5.30.3

▶ *Tetramethyl thiopyrophosphorodithionate* $(MeO)_2P(S)SP(S)(OMe)_2$ (**158**) (*191*). Dimethyl *H*-thiophosphonate (63 g, 0.5 mol) in petroleum ether (100 ml) was added dropwise to a solution of *N,N*-dimethylaminosulfenyl chloride (27 g, 0.24 mol) in petroleum ether (270 ml) at 0 °C. The mixture was stirred at this temperature for 1 h, warmed to room temperature, and stirred for a further 2 h. It was washed with water (100 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Distillation of the residue gave the desired product (15 g, 21%). Bp 82−83 °C/0.01 mmHg.

▶ *Tetramethyl thiopyrophosphorodithionate* $(MeO)_2P(S)SP(S)(OMe)_2$ (**158**) (*192*). Sulfur dichloride (1 mol equiv.) was added dropwise to a stirred 40% solution of *O,O*-dimethyl sodium

phosphorodithioate (2 mol equiv.) in water cooled to 0–5 °C. The temperature was maintained below 10 °C. The oily layer was separated, extracted with ether, dried, and the ether removed under reduced pressure to give a white crystalline solid (yield not stated). Mp 52–53 °C.

▶ *Tetraethyl thiopyrophosphorodithionate* (**159**) *$(EtO)_2P(S)SP(S)(OEt)_2$* (*187*). *O,O*-Diethyl potassium phosphorodithioate (45 g, 0.2 mol) and diethyl phosphorochloridothionate (37.5 g, 0.2 mol) were dissolved in ethanol (500 ml) and heated under reflux overnight. The mixture was filtered, concentrated under reduced pressure, and the residue purified by fractional distillation to give the title compound (40 g, 59%). Bp 88–90 °C/2 mmHg.

▶ *Diethyl diisopropyl thiopyrophosphorodithionate $(EtO)_2P(S)SP(S)(O\text{-}i\text{-}Pr)_2$* (**160**) (*193*). A solution of diisopropyl *H*-thiophosphonate (2.0 g, 11 mmol) in heptane (10 ml) was added dropwise to a stirred solution of *O,O*-diethyl *S*-chloro phosphorodithionate (2.4 g, 11 mmol) in anhydrous heptane (10 ml) at 0 °C. The mixture was concentrated under reduced pressure and fractionated to give the product as a liquid (1.2 g, 29%). Bp 138 °C/0.4 mmHg.

Tetra-alkyl thiopyrophosphorodithionates can be prepared by treating the piperidinium or potassium salts of *O,O*-dialkyl hydrogen phosphorodithioates with 2-chloro-1-methylpyridinium salts (*194*). Thiopyrophosphorodithionates such as compound (**161**) are prepared similarly using 2-bromo-1-methylpyridinium iodide (Fig. 5.30.4) (*195*).

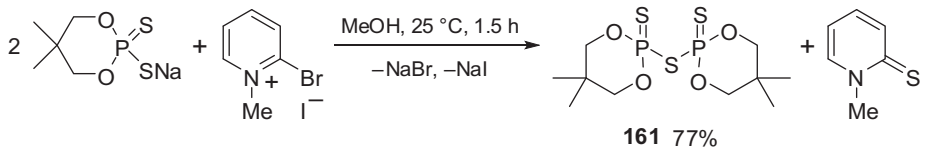


Figure 5.30.4

▶ *Bis(5,5-dimethyl-2-thiono-1,3,2-dioxaphospholane) 2-sulfide* (**161**) (*195*). A solution of sodium 5,5-dimethyl-2-mercapto-2-thiono-1,3,2-dioxaphospholane (440 mg, 2 mmol) in anhydrous methanol (70 ml) was added with stirring to 2-bromo-1-methylpyridinium iodide (300 mg, 1 mmol) suspended in anhydrous methanol (20 ml). The mixture was stirred at room temperature for 90 min. Removal of solvent and column chromatography of the residue on silica gel, eluting with 1:5 ethyl acetate–hexane, gave the pure product (279 mg, 77%). δ_P 78.5 ppm.

5.31 *BIS*(DIALKYLTHIOPHOSPHORYL) DISULFIDES $(RO)_2P(S)SSP(S)(OR)_2$

These are prepared by treating *O,O*-dialkyl hydrogen phosphorodithioates with oxidising agents such as potassium nitrite, potassium iodide, sodium hypochlorite, or by aerial oxidation (*130,196*). *O,O*-Dimethyl hydrogen phosphorodithioate in benzene and dimethylsulfoxide oxidises after 2 days at room temperature to the disulfide (57% yield) (*197*). Examples that use potassium nitrite and potassium iodide as the oxidising agents are shown in Fig. 5.31.1.

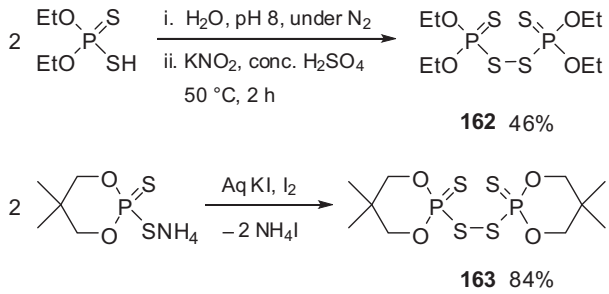


Figure 5.31.1

▶ *Bis(diethylthiophosphoryl) disulfide* (**162**) (*196*). A 250 ml-reaction vessel equipped with a digital thermometer, condenser and stirrer was charged with *O,O*-diethyl phosphorodithioate (6.3 g, 34 mmol) and water (100 ml). The mixture was stirred under nitrogen and the pH adjusted to 8 using 1 M aqueous potassium hydroxide. Potassium nitrite (3.86 g, 34 mmol) was added in one portion, and then concentrated sulfuric acid (4.96 g, 50 mmol) was added dropwise. The reaction mixture was heated to 50 °C for 2 h, cooled, and the product extracted with dichloromethane (3 × l00 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a yellow oil (3.00 g). Column chromatography on silica gel, eluting with dichloromethane, gave the pure material as a pale-yellow liquid (2.90 g, 46%).

▶ *Bis(5,5-dimethyl-2-thiono-1,3,2-dioxaphospholane) 2-disulfide* (**163**) (*130*). Anhydrous ammonia gas was passed over 30 min through a solution of 5,5-dimethyl-2-mercapto-2-thiono-1,3,2-dioxaphospholane (63.4 g, 0.32 mol) in anhydrous benzene (1000 ml) at 0—5 °C. The white ammonium salt was filtered off, washed with benzene (2 × 200 ml) and dried under vacuum (64.6 g, 94%). A solution of this salt (21.5 g, 0.10 mol) in water (150 ml) was stirred at room temperature and a solution of iodine (12.7 g, 0.05 mol) and potassium iodide (25 g, 0.15 mol) in water (100 ml) was added dropwise. The brown solid was filtered off, washed with water (200 ml) and recrystallised from ethanol to yield the disulfide (16.5 g, 84%). Mp 133—134 °C.

5.32 TETRA-ALKYL CARBONYL *BIS*(PHOSPHORODITHIOATES) $[(RO)_2P(S)S]_2C{=}O$

Few references to these materials are available. Compounds (**164**) are synthesised from ammmonium *O,O*-dialkyl phosphorodithioates and phosgene (Fig. 5.32.1) (*198,199*).

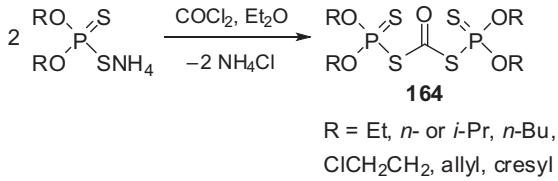


Figure 5.32.1

▶ *Tetra-ethyl carbonyl bis(phosphorodithioate)* (*198*). Phosgene (45 g, 0.46 mol) was passed rapidly into a stirred suspension of ammonium *O,O*-diethyl phosphorodithioate (153 g, 0.75 mol) in ether (600 ml) at 0 °C. The reaction completed a few minutes after the phosgene had been added. Water was added to dissolve the ammonium chloride produced and the water and ether phases were separated. The ether phase was evaporated under reduced pressure to give the product as a water-insoluble liquid (149 g, 99%).

▶ *Tetra-allyl carbonyl bis(phosphorodithioate)* (*199*). Liquefied phosgene (10 g, 0.10 mol) was added through a dropping funnel capped with a dry-ice condenser to a stirred solution of *O,O*-diallyl triethylammonium phosphorodithioate (62 g, 0.2 mol) in anhydrous ether (200 ml) at 0–10 °C. The mixture was stirred overnight at room temperature, filtered to remove the amine salt, and the ether removed under reduced pressure to give the title compound as a light brown viscous liquid (36 g, 81%).

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CHAPTER 6

Selenophosphorus Compounds

Guoxiong Hua and Derek Woollins
EaStCHEM School of Chemistry, University of St Andrews, Fife, KY16 9ST, UK

6.1 INTRODUCTION

Interest in organic selenophosphorus chemistry continues due to its important biological role, potential applications in the pharmaceutical industry, agrochemical industry and material science. The relatively high reactivity of many selenophosphorus compounds makes them interesting intermediates or building blocks, whose elaboration leads to more complicated and diverse molecules, and expands the horizon of this branch of chemistry. General properties, key applications and synthetic procedures to typical organic selenophosphorus compounds and their derivatives are now described. Although the role of phosphoroselenoates in the metabolism of selenium-containing compounds is well documented (*1*,*2*), the preparation of selenophosphorus derivatives has received relatively little attention, and structural variations are almost exclusively confined to P(V) compounds (*3*). 2,4-*Bis*(phenyl)-1,3-diselenadiphosphetane-2,4-diselenide [{PhP(Se)(μ-Se)}$_2$], the Woollins' Reagent (WR), has emerged in recent years as a powerful selenation reagent, which has found fertile application for the conversion of various organic substrates into organic phosphorus—selenium compounds, particularly phosphorus—selenium heterocycles. Some space will be devoted to its preparation and application as a selenation reagent or precursor for the synthesis of phosphorus—selenium derivatives. Notes on the nomenclature of phosphorus—selenium compounds appear in Chapter 1 (Section 1.6).

6.2 ALKALI METAL *O,O*-DIALKYL PHOSPHOROSELENOATES (RO)$_2$P(O)SeM

The earliest report of these compounds described the preparation of sodium *O,O*-diethyl phosphoroselenoate (EtO)$_2$P(O)SeNa by saponification of the triethyl ester (EtO)$_3$P═Se (*4*). Alkali metal *O,O*-dialkyl phosphoroselenoates (RO)$_2$P(O)SeM (**1a**—**l**) have been synthesised in quantitative yield by adding selenium to the sodium or potassium dialkyl phosphites dissolved in alcohol-ether (Fig. 6.2.1) (*5*). The starting dialkyl phosphite alkali metal salts are obtained by reaction of dialkyl *H*-phosphonates (RO)$_2$P(O)H with an alkali metal alkoxide in alcoholic solution; the starting *H*-phosphonates are conveniently obtained by treating phosphorus trichloride with 3 molar equivalents of the alcohol (*5*,*6*). *O,O*-Dialkyl phosphoroselenoate alkali metal salts are colourless and often hygroscopic. A red discolouration on their surface appears when they are exposed to atmospheric moisture and to bright daylight. The salts are readily soluble in water. Their solubilities in organic solvents increase as the number of carbon atoms in the alkyl group increases or when the alkyl group is branched; the isopropyl

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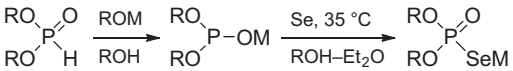
and *s*-butyl salts are considerably more soluble than the *n*-propyl and *n*-butyl salts. The sodium salts are generally more soluble in organic solvents than the corresponding potassium salts.



1a–l

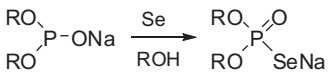
O,O-Dialkyl phosphoroselenoate alkali metal salts

	R	M		R	M		R	M
a	Me	Na	**e**	Me	K	**i**	*n*-Bu	K
b	Et	Na	**f**	Et	K	**j**	*i*-Bu	K
c	*n*-Pr	Na	**g**	*n*-Pr	K	**k**	*t*-Bu	K
d	*i*-Pr	Na	**h**	*i*-Pr	K	**l**	*i*-BuCH$_2$	K

Figure 6.2.1

▶ *O,O-Dialkyl phosphoroselenoate sodium or potassium salts* (**1a—l**) (*5*). A solution of the dialkyl *H*-phosphonate (0.201 mol) in ether (60—100 ml) was added dropwise to a stirred solution of the alkoxide salt prepared from sodium (4.6 g, 0.200 mol) or potassium (7.8 g, 0.200 mol) dissolved in the alcohol (30—75 ml) corresponding to that used to derive the *H*-phosphonate. The ether was essential in effecting a smooth and quantitative process. Selenium powder (15.9 g, 0.201 mol) was added in portions. A vigorous reaction took place with boiling of the ether, the end point being indicated through a colour change from pink to colourless upon adding an aliquot of the reaction mixture to phenolphthalein. The excess selenium was filtered off — crystals of phosphoroselenoate which separated were dissolved by heating — and in most cases the products were isolated by rotary evaporation of the alcohol-ether, partly or completely, under reduced pressure.

Addition of selenium to dialkyl phosphite alkali metal salts provides the corresponding *O,O*-dialkyl phosphoroselenoate salts (*7*). The reaction proceeds slowly, so warming is recommended. The use of well-dried alcohols having the same alkoxy group as that of the dialkyl *H*-phosphonate is preferred to prevent transesterication. *O,O*-Dialkyl phosphoroselenoate sodium salts (**1a—d**,**m—o**) were isolated in good yield after the solvent was removed (Fig. 6.2.2).

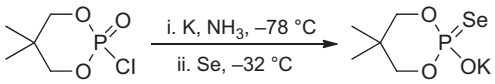


R = Me **1a**, Et **1b**, *n*-Pr **1c**, *i*-Pr **1d**
n-Bu **1m**, *i*-Bu **1n**, *i*-amyl **1o**

Figure 6.2.2

▶ *O,O-Dialkyl phosphoroselenoate sodium salts* (**1a–d,m–o**) (7). A slight excess of dialkyl *H*-phosphonate (0.201 mol) dissolved in ether (60–100 ml) was added to a stirred solution of sodium (4.6 g, 0.200 mol) in the respective alcohol (30–75 ml). Selenium powder (15.9 g, 0.201 mol) was added, which slowly caused the ether to boil (exothermic). The end point was determined by a colour change from pink to colourless upon testing an aliquot of the mixture with phenolphthalein. The excess selenium was filtered from the warm mixture and the solvent was removed from the filtrate by rotary evaporation to provide the title compounds.

2-Oxo-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane potassium salt (**2**) can be prepared by treating 2-chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane with potassium in liquid ammonia, followed by selenium, at low temperature (Fig. 6.2.3) (*6*).

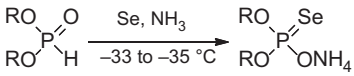


2 93%

Figure 6.2.3

▶ *2-Oxo-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane potassium salt* (**2**) (*6*). 2-Chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (0.460 g, 2.5 mmol) was added to a stirred solution of potassium (0.195 g, 5.0 mmol) in liquid ammonia (100–125 ml) at −78 °C. Once the blue colour disappeared (~30 min), selenium powder (0.198 g, 2.5 mmol) was added at −32 °C. After 5–6 h, the liquid ammonia was allowed to evaporate while stirring. Tetrahydrofuran (THF, 50 ml) was added to the residue and the mixture was stirred at room temperature for 12 h. The solids were filtered off and washed with THF (2 × 20 ml). The solvent was removed and the crude product was dissolved in acetone (3 ml). Dilution with carbon tetrachloride gave the title compound as crystals (0.62 g, 93%). Mp 198–201 °C. δ_P 47.8 ppm (s, $J_{P,Se}$ 793 Hz). IR (KBr) 548/cm (P═Se).

O,O-Dialkyl phosphoroselenoate ammonium salts (**3a–e**) are conveniently derived from dialkyl *H*-phosphonates and selenium in liquid ammonia (Fig. 6.2.4) (*6,8*). The liquid ammonia acts as both a reagent and a solvent. Pure products are obtained by filtration and solvent evaporation.



3a–e

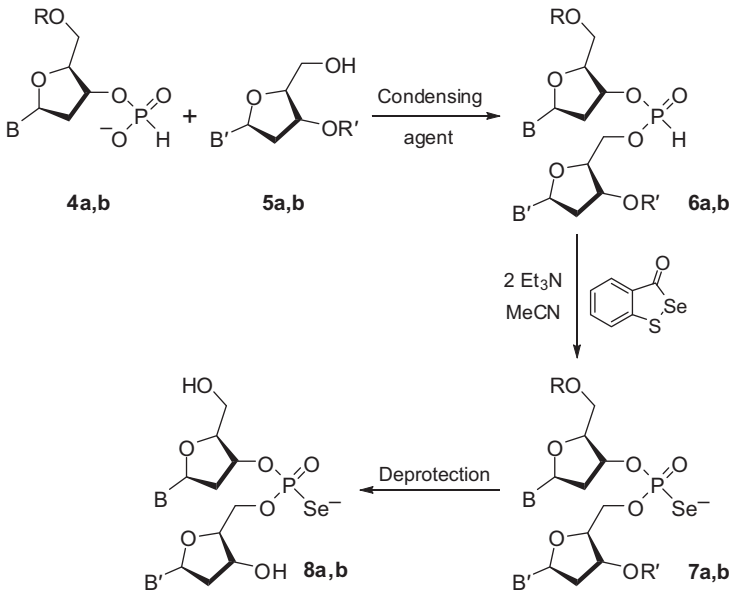
O,O-Dialkyl phosphoroselenoate ammonium salts

No.	R	Yield (%)	Mp (°C)	δ_P ppm (Hz)
a	Et	78	135–137	51.2 (775.8)
b	*n*-Pr	75	131–132	51.8 (775.4)
c	*i*-Pr	70	137–139	47.5 (765.4)
d	*n*-Bu	69	127–129	48.1 (744.9)
e	*t*-BuCH$_2$	75	151–152	51.3 (766.3)

Figure 6.2.4

▶ *O,O-Dialkyl phosphoroselenoate ammonium salts* (**3a—e**) (*8*). A flask containing finely powdered selenium (0.79—0.95 g, 10—12 mmol) suspended in dry liquid ammonia (15—25 ml) was cooled to −35 °C. The suspension was stirred magnetically for 20 min. A solution of the dialkyl *H*-phosphonate (10 mmol) dissolved in anhydrous ether (0.5 ml) was added at once and stirring was continued at −35 °C for 6—8 h. The cooling bath was removed and the mixture was stirred until the ammonia distilled off. The crude product was dissolved in anhydrous chloroform (10—15 ml) and the solution was filtered through Celite™. Evaporation of the solvent from the filtrate and drying of the resulting solid under reduced pressure gave the ammonium salts in quite high purities.

Nucleoside phosphoroselenoates can be prepared by stereospecific selenation of appropriate dialkyl *H*-phosphonates with the selenium-transfer reagent 3*H*-1,2-benzothiaselenol-3-one (*9*), which is soluble in common organic solvents, and shows an enhanced rate of selenium transfer compared to selenium or potassium selenocyanate (KSeCN). Nucleoside 3′-*H*-phosphonate monoesters (**4a—b**) react with protected nucleosides (**5a—b**) in the presence of pivaloyl chloride to provide dinucleoside *H*-phosphonates (**6a—b**), which react quickly and cleanly with 3*H*-1,2-benzothiaselenol-3-one and triethylamine in acetonitrile, to give the phosphoroselenoates (**7a—b**) (Fig. 6.2.5). Selenation occurs with retention of configuration at the phosphorus centre. The selenation reagent is unreactive towards dialkyl *H*-phosphonates in the absence of a base in neutral solvents. It also converts trialkyl phosphites into phosphoroselenonates under conditions compatible with solution- and solid-phase synthetic approaches to oligonucleotides (*10*).



a R = R′ = 4-methoxytriphenylmethyl B = B′ = thymin-1-yl

b R = 4,4′-dimethoxytriphenylmethyl R′ = benzoyl B = guanin-1-yl B′ = thymin-1-yl

Figure 6.2.5

▶ *Thymidin-3′-yl thymidin-5′-yl phosphoroselenoate sodium salt* (**8a**) (*9*). 3*H*-1,2-Benzothiaselenol-3-one (0.043 g, 0.20 mmol) then triethylamine (55.6 μl, 0.40 mmol) was added to a stirred solution of 5′-*O*-(4-methoxytrityl)thymidin-3′-yl 3′-*O*-(4-methoxytrityl)thymidin-5′-yl *H*-phosphonate **6a** (0.161 g, 0.15 mmol) [made from **4a** and **5a** and pivaloyl chloride and separated into the R_p and S_p diastereomers (*10*) in pyridine (7.5 ml)] in acetonitrile (5 ml). After 15 min the solvent was removed and the residue was purified on a short silica gel column using a stepwise gradient of methanol in chloroform (5—15% *v/v*). The purified phosphoroselenoate was detritylated with 80% aqueous acetic acid for 2 h and the solvent was removed. The residue was dissolved in water (1 ml) and passed through a short Dowex 50X-2 (H^+) and then an Amberlyst (Na^+) column. Water was removed by lyophilisation and the residue desalted on a Sephadex G 10 column, and lyophilised again to give from (R_p)-**6a** the product (S_p)-**8a** [0.060 g, 63%; δ_P (D_2O) 48.6 ppm ($J_{P,Se}$ 774 Hz)] and from (S_p)-**6a** the product (R_p)-**8a** [0.070 g, 74%; δ_P (D_2O) 49.4 ppm ($J_{P,Se}$ 777 Hz)].

▶ *Deoxyriboguanosin-3′-yl thymidin-5′-yl phosphoroselenoate sodium salt* (**8b**) (*9*). 3*H*-1,2-Benzothiaselenol-3-one (0.019 g, 0.088 mmol) then triethylamine (24.5 μl, 0.176 mmol) was added to a stirred solution of 5′-*O*-(4,4′-dimethoxytrityl)-N^2-isobutyryldeoxyriboguanosin-3′-yl 3′-*O*,N^3-dibenzoylthymidin-5′-yl *H*-phosphonate **6b** (0.050 g, 0.044 mmol) (made from **4b** and **5b** in the presence of pivaloyl chloride, separating the R_p and S_p diastereomers on a silica gel column using a stepwise gradient of methanol in chloroform (0—10% *v/v*) (*10*)) dissolved in pyridine (2 ml). After 15 min the solvent was removed and the residue was dissolved in 80% aqueous acetic acid (5 ml). After detritylation over 2 h, the solution was evaporated to dryness and the traces of acetic acid were removed by the evaporation of added toluene. The solid residue was purified on a short silica gel column using a stepwise gradient of chloroform—methanol (95:5—80:20 *v/v*). Fractions containing the product were combined and stirred overnight with 32% aqueous ammonia—ethanol (3:1 *v/v*, 5 ml). These fractions were evaporated, the residue partitioned between water and ether, and the aqueous layer concentrated. Conversion of the phosphoroselenoate into its sodium salt was carried out as described for **8a**, whereupon (R_p)-**6b** yielded (S_p)-**8b** [0.014 g, 49%; δ_P (D_2O) 48.5 ppm ($J_{P,Se}$ 775 Hz)] and (S_p)-**6b** yielded (R_p)-**8b** [0.015 g, 52%; δ_P (D_2O) 49.7 ppm ($J_{P,Se}$ 779 Hz)].

Triphenylphosphine selenide (TTPSe-1) and polymer-supported triphenylphosphine selenide (TTPSe-2) efficiently convert dialkyl *H*-phosphonates into *O,O*-dialkyl phosphoroselenoates (*11*). TPPSe-2 is prepared by shaking polystyryl-diphenylphosphine resin with 3 molar equivalents of KSeCN in THF for 4 h, whereupon the ^{31}P NMR spectrum of the suspended polymer beads shows disappearance of the broad signal at −5.4 ppm due to the phosphine and a new broad signal at 35.5 ppm due to the phosphine selenide. Treatment of dinucleoside *H*-phosphonate (**9**) with chlorotrimethylsilane in pyridine gave the silyl ester, which reacted within 15 min with 1.1 molar equivalents of TPPSe-1 or TPPSe-2 in pyridine to give the *O,O*-dialkyl *O*-trimethylsilyl phosphoroselenonate (δ_P 56.9 and 56.6 ppm) as the sole nucleotidic product (Fig. 6.2.6). Chromatography of this on silica gel resulted in desilylation and provided in high yield the dialkyl hydrogen phosphoroselenoate (**10**), identical to a specimen prepared by another method (*9*). Selenation of diethyl *H*-phosphonate with TPPSe-1 also completed in 5 min in pyridine in the presence of 5 molar equivalents of the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

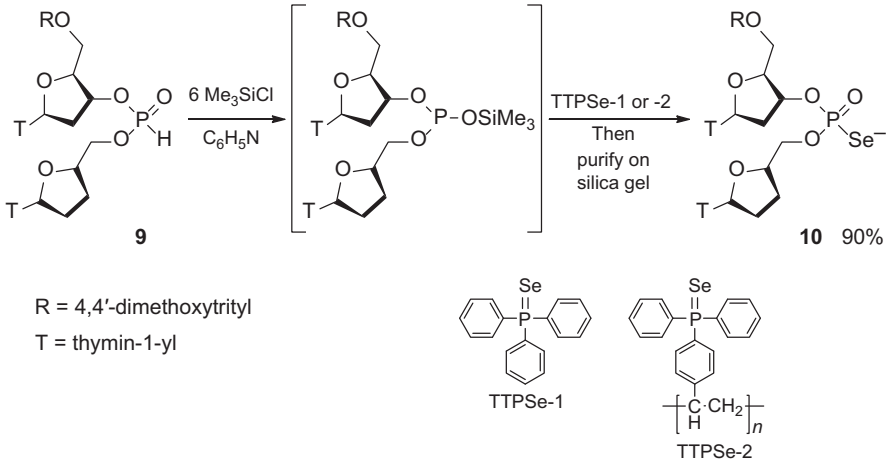


Figure 6.2.6

▶ *Disubstituted hydrogen phosphoroselenoate* (**10**) (*11*). The dialkyl *H*-phosphonate **9** (0.1 mmol) was dissolved in pyridine (4 ml) containing TPPSe-1 (0.068 g, 0.20 mmol). DBU (74.7 μl, 0.5 mmol) was added and after 5 min the mixture was diluted with dichloromethane (20 ml) and extracted with 0.5 M triethylammonium bicarbonate buffer (pH 6.5, 4 × 50 ml). The organic phase was chromatographed on silica gel using a stepwise gradient of methanol (0–2%) in chloroform containing 0.2% triethylamine, and the title species was isolated in 90% yield.

Treatment of potassium phthalimide with di(2-cyanoethyl) diselenide gives *Se*-(2-cyanoethyl) phthalimide, an efficient selenium-transfer reagent for the synthesis of oligonucleotide phosphoroselenoates (*12*). Coupling of 5′-*O*-(4,4-dimethoxytrityl) thymidine *H*-phosphonate (**11**) to 3′-*O*-phenoxyacetothymidine (**12**) in the presence of pivaloyl chloride provides dinucleotide *H*-phosphonate ester (**13**), which reacts in situ with *Se*-(2-cyanoethyl)phthalimide to afford the *Se*-(2-cyanoethyl) species (**14**) (Fig. 6.2.7). Removal of the 4,4-dimethoxytrityl (DMTr) group using dichloroacetic acid and pyrrole gives intermediate (**15**). Treatment of this with DBU and chlorotrimethylsilane resulted in loss of the 2-cyanoethyl group, and further deprotection of the phenoxyacetate protecting group gave the oligonucleotide dialkyl phosphoroselenoate (**16**) in excellent yield. A similar protecting group strategy (**11** + **17** → **18** → **19** → **20**) could be extended to the synthesis of Tp(Se)C dimer phosphoroselenoate (**21**) (Fig. 6.2.8).

A chemical approach is well suited for the synthesis of short oligonucleotides containing one P–Se bond (*13*). Introducing a selenium atom into the phosphate group of nucleic acids is achievable using KSeCN as a source of electrophilic selenium (*14*). A phosphoramidite can be coupled at the position where the selenium atom is to be placed. The column containing the oligomer is then removed from the synthesiser and treated with a saturated aqueous solution of KSeCN to introduce selenium and convert from P(III) to P(V). This approach allowed the preparation of an all P/Se oligomer using *H*-phosphonate chemistry (*15*). To obtain longer nucleic acids containing multiple P–Se bonds,

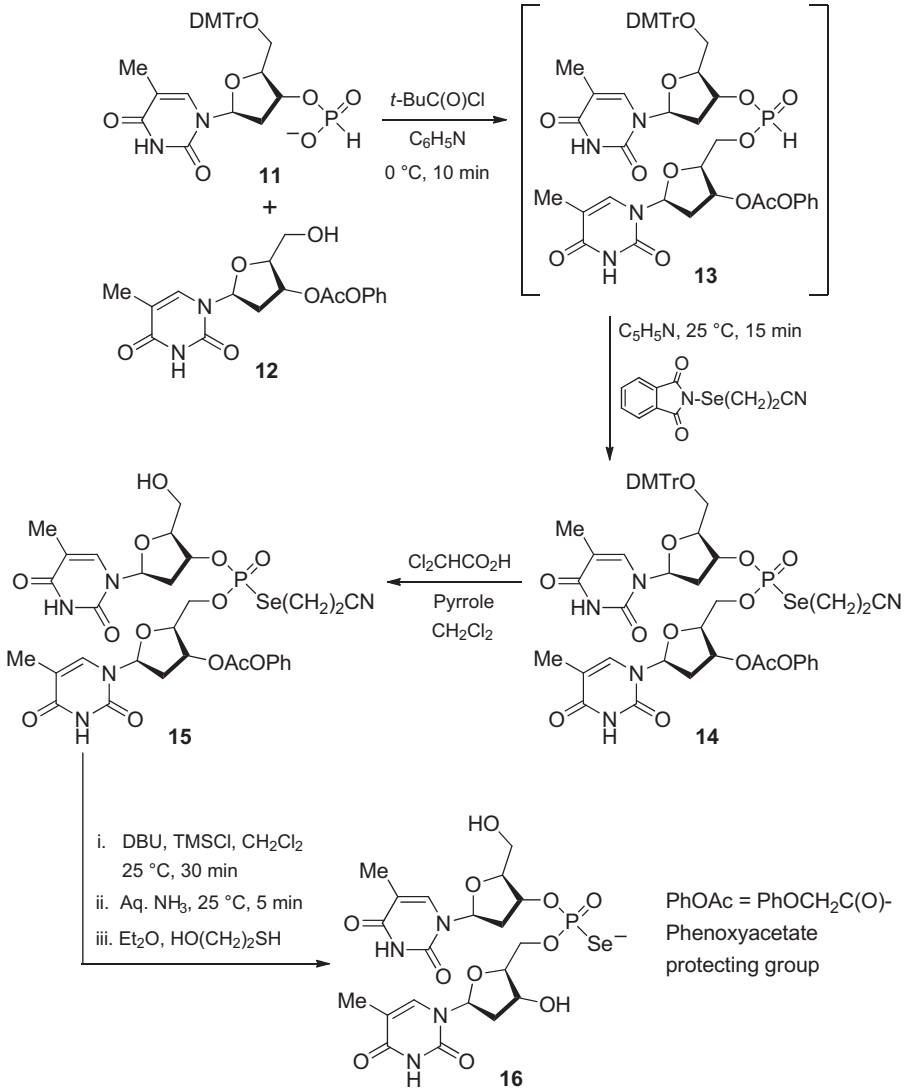


Figure 6.2.7

new enzymatic methods seem ideal for obtaining X-ray crystallography-quality samples. The first enzymatic conversion of thymidine 5′-(α-*P*-seleno) triphosphate (**22**) to phosphoroselenoate DNA (**23**) using DNA polymerase has been reported (Fig. 6.2.9) (*16*). The starting material (**22**) was made according to a modified method analogous to the one used for the nucleoside 5′-(α-*P*-thio)-triphosphate (*17*). The formed S_p and R_p diastereomers were separated by high-performance liquid chromatography. The enzymatic approach generates diastereomerically pure PSe-nucleic acids

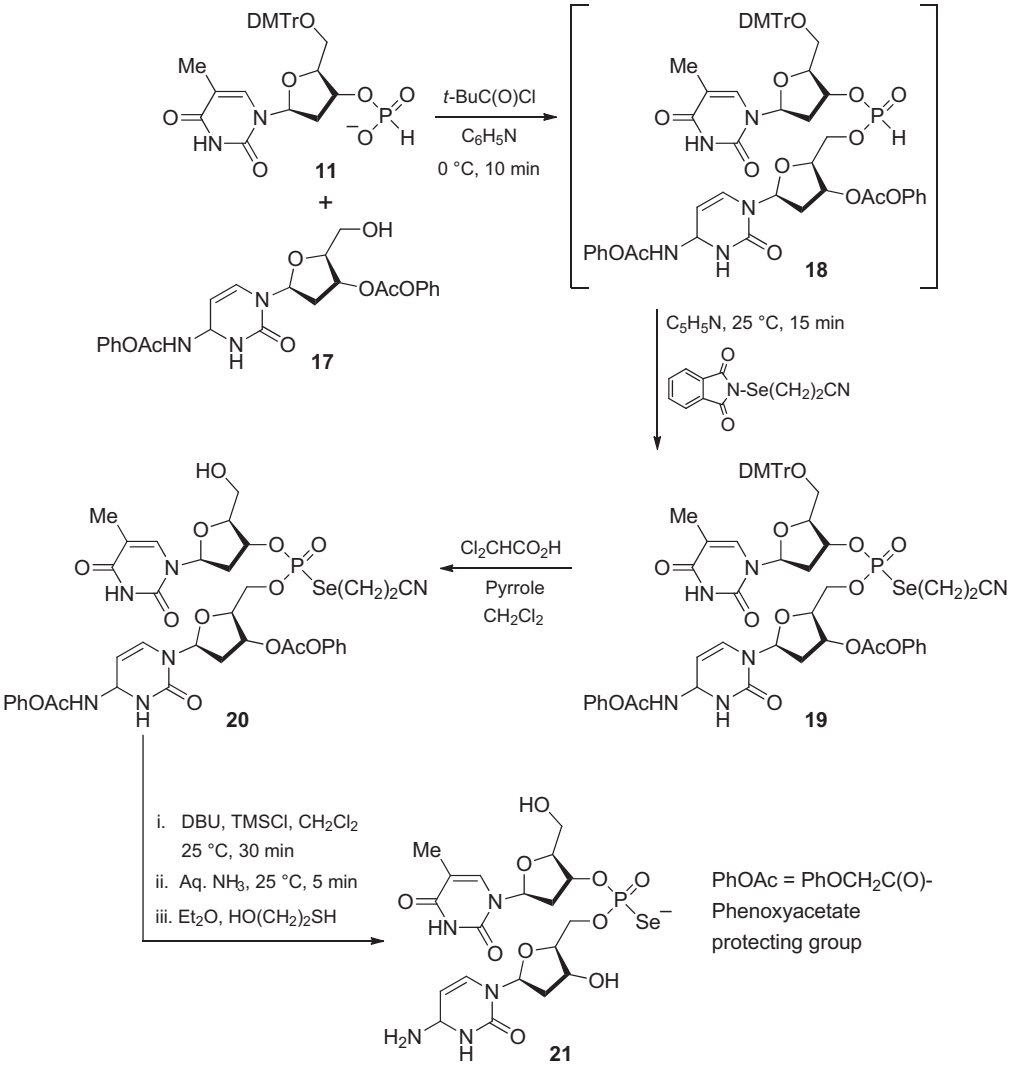
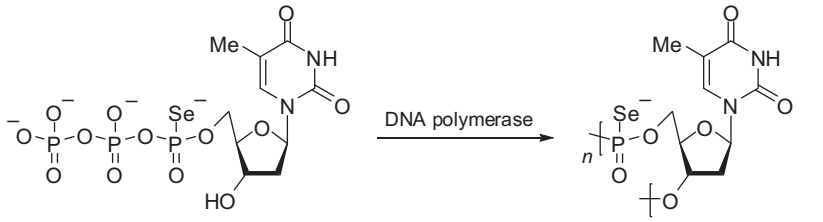


Figure 6.2.8



Thymidine 5′-(α-seleno)triphosphate **22** Phosphoroselenoate DNA **23**

Figure 6.2.9

without the need for separation of the P—Se diastereomers, due to the stereoselectivity of the polymerases, an advantage over chemical methods that usually require resolution of racemic products.

Transcription of adenosine 5′-(α-*P*-seleno) triphosphate (ATP-α-Se, **24**) with T7 RNA polymerase in vitro provided the first enzymatic synthesis of phosphoroselenoate RNA (**25**) (Fig. 6.2.10) (*18*).

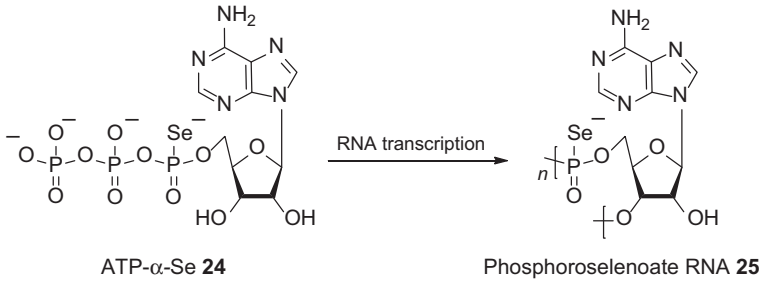


Figure 6.2.10

6.3 DIALKYL PHOSPHOROCHLORIDOSELENONATES $(RO)_2P(Se)Cl$

Dialkyl/aryl phosphorochloridoselenonates were first derived from the corresponding dialkyl/aryl phosphorochloridites $(RO)_2PCl$ or dialkyl *H*-selenophosphonates $(RO)_2P(Se)H$ (7). Heating diphenyl phosphorochloridite with selenium provides diphenyl phosphorochloridoselenonate (**26**) (Fig. 6.3.1), although overlong heating decreases the yield due to disproportionation to triphenyl phosphoroselenonate $(PhO)_3P{=}Se$, phosphorus trichloride and selenium; diaryl phosphorobromidoselenonates $(ArO)_2P(Se)Br$ are accessible by the same route starting from the diaryl phosphorobromidite. Treatment of diethyl *H*-selenophosphonate with sulfuryl chloride gives diethyl phosphorochloridoselenonate (**27**, bp 62 °C/1 mmHg) in acceptable yield.

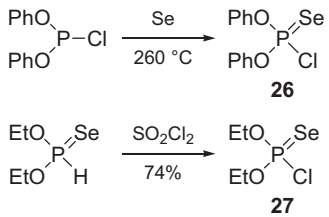
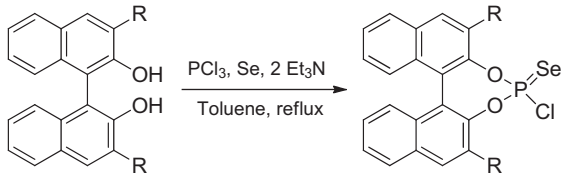


Figure 6.3.1

Substituted 1,1′-bi-2-naphthols react with phosphorus trichloride, selenium and triethylamine to give diaryl phosphorochloridoselenonates (**28a—d**) (Fig. 6.3.2) (*19—21*). Long reaction times are necessary for complete reaction. All products were purified by column chromatography on silica gel

and no decomposition was observed. Unlike the corresponding phosphorochloridates, which react vigorously with water (*20*), the phosphorochloridoselenonates are stable in water under neutral conditions even at elevated temperatures (*21*).



28a–d

O,O-Diaryl phosphorochloridoselenonates

No.	R	Time (h) [a]	Yield (%)	δ_P [b]	δ_{Se} [b]	$^1J_{P,Se}$ [c]
a	H	6.0	90	69.0	–69.2	1061
b	Br	9.5	48	64.4	–60.3	1079
c	$SiPh_3$	24	78	63.2	–41.0	1067
d	2,4,6-*i*-$Pr_3C_6H_2$	17	70	62.2	–41.0	1067

a. Reaction time. *b*. ppm. *c*. Hz.

Figure 6.3.2

▶ *Diphenyl phosphorochloridoselenonate (PhO)$_2$P(Se)Cl* (**26**) (*7*). A mixture of diphenyl phosphorochloridite (12.6 g, 50 mmol) and selenium (5.0 g, 63 mmol) was heated at 260 °C until the mixture clarified and a pale brown colour appeared. After 10 min the mixture was cooled and was distilled at 200 °C/11 mmHg with marginal decomposition. Multiple recrystallisations from methanol gave the pure title compound. Mp 59.0–59.5 °C. Di(2- and 4-methylphenyl) phosphorochloridoselenonate (heated to 220 and 200 °C respectively) and di(4-chlorophenyl) phosphorochloridoselenonate (heated to 275 °C) were obtained similarly.

▶ *(R_{ax})-1,1′-Binaphthyl-2,2′-diyl phosphorochloridoselenonate* (**28a**) (*21*). Triethylamine (8.4 ml, 60 mmol) was added dropwise to phosphorus trichloride (4.13 g, 30 mmol) in toluene (50 ml) at 0 °C with vigorous stirring under argon. A solution of (R_{ax})-1,1′-binaphthol (8.58 g, 30 mmol) in toluene (10 ml) was added dropwise at 0 °C. After 3 min, selenium (2.45 g, 31 mmol) was added and the mixture was warmed to 110 °C and stirred for another 6 h. The solvent was removed. Column chromatography of the solid residue on silica gel eluting with 3:2 hexane–dichloromethane gave the title compound as a white solid (12.12 g, 94%). Retention factor (R_f) 0.70. $[\alpha]_D^{20}$ −414 ($c = 1$, $CHCl_3$). Mp 240–241 °C. δ_P ($CDCl_3$) 69.0 ppm (s, $^1J_{P,Se}$ 1061 Hz). ^{77}Se NMR ($CDCl_3$) −69.2 ppm (d, $^1J_{P,Se}$ 1061 Hz).

6.4 DIALKYL HYDROGEN PHOSPHOROSELENOATES $(RO)_2P(Se)OH$ AND PHOSPHONO AND PHOSPHINO RELATIVES: RO(R)P(Se)OH AND $R_2P(Se)OH$

Three types of these materials exist: *O,O*-dialkyl hydrogen phosphoroselenoates $(RO)_2P(Se)OH$, *O*-alkyl hydrogen alkylphosphonoselenoates RO(R′)P(Se)OH, and dialkylphosphinoselenoic acids $R_2P(Se)OH$. They were first prepared in the 1960s (*22*). Treatment of dialkyl *H*-phosphonates with potassium metal and then selenium, followed by acidification and purification by vacuum distillation, gives the *O,O*-dialkyl hydrogen phosphoroselenoates (**29a–b**) (Fig. 6.4.1). A similar sequence starting from alkyl *H*-alkylphosphinates gives the *O*-alkyl hydrogen ethylphosphonoselenoates (**30a–b**).

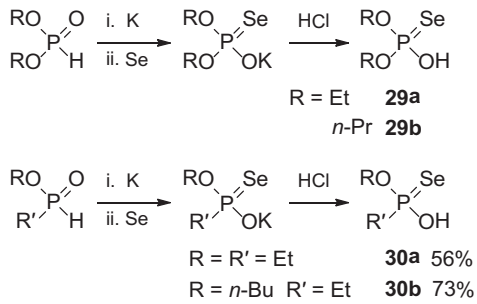


Figure 6.4.1

▶ *O,O-Di-n-propyl hydrogen phosphoroselenoate (n-PrO)$_2$P(Se)OH* (**29b**) (*22*). A solution of sodium *n*-propoxide, prepared from sodium (5.75 g, 0.25 mol) and *n*-propanol (150 ml), was placed in a 500-ml flask fitted with a mechanical stirrer, a dropping funnel and a thermometer. Di-*n*-propyl *H*-phosphonate (41.5 g, 0.25 mol) was added with stirring. The flask was placed in an ice–salt bath to maintain the temperature below 10 °C, and selenium (21.7 g, 0.275 mol) was added portionwise over 15 min, ensuring the temperature stayed below 25 °C. After addition the mixture was allowed to stand overnight. Unreacted selenium was filtered off and the *n*-propanol was removed from the filtrate by rotary evaporation. Water (30 ml) was added and the alkaline solution was extracted with benzene (30 ml). The aqueous layer was cooled in an ice-salt bath and aqueous hydrochloric acid (50 ml, 1:1 *v/v*) was added dropwise with efficient stirring and cooling to prevent decomposition. The combined extracts were dried ($MgSO_4$) and the solvent was removed. Distillation of the residue under reduced pressure gave the title compound (42.0 g, 69%). n_D^{25} 1.4855, d_4^{25} 1.3236.

Two methods can be used to make dialkylphosphinoselenoic acids: treatment of a dialkyl *H*-phosphonate with 3 molar equivalents of a Grignard reagent followed by addition of selenium (Fig. 6.4.2; *method 1*) or treatment of a dialkylchlorophosphine with selenium, and alkaline hydrolysis of the dialkylchlorophosphinoselenoyl chloride obtained (Fig. 6.4.2; *method 2*). The preparation of diethylphosphoroselenoic acid (**31**) illustrates such approaches (*22*).

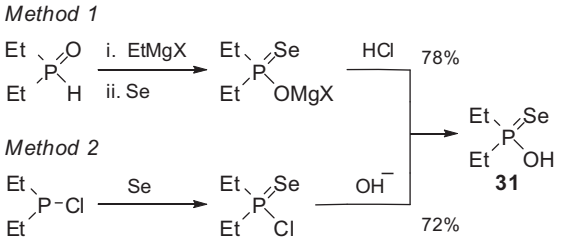


Figure 6.4.2

▶ *Diethylphosphinoselenoic acid $Et_2P(Se)OH$* (**31**) (*22*). *Method 1.* Ethyl bromide (37.6 g, 0.345 mol) was added to magnesium (7.8 g, 0.325 mol) in dry ether (100 ml). Diethyl *H*-phosphonate (13.8 g, 0.1 mol) in dry ether (15 ml) was added dropwise under nitrogen to this Grignard solution, with efficient stirring and cooling with an ice-salt bath, at a rate sufficient to allow the ether to boil. After addition the mixture was refluxed for 30 min. Selenium (9.85 g, 0.125 mol) was introduced and the mixture was refluxed for 2 h. Hydrochloric acid (30 ml, 1:1 *v/v*) was added dropwise with stirring, and cooling to 0–10 °C using an ice–salt bath, until the precipitate dissolved. Water was added (50 ml) and the ether layer was separated. The aqueous layer was extracted with ether (3 × 50 ml). The ether extracts were combined and the solvent was removed. Aqueous sodium carbonate was added to the residue and the alkaline solution was extracted with benzene. Hydrochloric acid (50 ml, 1:1 *v/v*) was added dropwise with efficient stirring to the aqueous solution cooled using an ice–salt bath. The yellow oil was extracted with ether (3 × 50 ml), the combined extracts were dried ($MgSO_4$), and the ether was removed. Distillation of the residue gave the title compound (14.5 g, 78%). Bp 76–77 °C/0.05 mmHg, $n_D^{31} = 1.5590$. *Method 2.* Selenium (6.0 g, 76 mmol) was added portionwise to diethylchlorophosphine (9.5 g, 76 mmol) with stirring under nitrogen at room temperature. After addition the mixture was heated to 100 °C for 15 min. Crude diethylphosphinoselenoyl chloride was decanted from any unreacted selenium. Aqueous sodium hydroxide (6.0 g in 40 ml water) was added dropwise with stirring at room temperature. The temperature of the mixture rose to 50 °C. The alkaline solution was extracted with benzene (50 ml). Hydrochloric acid (50 ml, 1:1 *v/v*) was added dropwise with efficient stirring to the aqueous solution, which was cooled using an ice-salt bath. The yellow oil was extracted with ether (3 × 50 ml), the combined extracts were dried ($MgSO_4$), and the ether was removed. Distillation of the residue under reduced pressure gave the title compound (8.4 g, 72%; bp 76–77 °C/0.05 mmHg), which solidified (mp 17 °C) when cooled using an ice bath.

Another route to *O,O*-dialkyl hydrogen phosphoroselenoates involves adding selenium to dialkyl trimethylsilyl phosphites. Treatment of 1,3-dioxa-6-aza-2-σ^4,λ^4-phosphacyclooctane (**32**) (*23*) with chlorotrimethylsilane and triethylamine provides 1,3-dioxa-6-aza-2-(*O*-trimethylsilyl ester)-σ^3, λ^3-phosphacyclooctane (**33**). In refluxing toluene this adds selenium almost quantitatively to give 1,3-dioxa-6-aza-2-(*O*-trimethylsilyl ester)-σ^4,λ^4-phosphacyclooctane selenide (**34**). This reacts with a molar equivalent of methanol in benzene at room temperature to generate the cyclic hydrogen phosphoroselenoate (**35**) (Fig. 6.4.3) (*24*).

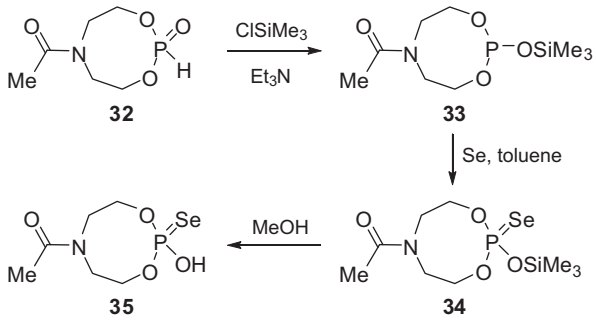


Figure 6.4.3

▶ *1-(2-Hydroxy-2-selenido-1,3,6,2-dioxazaphosphocan-6-yl)ethanone* (**35**) (*24*). A solution of chlorotrimethylsilane (0.565 g, 5.2 mmol) and triethylamine (0.525 g, 5.2 mmol) in toluene (10 ml) was added dropwise to the stirred cyclic dialkyl *H*-phosphonate **32** (1.0 g, 5.2 mmol) at room temperature. The mixture was stirred overnight. Triethylamine hydrochloride was filtered through Celite™ once a ^{31}P NMR spectrum of the solution showed only one resonance at 129 ppm. To the filtrate was added selenium (0.41 g, 5.2 mmol) and the mixture was refluxed for 24 h. Upon cooling to room temperature and filtering to remove all solid material, the filtrate was concentrated to 3–5 ml and was stored at 4 °C. Product **34** was isolated after a few days as colourless crystals (1.65 g, 92%). Mp 126–128 °C. δ_P (C_6D_6) 60.3 ppm (s, $^1J_{P,Se}$ 959 Hz). Methanol (0.046 g, 1.45 mmol) was added to a solution of this compound (0.5 g, 1.45 mmol) in toluene (5 ml) at 0 °C. Compound **35** precipitated and was filtered off and dried under vacuum to provide a white solid (0.36 g, 92%). Mp 192–197 °C. δ_P (d_6-dimethylsulfoxide (DMSO)) 63.3 ppm (s, $J_{P,Se}$ 894 Hz).

6.5 NUCLEOSIDE *H*-PHOSPHONOSELENOATE MONOESTERS (RO)P(O)(H)SeH AND DIESTERS $(RO)_2P(Se)H$

Nucleoside *H*-phosphonoselenoate monoesters are not a well-known class of compounds. For the preparation of the corresponding diesters, only two methods have been described in the literature. One of these involves treatment of dialkyl phosphorochloridites $(RO)_2PCl$ with hydrogen selenide (*25*,*26*) and the other, reduction of 2-chloro-4-methyl-1,3,2-dioxaphospholane (a phosphorochloridite) with tri-*n*-butyltin hydride to produce the corresponding phosphonite, followed by selenium addition (*27*). Unfortunately, these approaches do not appear to be applicable to natural product derivatives. 3*H*-1,2-Benzothiaselenol-3-one (*9*,*28*) and KSeCN (*29*) do not produce any *H*-phosphonoselenoate monoesters, but mixtures of the corresponding symmetrical phosphoroselenoates and *H*-phosphonate monoesters. A viable synthetic route to nucleoside 3′-*H*-phosphonoselenoate monoester (**38**) involved selenating phosphinate (**37**) (Fig. 6.5.1) (*30*). The generation of nucleoside phosphinate (**37**) (δ_P 14.2 ppm, $^1J_{P,H}$ 572 Hz, $^3J_{P,H}$ 9.8 Hz) in pyridine from the corresponding nucleoside (**36**) (1.5 mol equiv.) and triethylammonium phosphinate in the presence of

pivaloyl chloride (1.5 mol equiv.) proceeded in good yield (*method 1*). Considerable effort to select the best conditions for the selenation step was required. When pyridine was used as a solvent the formation of *H*-phosphonoselenoate monoester (**38**) was rather low after 3—4 h and its amount in the reaction mixture did not exceed 30—40%. The ^{31}P NMR spectrum of the mixture revealed significant amounts of selenophosphonic acid, *H*-phosphonate monoester (**38**) and *H*-phosphonate diester (**39**), in a total yield of 60—70%, due probably to competing selenation of the phosphinate salt and the high propensity of the phosphinate for disproportionation. Adding chloroform, acetonitrile or toluene in addition to the pyridine present in the reaction mixture tended to suppress some side-product formation, but unfortunately the reaction slowed, and more side-products formed as the reaction approached completion. The most favourable solvent system — chloroform, pyridine (2 equiv.) and triethylamine (2 equiv.) — led to a reasonably fast (4 h) and clean formation of *H*-phosphonoselenoate (**39**) in ~80% yield (*method 2*). Another convenient access to *H*-phosphonoselenoates uses TPPSe-1 (*31*) in combination with chlorotrimethylsilane to selenate the intermediate phosphinate rapidly and cleanly. This method has the advantage of homogenous conditions and the purification of nucleoside *H*-phosphonselenoate monoester in ~80% yield does not require additional reverse-phase chromatography.

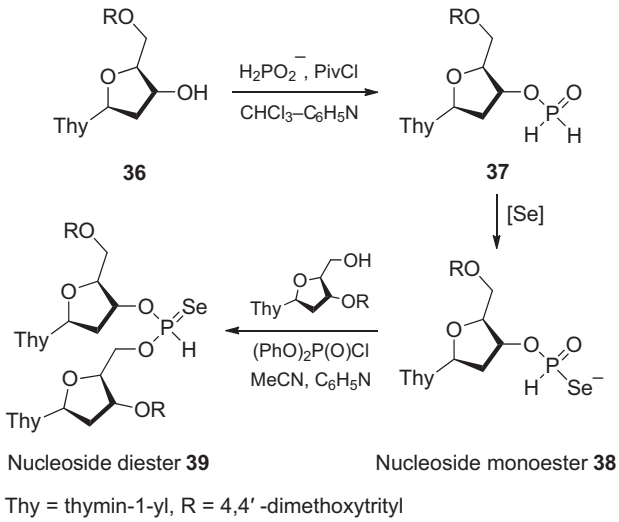


Figure 6.5.1.

▶ *Nucleoside H-phosphonoselenoate monoester* (**38**) (*31*). *Method 1.* Anhydrous nucleoside **36** (1.5 mol equiv.) and triethylammonium phosphinate (1.0 mmol) were dissolved in chloroform (16 ml) containing pyridine (2.0 mol equiv.). Selenium (3.0 mol equiv.) and pivaloyl chloride (1.5 mol equiv.) were added and after 10 min, triethylamine (2.0 mol equiv.). The mixture was stirred for ~ 4 h. Excess selenium was filtered off, the solvent removed, and the product purified by silica gel chromatography, using a stepwise gradient of methanol (0—4%) in dichloromethane containing 0.1% triethylamine. The product comprised monoester **38** contaminated with ~5% of diester **39**.

Reverse-phase silica gel chromatography, using a stepwise gradient of acetone in water, and precipitation with pentane, gave pure **38**, as a ~1:1 mixture of two diastereomers (triethylammonium salts), as an off-white powder (45–60%, >98% pure by ^{1}H NMR analysis). δ_P ($CDCl_3$) 48.1 ppm (dd, $^1J_{P,H}$ 564 Hz, $^3J_{P,H}$ 12.2 Hz, $^1J_{P,Se}$ 713 Hz) and 47.1 ppm (dd, $^1J_{P,H}$ 569 Hz, $^3J_{P,H}$ 12.8 Hz, $^1J_{P,Se}$ 713 Hz). *Method 2*. Nucleoside phosphinate **37** was generated by reacting anhydrous nucleoside **36** (1.5 mmol) with triethylammonium phosphinate (1.0 mmol) in chloroform–pyridine (16 ml, 3:1 *v/v*) in the presence of pivaloyl chloride (1.5 mmol). After 10 min TPPSe-1 (2.0 mol equiv.) and chlorotrimethylsilane (3.0 mol equiv.) were added. After 15 min the mixture was partitioned between saturated aqueous sodium bicarbonate (50 ml) and dichloromethane (150 ml). The *H*-phosphonoselenoate monoester triethylammonium salt was isolated (80%, >98% pure by ^{1}H NMR analysis).

▶ *Nucleoside H-phosphonoselenoate diester* (**39**) (*30*). *H*-Phosphonoselenoate monoester triethylammonium salt **38** (0.10 mmol) and the protected nucleoside (0.09 mmol) were dissolved in acetonitrile (4.00 ml) containing pyridine (0.50 ml), and diphenyl phosphorochloridate (0.25 mmol) was added. After ~ 10 min (thin layer chromatography (TLC) analysis) the reaction was quenched with saturated sodium chloride (1.0 ml) and partitioned between toluene (2 × 50 ml) and brine (20 ml). The organic phase was dried and the solvent was evaporated. Column chromatography of the residue on silica gel, eluting with 1:1 ethyl acetate–toluene containing 0.02% triethylamine, gave a white foam comprising a 1:1 mixture of diastereomers (81% yield, >98% pure by ^{1}H NMR analysis). δ_P ($CDCl_3$) 74.8 ppm (dq, $^1J_{P,H}$ 648 Hz, $^3J_{P,H}$ 11 Hz, $^1J_{P,Se}$ 877 Hz) and 76.7 ppm (dq, $^1J_{P,H}$ 644 Hz, $^3J_{P,H}$ 11 Hz, $^1J_{P,Se}$ 879 Hz).

6.6 *O,O,Se*-TRISUBSTITUTED PHOSPHOROSELENOLATES $(RO)_2P(O)SeR'$

Disubstituted *Se*-phenyl phosphoroselenolates (**40a–b**) are readily synthesised by adding the corresponding dialkyl phosphorochloridate to a solution of PhSeLi generated from reaction of PhLi with Se at −78 °C in THF (Fig. 6.6.1) (*31*). The phosphoroselenolates are easily purified by column chromatography on silica gel.

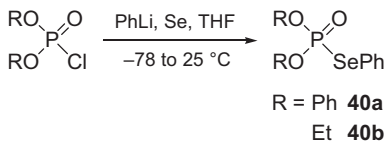


Figure 6.6.1

▶ *O,O-Disubstituted Se-phenyl phosphoroselenolates* (**40a–b**) (*31*). Phenyllithium (11 ml, 1.0 M in hexane–ether, 11.0 mmol) was added to a suspension of powdered selenium (0.869 g, 11.0 mmol) in anhydrous THF (15 ml) at 0 °C to produce a colourless solution of PhSeLi. This was cooled to −78 °C and the dialkyl phosphorochloridate (11.0 mmol) was added dropwise by syringe. After stirring at −78 °C for 0.5 h, the solution was allowed to warm slowly to room temperature, and was stirred for another 3 h. The mixture was poured into ice water (30 ml) and was extracted with ether (2 × 60 ml).

The extracts were dried ($MgSO_4$) and the solvent was removed. Flash column chromatography of the residue on silica gel eluting with 1:1 or 1:5 ether—hexane gave pale-yellow liquids: **40a** (2.26 g, 60%; mp 36—37 °C; δ_P 8.6 ppm, d, $J_{P,Se}$ 533 Hz) or **40b** (1.77 g, 55%; δ_P 16.7 ppm, d, $J_{P,Se}$ 466 Hz).

Alkylation of *O,O*-dialkyl phosphoroselenoate metal salts, $(RO)_2P(O)SeM$, with alkyl halides produces the *O,O,Se*-trialkyl phosphoroselenolates $(RO)_2P(O)SeR$ (7) — for example, the *O,O*-diethyl phosphoroselenoate lead(II) salt and iodoethane yield *O,O,Se*-triethyl phosphoroselenolate (**41**) (Fig. 6.6.2).

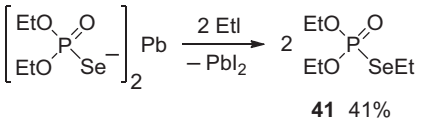
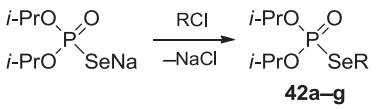


Figure 6.6.2

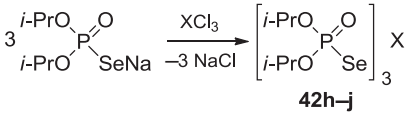
O,O-Dialkyl phosphoroselenoate metal salts also react with 1 molar equivalent of halides of carbon, silicon, germanium, tin, phosphorus, arsenic, sulfur and selenium (*32*). *O,O*-Diisopropyl phosphoroselenoate sodium salt reacts with EtI, PhCOCl, Me_3SiCl, Ph_3GeBr, Me_3SnCl, Ph_3SnCl, $PhSO_2Cl$, $PhSnCl_3$, PCl_3, and $AsCl_3$ to give the corresponding derivatives (**42a—j**) (Fig. 6.6.3). These involatile liquids are miscible with common organic solvents. They are stable in air, but are sensitive to heat and light, which causes loss of selenium. It is advisable to store them in the dark preferably at −30 °C.



42a–g

O,O-Diisopropyl phosphoroselenolates

No.	R	δ_P ppm	$^1J_{P,Se}$ (Hz)
a	Et	17.5	479.6
b	COPh	59.0	985.0
c	$SiMe_3$	18.1	466.8
d	$GePh_3$	19.7	507.9
e	$SnMe_3$	30.4	644.1
f	$SnPh_3$	16.5	479.7
g	SO_2Ph	8.9	495.0



42h–j

No.	X	δ_P ppm	$^1J_{P,Se}$ (Hz)
h	SnPh	33.1	–
i	P	58.3	874.2
j	As	12.4	473.3

Figure 6.6.3

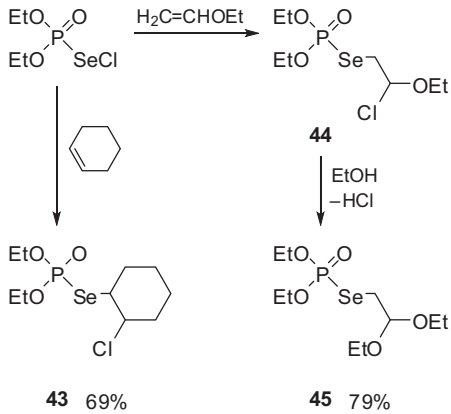


Figure 6.6.4

O,O-Diethyl *Se*-alkyl phosphoroselenoates

No.	R	Yield (%)	Bp (°C/mmHg)
41	Et	66	102–105/2
46a	*n*-Bu	63	122/3
46b	CH_2CH_2SMe	61	152/3
46c	*n*-C_6H_{13}	71	138/2
46d	*n*-$C_{10}H_{21}$	79	198/2
46e	4-C_6H_4Cl	91	172/1
46f	4-$C_6H_4NO_2$	85	mp 53–54
46g	4-$MeOC_6H_4$	83	182–184/2

Figure 6.6.5

Dialkyl *Se*-chloro phosphoroselenolates are useful reagents for the synthesis of *O,O,Se*-trialkyl phosphoroselenolates. Diethyl *Se*-chloro phosphoroselenolate adds to cyclohexene to give diethyl *Se*-(2-chlorohexyl) phosphoroselenolate (**43**) and to ethyl vinyl ether to generate intermediate (**44**) that reacts with ethanol to afford *O,O*-diethyl *Se*-(2,2-diethoxyethyl) phosphoroselenolate (**45**) (Fig. 6.6.4) (7).

O,O,Se-Trisubstituted phosphoroselenolates (e.g. **41**,**46a**–**g**) can be obtained by treating dialkyl *H*-phosphonates or their alkali metal salts $(RO)_2PONa$ or $(RO)_2POK$ with aliphatic or aromatic selenocyanates (Fig. 6.6.5). The by-products are hydrogen cyanide or the alkali metal cyanides.

▶ *O,O,Se-Trialkyl phosphoroselenolates* (**41**,**46a–g**) (7). Diethyl *H*-phosphonate (70 g, 0.51 mol) was added to a stirred suspension of powdered sodium (12 g, 0.52 mol) in toluene (100 ml) at 40–50 °C. Once the sodium had dissolved, the alkyl or aryl selenocyanate (0.51 mol) was added dropwise at 30–40 °C (intense foaming was observed). The mixture was stirred for another 30 min at 30 °C. Water (10 ml) was added to dissolve the sodium cyanide, and the toluene layer was isolated and dried ($MgSO_4$). The usual work-up gave the title compounds after distillation.

O,O,Se-Trialkyl phosphoroselenolates can also be obtained by Arbuzov reaction of trialkyl phosphites with alkyl selenocyanates or organic diselenides (7). Heating triethyl phosphite with ethyl selenocyanate gives *O,O,Se*-triethyl phosphoroselenolate (**41**) in high yield (Fig. 6.6.6); the method does not work when triaryl phosphites are used. Triethyl phosphite and diphenyl diselenide when heated together give *O,O*-diethyl *Se*-phenyl phosphoroselenolate (**40b**) in good yield. An analogous reaction with *bis*(diethylphosphoryl) diselenide provides *O,O,Se*-triethyl phosphoroselenolate (**41**) and tetraethyl pyrophosphoroselenonate (**47**).

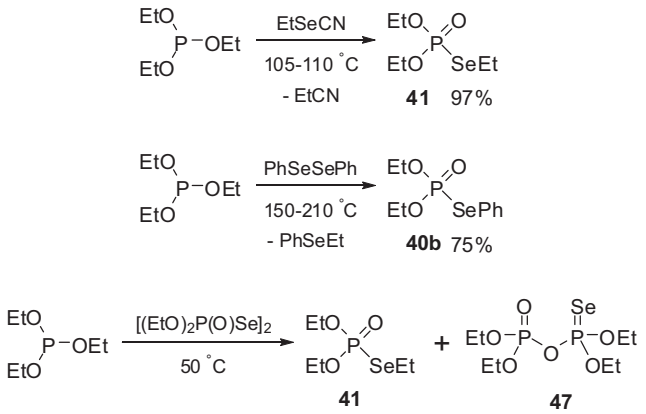


Figure 6.6.6

O,O,Se-Triethyl phosphoroselenolate (**41**) (7). A mixture of triethyl phosphite (41.5 g, 0.25 mol) and ethyl selenocyanate (26.8 g, 0.20 mol) was slowly heated. An exothermic reaction started at about 105 °C. The mixture was cooled with an ice bath and kept at 105–110 °C. After the reaction completed, the product was distilled to give the title compound (59.4 g, 97%).

Alkali metal or ammonium salts of *O,O*-dialkyl hydrogen phosphoroselenoates are amident nucleophiles that react with soft electrophiles, such as alkyl halides, through their selenium atom to give *O,O,Se*-trialkyl phosphoroselenolates $(RO)_2P(O)SeR$ (*33*). For example, triethylammonium salt (**48**) reacts with methyl iodide to furnish the *Se*-methyl derivative (**49**) (Fig. 6.6.7).

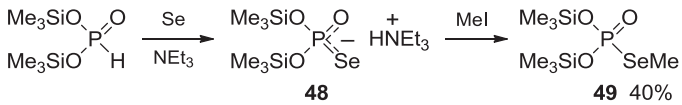


Figure 6.6.7

▶ *O,O-Bis(trimethylsilyl) Se-methyl phosphoroselenolate* $(Me_3SiO)_2P(O)SeMe$ (**49**) (*33*). A mixture of *bis*(trimethylsilyl) *H*-phosphonate (25 g, 0.1 mol) and triethylamine (10 g, 0.1 mol) in anhydrous benzene (100 ml) was stirred and selenium powder (8 g, 0.1 mol) was introduced slowly. The mixture was heated to 80 °C for 10 h, whereupon ^{31}P NMR analysis revealed complete conversion of the *H*-phosphonate to the triethylammonium salt **48**. To this solution was added methyl iodide (14.2 g, 0.1 mmol). Generation of heat and precipitation of triethylammonium iodide occurred. The precipitate was removed and the filtrate was distilled under vacuum to give the title compound (12.7 g, 40%).

O,O-Dineopentyl triethylammonium phosphoroselenoate (**50**) reacts with 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-*α*-D-mannopyranose bromide (**51**) to provide the corresponding phosphoroselenolate (**52**) with high stereoselectivity (Fig. 6.6.8) (*34*).

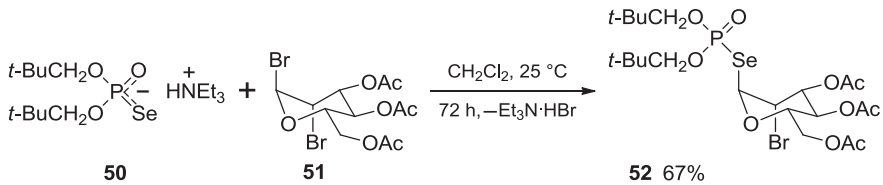


Figure 6.6.8

▶ *2-(Acetoxymethyl)-6-[(bis(neopentyl)phosphoryl)selenyl]-5-bromotetrahydro-2H-pyran-3,4-diyl diacetate* (**52**) (*34*). A solution of 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-*α*-D-mannopyranose bromide (0.432 g, 1.0 mmol) (*35*) in anhydrous dichloromethane (4 ml) was added to a solution of *O,O*-dineopentyl triethylammonium phosphoroselenoate (0.405 g, 1.0 mmol) in anhydrous dichloromethane (5 ml) and the mixture was stirred at room temperature for 72 h. The amine hydrobromide salt was filtered off; the filtrate was washed three times with water, dried ($CaCl_2$) and concentrated. The title compound was crystallised from petroleum ether to yield colourless crystals (0.430 g, 67%). Mp 69–71 °C. δ_P 11.7 ppm (s, $J_{P,Se}$ 495 Hz).

Treatment of *O,O*-dialkyl *N*-phenylphosphoramidoselenonates $(RO)_2P(Se)NHPh$ with sodium hydride then carbon dioxide, followed by methyl iodide, also provides *O,O*-dialkyl *Se*-alkyl phosphoroselenolates $(RO)_2P(O)SeR$ (e.g. **53a–c**) (Fig. 6.6.9) (*36*).

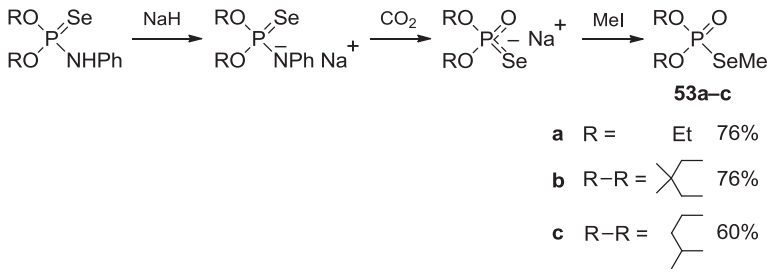


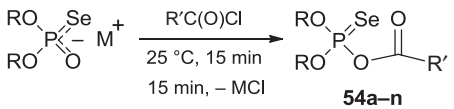
Figure 6.6.9

▶ *O,O-Diethyl Se-methyl phosphoroselenolate* (**53a**) (*36*). Reaction of diethyl phosphorochloridite, aniline and triethylamine in benzene gave diethyl *N*-phenylphosphoramidite $(EtO)_2PNHPh$ (bp 120 °C/4 mmHg, δ_P −129.0 ppm, n_D^{20} 1.5203) (*37*). Oxidation with *tert*-butyl hydroperoxide and addition of selenium gave *O,O*-diethyl *N*-phenylphosphoramidoselenonate (bp 122 °C/0.25 mmHg, δ_P −66.5 ppm). A solution of *O,O*-diethyl *N*-phenylphosphoramidoselenonate (14.6 g, 50 mmol) in dioxane (50 ml) was added dropwise to a suspension of sodium hydride (1.44 g, 60 mmol) in dioxane (100 ml) at 50 °C. Reaction was accompanied by evolution of hydrogen and a white precipitate. The mixture was stirred at 90 °C for another 1 h and dry carbon dioxide was bubbled through at that temperature for 2 h. An additional 1 h of stirring at 90 °C was followed by solvent evaporation. The residue was shaken with 1:5 *v/v* benzene—hexane (100 ml) and the resulting precipitate was filtered off and washed with hexane. The precipitate (100 ml) and iodomethane (14.2 g, 100 mmol) were combined. The suspension was refluxed for 2 h and cooled and the precipitate was filtered off and washed with benzene. The filtrate was evaporated and the residue was examined by ^{31}P NMR spectroscopy. Pure product was obtained by distillation (8.8 g, 76%). Bp 88—90 °C/1.5 mmHg. δ_P −19.7 ppm.

▶ *5,5-Dimethyl-2-(methylselenyl)-1,3,2-dioxaphosphorinane 2-oxide* (**54b**) (*36*). 2-*N*-Phenylamino-5,5-dimethyl-1,3,2-dioxaphosphorinane (mp 65—67 °C, δ_P −116.0 ppm) was obtained from the corresponding dialkyl phosphorochloridite, aniline and triethylamine in benzene (*38*). 5,5-Dimethyl-2-(phenylamino)-1,3,2-dioxaphosphinane 2-selenide (mp 167 °C, δ_P 2.6 ppm) was prepared by oxidation of this product with *tert*-butyl hydroperoxide and addition of selenium. A suspension of sodium hydride (1.44 g, 60 mmol) in dioxane (100 ml) was added dropwise at 50 °C to a solution of 5,5-dimethyl-2-(phenylamino)-1,3,2-dioxaphosphinane 2-selenide (15.2 g, 50 mmol) in dioxane (50 ml). Hydrogen gas and a white precipitate were evolved. The mixture was stirred at 90 °C for another 1 h and dry carbon dioxide was bubbled through at that temperature for 2 h. An additional 1 h of stirring at 90 °C was followed by solvent evaporation. The residue was shaken with 1:5 *v/v* benzene—hexane (100 ml) and the resulting precipitate was filtered off and washed with hexane. The precipitate (100 mmol) and methyl iodide (14.2 g, 100 mmol) were combined. The suspension was refluxed for 2 h, cooled, and the precipitate was filtered off and washed with benzene. The filtrate was evaporated and the residue was analysed by ^{31}P NMR spectroscopy. Pure product was obtained by crystallisation (9.2 g, 76%). Mp 90—92 °C. δ_P −13.8 ppm.

▶ *4-Methyl-2-(methylselenyl)-1,3,2-dioxaphosphinane 2-oxide* (**54c**) (*36*). 4-Methyl-2-(phenylamino)-1,3,2-dioxaphosphinane 2-selenide was prepared according to the literature (*39*,*40*). A suspension of sodium hydride (1.44 g, 60 mmol) in dioxane (100 ml) was added dropwise at 50 °C to 4-methyl-2-(phenylamino)-1,3,2-dioxaphosphinane 2-selenide (14.5 g, 50 mmol) in dioxane (50 ml). Hydrogen and a white precipitate formed. The mixture was stirred at 90 °C for another 1 h and dry carbon dioxide was bubbled through at that temperature for 2 h. An additional 1 h of stirring at 90 °C was followed by solvent evaporation. The residue was shaken with 1:5 *v*/*v* benzene—hexane (100 ml) and the resulting precipitate was filtered off and washed with hexane. The precipitate (100 mmol) and methyl iodide (14.2 g, 100 mmol) were combined. The suspension was refluxed for 2 h and cooled and the precipitate was filtered off and washed with benzene. The filtrate was evaporated and the residue was analysed by ^{31}P NMR spectroscopy. Pure product was obtained by crystallisation (6.9 g, 60%). Mp 58—59 °C. δ_P −12.5 ppm.

O,O-Dialkyl alkali metal phosphoroselenoates (M = Na or K) react with acyl and benzoyl chlorides to provide *O,O*-dialkyl *O*-acyl phosphoroselenonates (e.g. **54a—n**) (Fig. 6.6.10) (*6*). The reaction completes within 15 min at room temperature in THF. Subsequently, some mixed *O*-acyl derivatives isomerise to their *Se*-acyl derivatives, the rate depending on the nature of the substituents on the P and C_{acyl} atoms.



O,O–Dialkyl *O*–acyl phosphoroselenonates

No.	R	R′	Yield (%)	δ_P (ppm)	$^1J_{P,Se}$ (Hz)
a	$CH_2C(Me)_2CH_2$	4-ClC_6H_4	71	51.9	1056
b	$CH_2C(Me)_2CH_2$	*t*-Bu	*	53.0	1059
c	$CH_2C(Me)_2CH_2$	4-$MeOC_6H_4$	69	52.4	1057
d	$CH_2C(Me)_2CH_2$	4-$NO_2C_6H_4$	45	51.4	1064
e	$CH_2C(Me)_2CH_2$	Ph	*	52.1	1055
f	$CH_2C(Me)_2CH_2$	Me	*	51.2	1048
g	*i*-Pr	4-ClC_6H_4	75	60.1	990
h	*i*-Pr	*t*-Bu	71	60.4	983
i	*i*-Pr	4-$MeOC_6H_4$	67	60.0	984
j	*i*-Pr	4-$NO_2C_6H_4$	68	60.1	996
k	Ph	4-ClC_6H_4	66	53.2	1055
l	Ph	*t*-Bu	*	53.7	1049
m	Ph	4-$MeOC_6H_4$	*	53.4	1047
n	Ph	4-$NO_2C_6H_4$	53	53.0	1060

* Too unstable to isolate but presence confirmed by NMR analysis

Figure 6.6.10

▶ *O,O-Disubstituted O-acyl phosphoroselenonates* (**54a—n**) (*6*). The acid chloride (3.0 mmol) was added portionwise into a stirred solution of potassium 2-oxo-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane, potassium *O,O*-diisopropyl phosphoroselenoate or potassium *O,O*-diphenyl phosphoroselenoate (3.0 mmol) in THF (15 ml) at room temperature. The mixture was stirred for 15 min. The solvent was evaporated and the residue was suspended in chloroform or dichloromethane, filtered and the filtrate was washed sequentially with 1 M aqueous sodium bicarbonate and then water. The organic layer was dried ($MgSO_4$) and the solvent removed. Column chromatography on silica gel, eluting with 1:1 chloroform—hexane with increasing concentrations of chloroform, gave the *O,O*-disubstituted *O*-acyl phosphoroselenonates.

6.7 TETRA-ALKYL SELENOPYROPHOSPHATES $(RO)_2P(O)SeP(O)(OR)_2$ AND *BIS*(DIALKYLPHOSPHORYL) DISELENIDES $(RO)_2P(O)SeSeP(O)(OR)_2$

Bis(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl) selenide (**55**), the first example of a symmetrical tetra-alkyl selenopyrophosphate, is synthesised in low yield by treating 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane with selenous acid (Fig. 6.7.1) (*41*). This procedure gives complex mixtures of phosphorus products when extended to the synthesis of other symmetrical tetra-alkyl selenopyrophosphates (*42*). The asymmetric isomer, *P*-oxo-*P′*-seleno-*bis*-(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl) oxide (**56**), was prepared by a similar method used to synthesise the sulfur analogue (*43*) from 5,5-dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphorinane and the triethylammonium salt of 5,5-dimethyl-2-oxo-2-seleno-1,3,2-dioxaphosphorinane. The ^{31}P NMR spectrum of product (**56**) confirmed the presence of two different phosphorus nuclei ($\delta_{P=O}$ −22.9 ppm, $\delta_{P=Se}$ 43.6 ppm).

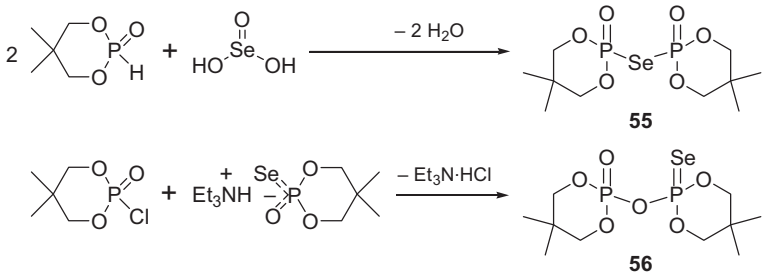
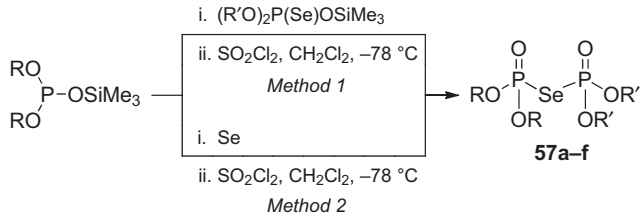


Figure 6.7.1

▶ *Bis(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl) selenide* (**55**) (*41*). Warming 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (2 mol) and selenous acid (1 mol) in benzene—methanol resulted in an exothermic reaction that had to be moderated by cooling in ice to avoid decomposition and formation of red selenium. The crystals obtained were recrystallised from chloroform—ether to give the title compound (25%). Mp 164—169 °C. δ_P 0.6 ppm.

An efficient synthesis of tetra-alkyl monoselenopyrophosphates (**57a—f**) has been developed based on the reaction of dialkyl trimethylsilyl phosphites with dialkyl *Se*-chloro phosphoroselenolates $(RO)_2P(O)SeCl$ (prepared in situ by chlorinating *O,O*-dialkyl *O*-trimethylsilyl phosphoroselenonates $(RO)_2P(Se)OSiMe_3$ with sulfuryl chloride) (Fig. 6.7.2; *method 1*) (*42*). Alternatively, the reaction of *O,O*-dialkyl *O*-trimethylsilyl phosphoroselenonates $(RO)_2P(Se)OSiMe_3$ with sulfuryl chloride in the presence of an equimolar amount of the starting dialkyl trimethylsilyl phosphites $(RO)_2POSiMe_3$ provides the same products (**57a—f**) in generally lower yield (Fig. 6.7.2; *method 2*).



O,O-Dialkyl symmetrical and unsymmetrical monoselenopyrophosphates

No.	R	R′	Yield (%) Method 1	Yield (%) Method 2	Mp (°C)	δ_P (ppm)
a	Me	Me	95	80	–	18.1
b	Et	Et	95	78	–	14.7
c	*i*-Pr	*i*-Pr	95	75	–	12.4
d	*t*-$BuCH_2$	*t*-$BuCH_2$	96	90	62–63	15.2
e	$CH_2C(Me)_2CH_2$	$CH_2C(Me)_2CH_2$	95	95	113–114	5.9
f	$CH_2C(Me)_2CH_2$	*t*-$BuCH_2$	95	95	186–187	14.3

Figure 6.7.2

▶ *O,O,O,O-Tetra-alkyl monoselenopyrophosphates* (**57a—f**) (*42*). *Method 1*. Sulfuryl chloride (1.35 g, 10 mmol) in dichloromethane (5 ml) was added dropwise to a vigorously stirred solution of the appropriate *O,O*-dialkyl *O*-trimethylsilyl phosphoroselenonate (10 mmol) and dialkyl trimethylsilyl phosphite (10 mmol) in dichloromethane (10 ml) at −78 °C. The mixture was allowed to warm slowly to ambient temperature. The solvent was evaporated under reduced pressure to afford the product. Further purification was achieved by column chromatography on silica gel, eluting with benzene and chloroform, or by recrystallisation from 1:1 *v/v* benzene—light petroleum. *Method 2*. Anhydrous selenium (0.40 g, 5 mmol) was added to the stirred dialkyl trimethylsilyl phosphite (10 mmol). The exothermic reaction was complete after several minutes. The mixture was diluted with dichloromethane (5 ml), cooled to −78 °C, and sulfuryl chloride (0.68 g, 5 mmol) in dichloromethane (5 ml) was added dropwise. The reaction mixture was worked up as described in the previous method.

Selective reaction of dialkyl trimethylsilyl phosphites with *O,O*-dialkyl *O*-trimethylsilyl phosphoroselenonates and sulfuryl chloride provides tetra-alkyl monoselenopyrophosphates (**58a—f**) in excellent

yields (Fig. 6.7.3) (*42*,*44*). The dialkyl trimethylsilyl phosphites are obtained by silylation of dialkyl *H*-phosphonates (*45*). The dialkyl trimethylsilyl phosphoroselenonates are available from addition of selenium to the dialkyl trimethylsilyl phosphites or by silylation of the anion $(RO)_2P(Se)O^-$ (*33*,*45*). Tetra-alkyl monoselenopyrophosphates (**58a–f**) are highly reactive towards nucleophiles and are potent phosphorylating reagents due to the excellent leaving group present [the anion $(RO)_2P(Se)O^-$ is very stable and the P-Se the bond is of low energy]. They isomerise to the tetra-alkyl pyrophosphoroselenonates $(RO)_2P(Se)OP(O)(OR)_2$ when warmed above 60 °C. This isomerisation is analogous to that observed for the symmetrical tetra-alkyl thiopyrophosphates (*46*).

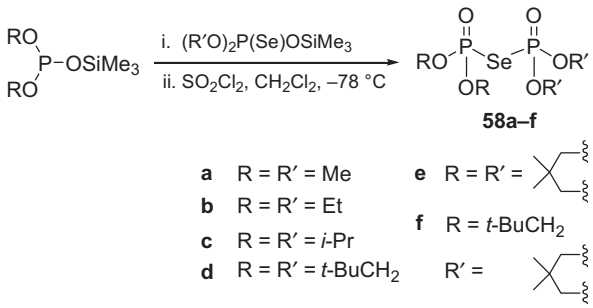


Figure 6.7.3

The reaction of phosphorus pseudohalogens with tricoordinate phosphorus compounds offers an alternative route to symmetrical monoselenopyrophosphates (*47*,*48*). The reaction of *bis*(dialkyl phosphoryl) diselenides with trialkyl phosphites follows a complex course (Fig. 6.7.4). Tetra-alkyl monoselenopyrophosphates form alongside other by-products. Phosphonium salts (**59**) are the key intermediates and can transform via nucleophilic attack of the phosphoroselenoate anion on each of the phosphorus and carbon atoms of the phosphonium counter-ion, depending on the stereo-electronic properties of the surrounding substituents. The ratio of the products **60**, **62**, **65** and **66** differ depending on the structure of the starting *bis*(dialkylphosphoryl) diselenides. *O,O*-Diethyl *O′,O′*-dimethyl monoselenopyrophosphate was obtained in 80% yield when R = Et and R′ = Me. However, in the case of R = R′ = Et, the reaction gave only *O,O,O,O*-tetraethyl monoselenopyrophosphate in 20% yield. The two results can be explained since nucleophilic displacement of an ethoxyl carbon is approximately 2000 times slower than that of a methoxyl carbon (*49*).

The course of the reaction can change strikingly upon replacing trialkyl phosphites with dialkyl trimethylsilyl phosphites. Here selective attack of the phosphoroselenoate anion on the silicon atom of the intermediate phosphonium salts (**68a–e**) gives exclusively the *O,O,O,O*-tetra-alkyl monoselenopyrophosphates (**69a–e**) (Fig. 6.7.5) (*49*). This extremely exothermic reaction must be conducted at −100 to −95 °C under anhydrous conditions. Monoselenopyrophosphates (**69a–e**) are readily isolated and purified by crystallisation or column chromatography on silica gel. The approach

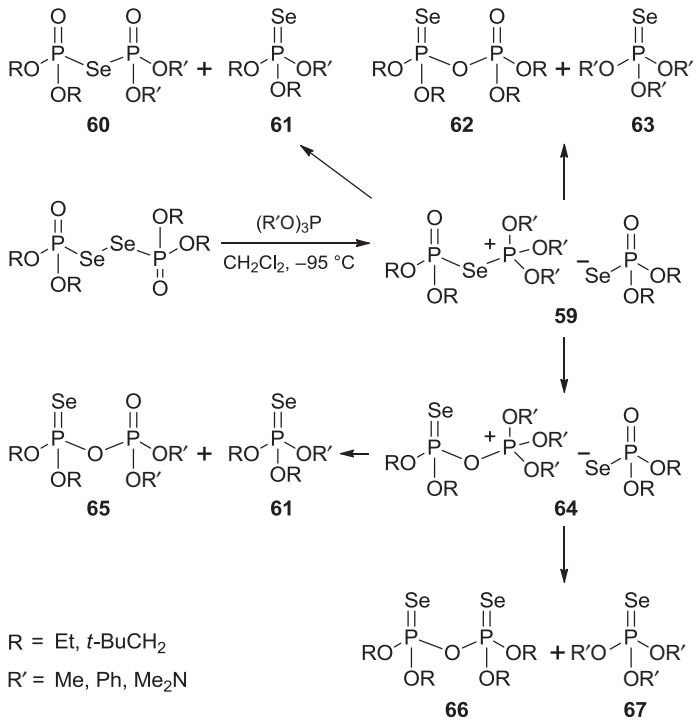


Figure 6.7.4

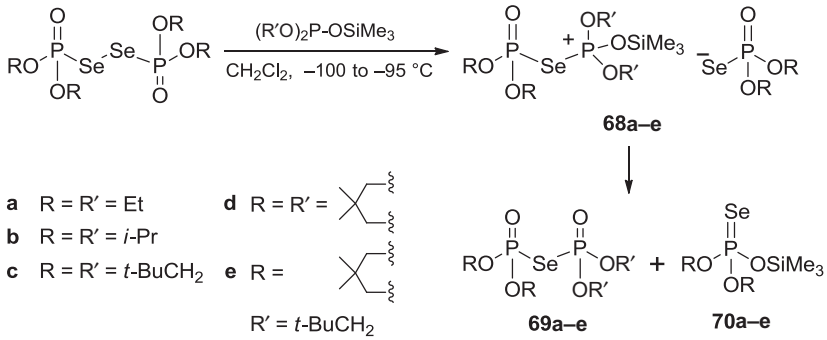


Figure 6.7.5

suits the synthesis in good yields of simple R = R′ and mixed R ≠ R′ monoselenopyrophosphates. These are moisture sensitive and hydrolyse readily to give dialkyl hydrogen phosphates (**71a–e**), *O,O*-dialkyl hydrogen phosphoroselenoates (**72a–e**), *O,O,O,O*-tetra-alkyl pyrophosphates (**73a–e**) and tetra-alkyl pyrophosphoroselenonates (**74a–e**) (Fig. 6.7.6).

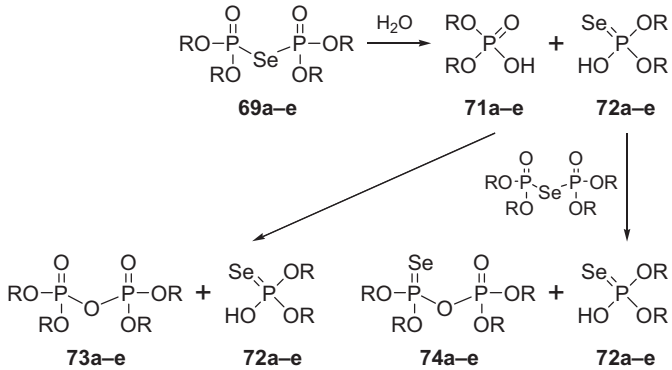


Figure 6.7.6

▶ *O,O,O,O-Tetra-alkyl monoselenopyrophosphates* $(RO)_2P(O)SeP(O)(OR')_2$ (**69a–e**) (*49*). The *bis*(dialkylphosphoryl) diselenide (1.5 mmol) in dichloromethane (5 ml) was added to a solution of the corresponding dialkyl trimethylsilyl phosphite (1.5 mmol) in dichloromethane (5 ml) at −100 to −95 °C. Then, the mixture was slowly warmed to room temperature, and monitored by ^{31}P NMR spectroscopy until complete conversion of the starting materials to the tetra-alkyl monoselenopyrophosphate was indicated. Addition of 1:1 *v/v* petroleum ether–diethyl ether (10 ml) caused the tetra-alkyl monoselenopyrophosphate to crystallise after standing for a few days in the refrigerator. Pure product was obtained by two recrystallisations from 1:1 *v/v* petroleum ether–diethyl ether in the case of solid products. Pure liquid products were obtained by column chromatography on silica gel 60, eluting with 1:1 benzene–chloroform.

Treatment of an aqueous solution of a sodium or potassium *O,O*-dialkyl phosphoroselenoate with iodine in diethyl ether gives *bis*(dialkylphosphoryl) diselenides (e.g. **75** or **76**) (Fig. 6.7.7) (*5*). Treatment of the same salts with aqueous solutions of *bis*(dialkylphosphoryl) diselenides affords *bis*(dialkylphosphoryl) diselenides containing the same R groups as those in the salts (e.g. **77** or **78**) (Fig. 6.7.8). Interestingly, *bis*(dialkylphosphoryl) diselenides (**76**) and (**79**) are obtained from an analogous reaction of the salts of *O,O*-dialkyl hydrogen phosphoroselenoates with *bis*(dialkylphosphoryl) disulfides (*5*). Compound (**75**) is a pale greenish crystalline solid (mp 34 °C), while the other seleno products (**76–79**) are liquids.

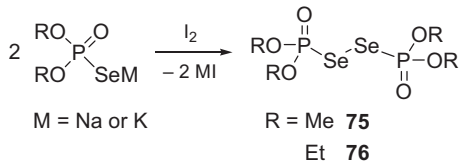


Figure 6.7.7

▶ *Bis(dialkylphosphoryl) diselenides [(RO)$_2$P(O)Se]$_2$* (**75**–**76**) (*5*). A solution of iodine (2 g) in ether (50 ml) was added to a solution of (RO)$_2$P(O)SeNa (5 g) in water (5 ml). Upon stirring, the aqueous and ether layers assumed brown and brownish-green colours, respectively. The layers were separated and the aqueous layer was extracted with ether (2 × 25 ml). The combined ether solutions were dried (Na_2SO_4) and the solvent was evaporated until 20 ml of solution remained. Cooling in a carbon dioxide–acetone freezing mixture caused pale greenish crystals of *bis*(dimethylphosphoryl) diselenide (**75**) to separate. In a separate experiment, the mother liquor was decanted and the crystals of *bis*(diethylphosphoryl) diselenide (**76**) were washed twice with cold petroleum ether.

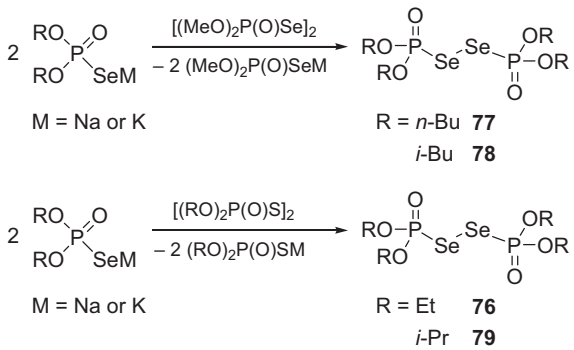


Figure 6.7.8

6.8 *O,O*-DIALKYL PHOSPHOROSELENOTHIOATE SALTS (RO)$_2$P(S)SeM OR (RO)$_2$P(Se)SM AND *O,O,Se*-TRIALKYL PHOSPHOROSELENOTHIONATES (RO)$_2$P(S)SeR OR *O,O,S*-TRIALKYL PHOSPHOROSELENOTHIOLATES (RO)$_2$P(Se)SR

Treatment of dialkyl phosphorochloridites with hydrogen sulfide and a trialkylamine provides dialkyl *H*-thiophosphonates, which add selenium in the presence of a trialkylamine, to give the *O,O*-dialkyl phosphoroselenothioate trialkylammonium salts (**80**) (Fig. 6.8.1) (*50*). These react with α-glycosyl bromides in boiling benzene to give *Se*- and *S*-glycosyl derivatives (**81a**–**d**) and (**82a**–**d**) respectively with inversion of configuration at the glycosylic centre (Fig. 6.8.2) (*50*). Glycosylation completes in a few hours and for more reactive reagents such as α-xylopyranosyl bromide in a few minutes, and generates almost quantitatively *Se*- and *S*-glycosyl derivatives as a mixture of isomers.

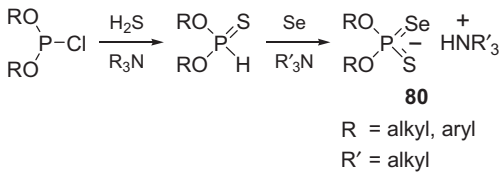
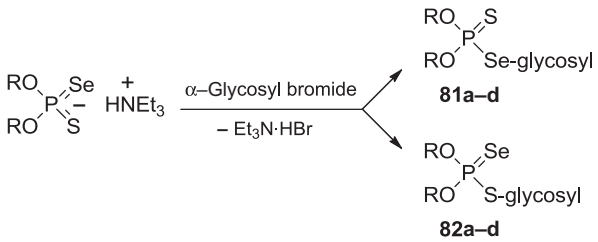


Figure 6.8.1



Product	R''R	Yield (%)	δ_P (ppm)	$J_{P,Se}$ (Hz)
81a	$H_2CC(Me)_2CH_2$	62	–76	422
81b	$H_2CC(Me)_2CH_2$	67	–73	424
81c	$H_2CC(Me)_2CH_2$	76	–74	440
81d	*t*-$BuCH_2$, *t*-$BuCH_2$	76	–84	431
82a	$H_2CC(Me)_2CH_2$	38	–85	972
82b	$H_2CC(Me)_2CH_2$	33	–82	972
82c	$H_2CC(Me)_2CH_2$	24	–83	880
82d	*t*-$BuCH_2$, *t*-$BuCH_2$	24	–93	924

Figure 6.8.2

▶ *5,5-Dimethyl-2-(2,3,4,6-tetra-O-acetyl-o-glucopyranosylselenyl)-1,3,2-dioxaphosphinane 2-sulfide* (**81a**) *and 5,5-dimethyl-2-(2,3,4,6-tetra-O-acetyl-o-glucopyranosylthio)-1,3,2-dioxaphosphinane 2-selenide* (**82a**) (*50*). A solution of α-acetobromoglucose (3.0 g, 7.2 mmol) and triethylammonium 2-thio-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane (2.6 g, 7.2 mmol) was refluxed in benzene (50 ml) for 8 h. Upon cooling to room temperature triethylammonium hydrobromide was filtered off, and the filtrate was washed with water and dried ($MgSO_4$). After removing the solvent, the syrupy residue was refluxed in carbon tetrachloride-heptane to give a mixture of isomers as colourless needles (3.1 g, 75%). Mp 144—146 °C. The ^{31}P NMR signals integrated as 38:62.

▶ *5,5-Dimethyl-2-[(2,3,4,6-tetra-O-acetyl-o-galactopyranosyl)selenyl]-1,3,2-dioxaphosphinane 2-sulfide* (**81b**) *and 5,5-dimethyl-2-[(2,3,4,6-tetra-O-acetyl-o-galactopyranosyl)thio]-1,3,2-dioxaphosphinane 2-selenide* (**82b**) (*50*). A solution of α-acetobromogalactose (2.0 g, 4.8 mmol) and triethylammonium 2-thio-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane (1.65 g, 4.8 mmol) was refluxed in benzene (30 ml) for 8 h. Upon cooling to room temperature triethylammonium hydrobromide was filtered off, and the filtrate was washed with water and dried ($MgSO_4$). After removing the solvent, the syrupy residue was refluxed in carbon tetrachloride-heptane to give a mixture of isomers as colourless needles (2.2 g, 80%). Mp 165—167 °C. The ^{31}P NMR signals integrated as 33:67.

▶ *5,5-Dimethyl-2-[(2,3,4-tri-O-acetyl-o-xylopyranosyl)selenyl]-1,3,2-dioxaphosphinane 2-sulfide* (**81c**) *and 5,5-dimethyl-2-[(2,3,4-tri-O-acetyl-o-xylopyranosyl)thio]-1,3,2-dioxaphosphinane 2-selenide* (**82c**) (*50*). A solution of α-acetobromoxylose (2.0 g, 5.9 mmol) and triethylammonium 2-thio-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane (2.0 g, 5.9 mmol) was heated in boiling benzene (30 ml) for 2 min. Upon cooling to room temperature triethylammonium hydrobromide

was filtered off, and the filtrate was washed with water and dried ($MgSO_4$). After removing the solvent, the syrupy residue was refluxed in 1:1 *v/v* carbon tetrachloride—heptane (30 ml) to give a mixture of isomers as colourless needles (2.5 g, 87%). Mp 134—136 °C. The ^{31}P NMR signals integrated as 24:76.

▶ *O,O-Dineopentyl-Se-(2,3,4,6-tetra-O-acetyl-o-glucopyranosyl)phosphoroselenothionate* (**81d**) *and O,O-dineopentyl-S-(2,3,4,6-tetra-O-acetyl-o-glucopyranosyl)phosphoroselenothiolate* (**82d**) (*50*). A solution of α-acetobromoglucose (0.82 g, 2.0 mmol) and triethylammonium *O,O*-dineopentyl phosphoroselenothioate (0.84 g, 2.0 mmol) was refluxed in benzene (10 ml) for 5 h. Upon cooling to room temperature triethylammonium hydrobromide was filtered off, and the filtrate was washed with water and dried ($MgSO_4$). The solvent was evaporated and the semicrystalline residue crystallised twice from light petroleum to give a mixture of isomers as colourless prisms (1.1 g, 84%). Mp 120—122 °C.

The *Se*-glycosyl phosphoroselenothionates (**83a—d**) and *S*-glycosyl phosphorothioselenonates (**84a—d**) were prepared by glycosidation of the β-D-hexopyranoses (1 mol) with the appropriate phosphoroselenothioate anion (1 mol) in the presence of $BF_3 \cdot Et_2O$ (3 mol) in 1,2-dichloroethane at room temperature (Fig. 6.8.3) (*51*). Peracetylated gluco-, galacto-, 2-deoxy-arabina- and per-*O*-benzylated unprotected 1-*OH*-gluco-β-D-hexopyranoses react to give a mixture of *Se*- and *S*-isomers (major and minor respectively).

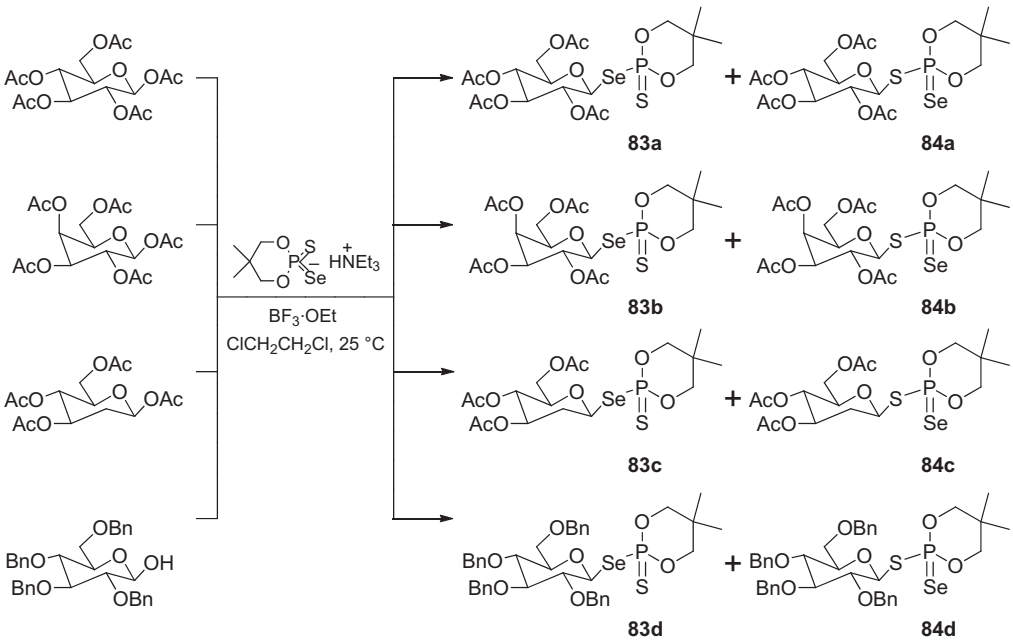


Figure 6.8.3

▶ *(2R,3R,5R,6S)-2-(Acetoxymethyl)-6-((5,5-dimethyl-2-selenido-1,3,2-dioxaphosphinan-2-yl)thionyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate* (**83a**) *and (2R,3R,5R,6S)-2-(acetoxymethyl)-6-((5,5-dimethyl-2-sulfido-1,3,2-dioxaphosphinan-2-yl)selenyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate* (**84a**) (*51*). To a solution of triethylammonium 5,5-dimethyl-1,3,2-dioxaphosphinane-2-thioate 2-selenide (1.33 g, 3.84 mmol) and (*2S,3R,5R,6R*)-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2,3,4,5-tetrayl tetraacetate (1.50 g, 3.83 mmol) in 1,2-dichloroethane (75 ml) was added $BF_3 \cdot Et_2O$ (1.63 g, 1.45 ml, 11.48 mmol). The mixture was stirred at room temperature for 30 h, washed with saturated aqueous $NaHCO_3$ (2 × 85 ml), water (85 ml) and dried ($MgSO_4$). The solvent was evaporated and the syrupy residue was crystallised twice from CCl_4—heptane to give a mixture of two isomers as colourless needles (1.0 g, 45%). Mp 144—145 °C. δ_P 85.2 ppm (s, $J_{P,Se}$ 976 Hz) for *S*-isomer and 76.2 ppm (s, $J_{P,Se}$ 424 Hz) for *Se*-isomer; integration ~1.0:2.3.

▶ *(2R,3S,5R,6S)-2-(Acetoxymethyl)-6-((5,5-dimethyl-2-selenido-1,3,2-dioxaphosphinan-2-yl)thionyl) tetrahydro-2H-pyran-3,4,5-triyl triacetate* (**83b**) *and (2R,3S,5R,6S)-2-(acetoxymethyl)-6-((5,5-dimethyl-2-sulfido-1,3,2-dioxaphosphinan-2-yl)selenyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate* (**84b**) (*51*). To a solution of triethylammonium 5,5-dimethyl-1,3,2-dioxaphosphinane-2-thioate 2-selenide (1.33 g, 3.84 mmol) and (*2S,3R,5S,6R*)-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2,3,4,5-tetrayl tetraacetate (1.50 g, 3.83 mmol) in 1,2-dichloroethane (75 ml) was added $BF_3 \cdot Et_2O$ (1.63 g, 1.45 ml, 11.48 mmol). The mixture was stirred at room temperature for 25 h, washed with saturated aqueous $NaHCO_3$ (2 × 85 ml), water (85 ml) and dried ($MgSO_4$). The solvent was removed and the syrupy residue was crystallised twice from CCl_4—heptane to give a mixture of two isomers as colourless needles (1.5 g, 68%). Mp 167—170 °C. δ_P 85.6 ppm (s, $J_{P,Se}$ 974 Hz) for *S*-isomer and 76.5 ppm (s, $J_{P,Se}$ 426 Hz) for *Se*-isomer; integration ~1.0:2.4.

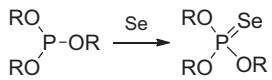
▶ *(2R,3S,6S)-2-(Acetoxymethyl)-6-((5,5-dimethyl-2-selenido-1,3,2-dioxaphosphinan-2-yl)thionyl)tetrahydro-2H-pyran-3,4-diyl diacetate* (**83c**) *and (2R,3S,6S)-2-(acetoxymethyl)-6-((5,5-dimethyl-2-sulfido-1,3,2-dioxaphosphinan-2-yl)selenyl)tetrahydro-2H-pyran-3,4-diyl diacetate* (**84c**) (*51*). To a solution of triethylammonium 5,5-dimethyl-1,3,2-dioxaphosphinane-2-thioate 2-selenide (1.35 g, 3.90 mmol) and (*2S,5S,6R*)-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2,4,5-triyl triacetate (1.30 g, 3.90 mmol) in 1,2-dichloroethane (80 ml) was added $BF_3 \cdot Et_2O$ (1.66 g, 1.47 ml, 11.7 mmol). The mixture was stirred at room temperature for 6 h, washed with saturated aqueous $NaHCO_3$ (2 × 85 ml), water (85 ml) and dried ($MgSO_4$). The solvent was evaporated and the syrupy residue was crystallised twice from CCl_4—heptane to give a mixture of two isomers as colourless needles (0.955 g, 47%). Mp 109—110 °C. δ_P 84.0 ppm (s, $J_{P,Se}$ 965 Hz) for *S*-isomer and 75.2 ppm (s, $J_{P,Se}$ 450 Hz) for *Se*-isomer; integration ~1.0:1.7.

▶ *5,5-Dimethyl-2-(((2S,3R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)thionyl)-1,3,2-dioxaphosphinane 2-selenide* (**83d**) *and 5,5-dimethyl-2-(((2S,3R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)selenyl)-1,3,2-dioxaphosphinane 2-sulfide* (**84d**) (*51*). To a solution of triethylammonium 5,5-dimethyl-1,3,2-dioxaphosphinane-2-thioate 2-selenide (0.96 g, 2.77 mmol) and (*2R,3R,5R,6R*)-3,4,5-*tris*(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2*H*-pyran-2-ol (1.50 g, 2.77 mmol) in 1,2-dichloroethane (55 ml) was added $BF_3 \cdot Et_2O$ (1.18 g, 1.05 ml, 8.31 mmol). The mixture was stirred at room temperature for 7 days. Then it was

washed with saturated $NaHCO_3$ (2 × 85 ml), water (85 ml) and dried ($MgSO_4$). The solvent was evaporated and the syrupy residue was crystallised twice from CCl_4—heptane to give a mixture of two isomers as colourless needles (0.775 g, 36%). Mp 135—138 °C. δ_P 87.3 ppm (s, $J_{P,Se}$ 962 Hz) for *S*-isomer and 77.8 ppm (s, $J_{P,Se}$ 463 Hz) for *Se*-isomer; integration ~1:1.9.

6.9 *O,O,O*-TRISUBSTITUTED PHOSPHOROSELENONATES $(RO)_3P{=}Se$

Addition of selenium to trialkyl phosphites to give *O,O,O*-trisubstituted phosphoroselenonates $(RO)_3P{=}Se$ (e.g. **85a—f**; Fig. 6.9.1) occurs much less easily than the analogous addition of sulfur to give *O,O,O*-trisubstituted phosphorothionates $(RO)_3P{=}S$ (*7*). Normally selenation occurs above 200 °C — aryl substituents when present influencing the reaction rate little — although 2-ethoxy-4-methyl-1,3,2-dioxaphospholane 2-selenide (**86**; Fig. 6.9.2) is obtained in poor yield (5%) possibly due to instability during distillation. Selenium addition to *tris*(-trimethylsilyl) phosphite provides *O,O,O-tris*(trimethylsilyl) phosphoroselenonate (**87**) in acceptable yield (*52*).

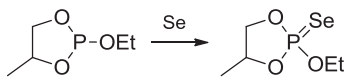


85a–f

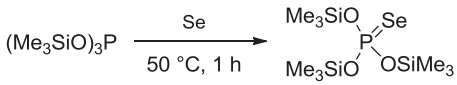
O,O,O-Triorganyl phosphoroselenonates

Product	R	Bp (°C/mmHg)
a	Me	95/20
b	Et	117/20
c	Ph	73–74/760
d	2-MeC_6H_4	50–51/760
e	4-MeC_6H_4	111–112/760
f	4-ClC_6H_4	88/760

Figure 6.9.1



86 5%



87 67%

Figure 6.9.2

▶ *Tris(trimethylsilyl)phosphoroselenonate* (**87**) (*52*). A mixture of *tris*(trimethylsilyl) phosphite (12 g, 40 mmol) and powdered selenium (3.32 g, 42 mmol) was heated at 50 °C for 1 h. After cooling to room temperature the excess selenium was filtered off. Vacuum distillation of the filtrate gave the title compound (9.1 g, 60%).

Strained *O,O,O*-trialkyl phosphoroselenonates (**88a–e**) can be obtained by treating the appropriate trialkyl phosphites with selenium or KSeCN (Fig. 6.9.3) (*53*). The starting trialkyl phosphites are prepared by known methods: 2-methoxy-4,6-dimethyl-1,3,2-dioxaphosphinane (*54*), 2-methoxy-1,3,2-dioxaphospholane (*53*), 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane (*55*), 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.1]heptane (*56*) and 2-methoxy-1,3,2-dioxaphosphinane (*53*).

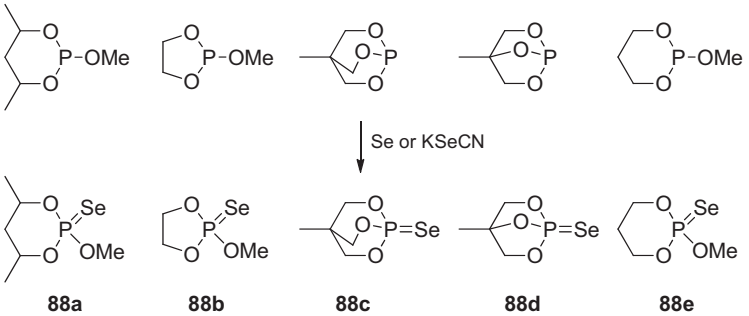


Figure 6.9.3

▶ *2-Methoxy-4,6-dimethyl-1,3,2-dioxaphosphinane 2-selenide* (**88a**) (*53*). *Method 1*. A mixture of 2-methoxy-4,6-dimethyl-1,3,2-dioxaphosphinane (2.00 g, 12.2 mmol) and red selenium powder (1.60 g, 20.3 mmol) in toluene (15 ml) was heated at 80 °C for 18 h. The hot mixture was filtered to remove solid material. Upon cooling to room temperature the filtrate was reduced to dryness and the residue was recrystallised from *n*-hexane at −78 °C to give the title compound (2.46 g, 83%). *Method 2*. A mixture of 2-methoxy-4,6-dimethyl-1,3,2-dioxaphosphinane (1.19 g, 7.23 mmol) and KSeCN (1.05 g, 7.31 mmol) in anhydrous acetonitrile (25 ml) was stirred at room temperature under nitrogen for 90 min. The solvent was removed and the white residue was extracted with anhydrous benzene (20 ml) and filtered under nitrogen. Evaporation of the filtrate gave the title compound (1.40 g, 80%). Mp 68–70 °C.

▶ *2-Methoxy-1,3,2-dioxaphospholane 2-selenide* (**88b**) (*53*). A mixture of 2-methoxy-1,3,2-dioxaphospholane (2.51 g, 20.6 mmol) and KSeCN (3.01 g, 20.9 mmol) in anhydrous acetonitrile (25 ml) was stirred at room temperature under nitrogen for 2 h. The solvent was removed and the white residue was extracted with anhydrous benzene (20 ml) and filtered under nitrogen. Evaporation of the solvent from the filtrate gave the title compound (78% pure by ^{31}P NMR analysis). Attempted further purification including chromatography resulted in decomposition.

▶ *4-Methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-selenide* (**88c**) (*53*). A mixture of freshly sublimed 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane (4.74 g, 32.0 mmol) and red selenium (3.80 g, 48.0 mmol) in toluene (25 ml) was heated at 80 °C for 10 h. The hot mixture was

filtered and the solid residue was extracted with toluene (150 ml) using a Soxhlet apparatus for 2 days under nitrogen. The harvested solid, which precipitated upon cooling to room temperature, was recrystallised from boiling toluene (300 ml), washed with hexane (2 × 30 ml) and dried under vacuum to afford the title compound as a white solid (6.36 g, 88% yield). Mp 246–248 °C.

▶ *4-Methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.1]heptane 1-selenide* (**88d**) (*53*). A mixture of 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.1]heptane (0.60 ml, 5.8 mmol) and red selenium (0.86 g, 11.0 mmol) in anhydrous toluene (15 ml) was heated at 75 °C for 10 h. Upon cooling to room temperature the mixture was filtered. The filtrate was cooled to −78 °C and the product crystallised to give a white solid (0.78 g, 63%). It is moisture sensitive and decomposes slowly at room temperature even under nitrogen. Mp 74–76 °C.

▶ *2-Methoxy-1,3,2-dioxaphosphinane 2-selenide* (**88e**) (*53*). A mixture of 2-methoxy-1,3,2-dioxaphosphinane (1.34 g, 9.84 mmol) and KSeCN (1.42 g, 9.86 mmol) in anhydrous acetonitrile (25 ml) was stirred at room temperature under nitrogen for 2 h. The solvent was removed and the white residue was extracted with anhydrous benzene (20 ml) and filtered under nitrogen. The benzene was removed from the filtrate to afford the crude product. No attempt was made to distil the product due to the Pistschimuka rearrangement previously reported to occur upon distillation.

6.10 *O,O*-DIALKYL PHOSPHORODISELENOATE SALTS $(RO)_2P(Se)SeM$ AND *O,O,Se*-TRIALKYL PHOSPHORODISELENOATES $(RO)_2P(Se)SeR'$

The first *O,O,Se*-trialkyl phosphorodiselenoates $(RO)_2P(Se)SeR$ (**89**) were made by treating phosphorus pentaselenide with alcohols (Fig. 6.10.1) (*7*). A mixture of phosphorus pentaselenide and ethanol, for example, requires warming initially for reaction to occur; red selenium precipitates and hydrogen selenide forms, and addition of water to the mixture causes *O,O,Se*-triethyl phosphorodiselenoate $(EtO)_2P(Se)SeEt$ to separate (this product cannot be isolated by distillation). Reaction of an alcohol (4 mol) with phosphorus pentaselenide (1 mol) in refluxing heptane gives *O,O*-dialkyl hydrogen phosphorodiselenoates $(RO)_2P(Se)SeH$, which on treatment with ethanolic potassium hydroxide provide *O,O*-dialkyl phosphorodiselenoate potassium salts (**90**) (*57*). These are rather unstable and turn red upon storage. *O,O*-Dialkyl phosphorodiselenoate ammonium salts $(RO)_2P(Se)SeNH_4$ are much easier to handle and are obtained as colourless powders by treating *O,O*-dialkyl hydrogen phosphorodiselenoates with anhydrous gaseous ammonia at 0 °C (*58*).

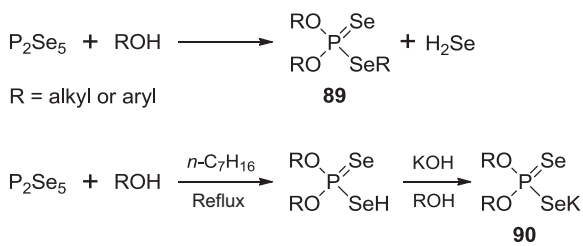


Figure 6.10.1

Only a few examples of *O,O*-dialkyl phosphorodiselenoate salts $(RO)_2P(Se)SeM$ have been reported since the 1970s. The ammonium salts have been used as nucleophiles to attack electrophiles to form esters of general formula $(RO)_2P(Se)SeR'$ (**91–95**) (*59–62*). Such reactions include Michael addition, epoxide ring opening, acylation and α-alkynation (Fig. 6.10.2) (*63*).

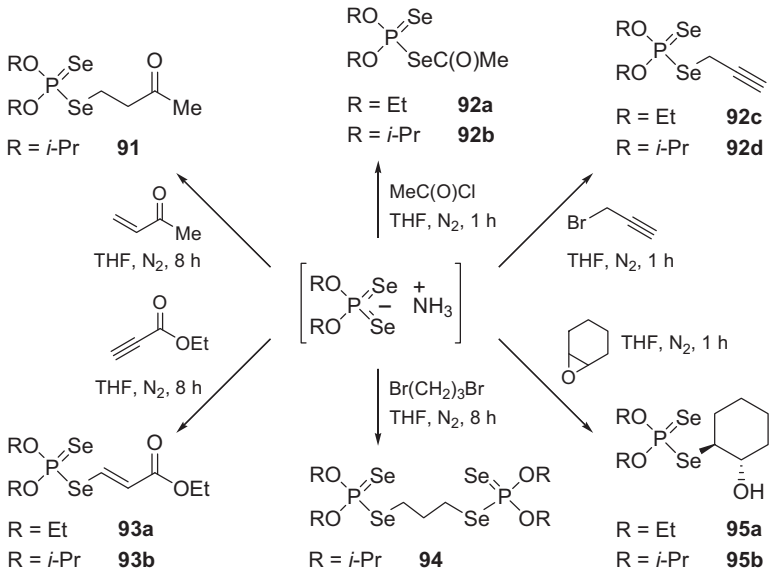


Figure 6.10.2

▶ *O,O-Diisopropyl Se-(3-oxobutyl) phosphorodiselenoate* $(i\text{-}PrO)_2P(Se)SeCH_2CH_2C(O)Me$ (**91**) (*63*). But-3-en-2-one (100 µl, 1.35 mmol) was added to a stirred suspension of $(i\text{-}PrO)_2P(Se)SeNH_4$ (0.439 g, 1.35 mmol) in THF (20 ml). The mixture was stirred at room temperature for 8 h under nitrogen. Volatile material was removed under vacuum. The product was isolated by preparative TLC eluting with 5% ethyl acetate in hexane. After running the TLC plate, four spots were isolated and the second spot from the top was the desired compound. After cutting the silica gel from the TLC plate, dichloromethane was added to extract the title compound, and the suspension was filtered to afford a greenish-yellow liquid (0.15 g, 30%). δ_P 80.5 ppm (s, $J_{P,Se}$ 478 Hz, $J_{P,Se}$ 883 Hz); δ_{Se} 377.9 (d, $J_{P,Se}$ 478 Hz); and −93.5 ppm (d, $J_{P,Se}$ 883 Hz).

▶ *O,O-Dialkyl Se-(propargyl) phosphorodiselenoates* $(RO)_2P(Se)SeCH_2C{\equiv}CH$ (**92c–d**) (*63*). Propargyl bromide (80% solution in toluene, 100 µl, 0.93 mmol) was added to a solution of $(RO)_2P(Se)SeNH_4$ (0.93 mmol) in THF (20 ml). The mixture was stirred at room temperature for 1 h under nitrogen and was filtered to remove the ammonium bromide. Rotary evaporation of the filtrate under vacuum gave the title species.

▶ *Ethyl 3-[(O,O-dialkylphosphoroselenoyl)selenyl]acrylates* $(RO)_2P(Se)SeCH{=}CHCO_2Et$ (**93a–b**) (*63*). Ethyl propiolate (130 µl, 1.24 mmol) was added to a suspension of $(RO)_2P(Se)SeNH_4$

(1.23 mmol) in THF (20 ml). The mixture was stirred at room temperature for 8 h under nitrogen, filtered, and the filtrate evaporated to dryness under vacuum to give the product.

▶ *O,O,O′,O′-Tetra-isopropyl Se,Se′-propane-1,3-diyl diphosphorodiselenoate (i-PrO)$_2$P(Se)Se(CH$_2$)$_3$ SeP(Se)(O-i-Pr)$_2$* (**94**) (*63*). 1,3-Dibromopropane (25 μl, 0.25 mmol) was added to a stirred suspension of (*i*-PrO)$_2$P(Se)SeNH$_4$ (0.163 g, 0.5 mmol) in THF (10 ml) in a Schlenk flask and stirred for 8 h under nitrogen. The mixture was filtered to remove the ammonium bromide. The solvent was evaporated under vacuum at room temperature to give a colourless liquid (0.28 g, 88%). δ_P 79.7 ppm (s, $J_{P,Se}$ 481 Hz, $J_{P,Se}$ 885 Hz); δ_{Se} 352.7 (d, $J_{P,Se}$ 481 Hz); and −90.1 ppm (d, $J_{P,Se}$ 885 Hz).

▶ *O,O-Dialkyl Se-[(1S,2S)-2-hydroxycyclohexyl] phosphorodiselenoates (RO)$_2$P(Se)SeC$_6$H$_{10}$(OH)-2* (**95a–b**) (*63*). Cyclohexene oxide (100 μl, 1.38 mmol) was added to a stirred suspension of (RO)$_2$P(Se)SeNH$_4$ (1.23 mmol) in THF (20 ml). The mixture was stirred at room temperature for 3 h under nitrogen. The mixture was filtered to remove the salt and the filtrate was evaporated to dryness. The resulting residue was vacuum-dried to give the title compounds.

6.11 HALOGENOSELENOPHOSPHONIUM SALTS [R$_3$P$^+$SeX]X$^-$ AND [(RO)$_3$P$^+$SeX]X$^-$

Interaction of bromine with *O,O,O*-trialkyl phosphoroselenonates (RO)$_3$P═Se (R = Et or *t*-BuCH$_2$) in dichloromethane at −20 °C provides the bromoselenophosphonium salts (**96a–b**) (Fig. 6.11.1) (*64*). The reaction proceeds at temperatures as low as −85 °C to give the same products. The salts are stable below −20 °C, and the bromide anion can be readily exchanged using silver(I) trifluoromethanesulfonate to produce the corresponding triflate (**97**).

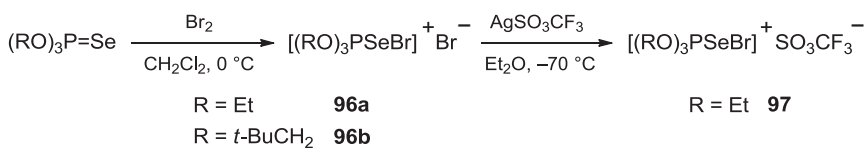


Figure 6.11.1

▶ *O,O,O-Trineopentylbromoselenophosphonium bromide (t-BuCH$_2$O)$_3$PSeBr$^+$Br$^-$* (**96b**) (*64*). A solution of bromine (1.60 g, 10 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of *O,O,O*-trineopentyl phosphoroselenonate (3.35 g, 10 mmol) in dichloromethane (25 ml) at 0 °C. The mixture was stirred at that temperature for 15 min. After filtering to remove solid material the filtrate was evaporated to yield a brown solid (5.22 g, 88%). Mp 43–47 °C. δ_P 30.6 ppm ($^1J_{P,Se}$ 854 Hz).

▶ *O,O,O-Triethylbromoselenophosphonium trifluoromethanesulfonate (EtO)$_3$PSeBr$^+$SO$_3$CF$_3^-$* (**97**) (*64*). A solution of silver(I) trifluoromethanesulfonate (3.08 g, 12 mmol) in dry ether (15 ml) was added dropwise at −70 °C to a stirred solution of *O,O,O*-triethylbromoselenophosphonium bromide (4.86 g, 12 mmol) in dichloromethane (15 ml) and acetonitrile (15 ml). The mixture was stirred at that

temperature for ~10 h until completion, as determined by ^{31}P NMR spectroscopy. After filtering to remove silver bromide at −30 °C under N_2 the filtrate was evaporated to give the title compound (5.12 g, 90%). δ_P 36.4 ppm ($^1J_{P,Se}$ 810 Hz). The compound is stable in solution below −20 °C.

Addition of bromine to triarylphosphine selenides $Ar_3P{=}Se$ (Ar = Ph, *m*- or *p*-MeC_6H_4) to give yellow solids (**98a–c**) was first reported by Williams and Wynne (Fig. 6.11.2) (*63*). Although these solids are stable in moist air for about 1 h, their solutions decompose more easily, depositing red or grey selenium. Grey selenium deposits slowly from solutions in acetonitrile, chloroform, or dichloromethane, while decomposition is rapid in acetone or water.

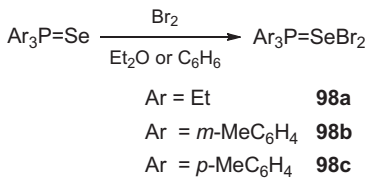


Figure 6.11.2

▶ *Dibromo(trisubstituted phosphine)selenides $Ar_3P{=}SeBr_2$* (**98a–c**) (*64,65*). A suspension of the triarylphosphine selenide (20 mmol) in anhydrous benzene or ether (30 ml) was prepared in a 250-ml three-necked round-bottomed flask equipped with a pressure-equalising dropping funnel and a dry nitrogen purge. A solution of bromine (2.9 g, 18 mmol) in dichloromethane (70 ml) was added over 30 min to the stirred suspension at 0 °C. The resulting yellow precipitate was filtered under nitrogen, washed with anhydrous ether, dried and recrystallised from ether–benzene at −20 °C to give yellow powders: **98a** [88%, mp 88–89 °C dec.; δ_P 50.7 (br s, $CDCl_3$); δ_P 42.0 ppm (br s, C_6D_6)], **98b** (99%, mp 112–113 °C dec.) and **98c** (80%, mp 97–98 °C dec.).

The reaction of triphenyl or tri-*n*-butylphosphine selenides with chlorine at −90 °C gives ionic selenophosphonium salts (**99a–b**) (Fig. 6.11.3) (*64*). These decompose to chlorophosphonium chlorides (**100a–b**), which can be observed by NMR spectroscopy at −90 °C. The phosphonium salt

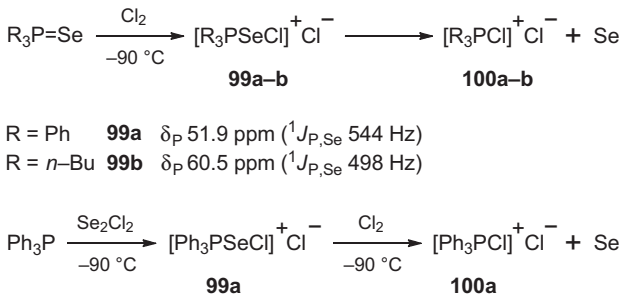


Figure 6.11.3

structure is supported by the ^{31}P NMR chemical shifts and $^{1}J_{P,Se}$ coupling constants that indicate a selenium atom singly bonded to a phosphorus centre. Products (**99a**) and (**100a**) were also observed during the reaction of triphenylphosphine with diselenium dichloride in dichloromethane at −90 °C.

Three iodine adducts R_3PSeI_2 (**101a–c**; R = Ph, Me_2N and Et_2N) were synthesised from reaction of the appropriate tertiary phosphine selenides with iodine in ether at room temperature (Fig. 6.11.4) (*66*). They were isolated in quantitative yield and were stable to air and moisture. Recrystallisation of the red powders from 1:1 *v/v* dichloromethane–ether at 50 °C produced large quantities of dark red crystals on standing at room temperature for approximately 2 days.

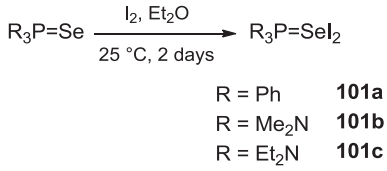


Figure 6.11.4

Another three iodophosphane selenides have been reported (*67*). Crystalline dicyclohexyldiiodophosphane selenide $(c\text{-}C_6H_{11})_2P(Se)I_2$ (**102**) and di-*tert*-butyliodophosphane selenide $(t\text{-}Bu)_2P(Se)I$ (**103**) were prepared by adding selenium to the related iodophosphines (Fig. 6.11.5). The iodophosphines were obtained in situ by reacting the chloro- or bromophosphines with an excess of sodium iodide in toluene. Addition of iodine to a toluene solution of di-*tert*-butyliodophosphane selenide (**103**) gave di-*tert*-butyliodophosphane selenide-diiodine (**104**). A similar reaction of dicyclohexyldiiodophosphane selenide (**102**) with iodine in dichloromethane produced insoluble, amorphous black solids that were not simple 1:1 adducts.

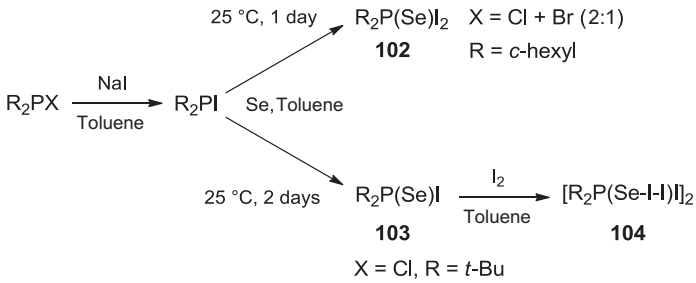


Figure 6.11.5

▶ *Dicyclohexyldiiodophosphane selenide* $(c\text{-}C_6H_{11})_2P(Se)I_2$ (**102**) (*67*). A chloro/bromodicyclohexylphosphine mixture (18.36 g, ~80 mmol, Cl:Br ratio about 2:1), obtained after distillation from the reaction of cyclohexylmagnesium bromide with phosphorus trichloride, was added to

a suspension of sodium iodide (30 g, 200 mmol) in toluene (40 ml). The mixture was refluxed for 1 h. After a further 18 h stirring at room temperature, the solid was removed by filtration, and powdered selenium (6.32 g, 80 mmol) was added. After stirring at room temperature for 1 day, the mixture was heated to 90 °C for 30 min to complete the reaction. After filtration of the hot solution, slow cooling led to crystallisation of the title compound as red-orange prisms (18.23 g, ~50%). Mp 74 °C. δ_P −79 ppm ($^1J_{P,Se}$ 755 Hz).

▶ *Di-tert-butyliodophosphane selenide (t-Bu)$_2$P(Se)I* (**103**) (*67*). Di-*tert*-butylchlorophosphine (7.83 g, 50 mmol) was added to a suspension of sodium iodide (15.0 g, 100 mmol) in toluene (50 ml). After stirring for 4 days the solid was removed by filtration, half of the solvent was evaporated under reduced pressure, and powdered grey selenium (3.16 g, 40 mmol) was added. After stirring for 3 days, unconsumed selenium was removed by filtration, the solvent was evaporated under reduced pressure, and the yellowish residue was recrystallized from hexane to give yellow crystals (11.45 g, 65%). Mp 83 °C. δ_P 126 ppm ($^1J_{P,Se}$ 775 Hz).

▶ *Di-tert-butyliodophosphane selenide-diiodine [(t-Bu)$_2$P(Se-I-I)I]$_2$* (**104**) (*67*). Iodine (0.76 g, 3.0 mmol) was added to a solution of di-*tert*-butyliodophosphane selenide (*t*-Bu)$_2$P(Se)I **103** (1.11 g, 3.4 mmol) in toluene (10 ml). Stirring was continued until all the iodine had dissolved. Subsequently hexane (10 ml) was carefully added and allowed to diffuse into the toluene solution to give black-brown crystals (1.45 g, 80%). Mp 96 °C. δ_P 129 ppm ($^1J_{P,Se}$ 600 Hz).

The dibromine adducts R_3PSeBr_2 (**105a–c**; R = Me_2N, Et_2N and *c*-C_6H_{11}) were also prepared by reaction of $R_3P{=}Se$ with bromine in ether at room temperature (Fig. 6.11.6) (*68*). The $R_3P{=}Se$ starting materials are easily prepared by selenium addition to the R_3P precursors. Dibromine adducts (**105a–c**) were isolated in almost quantitative yield. In contrast to the analogous diiodo compounds R_3PSeI_2 (R = Ph, Me_2N and Et_2N), which are air- and moisture stable, the dibromo compounds R_3PSeBr_2 are moisture sensitive and decompose in under an hour when exposed to the atmosphere.

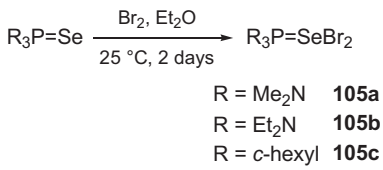


Figure 6.11.6

▶ *Synthesis of (c-C_6H_{11})$_3$P═SeBr$_2$* (**105c**) (*68*). Tricyclohexylphosphine selenide (2.00 g, 5.57 mmol) was suspended in diethyl ether (75 ml) and bromine (0.89 g, 5.57 mmol) was added. After 2 h stirring at room temperature the resultant yellow solid was isolated using standard Schlenk techniques and transferred to predried argon-filled ampoules that were flame sealed. δ_P 56.7 ppm. IR (P–Se) 517/cm.

6.12 SECONDARY PHOSPHINE SELENIDES $R_2P(Se)H$

Secondary phosphine selenides are excellent nucleophiles, as exemplified by the addition of secondary phosphine selenides to 3,7-dimethyl-2,6-octadienal, which results in polyfunctional products (*69*). Secondary phosphines can be prepared from red phosphorus and styrene or 2-vinylnaphthalene in one step under superbasic conditions (*70*–*72*). Treating phosphine with 1-(*tert*-butyl)-4-vinylbenzene in potassium hydroxide–DMSO in the presence of a small quantity of water at 70–120 °C for 3 h provides *bis*[4-(*tert*-butyl)phenethyl]phosphine and *tris*[4-(*tert*-butyl) phenethyl]phosphine (Fig. 6.12.1) (*71*). No reaction occurs in the absence of potassium hydroxide, confirming a nucleophilic addition mechanism presumed to be mediated by the phosphide anion formed from phosphine. The reaction usually gives a mixture of secondary and tertiary phosphines, but conditions for selective preparation can be elaborated. Selective 4-*tert*-butylphenethylation of phosphine occurs at 70–120 °C in the KOH–DMSO system in the presence of water (1.5 wt%). *Bis*- and *tris*-[4-(*tert*-butyl)phenethyl]phosphine react with selenium to give the corresponding selenides (**106**–**107**). *Bis*[2-(2-substituted aryl or heteroaryl)ethyl]phosphine selenides (**108**–**110**) are obtained similarly (Fig. 6.12.2) (*73*–*75*).

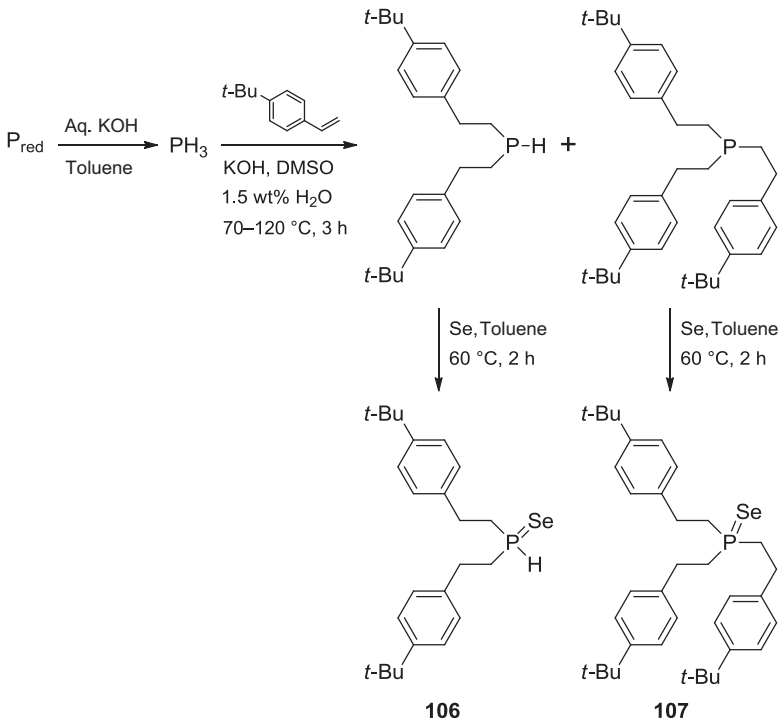


Figure 6.12.1

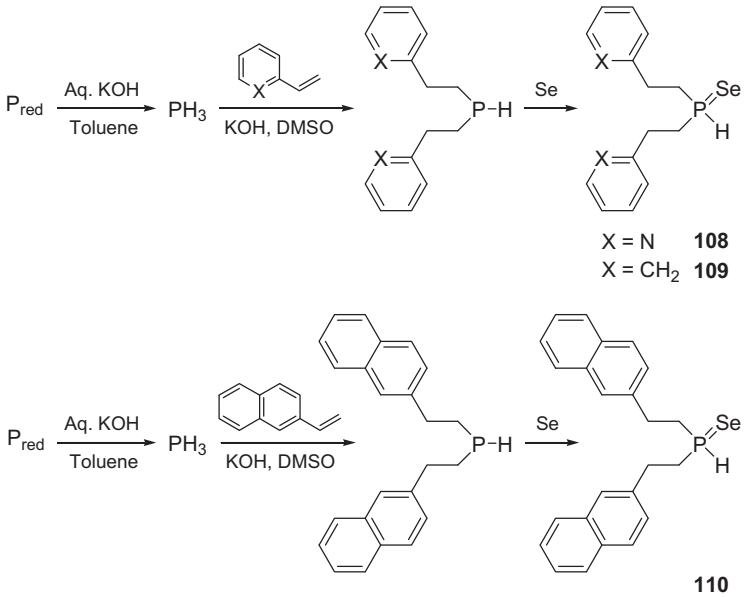


Figure 6.12.2

▶ *Bis[4-(tert-butyl)phenethyl]phosphine selenide* (**106**) (*70—72*). Red phosphorus (15.5 g, 0.5 mol) and toluene (50 ml) were placed in a 500-ml three-necked flask fitted with a gas inlet, a pressure-equalizing dropping funnel, a magnetic stirrer, a reflux condenser and a gas outlet. An aqueous solution of 50 wt% KOH (50 g, 0.893 mol) was added to the dropping funnel. The flask was connected via a wash bottle containing a mixture of aqueous KOH and DMSO to a 200-ml four-necked flask containing KOH—DMSO—H_2O. This second flask was equipped with an efficient mechanical stirrer, a gas-inlet tube and a dropping funnel containing a mixture of the styrene and DMSO, and a gas-outlet and thermometer. The outlet was connected to another wash bottle containing an aqueous solution of $CuSO_4$. The contents of the first flask were refluxed to 60—70 °C, those of the second flask to 70 °C. The rate of addition was adjusted so that phosphine was evolved at a rate of 45—50 bubbles per minute. The addition of the styrene—DMSO mixture was started 10 min after evolution of phosphine began. A solution of 1-(*tert*-butyl)-4-vinylbenzene (7.7 g, 51.8 mmol) in DMSO (5 ml) was added dropwise over 2 h to a stirred suspension of KOH (10.0 g, 178.6 mmol), DMSO (40 ml) and water (1.5 ml), blanketed by argon and saturated with phosphine, at 70 °C with continuous bubbling of phosphine. The mixture was heated at that temperature for an additional 1 h while continuing the flow of phosphine. The phosphine feed was then stopped. The mixture was purged with argon, cooled, diluted with water, dried (K_2CO_3), the benzene was distilled off, and the residue was fractionated under vacuum to recover 1-(*tert*-butyl)-4-vinylbenzene (2.1 g). The residue was washed with hexane (10 ml) and dried under vacuum to furnish *bis*[(4-(*tert*-butyl)phenethyl)] phosphine as a colourless powder (6.0 g, 87%). Mp 138—139 °C. δ_P −68.7 ppm (s, $J_{P,H}$ 195.93 Hz). To a 100-ml three-necked flask equipped with a reflux condenser, a calcium chloride tube, a dropping

funnel, a thermometer, and a bubbler, charged with toluene (30 ml) and selenium (0.79 g, 10 mmol), a solution of *bis*[4-(*tert*-butyl)phenethyl]phosphine (3.54 g, 10 mmol) in toluene (20 ml) was added. The stirred suspension was boiled for 2 h, the solvent was removed under vacuum and the residue was left to crystallise for 72–80 h. The product was rinsed with ethanol (3 × 1.5–2.0 ml) to give the title compound as a colourless powder (3.95 g, 91%). Mp 93–95 °C. δ_P 3.4 ppm (s, $J_{P,H}$ 433 Hz, $J_{P,Se}$ 706.9 Hz). δ_{Se} −417.8 ppm (d, $J_{P,Se}$ 707 Hz).

6.13 TERTIARY PHOSPHINE SELENIDES $R_3P{=}Se$

Tertiary phosphine selenides are prepared by treating the appropriate tertiary phosphine with selenium (*54*,*76*,*77*), KSeCN (*29*) or organic diselenides (*76*,*77*). Preparation of a phosphine selenide from the appropriate tertiary phosphine and selenium often requires numerous extractions to obtain pure material (*78*). An efficient route to arylphosphine selenides from reaction of tertiary phosphines with KSeCN has been reported (*29*). The reaction of triarylphosphines with KSeCN in acetonitrile rapidly produces quite pure triarylphosphine selenides (**111a–f**) in high yield (Fig. 6.13.1) (*79*,*80*).

$$Ar_3P + KSeCN \xrightarrow{MeCN} \underset{\textbf{111a–f}}{Ar_3P{=}Se} + KCN$$

No.	Ar (or P=Se product)	Yield (%)	Mp (°C)	$\nu_{P=Se}$ (/cm)
111a	Ph	96	187–188	562
111b	*p*-MeC_6H_4	95	198	544
111c	*m*-MeC_6H_4	94	139–140	574
111d	$Me_2N(CH_2)_3P(Se)Ph_2$	87	90–91	532
111e	$Ph_2P(Se)(CH_2)_2P(Se)Ph_2$	84	194–195	539
111f	$CH_2{=}CHCH_2P(Se)Ph_2$	89	78–79	–

Figure 6.13.1

▶ *Triphenylphosphine selenide* (**111a**, TPPSe-1) (*29*). Triphenylphosphine (13.1 g, 50 mmol) dissolved in warm anhydrous acetonitrile (60 ml) was added rapidly to a solution of KSeCN (7.2 g, 50 mmol) in anhydrous acetonitrile (60 ml). A white crystalline product began to precipitate immediately. The mixture was stirred for 1 h and the solvent was evaporated. The solid residue was transferred to a sintered glass funnel and was washed with distilled water (300 ml) to remove the potassium cyanide, and with cold absolute ethanol (10 ml), and finally with anhydrous ether. The crude product was dried under vacuum over P_4O_{10} for 1 h to give TPPSe-1 (16.4 g, 96%). Recrystallisation from absolute ethanol gave small white crystals. Mp 187–188 °C. IR (P=Se) 562/cm.

Exchange reactions can be used to obtain tertiary phosphine selenides. The reaction of $Ph_2P(Se)CH_2P(Se)Ph_2$ and $Ph_2PCH_2PPh_2$ at room temperature immediately affords $Ph_2P(Se)CH_2PPh_2$ (**112**) quantitatively (Fig. 6.13.2) (*81*,*82*). Mixtures of ethylene-bridged analogues react equally quickly and

produce a mixture of **113**, **114** and **115** in a 1:2:1 ratio. The difference in the equilibrium positions between mixtures of the methylene and ethylene reactants is due presumably to the more electron-deficient P(V) atom in $Ph_2P(Se)CH_2PPh_2$ deactivating its P(III) atom, whereas the phosphorus atoms in $Ph_2P(Se)CH_2CH_2PPh_2$ are separated by two CH_2 groups, lessening the effect. The effect operates in some compounds with NR groups as bridges: $Me_2NP(\mu\text{-N-}t\text{-Bu})_2PNMe_2$ and Me_2N-$P(Se)(\mu\text{-N-}t\text{-Bu})_2P(Se)NMe_2$ when mixed produce quantitatively the cyclodiphosphazine monoselenide $Me_2NP(Se)(\mu\text{-N-}t\text{-Bu})_2PNMe_2$ *(83)*.

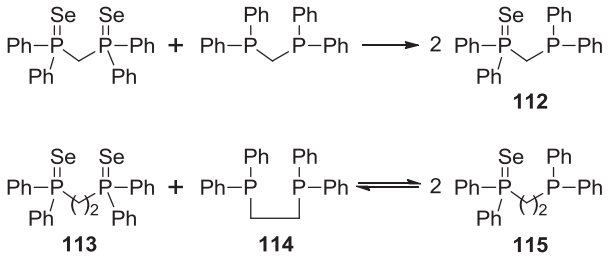


Figure 6.13.2

The alkylation of secondary phosphine selenides was first reported by Trofimov *(83)*. Treating di(2-phenethyl)phosphine selenide with methyl iodide in the presence of an equimolar amount of potassium hydroxide in THF at room temperature gives the tertiary phosphine selenide (**116**) in good yield (Fig. 6.13.3) *(84)*. This suggests that alkylation of secondary phosphine selenides may provide an opportunity to prepare some difficult-to-access and unsymmetrical phosphine selenides in satisfactory yields under mild conditions.

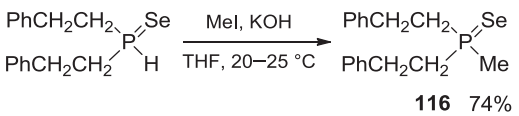
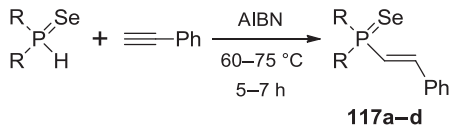


Figure 6.13.3

▶ *Methyl[di(2-phenethyl)]phosphine selenide* (**116**) *(84)*. A solution of di(2-phenethyl)phosphine selenide (0.321 g, 1.0 mmol) in THF (1.0 ml) was added to a stirred suspension of ground potassium hydroxide (0.056 g, 1.0 mmol) in THF (0.5 ml). Dry argon was bubbled through the mixture, and iodomethane (0.141 g, 1.0 mmol) in THF (0.5 ml) was added dropwise over 3 min. The mixture was stirred for 3.5 h at room temperature and was diluted with water (2.5 ml) and extracted with chloroform (3 × 2.5 ml). The chloroform extracts were dried (Na_2SO_4) and the solvent was removed to give a yellow liquid (0.25 g, 74%). δ_P 28.6 ppm (s, $J_{P,Se}$ 694 Hz). δ_{Se} −341.6 ppm (d, $J_{P,Se}$ 695 Hz).

A facile stereoselective free-radical addition of secondary phosphine selenides to aromatic and heteroaromatic alkynes to give dialkyl(alkenyl)phosphine selenides has been developed (*85*). In the presence of azobisisobutyronitrile (AIBN) the secondary phosphine selenides add to the alkynes to provide anti-Markovnikov adducts (**117a**–**d**) with predominantly *Z*-configuration (up to 97%) (Fig. 6.13.4). No noticeable substituent effect on the product yield was found despite the remarkable difference in the structures of the secondary phosphine selenides studied. For the most bulky phosphine selenide (**117c**) the *Z*-isomer composition in the adduct mixture was 75% due presumably to steric compression.



Dialkyl or diaryl (alkenyl)phosphine selenides

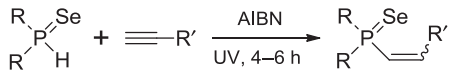
No.	R	Time [a] (h)	Yield [b] (%)	*Z*-isomer
117a	Ph	5	75	97
117b	$PhCH_2CH_2$	5	70	91
117c	4-*t*-$BuC_6H_4CH_2CH_2$	5	80	75
117d	2-$PyCH_2CH_2$	7	60	95

a. Reaction time. *b*. Isolated yield

Figure 6.13.4

▶ *Disubstituted (alkenyl)phosphine selenides* (**117a**–**d**) *in the presence of AIBN at 65–70 °C* (*85*). A mixture of the secondary phosphine selenide and aromatic or heteroaromatic alkyne (1:3 mol ratio) and AIBN (2 mass%) was stirred under argon at 65–70 °C. The reaction was monitored by ^{31}P NMR spectroscopy, which revealed the disappearance of peaks for the secondary phosphine selenides at ~2–5 ppm and the appearance of new peaks at ~22–35 ppm for the tertiary alkenylphosphine selenides. The excess alkyne was removed under vacuum, and the residue was washed twice with small amounts of ether, and dried to afford the title compounds.

Microwave irradiation (600 W) of the mixture of secondary phosphine selenides with alkynes for 4–6 h also provided dialkyl(alkenyl)phosphine selenides (**117a**,**c**,**e**–**g**) in 53–80% isolated yields (*85*). However, UV-irradiation caused rapid *Z*- to *E*-isomerisation of the products and the stereoselectivity was lower (Fig. 6.13.5).



117a,c,e–g

Dialkyl or diaryl (alkenyl)phosphine selenides

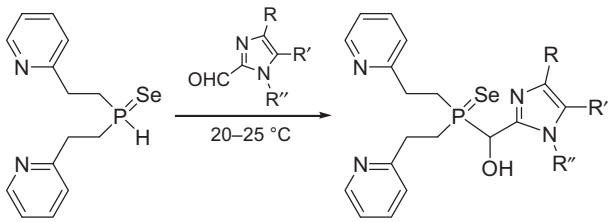
No.	R	R′	Time [a] (h)	Yield [b] (%)	*E*:*Z*
117a	Ph	Ph	4	80	60:40
117c	4-*t*-$BuC_6H_4CH_2CH_2$	Ph	4	65	60:40
117e	Ph	2-naphthyl	4	53	60:40
117f	2-$PhCH_2CH_2$	2-naphthyl	5	74	50:50
117g	2-$PhCH_2CH_2$	2-furyl	6	60	35:65

a. Reaction time. *b*. Isolated yield

Figure 6.13.5

▶ *Disubstituted (alkenyl)phosphine selenides* (**117a**,**c**,**e**–**g**) *in the presence of AIBN under UV-initiation* (*85*). An equimolar mixture of the secondary phosphine selenide and aromatic or heteroaromatic alkyne in dioxane was placed in a quartz ampoule under argon and irradiated using a 200 W Hg arc lamp for 4–6 h. The solvent was removed under vacuum; the residue was washed twice with small amounts of ether and dried to give the product.

Nucleophilic addition of secondary phosphine selenides to aldehydes leads readily to tertiary phosphine selenides (*74*). Treating *bis*[2-(2-pyridyl)ethyl]phosphine selenide with certain 1*H*-imidazole-based aldehydes at room temperature delivers the tertiary phosphine selenides (**118a**–**c**) in good yield (Fig. 6.13.6).



R = Et	R′ = R″ = H	**118a**	79%
R = vinyl	R′ = R″ = H	**118b**	81%
R = vinyl	R′ + R″ = $(CH_2)_4$	**118c**	78%

Figure 6.13.6

▶ *Bis[2-(2-pyridyl)ethyl]-α-imidazole phosphine selenides* (**118a**–**c**) (*74*). A mixture of *bis*[2-(2-pyridyl)ethyl]phosphine selenide (0.323 g, 1.0 mmol) and the appropriate aldehyde (1.1 mmol) in anhydrous THF (2 ml) was purged with argon and stirred at room temperature for 3 h. The solvent

was removed and the residue was washed with ethanol (3 × 0.3 ml) and dried under vacuum to give the title compounds as viscous liquids, soluble in chloroform, acetone and DMSO.

6.14 DISUBSTITUTED PHOSPHINOCHLORIDOSELENONATES $R_2P(Se)Cl$

Alkyl or aryl phenylphosphinochloridoselenonates (**119**) and (**120a–b**) are obtained by treating phenyldichlorophosphine with Grignard reagents and selenium or by treating phosphorus trichloride successively with two different Grignard reagents and selenium (Fig. 6.14.1) (*86*).

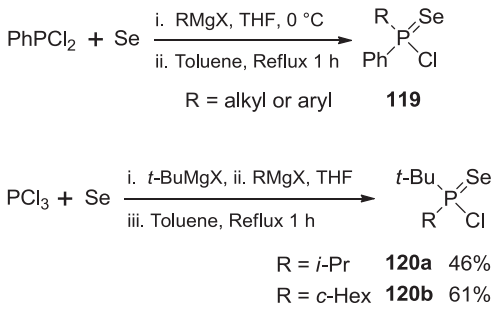


Figure 6.14.1

▶ *Alkyl(phenyl)phosphinochloridoselenonates Ph(R)P(Se)Cl* (**119**) (*86*). Phenyldichlorophosphine (1.09 ml, 8.00 mmol) was added to a stirred suspension of selenium (0.695 g, 8.80 mmol) in THF (40 ml) at room temperature under argon. To this was added RMgCl (8.00 mmol) in THF (36 ml) dropwise over 1 h at 0 °C with stirring. After the solvent was removed, toluene (20 ml) was added to the residue. The mixture was heated under reflux in toluene for 1 h and insoluble material was filtered off. The solvent was removed and the residue was purified by column chromatography on silica gel, eluting with hexane–dichloromethane.

▶ *Alkyl(tert-butyl)phosphinochloridoselenonates t-Bu(R)P(Se)Cl* (**120a–b**) (*86*). Phosphorus trichloride (0.872 ml, 10.0 mmol) was added to a stirred suspension of selenium (0.868 g, 11.0 mmol) in THF (50 ml) at room temperature under argon. To this was added *t*-BuMgCl (1.0 mol/l in THF, 10.0 ml, 10.0 mmol) in THF (40 ml) dropwise over 1 h at 0 °C. The mixture was stirred at room temperature for 2 h. To it was added RMgCl (10 mmol) in THF (45 ml) dropwise over 1 h at 0 °C. Again the mixture was stirred at room temperature for 2 h. The solvent was removed and toluene (25 ml) was added to the residue. The mixture was heated under reflux in toluene for 1 h and insoluble material was filtered off. After the solvent was removed, the residue was purified by column chromatography on silica gel, eluting with hexane–dichloromethane, and gel permeation chromatography eluting with chloroform, to give the title compounds.

6.15 DISELENOPHOSPHINOIC ACID SALTS $R_2P(Se)SeM$

The chemistry of diselenium—phosphorus compounds is of interest due to their unique properties (*87—89*). Alkali metal derivatives have been used widely as intermediates for the preparation of conducting nanomaterials (*88—90*), as precursors for vapour deposition processes for semiconducting films (*91—104*), as extractants for rare earth and transuranic elements (*91,97,105—108*), as biologically active compounds (e.g. antimicrobials) (*109*) and as versatile building blocks in organic synthesis (*88,110—112*).

Conventional syntheses of dialkyl diselenophosphinate salts are based on the reactions of disubstituted phosphinochloridoselenonates $R_2P(Se)Cl$ or monochlorophosphines R_2PCl with sodium selenide Na_2Se or polyselenides Na_xSe_y. However, these methods have limitations. Sodium diethyl diselenophosphinate (**121**), the first representative of a family of such compounds, was prepared as a dihydrate in an overall yield of 34% by a multistep route (Fig. 6.15.1) (*112*). The key reagent sodium hydroselenide was prepared from hydrogen selenide and sodium ethoxide.

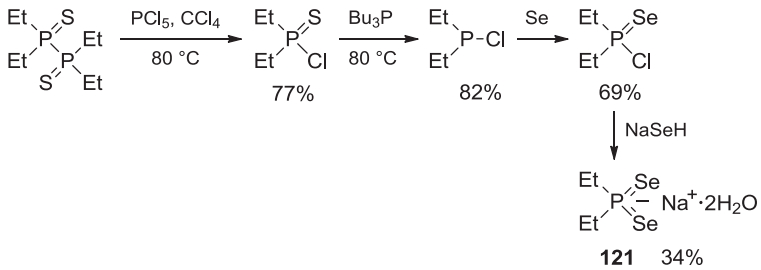


Figure 6.15.1

Treating diphenylphosphinochloridoselenonate (prepared from diphenylchlorophosphine and selenium) with a molar equivalent of sodium hydroselenide gives sodium diphenyldiselenophosphinate (**122**) in 65% yield (Fig. 6.15.2) (*103*). Note that the oxidation of diphenylchlorophosphine requires the use of the more reactive red selenium (obtained from the action of reducing agents such as formalin, hydrazine or sulfur dioxide on selenous acid H_2SeO_3) instead of amorphous grey selenium.

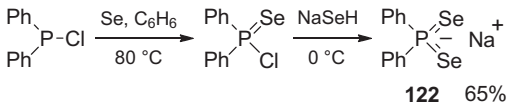


Figure 6.15.2

▷ *Sodium diphenyldiselenophosphinate $Ph_2P(Se)SeNa$* (**122**) (*103*). Red selenium (2.0 g, 25 mmol) was added to a solution of freshly distilled diphenylchlorophosphine (4.4 g, 20 mmol) in benzene (50 ml). The suspension was stirred for 4—6 h under nitrogen and cooled. The black selenium that formed was filtered off. Red selenium (2.0 g, 25 mmol) was added to the filtrate and the reaction was repeated. The

solution was cooled to 0 °C and added dropwise to a solution of sodium hydroselenide in ethanol. The mixture was heated on a water bath and allowed to stand overnight. The crystals that precipitated were recrystallised from acetone—hexane, washed with ether and dried to give the product (4.8 g, 65%).

Treatment of *tert*-butyl(phenyl)phosphinochloridoselenonate with Na_2Se (instead of NaSeH) in acetonitrile gives sodium *tert*-butyl(phenyl)diselenophosphinate (**123**). This reacts with iodomethane to afford the *Se*-methyl ester (**124**) in excellent yield (Fig. 6.15.3) (*86*).

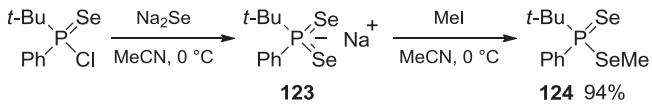


Figure 6.15.3

▶ *Methyl tert-butyl(phenyl)diselenophosphinate t-Bu(Ph)P(Se)SeMe* (**124**) (*86*). *t*-Bu(Ph)P(Se)Cl (0.140 g, 0.50 mmol) was added to a suspension of Na_2Se (0.069 g, 0.55 mmol) in acetonitrile (5 ml) at 0 °C. The mixture was stirred at 0 °C for 4 h. After insoluble material was filtered off, iodomethane (1.0 mmol) was added to the filtrate at 0 °C, and the mixture was stirred at that temperature for 1 h. The mixture was quenched with water and extracted with ether (20 ml). The organic layer was dried ($MgSO_4$) and concentrated. Column chromatography of the residue on silica gel, eluting with hexane-ether, gave a pale yellow liquid (0.159 g, 94%).

Using monochlorophosphines R_2PCl instead of phosphinochloridoselenonates $R_2P(Se)Cl$ as precursors is preferable for the synthesis of sodium diselenophosphinates. A protocol for their preparation based on monochlorophosphine R_2PCl and sodium polyselenide Na_xSe_y has been developed (*113*). Polyselenide Na_xSe_y, prepared from sodium metal and selenium in liquid ammonia, reacted with diphenylchlorophosphine to form a mixture of products, from which sodium diphenyldiselenophosphinate (**125**) was isolated (Fig. 6.15.4).

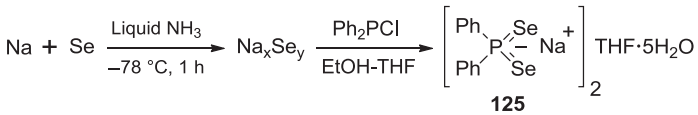


Figure 6.15.4

▶ *Synthesis of* $(Ph_2PSe_2Na)_2 \cdot THF \cdot 5\ H_2O$ (**125**) (*113*). Sodium (0.80 g, 35 mmol) and selenium (3.95 g, 50 mmol) were added gradually to liquid ammonia (10 ml) at −78 °C and stirred together for 1 h before warming to room temperature, whereupon the ammonia evaporated. Ethanol (10 ml) and THF (15 ml), followed by Ph_2PCl (7.72 g, 35 mmol), were added and the mixture was stirred at room temperature overnight. Addition of hexane enabled the isolation of crystals of the title compound.

The reproducible syntheses of triethylammonium salts of disubstituted diselenophosphinates (**126a–c**) in high yield are further examples of the use of disubstituted chlorophosphine-starting materials (Fig. 6.15.5) (*92*). These syntheses require triethylsilane, triethylamine and selenium. Excess triethylsilane and triethylamine are used to deliver the $R_2P(Se)Se^-$ species. Triethylsilane is used instead of trichlorosilane because the latter reacts readily with triethylamine to precipitate triethylammonium chloride, making selenium insertion difficult. The synthesised ionic compounds are air and moisture stable and dissolve in most common organic solvents.

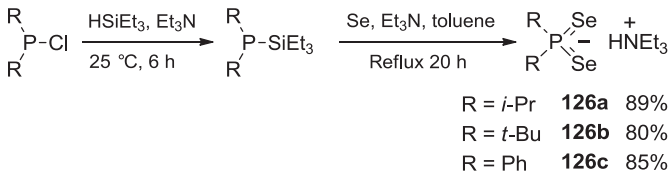


Figure 6.15.5

▶ *Triethylammonium salts of disubstituted diselenophosphinates* (**126a–c**) (*92*). R_2PCl (30 mmol) and $HSiEt_3$ (9.6 ml, 60 mmol) were dissolved in cold dry toluene (150 ml) under nitrogen followed by triethylamine (8.3 ml, 60 mmol). The mixture was stirred at room temperature for 6 h to give a white cloudy precipitate. Grey selenium powder (4.7 g, 60 mmol) was added and the solution was heated under reflux for 20 h, giving a dark red solution and white precipitate. Upon cooling to room temperature the white precipitate was filtered off. The filtrate was reduced to ~50 ml and kept at 0 °C to produce yellow crystals. These were collected by filtration and washed with cold hexane to give **126a** (10.0 g, 89%), δ_P 64.9 ppm (s, $J_{P,Se}$ 574 Hz); **126b** (9.6 g, 80%), δ_P 92.3 ppm (s, $J_{P,Se}$ 567 Hz) and **126c** (13.4 g, 85%), δ_P 20.5 ppm (s, $J_{P,Se}$ 602 Hz).

Novel methods for the synthesis of diselenophosphinate salts based on the reactions of *P*-nucleophilic organophosphorus compounds, such as R_2PM, R_2PH or $R_2P(Se)H$, with selenium have been developed in recent years. The synthesis of alkali metal diselenophosphinates from alkali metal diorganophosphides and selenium was first accomplished by Davies et al. in 2002 (*87*). Treating Ph_2PH with *n*-butyllithium, selenium and *N,N,N′,N′*-tetramethylethylene-1,2-diamine (TMEDA) gives $[Ph_2PSeLi.TMEDA]_2$ (**127**), which is transformed by treatment with another molar equivalent of selenium to $[Ph_2P(Se)SeLi.TMEDA.THF]$ (**128**) (Fig. 6.15.6). This complex was isolated as a colourless air-sensitive crystalline solid. Its ^{31}P NMR spectrum showed a single peak with ^{77}Se satellites and a $^1J_{PSe}$ coupling of 585 Hz; the doublet in the ^{77}Se NMR spectrum was downfield at δ −41 ppm.

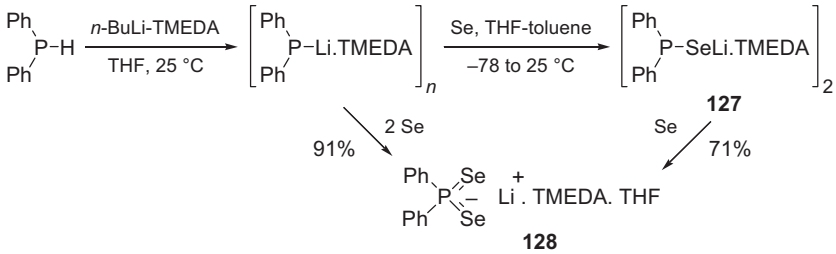


Figure 6.15.6

▶ *Synthesis of $Ph_2P(Se)SeLi.TMEDA.THF$* (**128**) (*87*). *n*-Butyllithium (1.6 M in hexane, 3.2 ml, 5 mmol) was added to diphenylphosphine (0.86 ml, 5 mmol) and TMEDA (0.75 ml, 5 mmol) in toluene (2 ml) and THF (4 ml) and treated with a suspension of grey selenium powder (0.80 g, 10 mmol) in toluene (4 ml) at −78 °C. The mixture was warmed to room temperature to afford a clear yellow solution from which crystals of the title compound (2.46 g, 91%) grew over 24 h.

Potassium diphenylphosphide Ph_2PK also reacts with selenium to provide diselenophosphinate salts. The THF solvate of potassium diphenyldiselenophosphinate (**129**) is obtained from potassium diphenylphosphide and 2 molar equivalents of grey selenium powder in THF−toluene (Fig. 6.15.7) (*88*). Using modified methods, potassium diphenyldiselenophosphinate monohydrate (**130**) and anhydrous form (**131**) are synthesised from potassium diphenylphosphide and selenium (*111*,*114*).

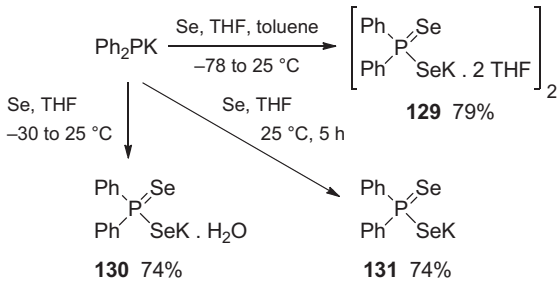


Figure 6.15.7

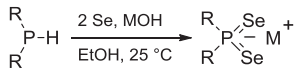
▶ *Synthesis of $[Ph_2P(Se)SeK\cdot 2\ THF]_2$* (**129**) (*88*). Ph_2PK (5 ml, 0.5 M in THF, 2.5 mmol) was added to a stirred suspension of selenium (0.39 g, 5 mmol) in toluene (5 ml) and THF (2 ml) at −78 °C. The resulting mixture was allowed to warm to room temperature to give a clear yellow solution. Crystals of the title compound (0.52 g, 79%) were grown from this at −30 °C over 24 h.

▶ *Synthesis of $Ph_2P(Se)SeK\cdot H_2O$* (**130**) (*111*). Grey selenium powder (0.155 g, 2 mmol) was added to a suspension of potassium diphenylphosphine (5 M in 10 ml of THF, 0.9 mmol) and the mixture was stirred for 6 h under argon at −30 °C. The mixture was filtered and the filtrate was concentrated. Crystallisation from hexane gave white crystals (74%).

▶ *Synthesis of $Ph_2P(Se)SeK$* (**131**) (*114*). Potassium *tert*-butoxide (1.18 g, 11.0 mmol) and diphenylphosphine (1.86 g, 10.0 mmol) in THF (100 ml) were combined in a round-bottomed flask under argon. The solution coloured red and was stirred for 2 h at room temperature. Selenium (1.58 g, 20 mmol) was added and agitation was continued for 5 h at room temperature; the solution turned yellow. The mixture was filtered to remove unreacted selenium and the filtrate was concentrated. Reprecipitation with hexane gave a white solid (2.82 g, 74%).

Recently a one-pot method for the synthesis of alkali metal (Li, Na, K, Rb, Cs) diselenophosphinates from secondary phosphines, selenium and alkali metal hydroxides was reported

(*115*). The reaction was conducted in ethanol at room temperature to afford alkali metal salts of diselenophosphinates (**131**,**132a–o**) in high yield (Fig. 6.15.8).



131,132a–o

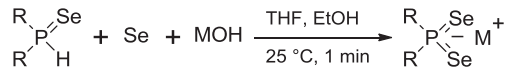
Alkali metal salts of disubstituted diselenophosphinates

No.	R	M	Yield (%)	Mp (°C)	δ_P (ppm)	$^1J_{P,Se}$ (Hz)
131	Ph	K	92	134–136	21.6	583
132a	$PhCH_2CH_2$	Li	93	99–100	26.7	556
132b	$PhCH_2CH_2$	Na	97	182–184	26.8	559
132c	$PhCH_2CH_2$	K	95	209 211	26.5	557
132d	$PhCH_2CH_2$	Rb	92	202–204	26.6	559
132e	$PhCH_2CH_2$	Cs	98	187–189	26.9	555
132f	$PhCH(Me)CH_2$	K	88	198–200	25.9, 27.0	557, 559
132g	$PhCH(Me)CH_2$	Rb	97	180–182	24.9, 26.0	550, 557
132h	$PhCH_2CHMe$	K	81	>200	67.6, 67.8	569, 571
132i	4-*t*-$BuC_6H_4CH_2CH_2$	K	92	185–187	25.4	559
132j	4-$MeOC_6H_4CH_2CH_2$	K	89	190–193	27.1	558
132k	2-Naphthyl-CH_2CH_2	K	94	192–194	23.8	613
132l	6-Me-3-$PyCH_2CH_2$	Cs	96	189–191	26.2	563
132m	4-$PyCH_2CH_2$	Na	93	>200	28.3	566
132n	2-Furyl-CH_2CH_2	Cs	96	200–202	26.1	565
132o	Ph	Cs	94	224–226	21.8	582

Figure 6.15.8

▶ *Alkali metal diselenophosphinates* (**131**,**132a–o**) (*115*). A mixture of $MOH \cdot n\ H_2O$ ($n = 0$ for M = Li or Na; $n = 0.5$ for M = K; $n = 1$ for M = Rb or Cs; 1.0 mmol) in ethanol (5 ml) and amorphous grey selenium (0.158 g, 2.0 mmol) were added sequentially to a solution of the appropriate secondary phosphine (1.05 mmol) in ethanol (6 ml) at room temperature under argon. The suspension was stirred vigorously at room temperature until the selenium dissolved completely. The colourless solution was filtered and concentrated. The residue was ground in ether (10 ml) and the solvent was decanted to give, after washing with ether (10 ml) and drying under vacuum, the title compounds as white crystalline powders.

Alkali metal diselenophosphinates can be obtained from a three-component reaction between secondary phosphine selenides, selenium and alkali metal hydroxides (*73*,*116*). The secondary phosphine selenides $R_2P(Se)H$ (R = Ph, $PhCH_2CH_2$, $PhCH(Me)CH_2$, 4-$MeOC_6H_4CH_2CH_2$, and 2-naphthyl-CH_2CH_2) reacted with Se and MOH (M = Li, Na, K, Rb, Cs) in THF–ethanol at room temperature. The alkali metal diselenophosphinates (**131**,**132a–e**,**g**,**j**,**k**) were obtained in 94–100% yield (Fig. 6.15.9). The proposed mechanism involves deprotonation of the secondary phosphine



131,132a–e,g,j,k

Alkali metal salts of disubstituted diselenophosphinates

No.	R	M	Yield (%)
131	Ph	K	95
132a	$PhCH_2CH_2$	Li	96
132b	$PhCH_2CH_2$	Na	97
132c	$PhCH_2CH_2$	K	100
132d	$PhCH_2CH_2$	Rb	98
132e	$PhCH_2CH_2$	Cs	98
132g	$PhCH(Me)CH_2$	Rb	97
132j	$4\text{-}MeOC_6H_4CH_2CH_2$	K	100
132k	$2\text{-Naphthyl-}CH_2CH_2$	K	94

Figure 6.15.9

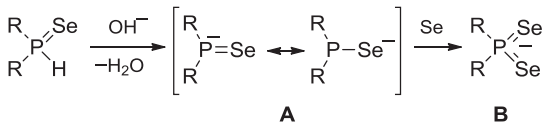


Figure 6.15.10

selenide by hydroxide to provide anion **A**, which cleaves the Se—Se bond of selenium, to yield the diselenophosphinate anion **B** (Fig. 6.15.10).

▶ *Alkali metal bis(2-aryl)diselenophosphinates* (**131**,**132a—e**,**g**,**j**,**k**) (*73*). Amorphous grey selenium (0.049 g, 0.623 mmol) was added to a solution of the appropriate secondary phosphine selenide (0.623 mmol) in THF (2 ml) under argon, followed by MOH (0.623 mmol) in absolute ethanol (6 ml). The selenium dissolved instantly (∼20—30 s) to give a colourless transparent solution. The solvent was removed and the residue was dissolved in ether (2 ml). Evaporation of the ether under vacuum (1 mmHg, room temperature) gave the alkali metal salts.

The synthesis of ammonium disubstituted diselenophosphinates is conducted by treating the secondary phosphine selenides with selenium and ammonia (*117*). The reaction proceeds readily in aqueous ethanol at room temperature and delivers products (**133a—b**) in high yield (Fig. 6.15.11). *Bis*(2-phenethyl)phosphine selenide reacts similarly with hydrazine hydrate in warm ethanol to yield the hydrazinium diselenophosphinate (**134**) (*110*).

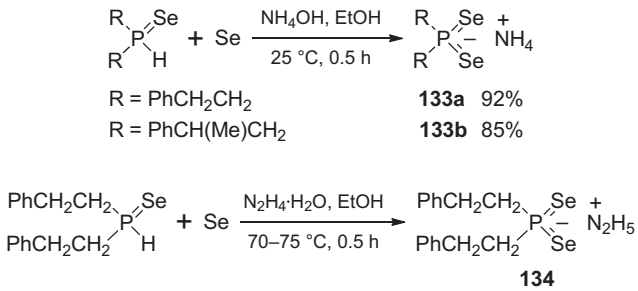
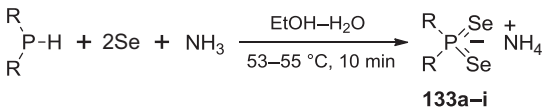


Figure 6.15.11

▶ *Ammonium bis(2-phenethyl)diselenophosphinate* (**133a**) (*117*). Grey selenium (0.08 g, 1.0 mmol) and 25% aqueous ammonia (0.12 ml, 1.6 mmol) were added to a stirred solution of *bis*(2-phenethyl) phosphine selenide (0.32 g, 1.0 mmol) in ethanol (8 ml) at room temperature. After 30 min, the mixture was filtered and the filtrate was evaporated. The residue was ground in hexane (2 × 10 ml), the hexane was decanted and the residue was dried under vacuum to afford the product (0.38 g, 92%).

▶ *Hydrazinium bis(2-phenethyl)diselenophosphinate* (**134**) (*110*). Amorphous grey selenium (0.079 g, 1.0 mmol) was added to a stirred solution of *bis*(2-phenethyl)phosphine selenide (0.321 g, 1.0 mmol) and hydrazine hydrate (0.051 g, 1.0 mmol) in ethanol (10 ml) at room temperature. The mixture was stirred for 30 min at 70—75 °C and filtered. The solvent was removed and the residue was washed with ether (2 × 10 ml) and dried under vacuum to give the title species.

An efficient method for the synthesis of ammonium disubstituted diselenophosphinates has been developed from secondary phosphines (*118*). These react readily with selenium and aqueous ammonia in warm ethanol (*method 1*) or with selenium and liquid ammonia in ethanol at room temperature (*method 2*) to provide ammonium salts **133a—i** in high yields (Fig. 6.15.12). The salts are powders, stable under argon and soluble in organic solvents such as alcohols, DMSO, dioxane and THF.



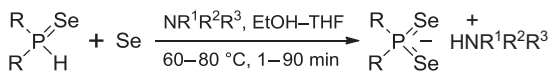
Ammonium salts of dialkyl or diaryl diselenophosphinates

No.	R	Yield (%) method 1	Yield (%) method 2	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
133a	$PhCH_2CH_2$	94	96	24.3	–36	616
133b	$PhCH(Me)CH_2$	87	85	22.9, 24.1	–23, –23	607
133c	$PhCH_2CH(Me)$	76	–	63.5, 63.9	–160, –158, –156	584
133d	4-*t*-$BuC_6H_4CH_2CH_2$	–	88	26.8	–48	640
133e	4-$MeOC_6H_4CH_2CH_2$	89	88	24.0	–35	608
133f	4-$PyCH_2CH_2$	95	–	24.2	–51	616
133g	2-Me-5-$PyCH_2CH_2$	93	95	26.4	–63	564
133h	2-Furyl-CH_2CH_2	92	92	23.0	–42	607
133i	Ph	94	89	23.6	15	631

Figure 6.15.12

▶ *Ammonium disubstituted diselenophosphinates* (**133a–i**) (*118*). *Method 1.* 25% Aqueous ammonia (0.12 ml, 1.6 mmol) and amorphous grey selenium (0.158 g, 2.0 mmol) were added consecutively to a solution of the secondary phosphine (1.0 mmol) in ethanol (10 ml) at room temperature under argon. The suspension was stirred vigorously at 53–55 °C until the selenium disappeared. The colourless solution was filtered and the filtrate was dried under vacuum. The residue was ground in hexane (10 ml). The hexane was decanted; the white powder was washed with more hexane (10 ml) and dried to afford the product. *Method 2.* Liquid ammonia (0.04 ml, 1.6 mmol) and selenium (0.158 g, 2.0 mmol) were added consecutively to a solution of the secondary phosphine (1.0 mmol) in ethanol (10 ml) at room temperature under argon. The suspension was stirred vigorously until the selenium disappeared. The colourless solution was filtered and the filtrate was dried. The residue was ground in hexane (10 ml). The latter was decanted; the white powder was washed with more hexane (10 ml) and dried to give the product.

One-pot reaction of secondary phosphine selenides with selenium and nitrogen bases can provide new diorganodiselenophosphinates. The reaction of a secondary phosphine selenide, selenium and an amine (primary, secondary, tertiary, or a diamine) proceeds under mild conditions in THF–ethanol to give mono-, di-, and triorganoammonium salts of diorganodiselenophosphinates (**126c**,**135a–l**) in high yields (Fig. 6.15.13) (*119*).



126c,135a–l

Mono-, di- and tri-organoammonium salts of diorganodiselenophosphinates

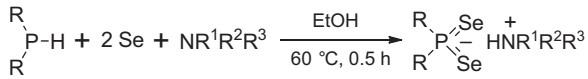
Salt	R	$NR^1R^2R^3$	Time [a] (min)	Yield (%)	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
126c	Ph	Et_3N	50	88	22.1	–24.4	603
135a	$Ph(CH_2)_2$	Et_3N	60	94	24.8	–48.5	575
135b	$Ph(CH_2)_2$	Allyl-NH_2	15	91	24.8	–59.0	556
135c	$PhCH(Me)CH_2$	*i*-Pr_2NH	15	95	24.2, 25.2	–34.9	567, 564
135d	4-*t*-$BuC_6H_4(CH_2)_2$	Et_3N	60	99	25.2	–48.5	572
135e	2-Me-5-$Py(CH_2)_2$	*n*-Pr_2NH	15	87	24.3	–59.0	574
135f	$Ph(CH_2)_2$	*n*-Bu_2NH	50	95	24.5	–45.6	573
135g	$Ph(CH_2)_2$	*n*-Pr_2NH	10	93	25.4	–59.8	566
135h	$Ph(CH_2)_2$	*c*-Hex-NH_2	10	98	24.8	–59.0	558
135i	$Ph(CH_2)_2$	$[HO(CH_2)_2]_3N$	60	79	26.4	–48.1	566
135j	$Ph(CH_2)_2$	$Allyl_3N$	90	90	24.6	–43.9	576
135k	$Ph(CH_2)_2$	DABCO	60	84	25.1	–69.6	571
135l	$Ph(CH_2)_2$	DBU	1	99	25.1	–66.9	583

a. Reaction time. DABCO = 1,4-diazabicyclo[2.2.2]octane. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Figure 6.15.13

▶ *Mono-, di- and trialkylammonium diselenophosphinates* (**126c, 135a–l**) (*119*). Amorphous grey selenium (0.049 g, 0.623 mmol) was added to the secondary phosphine selenide (0.623 mmol) in THF (4 ml) at 85 °C under argon. A solution of the appropriate amine (0.810 mmol) in ethanol (5 ml) was added to the stirred suspension. The suspension was heated until dissolution of selenium occurred (60 min) to give a colourless solution. Upon cooling to room temperature the solvent was removed and the residue was washed with ether (7 ml) and dried to give the title species.

Mono-, di-, and triorganoammonium salts of the diorganodiselenophosphinates can also be obtained from the one-pot reaction of secondary phosphines, selenium and an amine (primary, secondary or tertiary) (*120*,*121*). The reactions are completed under mild conditions and give the diselenophosphinates (**126c**,**135a–e**,**g**,**m–s**) in high yield (Fig. 6.15.14).



126c, 135a–e,g,m–s

Trialkylammonium salts of disubstituted diselenophosphinates

Salt	R	$NR^1R^2R^3$	Yield (%)
126c	Ph	Et_3N	92
135a	$Ph(CH_2)_2$	Et_3N	94
135b	$Ph(CH_2)_2$	Allyl-NH_2	85
135c	$PhCH(Me)CH_2$	*i*-Pr_2NH	87
135d	4-*t*-$BuC_6H_4(CH_2)_2$	Et_3N	85
135e	6-Me-3-$Py(CH_2)_2$	*i*-Pr_2NH	94
135g	$Ph(CH_2)_2$	*n*-Pr_2NH	94
135m	Ph	Allyl-NH_2	97
135n	$Ph(CH_2)_2$	Et_2NH	91
135o	4-$Py(CH_2)_2$	Et_3N	91
135p	2-$Py(CH_2)_2$	Et_3N	89
135q	2-$Py(CH_2)_2$	Allyl-NH_2	94
135r	2-Furyl$(CH_2)_2$	Et_3N	87
135s	2-Furyl$(CH_2)_2$	Allyl-NH_2	96

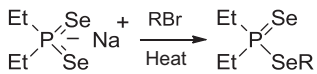
Figure 6.15.14

▶ *Mono-, di- and trialkylammonium diselenophosphinates* (**126c**,**135a–e**,**g**,**m–s**) (*120*,*121*). Amorphous grey selenium (0.158 g, 2.0 mmol) was added to a mixture of the secondary phosphine (1.0 mmol) and aliphatic amine (1.1 mmol) in absolute ethanol (10 ml) at room temperature under argon. The suspension was stirred at 60 °C until the selenium dissolved (~30 min) to give a colourless solution. Upon cooling to room temperature the solvent was removed and the residue was washed with ether (2 × 10 ml) and dried (45 °C/1 mmHg).

6.16 ESTERS OF DISELENOPHOSPHINOIC ACIDS $R_2P(Se)SeR'$

Considerable attention has been paid recently to the preparation of diselenophosphinates $R_2P(Se)SeR'$ (R and R′ = alkyl or aryl) because of their wide applications – for example as agents for Reversible Addition-Fragmentation Chain Transfer (RAFT) polymerisation (*88*,*110–112*,*122*) and as promising candidates for a new generation of pesticides (*123*). Therefore the development of efficient methods of synthesis of such compounds is highly desirable.

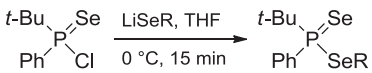
The reaction of diselenophosphinate salts with organohalides represents an efficient method for the synthesis of products of structure $R_2P(Se)SeR'$. So far, only a few reports of the alkylation of diselenophosphinates $R_2P(Se)Se^-$ have been reported (*86*,*112*). Unsurprisingly the method has attracted much attention as the diselenophosphinate salts were for a long time inaccessible. The first examples of diselenophosphinates (**136a–b**) were prepared by the reaction of sodium diethyldiselenophosphinate with ethyl or *n*-propyl bromide (Fig. 6.16.1) (*112*). Unfortunately no experimental details were given. A more recent example is the synthesis of methyl *tert*-butyl(phenyl)diselenophosphinate (**124**) from the reaction of *t*-Bu(Ph)P(Se)SeNa (**123**) with iodomethane (refer to Fig. 6.15.3) (*86*).



R = Et **136a**
R = *n*-Pr **136b**

Figure 6.16.1

Another route to esters of structure $R_2P(Se)SeR$ is the reaction of phosphinochloridoselenonates with organoselenolates. For example, treating *tert*-butyl(phenyl)phosphinochloridoselenonate with a molar equivalent of lithium selenolates in THF gives the diselenophosphinates (**137a–c**) in acceptable yield (Fig. 6.16.2) (*86*).



R = *n*-Bu **137a** 96%
R = *t*-Bu **137b** 66%
R = Ph **137c** 96%

Figure 6.16.2

▶ *Se-n-Butyl tert-butyl(phenyl)diselenophosphinate t-Bu(Ph)P(Se)Se-n-Bu* (**137a**) (*86*). *n*-Butyllithium (1.6 M hexane, 0.625 ml, 1.0 mmol) was added to a stirred suspension of selenium (0.079 g, 1.0 mmol) in THF (5 ml) at 0 °C and the mixture was stirred at 0 °C for 10 min. Next, *t*-Bu(Ph)P(Se)Cl (0.252 g, 0.9 mmol) was added, and the mixture was stirred for 15 min, before being poured into water and extracted with ether (20 ml). The organic layer was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel eluting with hexane–ether gave a pale-yellow liquid (0.330 g, 96%).

Syntheses of diselenophosphinates $R_2P(Se)SeR$ by the reaction of phosphinochloridoselenonates with organolithium or Grignard reagents have been documented (*110*). The reaction of a 2.0:1.6 molar ratio of *t*-Bu(R)P(Se)Cl and *n*-butyllithium in THF gives a mixture of *Se*-(*n*-butyl) diselenophosphinates (**137a–b**), *Se*-(*n*-butyl)phosphinoselenolates (**138a–b**) and tertiary phosphine selenides (**139a–b**) in low yield (Fig. 6.16.3). Reaction of a 1.0-1.0-2.0 molar ratio of various phosphinochloridoselenonates, organolithium or magnesium reagents, and selenium generates *Se*-esters **137a–e** (12–63%) and selenides **139a–e** (3–26%) selectively (Fig. 6.16.4).

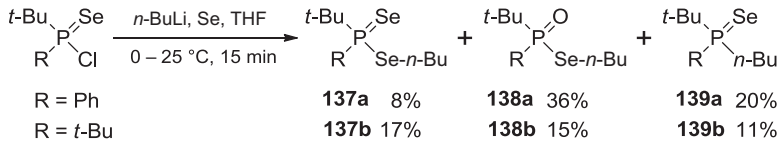
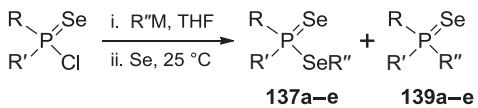


Figure 6.16.3



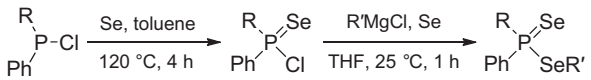
Unsymmetrical tertiary phosphine selenides

No.	R	R′	R″M	Yield (%) **137**	Yield (%) **139**
a	*t*-Bu	Ph	*n*-BuLi	37	24
b	*t*-Bu	Ph	*t*-BuLi	54	3
c	*t*-Bu	Ph	PhLi	63	6
a	*t*-Bu	Ph	*n*-BuMgCl	12	26
d	*t*-Bu	*t*-Bu	*n*-BuLi	46	19
e	Ph	Ph	*n*-BuLi	19	25

Figure 6.16.4

▶ *n-Butyl tert-butyl(phenyl)diselenophosphinate t-Bu(Ph)P(Se)Se-n-Bu* (**137a**) *and tertiary phosphine selenide t-Bu(Ph)P(Se)-n-Bu* (**139a**) (*110*). *n*-Butyllithium (1.6 M in hexane, 0.63 ml, 1.0 mmol) was added to a stirred solution of *t*-Bu(Ph)P(Se)Cl (0.28 g, 1.0 mmol) in THF (10 ml) at 0 °C. Selenium (0.158 g, 2.0 mmol) was added after 15 min. The mixture was stirred at room temperature for 1 h and then poured into water and extracted with dichloromethane (50 ml). The organic layer was dried ($MgSO_4$) and concentrated. Column chromatography of the residue on silica gel eluting with hexane–dichloromethane gave **137a** (0.141 g, 37%) and **139a** (0.071 g, 24%).

Another efficient preparative approach for the synthesis of diselenophosphinates $R_2P(Se)SeR$ is based on selenium insertion into monochlorophosphines, followed by treatment with RSeMgCl (prepared from Grignard reagents and selenium) (*112*,*122*). For example, the diselenophosphinates **137e** and **140a–h** were obtained this way in moderate to good yields (Fig. 6.16.5).



137e,**140a–h**

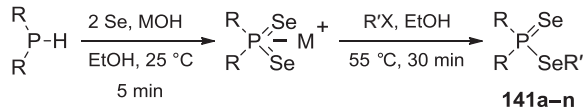
P-Disubstituted *Se*-(alkyl or aryl) phenyldiselenophosphinates

No.	R	R′	Yield (%)
137e	Ph	*n*-Bu	68
140a	Ph	phenyl	91
140b	Ph	4-$MeOC_6H_4$	74
140c	Ph	2,4,6-$Me_3C_6H_2$	67
140d	Ph	*t*-Bu	83
140e	Ph	*i*-Pr	73
140f	Ph	cyclohexyl	77
140g	Ph	benzyl	80
140h	*i*-Pr	4-$MeOC_6H_4$	51

Figure 6.16.5

▶ *Se-Phenyl diphenyldiselenophosphinate* $Ph_2P(Se)SePh$ (**140a**) (*112*). Phenylmagnesium chloride (11.0 mmol) was added to a suspension of selenium (0.870 g, 11.0 mmol) in THF (50 ml) at 0 °C, and the mixture was stirred at 0 °C for 30 min before being added dropwise to a stirred solution of diphenylphosphinochloridoselenonate (3.14 g, 10.5 mmol) in THF (30 ml) over 30 min at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 1 h. The solvent was removed and the residue was chromatographed on silica gel to afford the title compound (4.10 g, 91%). δ_P 43.5 ppm (s, $J_{P,Se}$ 366 and 774 Hz).

A convenient approach for the synthesis of diselenophosphinates based on the reaction of alkali metal diselenophosphinates with organic halides has been reported recently (*111*). The alkali metal diselenophosphinates can be prepared from readily available secondary phosphine or secondary phosphine selenides, selenium and alkali metal hydroxides, under environmentally friendly conditions (*71*,*115*,*124*). The reaction of alkali metal diselenophosphinates with organic halides occurs in ethanol under mild conditions to afford the *Se*-esters (**141a–n**) in high yields (Fig. 6.16.6).



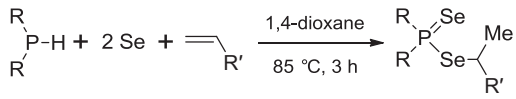
Se-Substituted dialkyl or diaryl diselenophosphinates

No.	R	M	R'X	Yield (%)	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
141a	Ph	Cs	MeI	95	42.6	–188	788, 351
141b	Ph	K	MeI	91	40.5	–177	766, 367
141c	Ph	K	$Me(CH_2)_4Br$	87	40.8	–175	766, 369
141d	Ph	K	$Me(CH_2)_5Br$	89	40.9	–175	765, 367
141e	Ph	K	$CH_2{=}CHCH_2Br$	92	40.9	–167	769, 362
141f	Ph	Cs	≡–CH_2Br	94	43.3	–174	791, 344
141g	$Ph(CH_2)_2$	Na	MeI	95	49.9	–254	768, 340
141h	$Ph(CH_2)_2$	Na	EtI	84	48.5	–251	747, 354
141i	$Ph(CH_2)_2$	K	$Me(CH_2)_4Br$	90	48.7	–248	746, 355
141j	$Ph(CH_2)_2$	K	$Me(CH_2)_5Br$	87	48.7	–248	747, 356
141k	$Ph(CH_2)_2$	K	$PhCH_2$	90	49.2	–230	748, 353
141l	$Ph(CH_2)_2$	K	$CH_2{=}CHCH_2Br$	77	49.6	–237	743, 353
141m	$Ph(CH_2)_2$	Na	≡–CH_2Br	91	52.5	–250	770, 334
141n	2-$Py(CH_2)_2$	Na	EtI	79	49.4	–253	745, 359

Figure 6.16.6

▶ *Se-Substituted dialkyl or diaryl diselenophosphinates $R_2P(Se)SeR'$* (**141a–n**) (*111*). To a solution of the alkali metal diselenophosphinates (0.50 mmol) in ethanol (6 ml) was added at room temperature, the corresponding organic halide (0.51 mmol). The mixture was stirred at 50–55 °C for 30 min. The solvent and the excess organic halide were removed under reduced pressure, and ether (10 ml) was added to the residue. The precipitated white powder (alkali metal halide) was filtered off, and the ether was evaporated from the filtrate. The residue was dried (40–45 °C, 2 mmHg) to afford the title species.

An approach to the preparation of diselenophosphinates **142a–i** has been developed using the reaction between aryl- or hetarylalkenes, secondary phosphines and selenium (Fig. 6.16.7) (*125*). The reaction occurs in warm 1,4-dioxane in the absence of catalyst leading to the target compounds in good to excellent yields.



142a–i

Se-Alkyl aryl/heteroaryl diselenophosphinates

No.	R	R′	Yield (%)	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
142a	$Ph(CH_2)_2$	Ph	85	49.3	–231	758, 356
142b	$Ph(CH_2)_2$	4-*t*-BuC_6H_4	90	48.1	–235	756, 358
142c	$Ph(CH_2)_2$	4-ClC_6H_4	86	49.2	–248	760, 352
142d	$Ph(CH_2)_2$	2-naphthyl	54	49.3	–237	758, 356
142e	$Ph(CH_2)_2$	2-furyl	91	49.6	–237	760, 353
142f	$Ph(CH_2)_2$	1-pyrrolyl	95	50.6	–229	750, 349
142g	4-$MeOC_6H_4(CH_2)_2$	4-*t*-BuC_6H_4	89	47.1	–230	744, 364
142h	2-Furyl$(CH_2)_2$	2-furyl	90	49.4	–245	750, 358
142i	2-Furyl$(CH_2)_2$	1-pyrrolyl	94	47.9	–236	750, 346

Figure 6.16.7

▶ *Se-2-[2-(Phenyl)ethyl] diphenethyldiselenophosphinate* $(PhCH_2CH_2)_2P(Se)SeCH(Me)Ph$ (**142a**) (*125*). Styrene (0.125 g, 1.2 mmol) and grey selenium powder (0.079 g, 1.0 mmol) were added consecutively to a solution of *bis*(2-phenethyl)phosphine selenide (0.321 g, 1.0 mmol) in 1,4-dioxane (8 ml) at room temperature under argon. The suspension was stirred at 85 °C until the selenium dissolved to give a yellow solution (~3 h). The solvent was removed and the residue was flash chromatographed on neutral alumina, eluting with hexane, to give the product (0.43 g, 85%).

6.17 *BIS*(DIALKYLSELENOPHOSPHINYL) SELENIDES $[R_2P(Se)]_2Se$ AND DISELENIDES $[R_2P(Se)]_2Se_2$

Bis(diorganoselenophosphinyl) selenides $[R_2P(Se)]_2Se$ have received attention due to their potential as precursors in metal organic chemical vapour deposition for semiconducting thin films (*91*), for nanoparticle studies (*92*,*126*) and because of their magneto-optical (*111*,*127*), electrical and other properties (*98*). They are also promising extractants of transuranium elements (*128*), biologically active (*124*), and useful as RAFT agents (*112*) and intermediates for the preparation of diselenophosphinate anions as precursors to nanomaterials (*97*). Methods for preparing *bis*(diorganoselenophosphinyl) selenides have been noted as low yielding, time-consuming and requiring toxic phosphorus halides. For example, such selenides can be obtained from Ph_2PCl and Na_xSe_y generated from sodium metal and selenium in liquid ammonia at −78 °C (*103*,*104*,*129*). The method normally leads to a mixture of products along with unreacted selenium and is poorly reproducible (*113*).

A facile and reproducible method for preparing *bis*(dialkylselenophosphinyl) selenides (**143a**–**b**) and *bis*(dialkylselenophosphinyl) diselenide (**144**) in moderate yields (41–43%) involves the multistep

reaction of monochlorophosphines R_2PCl with trichlorosilane, triethylamine and selenium in toluene (Fig. 6.17.1) (*130*). The selenated products are soluble in common nonpolar organic solvents and are stable to air and moisture for several months without apparent decomposition.

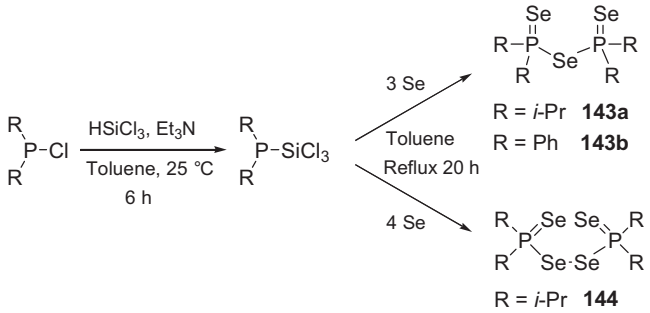


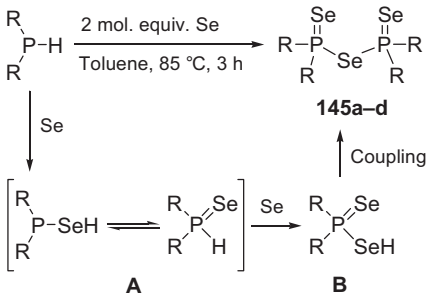
Figure 6.17.1

▶ *Bis(diisopropylselenophosphinyl) selenide [(i-Pr)$_2$P(Se)]$_2$Se* (**143a**) (*130*). Triethylamine (3.03 g, 30 mmol) was added to a stirred solution of diisopropylchlorophosphine (4.58 g, 30 mmol) and trichlorosilane (4.07 g, 30 mmol) in cold toluene (60 ml). The solution was allowed to warm to room temperature and was stirred for 6 h producing a white cloudy precipitate. The precipitate was filtered off and the resulting colourless solution was refluxed with grey selenium powder (3.56 g, 45 mmol) for 20 h until it had dissolved to form a yellow solution. The solvent was removed and the yellow residue was washed with cold hexane (2 × 20 ml) to obtain yellow crystals (2.90 g, 41%).

▶ *Bis(diisopropylselenophosphinyl) diselenide [(i-Pr)$_2$P(Se)Se]$_2$* (**144**) (*130*). A similar process to that described in the previous recipe was used, but using 60 mmol of selenium powder. After heating under reflux for 20 h, the selenium dissolved to form a clear dark-orange solution. The solvent was removed under vacuum and the orange residue was washed with cold hexane (2 × 20 ml) and recrystallised from toluene to provide orange crystals (3.55 g, 43%).

The use of secondary phosphines to prepare *bis*(diorganoselenophosphinyl) selenides has been reported recently (*70*). The phosphines were prepared easily from red phosphorus, styrenes and 2-vinylnaphthalene in one step. They reacted with 2 molar equivalents of selenium in warm toluene to give selenide products (**145a–d**) in 83–92% yield (Fig. 6.17.2). The proposed mechanism for their formation involves the secondary phosphines in the first stage reacting with selenium to give intermediates **A**, followed by reaction with a second molar equivalent of selenium to furnish intermediates **B**. Intermolecular coupling of two molecules of **B** and loss of hydrogen selenide leads to species (**145a–d**). Their ^{77}Se NMR spectra show a doublet of doublets at δ −138 to −140 ppm ($^1J_{P=Se}$ 745–749 Hz) assignable to the P═Se bond. The signals of the bridging selenium atom appear at δ 284–285 ppm ($^1J_{P-Se}$ 377–379 Hz) as triplets due to coupling to the two magnetically equivalent phosphorus atoms. In the ^{31}P NMR spectra the signals of the equivalent phosphorus atoms are observed as a singlet at

~56 ppm showing a set of satellite signals from the ^{77}Se nuclei (a characteristic of such systems). Detailed analysis of the satellites allowed the $^{2}J_{P,P}$ coupling to be determined as 17–20 Hz.

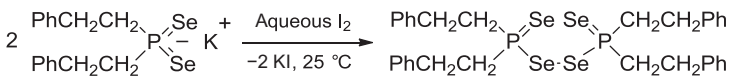


145a R = $PhCH_2CH_2$
145b R = *p*-(*t*-Bu)$C_6H_4CH_2CH_2$
145c R = *p*-$MeOC_6H_4CH_2CH_2$
145d R = naphthalen-2-yl

Figure 6.17.2

▶ *Bis(diorganoselenophosphinyl) selenides* (**145a–d**) (*70*). Selenium (0.158 g, 2.0 mmol) was added to a solution of the secondary phosphine (1.0 mmol) in toluene (8 ml) at 85 °C under argon. The suspension was stirred at this temperature for 3 h. The solvent was removed and the residue was washed with cold hexane (3 × 5 ml) and dried under vacuum.

Bis[di(2-phenethyl)selenophosphinyl] diselenide $[(PhCH_2CH_2)_2P(Se)]_2Se_2$ (**146**) is prepared in high yield from the reaction of potassium *bis*(2-phenylethyl)diselenophosphinate with iodine (Fig. 6.17.3) (*70*). Its physicochemical and spectral characteristics differ from the corresponding *bis* [di(2-phenethyl)selenophosphinyl] selenide $[(PhCH_2CH_2)_2P(Se)]_2Se$.



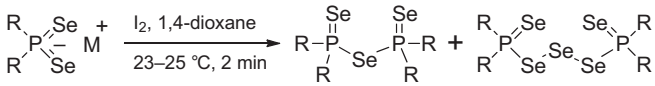
146 81% δ_P 55.6

Figure 6.17.3

▶ *Bis[di(2-phenethyl)selenophosphinyl] diselenide* $[(PhCH_2CH_2)_2P(Se)Se]_2$ (**146**) (*70*). A solution of iodine (0.127 g, 0.5 mmol) in ethanol (10 ml) was added to a solution of potassium *bis*(2-phenylethyl)diselenophosphinate (0.438 g, 1.0 mmol) in water (10 ml) at room temperature under argon. The mixture was stirred for 10 min, diluted with water (30 ml) and extracted with

toluene (2 × 25 ml). The toluene extract was dried (K_2CO_3) and concentrated to 10 ml. The remaining solution was diluted with hexane (15 ml) and kept overnight at 5–10 °C. The solvent was removed from the precipitate by decanting. The residue was washed with cold hexane (1 × 5 ml) and dried to give orange-red crystals (0.323 g, 81%). Mp 117–118 °C. δ_P 55.6 ppm (d, $J_{P,Se}$ 379 and 747 Hz).

A 2:1 molar ratio of alkali metal diselenophosphinates and iodine in 1,4-dioxane furnishes triselenides $[R_2P(Se)]_2Se$ (**147a–b**) and pentaselenides $[R_2P(Se)]_2Se_3$ (**148a–b**) (Fig. 6.17.4) (*131*). The ^{31}P NMR data showed that the tri- and pentaselenides formed in equimolar amounts. When R was $C_6H_5CH_2CH_2$, the triselenide (**147a**) and pentaselenide (**148a**) were isolated as co-crystals in 1:1 molecular ratio, as confirmed by X-ray diffraction analysis.



R = $PhCH_2CH_2$ M = Na or K **147a** **148a**

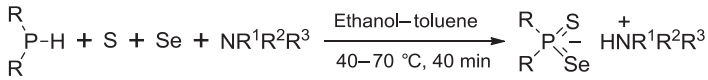
R = 2-Fur$(CH_2)_2$ M = Na or K **147b** **148b**

Figure 6.17.4

▶ *Triselenides $[R_2P(Se)]_2Se$* (**147a–b**) *and pentaselenides $[R_2P(Se)]_2Se_3$* (**148a–b**) (*131*). A solution of iodine (0.127 g, 0.5 mmol) in 1,4-dioxane (10 ml) was added dropwise over 2 min to the alkali metal diselenophosphinate (1.0 mmol) in 1,4-dioxane (6 ml) with stirring at room temperature. The mixture was diluted with water (20 ml) and extracted with toluene (2 × 20 ml). The extract was dried (K_2CO_3) and concentrated to one tenth of its volume. Addition of hexane (10 ml) and storage at 5–8 °C overnight gave the corresponding mixture of tri- and pentaselenides.

6.18 DIALKYL PHOSPHINOSELENOTHIOATE SALTS $R_2P(S)SeM$ AND *Se*-ESTERS $R_2P(S)SeR'$

A multicomponent reaction of secondary phosphines R_2PH (R = aryl, arylalkyl, hetarylalkyl), sulfur, selenium and primary, secondary or tertiary amines leading to the corresponding mono-, di- and trialkylammonium phosphinoselenothioates (**149a–l**) has been discovered recently (Fig. 6.18.1) (*132*). Reaction proceeds in a mixed solvent system and gives the products in high yields. Advantages include a simple one-pot procedure, short reaction time, low temperature and the avoidance of hazardous reagents. Products (**149a–l**) are white powders that are air- and moisture stable at room temperature; they are soluble in most organic solvents.



149a–l

Dialkyl or diaryl phosphinoselenothioate alkylammonium salts

No.	R	$NR^1R^2R^3$	Yield (%)	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
149a	$Ph(CH_2)_2$	Allyl-NH_2	91	49.3	–61	560
149b	$Ph(CH_2)_2$	*n*-Pr_2NH	92	48.7	–77	564
149c	$Ph(CH_2)_2$	Et_3N	85	47.2	–73	565
149d	$PhCH(Me)CH_2$	Et_2NH	76	46.8	–73	561
149e	*p*-(*t*-Bu)$C_6H_4C_6H_4(CH_2)_2$	*n*-Pr_2NH	79	48.1	–82	576
149f	*p*-$MeOC_6H_4C_6H_4(CH_2)_2$	Et_2NH	92	48.4	–84	576
149g	2-Furyl$(CH_2)_2$	*n*-Pr_2NH	89	47.9	–79	571
149h	2-Furyl$(CH_2)_2$	Et_3N	94	47.8	–80	578
149i	6-Me-3-Py$(CH_2)_2$	*n*-Pr_2NH	78	47.1	–83	567
149j	Ph	Allyl-NH_2	88	43.6	4	585
149k	Ph	*n*-Pr_2NH	82	43.0	–1	600
149l	Ph	Et_3N	91	44.4	2	606

Figure 6.18.1

▶ *Dialkyl or diaryl phosphinoselenothioate alkylammonium salts* (**149a–l**) (*132*). Amorphous grey selenium (78.9 mg, 1.0 mmol) was added to a solution of the appropriate dialkyl or diaryl phosphine (1.1 mmol) in absolute ethanol (7 ml) and the mixture was stirred for 20 min at 40 °C until dissolution of the residue to give a transparent solution. To this was added consecutively a solution of sulfur (32.1 mg, 1.0 mmol) in toluene (3 ml) and a solution of the appropriate alkylamine (1.1 mmol) in absolute ethanol (2 ml). The resulting solution was stirred for 20 min at 70 °C. The solvent was removed under reduced pressure and the residue was washed with ether (2 × 10 ml). The ether was decanted and the white powder remaining was dried under vacuum (40–45 °C, 1 mmHg).

Mixed phosphinoselenothioate salts $R_2P(S)Se^-$ are virtually neglected due to their poor availability. Sodium diethylphosphinoselenothioate (**150**) was first obtained by the solventless reaction of 1,1,2,2-tetraethyldiphosphine-1,2-disulfide with sodium selenide and selenium at ~200 °C for 2 h or by the reaction of diethylphosphinothionic chloride with sodium hydrogen selenide in absolute alcohol at 0 °C (Fig. 6.18.2) (*133*). Salt (**150**) was isolated as a crystalline dihydrate $Et_2P(S)SeNa \cdot 2H_2O$ (mp 124–125 °C). An aqueous solution of diethylselenothiophosphinic acid $Et_2P(S)SeH$ (**151**) can be obtained from $Et_2P(S)SeNa \cdot 2H_2O$ and a strong acid cation exchanger. Diethylselenothiophosphinic acid gradually decomposes on standing for a few hours at room temperature in diffuse daylight. Heating the salt (**150**) with alkyl bromides gives the *Se*-alkyl diethylphosphinoselenothionates **152a** (bp 135 °C/10 mmHg) and **152b** (bp 86–87 °C/0.06 mmHg) (Fig. 6.18.2).

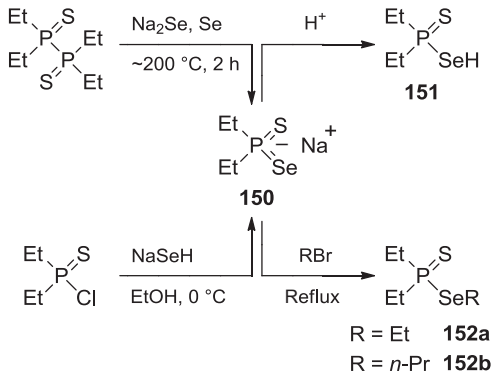
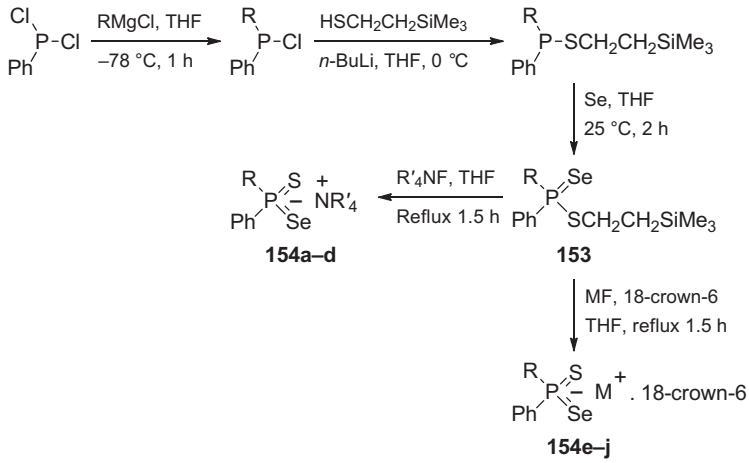


Figure 6.18.2

The most modern preparation of ammonium phosphinoselenothioates involves using air- and moisture-sensitive phenyldichlorophosphine, Grignard and organolithium reagents, and the not easily accessible reagent 2-(trimethylsilyl)ethanethiol. A typical example is the preparation of a series of tetraalkylammonim salts and alkali metal salts (*134*). Treating *S*-[2-(trimethylsilyl)ethyl] alkyl/aryl(phenyl) phosphinoselenothioates (**153**) with a tetraalkylammonium fluoride results in elimination of ethylene and trimethylsilyl fluoride and gives the alkylammonium phosphinoselenothioates (**154a—d**) in good yields (Fig. 6.18.3). Similarly, treatment of the phosphinoselenothioate-starting materials with alkali metal fluorides and 18-crown-6 provides in excellent yields the alkali metal phosphinoselenothioates as crown ether complexes (**154e—j**). These are air- and moisture stable; no appreciable change is observed after exposure to air for one week. The salts are soluble in organic solvents (e.g. CH_2Cl_2 and THF) and water.

▷ *Tetrabutylammonium diphenylphosphinoselenothioate* (**154a**) (*134*). *n*-Butyllithium (1.6 M in hexane, 1.25 ml, 2.0 mmol) was added to a stirred solution of 2-(trimethylsilyl)ethanethiol (0.32 ml, 2.0 mmol) in THF (20 ml) at 0 °C. After 10 min, diphenylphosphinoselenoic chloride (0.599 g, 2.0 mmol) was added at 0 °C, and the mixture was stirred at 0 °C for 1 h. The mixture was poured into water and extracted with ether (20 ml). The organic layer was dried ($MgSO_4$) and concentrated. Column chromatography of the residue on silica gel eluting with hexane-ether afforded *S*-[2-(trimethylsilyl)ethyl] diphenylphosphinoselenothioate as a colourless solid [0.715 g, 90%; mp 66—67 °C dec.; δ_P 54.0 ppm (s, $J_{P,Se}$ 774 Hz), δ_{Se} −217.9 ppm (d, $J_{P,Se}$ 774 Hz)]. A portion of this (0.397 g, 1.0 mmol) dissolved in THF (10 ml) was treated with tetrabutylammonium fluoride (1.0 M in THF, 1.1 ml, 1.1 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. It was extracted with dichloromethane (50 ml) and the organic layer was washed with water (3 × 50 ml), dried ($MgSO_4$), filtered and the filtrate concentrated. Ether (5 ml) was added to the residue and the mixture was stirred for 10 min. The resulting precipitate was collected by filtration to give the title compound as a colourless solid (0.499 g, 93%). Mp 78—80 °C dec.

▷ *Potassium tert-butyl(phenyl)phosphinoselenothioate 18-crown-6 complex* (**154e**) (*134*). *S*-[2-(Trimethylsilyl)ethyl] *tert*-butyl(phenyl)phosphinoselenothioate (0.377 g, 1.0 mmol) was added to

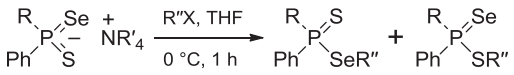


No.	R	R'$_4$NF or MF	Yield (%)	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
154a	Ph	*n*-Bu$_4$NF	93	44.8	–5.2	632
154b	*t*-Bu	*n*-Bu$_4$NF	94	75.3	–125.0	619
154c	Ph	Me$_4$NF	90	44.3	–7.0	646
154d	*t*-Bu	Me$_4$NF	92	75.1	–113.2	636
154e	*t*-Bu	KF	94	74.8	–128.4	607
154f	Ph	RbF	87	44.5	–10.2	624
154g	2-MeOC$_6$H$_4$	RbF	92	38.0	9.1	612
154h	*i*-Pr	RbF	92	64.4	–120.6	618
154i	*t*-Bu	RbF	94	74.9	–126.6	615
154j	*t*-Bu	CsF	91	74.8	–124.5	610

Figure 6.18.3

a stirred mixture of potassium fluoride (0.116 g, 2.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (5 ml) at room temperature. The mixture was heated under reflux for 1.5 h. THF (20 ml) was added, the insoluble solid was filtered off and the filtrate was concentrated. Ether (5 ml) was added to the residue and the mixture was stirred for 10 min. The resulting precipitate was collected by filtration to give a colourless solid (0.544 g, 94%). Mp 220—222 °C (dec.).

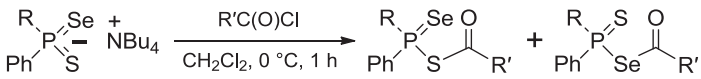
The salts (**154a–j**) react with electrophiles to give the corresponding derivatives (*134*). Alkylation of the tetraalkylammonium salts gives the *Se*-alkyl esters selectively. Tetrabutylammonium salts (**154a—b**) and iodomethane in THF give the *Se*-methyl esters (**155a—b**); the alternative *S*-esters (**156a—b**) hardly form at all (Fig. 6.18.4). In contrast, the acylation of salts (**154a—b**) with acyl chlorides preferentially produces the *S*-alkyl esters (**157a—e**) (Fig. 6.18.5) (*134*).



154a,b,d **155a–d** >99:<1 **156a–d**

Salt	R	R′	R″	Product	Yield (%)	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
154a	Ph	*n*-Bu	Me	**155a**	99	53.9	209.3	360
154b	*t*-Bu	*n*-Bu	Me	**155b**	91	97.6	3.2	492
154d	*t*-Bu	Me	Me	**155c**	93	97.6	3.2	492
154a	Ph	*n*-Bu	$CH_2CH{=}CH_2$	**155d**	88	54.0	320.5	360

Figure 6.18.4



154a,b **157a–e** **158a–e**

Salt	R	R′	Product	Ratio **157:158**	Yield (%)	δ_P (ppm) **157:158**	δ_{Se} (ppm) **157:158**	$^1J_{P,Se}$ (Hz) **157:158**
154a	Ph	C_6H_5	**a**	87:13	60	47.8/54.6	–153.0/683.2	794/346
154a	Ph	4-$MeOC_6H_4$	**b**	83:17	42	47.5/54.2	–151.6/668.8	793/349
154a	Ph	4-MeC_6H_4	**c**	82:18	47	47.5/54.3	–153.3/677.5	793/347
154b	*t*-Bu	4-MeC_6H_4	**d**	90:10	41	81.2/89.5	–250.7/593.0	803/349
154a	Ph	4-ClC_6H_4	**e**	85:15	67	48.4/55.3	–151.9/685.6	800/340

Figure 6.18.5

▶ *4-Chlorobenzoic diphenylphosphinoselenoic thioanhydride* (**157e**) *and 4-chlorobenzoic diphenylphosphinothioic selenoanhydride* (**158e**) (*134*). A solution of 4-chlorobenzoyl chloride (0.263 g, 1.5 mmol) in dichloromethane (5 ml) was added to tetrabutylammonium diphenylphosphinoselenothioate **154a** (0.539 g, 1.0 mmol) in dichloromethane (5 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, poured into water and extracted with dichloromethane (50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated, and the residue was recrystallised from dichloromethane-hexane to give an 85:15 mixture of **157e** and **158e** as a pale yellow solid (0.292 g, 67%).

6.19 WOOLLIN'S REAGENT (WR) AND PHOSPHORUS–SELENIUM-CONTAINING DERIVATIVES

6.19.1 Synthesis of WR

The diselenaphosphetane diselenides $(RPSe_2)_2$ have received very little attention compared to their sulfur analogues, the dithiadiphosphetane disulphides $(RPS_2)_2$. The first report was the

synthesis of $(t\text{-BuPSe}_2)_2$ from the reaction of dichloro-*tert*-butylphosphine and Li_2Se_2 (*135*). Since then, the same compound and its methyl and phenyl analogues have been obtained from the reaction of the silyl esters of triselenophosphonic acids and DMSO, though no detailed experimental procedures or spectroscopic data have been reported (*136*). A wide range of diselenaphosphetane diselenides $(RPSe_2)_2$ have followed from oxidation of the corresponding homocyclic pentamers $[(RP)_5$, R = Me, Et, 4-$Me_2NC_6H_4$, and Ph] by 10 molar equivalents of selenium (*137–141*). Among them, the chemistry of 2,4-*bis*(phenyl)-1,3-diselena-2,4-diphosphetane-2,4-diselenide $(PhPSe_2)_2$ has received special attention since it was named WR (*142*). However, a major obstacle to developing the chemistry of WR was its unwieldy synthesis from the cyclophosphine $(PhP)_5$, which could not be readily scaled up. It was not until 2005 that a large scale method for the preparation of WR was successfully developed, which gave a product of excellent purity in high yield, and permitted the synthesis of up to 150 g in normal laboratory glassware (*143*). So far, WR (available from Sigma-Aldrich Ltd.) has become a very useful selenium source or selenation reagent in synthetic chemistry (*144–154*).

WR was originally synthesised from the oxidation of the homocyclic pentamer $(PhP)_5$ by selenium (Fig. 6.19.1.1) (*139*). Although the desired product was obtained, the method has limitations for large-scale synthesis because the pentamer $(PhP)_5$ is a highly unpleasant, air-sensitive precursor of limited availability (it can be easily prepared on a small scale: 5–10 g only).

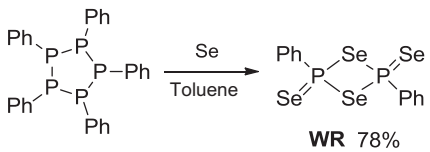


Figure 6.19.1.1

WR can be obtained using a large-scale procedure in high purity and high yield (*143*). Selenium is added to sodium metal dissolved in liquid ammonia at −78 °C, and the mixture is allowed to stir at −34 °C to give Na_2Se as an off-white solid after the ammonia is removed. Toluene is then added, followed by $PhPCl_2$, and the mixture is then heated under reflux. The mixture is filtered to remove the precipitated sodium chloride and a second portion of selenium is added and the reflux continued. WR is obtained as red crystals in excellent yield (Fig. 6.19.1.2). The method involves the use of the unpleasant dichlorophenylphosphine and the potentially hazardous liquid ammonia; however, it avoids the handling of the pentamer $(PhP)_5$. In addition, it produces a product of high purity in higher yield and by a cleaner process. However, the major advantage is that WR can be prepared on a much larger scale – up to 150 g using normal glassware. WR is insoluble in many organic solvents but dissolves in hot toluene, and can be stored at room temperature for several months without apparent decomposition.

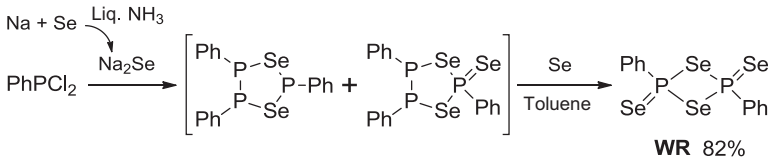


Figure 6.19.1.2

WR from (PhP)$_5$ (143). $PhPCl_2$ (8.9 g, 50 mmol) and Mg turnings (1.2 g, 50 mmol) were stirred together in THF (50 ml) at room temperature for 4 h. Acetone (5 ml) was added and excess Mg was filtered off. Upon the addition of water (2 × 30 ml), an oily off-white precipitate formed. The mixture was stirred vigorously for 40 min. The product was collected by suction filtration and dried under vacuum to give $(PhP)_5$ as a white solid (1.41 g, 26%). A mixture of $(PhP)_5$ (1.01 g, 1.87 mmol) and selenium (1.49, 18.7 mmol) was stirred and refluxed in toluene (30 ml) for 5 h. The reaction mixture was allowed to cool to room temperature. The product was collected by suction filtration, washed with toluene (2 × 15 ml) and dried under vacuum to give WR as a red solid (1.96 g, 78%).

WR from PhPCl$_2$ (143). Sodium (1.200 g, 52.2 mmol) was dissolved in liquid ammonia (50 ml) at −78 °C. Selenium (2.061 g, 26.1 mmol) was added resulting in a dark red mixture. After 15 min of stirring, the ammonia was allowed to evaporate and was replaced by toluene (50 ml). An excess of $PhPCl_2$ (6.60 ml) was added and the mixture was heated under reflux for 64 h. Progress was monitored by ^{31}P NMR spectroscopy. More selenium (3.435 g, 43 mmol) was added and the mixture was refluxed for another 3.5 h. The product was collected by suction filtration, washed with toluene (2 × 15 ml) and dried to give WR as a red solid (5.68 g, 82%). ^{31}P NMR (solid state) δ 18.7 ppm (s).

Woollins' Reagent reacts with organic substrates to cause oxygen–selenium exchange and to provide phosphorus–selenium heterocycles and surprising phosphorus selenium-free products. Only the synthesis of phosphorus–selenium derivatives is now summarised.

6.19.2 Organophosphorus–selenium noncyclic derivatives

WR is believed to be in equilibrium with a diselenophosphorane $PhP(=Se)_2$, the reactive species in solution (*155*). Nucleophilic addition of the phosphorus atom of the P=Se bond of diselenophosphorane can be used to prepare diselenophosphinates. 2-Phosphaindolizine (**159**) reacts with an equimolar amount of WR in benzene at ambient temperature for 2 h to give the zwitterionic diselenophosphinate (**160**) in low yield (Fig. 6.19.2.1) (*156*). A 2:1:2 molar ratio of 2-phosphaindolizine (**159**), WR or its analogues, and triethylamine in benzene at ambient temperature for 2 h affords triethylammonium diselenophosphinates (**161a–c**) in 60–87% yield (*157*). Similarly, 1-aza-2-phosphaindolizine (**162**) reacts with WR or its analogues in the presence of triethylamine to give the diselenophosphinates (**163a–b**) in moderate yield.

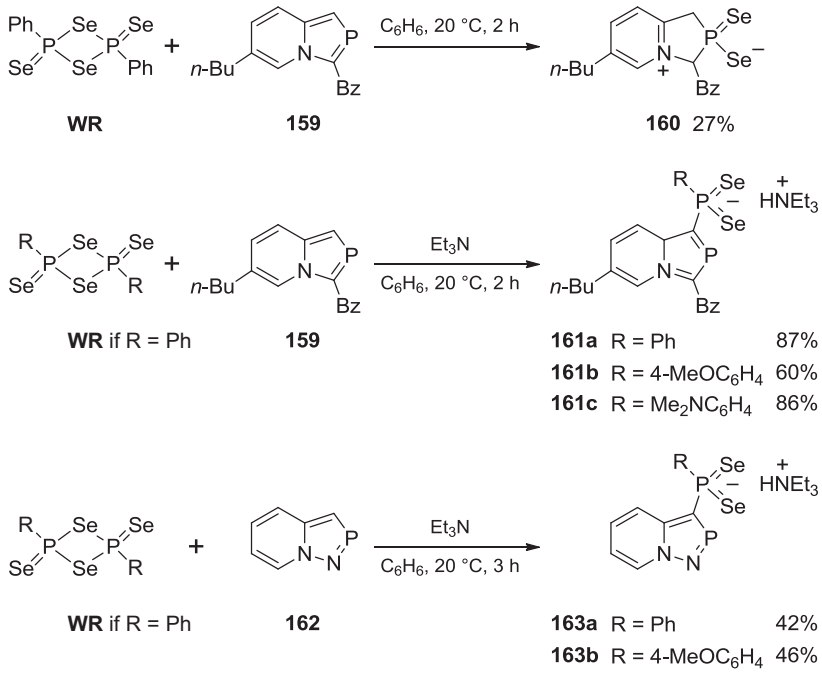


Figure 6.19.2.1

▷ *Triethylammonium diselenophosphinate* (**161a**) (*157*). To a mixture of 2-phosphaindolizine **159** (1.1 g, 3.6 mmol) and WR (0.96 g, 1.8 mmol) in anhydrous benzene (10 ml) was added triethylamine (0.4 g, 3.7 mmol) and the mixture was stirred at ambient temperature for 2 h. After 15 min, the colour of the mixture changed to yellow and the WR began to disappear. The reaction was completed when no solid WR remained. The solvent was removed and the solid residue was washed with ether (3 × 40 ml) and dried to yield a yellow crystalline solid (2.02 g, 87%).

The preparation of a series of novel zwitterionic diselenophosphinates by the reaction of cyanamides R^1R^2NCN with WR has been developed recently (*150*). Refluxing equimolar amounts of WR and cyanamides in toluene for 10 h followed by treatment with water for 1 h provides zwitterionic diselenophosphinates (**164a–d**) in 29–57% yields and cyclic selenazadiphosphoaminediselenides (**165a–d**) in 11–41% yields (Fig. 6.19.2.2). Treatment of the latter with water in refluxing THF for 3 h gave the zwitterionic diselenophosphinates (**164a–d**) almost quantitatively.

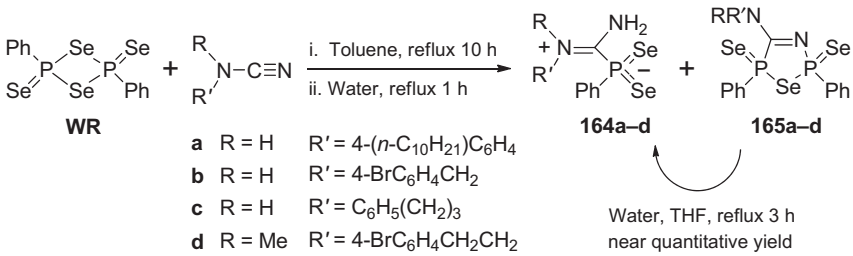
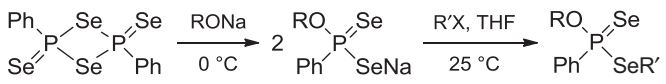


Figure 6.19.2.2

▶ *Zwitterionic diselenophosphinates* (**164a–d**) *and selenazadiphosphoaminediselenides* (**165a–d**) (*150*). A suspension of WR (1.06 g, 2.0 mmol) and the appropriate cyanamide (2.0 mmol) in toluene (30 ml) was heated under reflux for 10 h. The red suspension disappeared and a pale yellow solution formed. After cooling to 90 °C, the mixture was added to water (2 ml) and was refluxed for another 1 h. A yellow suspension and a mixture of dark and white precipitates was obtained. Toluene and excess water were removed under vacuum and the residue was extracted with dichloromethane (3 × 30 ml). The organic layers were dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel, eluting with 1:9 ethyl acetate–dichloromethane, gave species **165a–d**, and eluting with 1:5 ethyl acetate–dichloromethane, species **164a–d**.

Sodium phenylphosphonodiselenoates (**166a–e**) are obtained in high yields as white or pale yellow solids through cleavage of the four-membered P_2Se_2 ring of WR by 2 molar equivalents of sodium alkoxides (Fig. 6.19.2.3) (*157*). Stirring the sodium *O*-alkyl phenylphosphonodiselenoates (**166a–e**) with a molar equivalent of haloalkane in THF yields the *O,Se*-dialkyl phenylphosphonodiselenoates (**167a–k**) (*158*). These were isolated as sticky oils or pastes soluble in chlorinated solvents and THF, and stable to air and moisture for months without obvious degradation. The esters bearing bulky R groups (*i*-Pr) were obtained in the lowest yields, suggesting the importance of steric factors during the formation of the products. The haloalkanes with the longer chain alkyl groups also gave lower yields; compound (**167f**) was isolated in the lowest yield as a mixture of two stereoisomers.



WR **166a–e** **167a–k**

O,Se-dialkyl phenylphosphonodiselenoates

No.	R	R′	Yield (%)	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
167a	Me	2-$BrC_6H_4CH_2$	99	84.3	321.6, –108.8	446, 826
167b	Me	$C_6H_5CH_2$	93	84.3	401.3, –95.4	448, 848
167c	Me	$C_6H_5C(O)CH_2$	89	84.5	402.4, –94.2	427, 833
168d	Me	$C_6H_5C(O)$	99	75.7	410.8, –69.8	423, 840
167e	Me	$Me(CH_2)_6$	99	84.8	409.8, –97.1	451, 826
167f *	Me	$EtC(O)CH_2C(O)CH_2$	75	85.5	387.4, –99.0	420, 832
	Me	$EtC(O)CH_2C(O)CH_2$		85.1	387.4, –99.0	434, 837
167g	Et	$C_6H_5CH_2$	99	80.0	386.9, –99.2	444, 824
167h	Et	2-$BrC_6H_4CH_2$	99	80.1	340.1, –101.3	444, 822
167i	*i*-Pr	2-$BrC_6H_4CH_2$	84	77.3	335.1, –101.6	439, 819
167j	*i*-Pr	$C_6H_5CH_2$	83	77.1	414.2, –88.5	441, 822
167k	*i*-Pr	$C_6H_5C(O)CH_2$	83	77.6	406.8, –94.2	418, 826

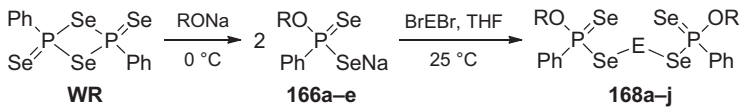
* This compound was isolated as a mixture of diastereomers

Figure 6.19.2.3

▶ *Sodium O-alkyl phenylphosphonodiselenoates RO(Ph)P(Se)SeNa* (**166a–e**) (*157*). Small pieces of sodium (0.118 g, 5.13 mmol) were stirred in the appropriate alcohol (20 ml) at 0 °C until they fully dissolved. To this solution was added WR (1.37 g, 2.57 mmol) and the mixture was heated at 60 °C for 45 min. The mixture was allowed to cool to room temperature and the resulting green solution was filtered through a small pad of Celite™. The filtrate was concentrated under vacuum to a volume of ~5 ml and hexane (30 ml) was added to precipitate the desired sodium salt as a white or pale yellow solid.

▶ *O,Se-Dialkyl phenylphosphonodiselenoates* (**167a–k**) (*158*). A solution of the haloalkane (2.0 mmol) and the appropriate sodium *O*-alkyl phenylphosphonodiselenoate (2.0 mmol) in anhydrous THF (50 ml) was stirred at room temperature under nitrogen for 20 h. Insoluble solid was filtered off and the filtrate was dried under vacuum. Column chromatography of the residue on silica gel, eluting with dichloromethane, gave the target compounds.

Similar reactions occur with dihaloalkanes. A dihaloalkane and 2 molar equivalents of sodium *O*-alkyl phenyldiselenophosphonates (**166a–e**) in THF stirred at room temperature give *O,O′,Se,Se′*-tetraalkyl *bis*(phenylphosphonodiselenoates) (**168a–j**) (Fig. 6.19.2.4) (*158*). These were isolated in high yields as sticky oils or pastes soluble in chloroform, dichloromethane and THF, and insoluble in ether or hexane. They were obtained as mixtures of two stereoisomers in various ratios owing to the presence of two phosphorus stereogenic centres.



O,O′,Se,Se′-tetraalkyl *bis*(phenylphosphonodiselenoates)

No.	R	E	Yield (%)	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
168a	Me	$CH_2CH_2CH_2$	94	84.9	321.6, –108.8	440, 829
168b *	Me	$CH_2C_6H_4CH_2$-*p*	82	84.4	401.3, –95.4	448, 827
	Me	$CH_2C_6H_4CH_2$-*p*		84.3	402.4, –94.2	446, 827
168c *	Et	CH_2	72	81.4	410.8, –69.8	420, 832
	Et	CH_2		81.2	409.8, –97.1	422, 832
168d *	Et	CH_2CH_2	78	80.6	387.4, –99.0	432, 829
	Et	CH_2CH_2		80.5	386.9, –99.2	432, 829
168e *	Et	$CH_2CH_2CH_2$	75	80.9	340.1, –101.3	437, 826
	Et	$CH_2CH_2CH_2$		80.6	335.1, –101.6	437, 826
168f	Et	$CH_2C_6H_4CH_2$-*p*	93	80.2	414.2, –88.5	444, 825
168g *	*i*-Pr	CH_2CH_2	68	77.6	406.8, –94.2	427, 826
	i-Pr	CH_2CH_2		77.5	399.7, –94.4	427, 826
168h *	*i*-Pr	$CH_2CH_2CH_2$	66	77.9	359.7, –96.5	434, 822
	i-Pr	$CH_2CH_2CH_2$		77.6	359.5, –96.7	432, 822
168i	*i*-Pr	$CH_2C_6H_4CH_2$-*p*	58	77.1	433.1, –87.1	439, 819
168j	*n*-Pr	$CH_2C_6H_4CH_2$-*p*	73	80.2	412.9, –88.1	446, 825

* Signifies that the numbered compound was isolated as a mixture of stereoisomers

Figure 6.19.2.4

▷ *Bis(O-alkyl phenylphosphonodiselenoyl) species (RO(Ph)P(Se)Se)$_2$E* (**168a–j**) (*158*). A mixture of dihaloalkane (1.0 mmol) and sodium phenylphosphonodiselenoate (2.0 mmol) in anhydrous THF (50 ml) was stirred at room temperature under nitrogen for 20 h. After filtering to remove insoluble material, the filtrate was concentrated to a volume of ~5 ml and purified by column chromatography on silica gel, eluting with dichloromethane, to afford the product.

Woollins' group have published the synthesis of alkylamine salts of *bis*-diselenophosphonic acids (**169a–g**) that react with iodomethane to afford the *Se,Se*-dialkyl diesters (**170a–g**) (Fig. 6.19.2.5) (*159*).

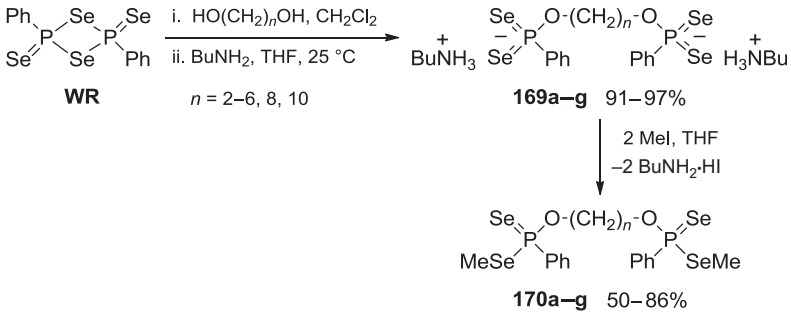
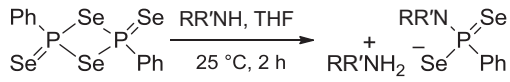


Figure 6.19.2.5

▷ *Di(butylammonium) bis(phosphonodiselenoate) salts* (**169a–g**) (*159*). A mixture of WR (0.54 g, 1.0 mmol) and diol (1.0 mmol) in anhydrous dichloromethane (20 ml) was stirred at room temperature for 20 h. The red suspension disappeared and a greenish yellow solution was formed along with a trace precipitate of grey selenium. The resulting mixture was filtered. The filtrate was concentrated to give a green paste that was dissolved in THF (50 ml) (yellow solution), and butylamine (0.5 ml) was added dropwise. A brown suspension and then a grey or pale grey suspension formed after 4 h stirring at room temperature. The target compounds were collected by filtration and were washed with dichloromethane and ether.

▷ *Bis(phenylphosphonodiselenoate) Se,Se′-dimethyl esters* (**170a–g**) (*159*). A THF solution of the appropriate di(butylammonium) *bis*(phosphorodiselenoate) (2.0 mmol) was cooled to 0 °C and iodomethane (0.26 ml, 4.2 mmol) was added dropwise to give a milky grey suspension. Stirring was continued overnight at room temperature and gave a pale green suspension that was concentrated. The residue was dissolved in ethyl acetate and washed with 2% aqueous $Na_2S_2O_4$, twice with water and brine, and dried ($MgSO_4$). Concentration left the crude diester, which was purified by column chromatography on silica gel, eluting with dichloromethane.

The reaction of WR with 2 molar equivalents of primary or secondary amines at room temperature yields alkylammonium phenylphosphonamidodiselenoates (**171a–f**) in good to excellent yields (Fig. 6.19.2.6). These products are off-white solids or pale yellow pastes, which are soluble in polar and chlorinated solvents (e.g. alcohols, dichloromethane or chloroform) but insoluble in less polar solvents



WR **171a–f**

N,N-Disubstituted phenylphosphonamidodiselenoate salts

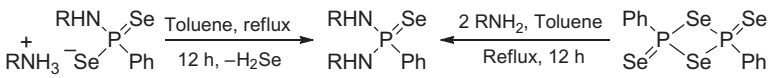
No.	R	R′	Yield (%)	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
171a	H	*n*-Bu	98	44.3	57.9	613
171b	H	Ph	70	46.2	39.0	636
171c	H	Bn	99	46.1	39.9	634
171d	Et	Et	97	55.8	62.8	615
171e	*i*-Bu	*i*-Bu	95	63.9	31.6	617
171f	Bn	$BnCH_2$	93	70.0	56.1	620

Figure 6.19.2.6

(e.g. ethers and hexane) (*160*). They are air stable for several weeks; after that degradation occurs, which includes the reddening of the solids due to expulsion of selenium, with evolution of a foul-smelling gas.

▶ *Alkylammonium phenylphosphonamidodiselenoates* (**171a–f**) (*160*). A mixture of WR (0.54 g, 1.0 mmol) and primary or secondary amine (4.0 mmol) in anhydrous THF (50 ml) was stirred at room temperature. The red suspension disappeared gradually and a greyish white suspension formed after 2 h. The solvent was evaporated to remove the solvent and the residue was dissolved in dichloromethane. Insoluble solid was removed by filtration thought a pad of Celite™. The filtrate was dried under vacuum to give the required products.

Refluxing a toluene solution of ammonium phenylphosphonamidodiselenoates (**171a–c**) for 12 h generated the *N,N′*-dialkyl phenylphosphonodiamidoselenonates (**172a–c**) in excellent yield with evolution of hydrogen selenide (Fig. 6.19.2.7). The same products were also obtained in slightly lower yield from the reaction of WR with 2 molar equivalents of the corresponding primary amine in refluxing toluene. Compounds (**172a–c**) are sticky oils or solids that dissolve in common chlorinated solvents and are air stable for several months (*161*).



171a–c *Method 1* **172a–c** *Method 2* **WR**

N,N′-Disubstituted phenylphosphonodiamidoselenonates

No.	R	Yield (%) Method 1	Yield (%) Method 2	δ_P (ppm)	δ_{Se} (ppm)	$^1J_{P,Se}$ (Hz)
172a	*n*-Bu	99	91	60.3	–243.2	763
172b	Ph	98	95	46.0	–180.4	812
172c	Bn	99	90	62.4	–250.4	775

Figure 6.19.2.7

▶ *N,N′-Dialkyl/aryl phenylphosphonodiamidoselenonates* (**172a–c**) (*160*). *Method 1.* A solution of the ammonium phenylphosphonamidodiselenoate **171a–c** (0.05 mmol) in toluene (20 ml) was heated under reflux under nitrogen for 12 h. Upon cooling the mixture was evaporated to remove solvent and the residue was chromatographed on silica gel, eluting with dichloromethane, to afford the products. *Method 2.* A suspension of primary amine (2.0 mmol) and WR (0.54 g, 1.0 mmol) in anhydrous toluene (20 ml) was heated under reflux under nitrogen for 12 h. The red suspension disappeared and a yellow suspension formed. After cooling and removing the unreacted solid by filtration, the filtrate was evaporated, and the residue was purified by chromatography on silica gel, eluting with dichloromethane, to give the title compounds.

6.19.3 Organophosphorus–selenium heterocyclic derivatives

One of the most attractive features of WR lies in its capacity to form phosphorus–selenium heterocycles. The earliest examples are the reactions of WR with small unsaturated molecules such as carbon disulfide or acetone (*137*,*138*). Woollins' Reagent reacts with carbon disulfide slowly giving a dimeric motif (**173**) of two five-membered CP_3Se rings bridged through their trigonal carbon atoms to the phosphorus atoms of a P_2Se_2 ring (Fig. 6.19.3.1). Treatment of WR with acetone gives colourless crystals of 4,4-dimethyl-5-oxa-1,3-diphenyl-1,3-diseleno-2-selena-1,3-diphospholane (**174**) by insertion of acetone into the P_2Se_2 ring.

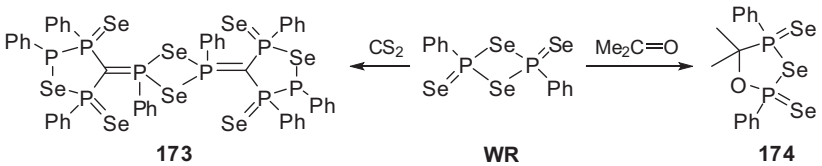


Figure 6.19.3.1

Syntheses of far more extensive series of P–Se heterocycles have been performed via the reaction of WR with a wide range of organic substrates containing reactive C=O, C=C and C≡C bonds. A mixture of WR and diphenylcyclopropenone gives the expected selenocarbonyl compound (**175**) and an unusual phosphorus-selenium spirocyclic heterocycle (**176**) (Fig. 6.19.3.2) (*143*).

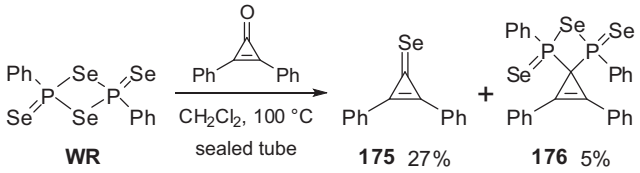


Figure 6.19.3.2

▶ *Selenocarbonyl compound* (**175**) *and phosphorus—selenium heterocycle* (**176**) (*143*). A solution of WR (0.200 g, 0.373 mmol) and diphenylcyclopropenone (0.154 g, 0.746 mmol) in dichloromethane (3 ml) was stirred at 100 °C in a sealed tube for 5 min, producing a dark-red solution plus a tiny amount of black solid (selenium). Column chromatography on silica gel eluting with toluene gave an orange fraction and a subsequent purple fraction. These were dried under vacuum to give an orange solid **175** (0.054 g, 27%; ^{77}Se NMR δ 330.0 ppm, singlet) and a purple solid **176** (0.012 g, 5%). δ_P 66.1 ppm (s, $^1J_{P,Se}$ 304, 816, $^2J_{P,Se}$ 124 Hz), ^{77}Se NMR −34.1 (d, $J_{P,Se}$ 820 Hz), 506.9 ppm (d, $J_{P,Se}$ 306 Hz).

The reaction of WR with azobenzene results in N═N bond cleavage and substitution of a bridging selenium atom in WR by an NPh unit, yielding selenaazadiphosphetane (**177**) (Fig. 6.19.3.3) (*161*). Chloroform solutions of this compound are susceptible to oxidation, depositing red selenium within 72 h, although the crystalline material is more inert.

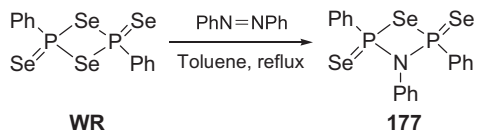


Figure 6.19.3.3

▶ *Selenaazadiphosphetane* (**177**) (*161*). A solution of WR (0.150 g, 0.28 mmol) and azobenzene (0.032 g, 0.18 mmol) in toluene (2 ml) was heated at 130 °C for 5 h, providing an orange solution containing some black selenium. The solvent was removed and the crude product was extracted with dichloromethane (2 ml) and was worked up in the usual way. Column chromatography on silica gel eluting with dichloromethane afforded a pale orange solid (0.02 g, 13%). δ_P 44.7 ppm (s, $J_{P,Se}$ 857, 263 Hz).

Treatment of WR with a solution of methyl phenylpropiolate in refluxing toluene provides three five-membered heterocycles (**178**–**180**) that are moderately stable in air, degrading over several weeks with expulsion of red selenium (Fig. 6.19.3.4) (*143*).

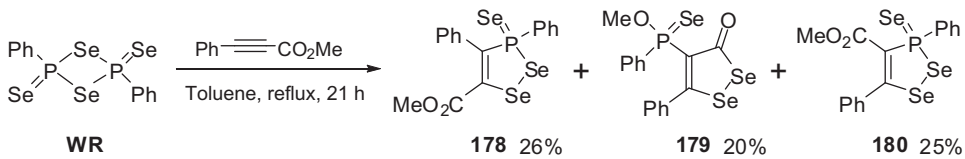


Figure 6.19.3.4

▶ *Synthesis of heterocycles* (**178**–**180**) (*143*). A mixture of WR (0.300 g, 0.56 mmol) and methyl phenylpropiolate (0.18 ml, 1.22 mol) in toluene (7 ml) was refluxed for 21 h, resulting in a red solution. After cooling to room temperature, the solution was chromatographed on silica gel, eluting

with toluene, to afford successively: orange **178**, yellow **179** and orange **180** fractions. The products precipitated as yellow (**178** and **179**) or orange (**180**) solids following the addition of hexane to dichloromethane solutions. Compound **178** (0.073 g, 26%). δ_P 76.0 ppm (s, $^1J_{P,Se}$ 366 and 789 Hz), ^{77}Se NMR 525.8 (d, $^2J_{P,Se}$ 10 Hz), 341.4 (d, $^1J_{P,Se}$ 367 Hz) and 26.8 ppm (d, $^1J_{P,Se}$ 796 Hz); **179** (0.056 g, 20%). δ_P 85.7 ppm (s, $^1J_{P,Se}$ 822 Hz), ^{77}Se NMR 687.5 (s, C(O)Se), 518.0 (s, C(Ph)Se) and 207.0 ppm (d, $^1J_{P,Se}$ 823 Hz); **180** (0.070 g, 25%). δ_P 71.4 ppm (s, $^1J_{P,Se}$ 343 and 798 Hz), ^{77}Se NMR 532.0 (d, $^2J_{P,Se}$ 7 Hz, C-Se), 420.6 (d, $^1J_{P,Se}$ 343 Hz), −25.0 ppm (d, $^1J_{P,Se}$ 799 Hz).

Similarly unexpected phosphorus—selenium heterocycles are obtained from the reaction of WR with alkynes and dialkylcyanamides. Heating WR and dimethyl but-2-ynedioate in toluene gives the five-membered heterocycles (**181**) and (**182**) and the six-membered heterocycle (**183**) in 5—19% yields (Fig. 6.19.3.5) (*162*). More straightforward products (**184a—b**) or (**185a—b**) are harvested from the reaction of WR with dialkylcyanamides or ethynylbenzenes (*162,163*).

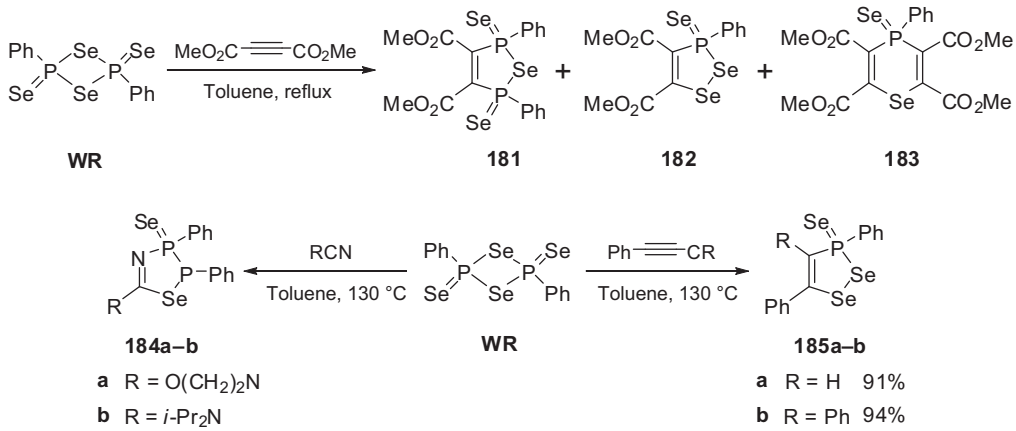


Figure 6.19.3.5

▶ *Synthesis of diselenaphosphole 3-selenides* (**185a—b**) (*163*). A mixture of WR (0.54 g, 1.0 mmol) and phenylacetylene or diphenylacetylene (1.0 mmol) in toluene (10 ml) was heated under reflux for 12 h resulting in a brown solution. Upon cooling to room temperature, the solution was chromatographed on silica gel, eluting with toluene to afford 3,5-diphenyl-1,2,3-diselenaphosphole 3-selenide **185a** (0.401 g, 91%); δ_P 67.1 ppm (s,$^1J_{P,Se}$ 350 and 771 Hz); δ_{Se} 559.9 (d, $^2J_{P,Se}$ 7 Hz), 411.7 (d, $^1J_{P,Se}$ 350 Hz), and −15.4 ppm (d, $^1J_{P,Se}$ 774 Hz); and 3,4,5-triphenyl-1,2,3-diselenaphosphole 3-selenide **185b** (0.495 g, 94%); δ_P 74.3 ppm (s,$^1J_{P,Se}$ 357 and 779 Hz); δ_{Se} 519.3 (d, $^2J_{P,Se}$ 7 Hz), 373.4 (d, $^1J_{P,Se}$ 358 Hz), and −28.6 ppm (d, $^1J_{P,Se}$ 777 Hz).

Several five-membered C_2PSe_2 heterocycles (**187a—d**) and (**188a—d**) result from reaction of WR and dialkynes by formal addition of a $PhP(Se)Se_2$ fragment to the alkyne triple bond (Fig. 6.19.3.6). The unusual diselenide (**189**) is generated by an intramolecular cycloaddition-rearrangement along

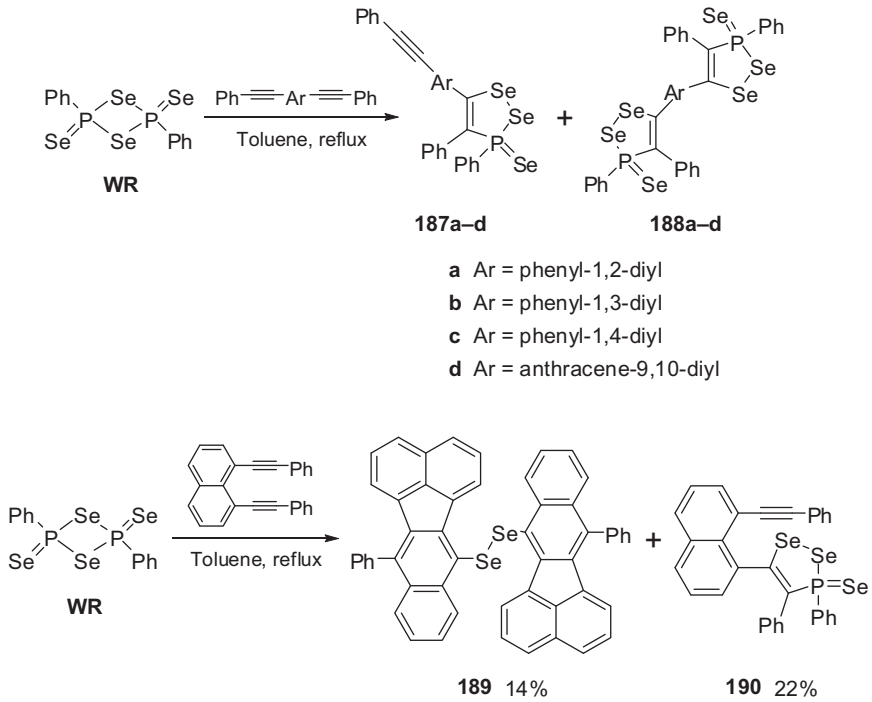


Figure 6.19.3.6

with a five-membered C_2PSe_2 heterocycle (**190**) formed when a sterically constrained naphthalene dialkyne is used (*163*,*164*).

Diselenide (**189**) *and 3,4-diphenyl-5-(8-(phenylethynyl)-1-naphthyl)-3H-1,2,3-diselenaphosphole 3-selenide* (**190**) (*163*). A mixture of WR (1.08 g, 2.0 mmol) and 1,8-*bis*(phenylethynyl)naphthalene (0.35 g, 1.0 mmol) in toluene (20 ml) was refluxed for 12 h resulting in a red solution. Upon cooling to room temperature, the solution was chromatographed on silica gel, eluting with toluene, to afford a red product **189** [0.057 g, 14%; δ_{Se} 279.9 ppm (s, 2 Se)] followed by a pale-yellow product **190** [0.147 g, 22%; δ_P 66.5 ppm (s, $^1J_{P,Se}$ 380 and 803 Hz); δ_{Se} 564.3 (d, $^2J_{P,Se}$ 11 Hz), 461.5 (d, $^1J_{P,Se}$ 383 Hz) and −14.7 ppm (d, $^1J_{P,Se}$ 802 Hz)].

Treating WR with symmetrical diynes RC≡C−C≡CR (R = Ph or $SiMe_3$) in a 2:1 molar ratio in refluxing toluene gives five-membered $C_2P(Se)Se_2$ heterocycles (**191a**−**b**) and *bis*-heterocycles (**192a**−**b**) with two five-membered $C_2P(Se)Se_2$ rings linked through a C−C bond (Fig. 6.19.3.7). WR reacts differently with *t*-Bu-C≡C−C≡C-*t*-Bu and affords the four-membered $C_2P(Se)Se$ heterocycle (**193**) and a heteropentalene (**194**) with two $C_3P(Se)Se$ rings fused at the central two carbons of the diyne (*164*).

Unusual phosphorus−selenium heterocycles, 1,6,6λ^4-triselena-3*a*-phospha-3,4-diazapentalenes (**195a**−**c**), have been isolated in ∼5% yield from the reaction mixture of WR and a ten-fold

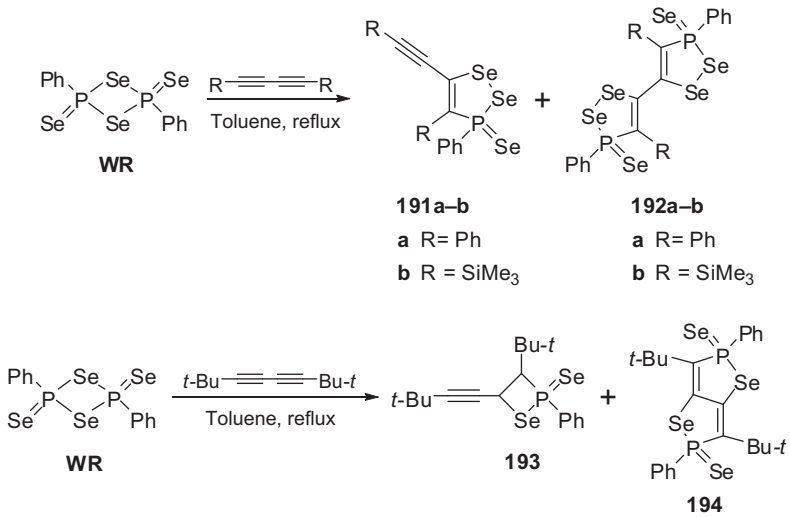


Figure 6.19.3.7

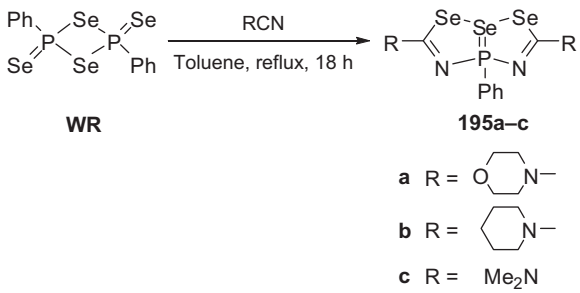


Figure 6.19.3.8

molar excess of dialkylcyanamides (Fig. 6.19.3.8) (*165*). These heterocycles contain a core of two fused five-membered PSe_2CN rings with the imino substituents lying approximately in the same plane.

▶ *Phosphorus—selenium heterocycles* (**195a—c**) (*165*). A toluene solution (10 ml) of WR (0.15 mmol) and R_2NCN (1.5 mmol) was heated under reflux for 18 h. It changed colour from red to lime green with precipitation of some selenium. After cooling to room temperature, the solvent was removed and the products were extracted into dichloromethane (2 ml). Column chromatography on silica gel, eluting with dichloromethane, afforded **195a—c** as yellow solids (~5% yield): **195a** δ_P 82.7 ppm ($J_{P,Se}$ 317 Hz), **195b** δ_P 83.9 ppm ($J_{P,Se}$ 324 Hz) and **195c** δ_P 81.7 ppm ($J_{P,Se}$ 318 Hz).

Treatment of WR with norbornene proceeds with cleavage of the $P_2(\mu\text{-Se})_2$ ring resulting in the formation of the 1,2-diselena-3-phospholane (**196**) with a five-membered C_2PSe_2 ring, via a [2 + 3] cycloaddition between the alkene and a Se—P═Se unit (Fig. 6.19.3.9) (*161*). This compound differs from the product 1,2-thiaphosphetane (C_2PS ring) formed from the reaction between norbornene and

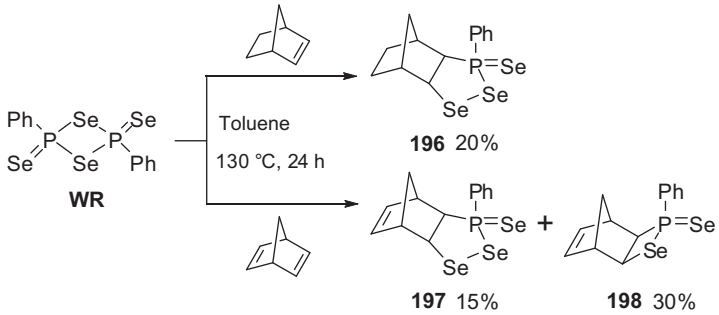


Figure 6.19.3.9

$[RP(S)(\mu\text{-}S)]_2$ (R = ferrocenyl) (*166*). However, treating WR with norbornadiene gave a five-membered C_2PSe_2 product (**197**) and a four-membered C_2PSe heterocycle (**198**), although the reaction was slower than with norbornene (*166*,*167*).

▶ *Phosphorus—selenium heterocycle* (**196**) (*161*). A toluene solution (2 ml) of WR (0.15 g, 0.28 mmol) and norbornene (0.052 g, 0.56 mmol) was heated under reflux for 24 h and gave an orange solution and a small amount of selenium. Upon cooling to room temperature, the solvent was removed and the residue was dissolved in dichloromethane (2 ml) and purified by column chromatography on silica gel, eluting with dichloromethane. Recrystallisation of the resulting orange solid by slow evaporation of a dichloromethane-hexane solution over several days at room temperature gave crystals of the title compound (0.025 g, 20%).

Reaction of WR with 2 molar equivalents of difunctional substrates (e.g. diamines, dialcohols, diphenols, dithiophenols, or mixed forms of these functional groups, even the oxidised form of dithiols, diselenols or thioselenols) proceeds with cleavage of its central $P_2(\mu\text{-}Se)_2$ bridge to furnish heterocycles (**199a—d**), (**200a—e**) and (**201a—c**) (Figs 6.19.3.10—6.19.3.12) (*151*,*168*).

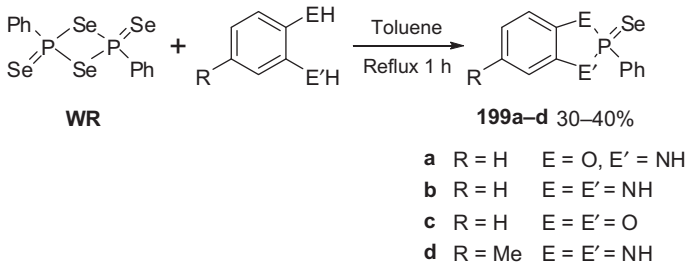


Figure 6.19.3.10

▶ *Phosphorus—selenium heterocycles* (**199a—d**) (*168*). A mixture of 2-aminophenol, 1,2-phenylenediamine, catechol or 3,4-diaminotoluene (0.50 mmol) and WR (0.25 mmol) in dry toluene (2 ml) was heated under reflux for 1 h, and the dark-red suspension became colourless or pale

yellow, with deposition of some selenium. Upon cooling to room temperature and removal of the solvent the residue was extracted into dichloromethane (2 ml) and purified by column chromatography on silica gel, eluting with dichloromethane. The products were isolated by concentration of the pale green dichloromethane eluate to a volume of ~5 ml, addition of hexane (5 ml) and concentration under vacuum until precipitation occurred. Isolated yields were typically 30–40%: **199a** δ_P (CD_2Cl_2) 97.5 ppm (s, $J_{P,Se}$ 895 Hz), **199b** 71.3 ppm (s, $J_{P,Se}$ 831 Hz), **199c** 116.0 ppm (s, $J_{P,Se}$ 952 Hz), and **199d** 71.8 ppm (s, $J_{P,Se}$ 824 Hz).

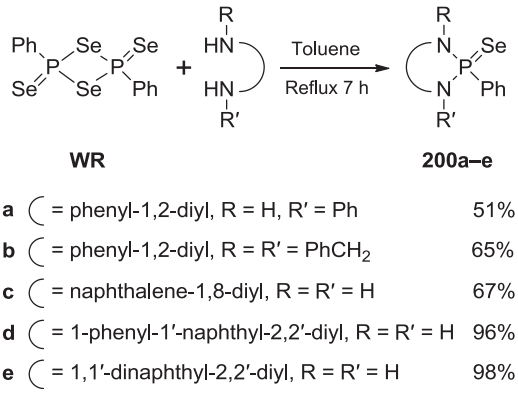


Figure 6.19.3.11

▶ *Phosphorus–selenium hetercycles* (**200a–e**) *(151)*. A mixture of the appropriate diamine (2.0 mmol) and WR (0.54 g, 1.0 mmol) in anhydrous toluene (20 ml) was heated under reflux for 7 h. The red suspension disappeared and a grey solution formed along with a small amount of black selenium. Upon cooling to room temperature and removing the solvent the residue was purified by column chromatography on silica gel, eluting with toluene, to give the following products: pale white solid **200a** (190 mg, 51%). Mp 188–190 °C. δ_P ($CDCl_3$) 75.5 ppm (s, $J_{P,Se}$ 842 Hz), δ_{Se} ($CDCl_3$) −115.7 ppm (d, $J_{P,Se}$ 842 Hz); white solid **200b** (306 mg, 65%). Mp 211–121 °C, δ_P ($CDCl_3$) 84.7 ppm (s, $J_{P,Se}$ 842 Hz), δ_{Se} ($CDCl_3$) −188.7 ppm (d, $J_{P,Se}$ 842 Hz); milky-white solid **200c** (250 mg, 67%). Mp 195–197 °C. δ_P ($CDCl_3$) 40.5 ppm (s, $J_{P,Se}$ 817 Hz), δ_{Se} ($CDCl_3$) −182.1 ppm (d, $J_{P,Se}$ 820 Hz); white solid **200d** (402 mg, 96%). Mp 201–203 °C. The ^{31}P and ^{77}Se NMR spectra indicated two diastereomers: δ_P (CD_2Cl_2) 83.5 (s, $J_{P,Se}$ 805 Hz) and 84.5 ppm (s, $J_{P,Se}$

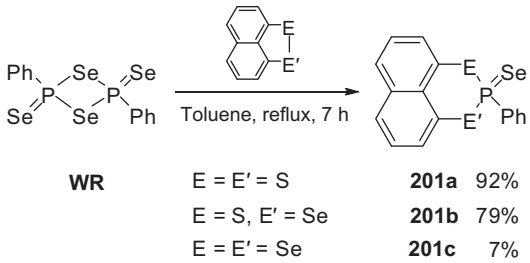


Figure 6.19.3.12

805 Hz), δ_{Se} (CD_2Cl_2) −207.0 (d, $J_{P,Se}$ 805 Hz) and −209.8 ppm (d, $J_{P,Se}$ 805 Hz); slightly pink solid **200e** (460 mg, 98%). Mp 198−199 °C. δ_P (d_6-acetone) 82.5 ppm (s, $J_{P,Se}$ 810 Hz), δ_{Se} (d_6-acetone) −193.5 ppm (d, $J_{P,Se}$ 810 Hz).

▶ *Phosphorus−selenium hetercycles* (**201a−c**) (*151*). A mixture of naphtho[1,8-*cd*][1,2]dithiole, naphtho[1,8-*cd*][1,2]thiaselenole or naphtho[1,8-*cd*][1,2]selenole (2.0 mmol) and WR (0.54 g, 1.0 mmol) in anhydrous toluene (10 ml) was stirred at room temperature for 7 h. The red suspension appeared unchanged. The mixture was heated under reflux for 7 h and a solution and a black precipitate of selenium formed. Upon cooling to room temperature and removing the solvent, the residue was chromatographed on silica gel, eluting with toluene, to give the following products: white solid **201a** (0.348 g, 92%). Mp 154−155 °C. δ_P (CD_2Cl_2) 21.7 ppm (s, $J_{P,Se}$ 810 Hz), δ_{Se} (CD_2Cl_2) −81.2 ppm (d, $J_{P,Se}$ 810 Hz); pale brown solid **201b** (0.335 g, 79%). Mp 130−131 °C. δ_P (CD_2Cl_2) 3.7 ppm (s, $J_{P,Se}$ 798 Hz, $J_{P,Se}$ 390 Hz), δ_{Se} (CD_2Cl_2) 502.6 (d, $J_{P,Se}$ 390 Hz) and −50.9 ppm (d, $J_{P,Se}$ 799 Hz); yellow solid **201c** (0.033 g, 7%). Mp 90−91 °C. δ_P (CD_2Cl_2) 76.6 ppm (s, $J_{P,Se}$ 819 Hz, $J_{P,Se}$ 439 Hz), δ_{Se} (CD_2Cl_2) 386.9 ppm (d, $J_{P,Se}$ 441 Hz) and −26.0 ppm (d, $J_{P,Se}$ 820 Hz).

When aliphatic or aromatic diols are used, the reaction course becomes more complicated, depending upon the substrates. Apart from the common products (**202a−b**) bearing the PhP(Se) unit, other larger heterocycles containing PhP(Se)SeP(Se)Ph units (**203a−b** and **205a**) (Fig. 6.19.3.13) and/or PhP(Se)SeSeP(Se)Ph units (**205b-c**, **206** and **207**) form (Fig. 6.19.3.14) (*159*,*169*,*170*).

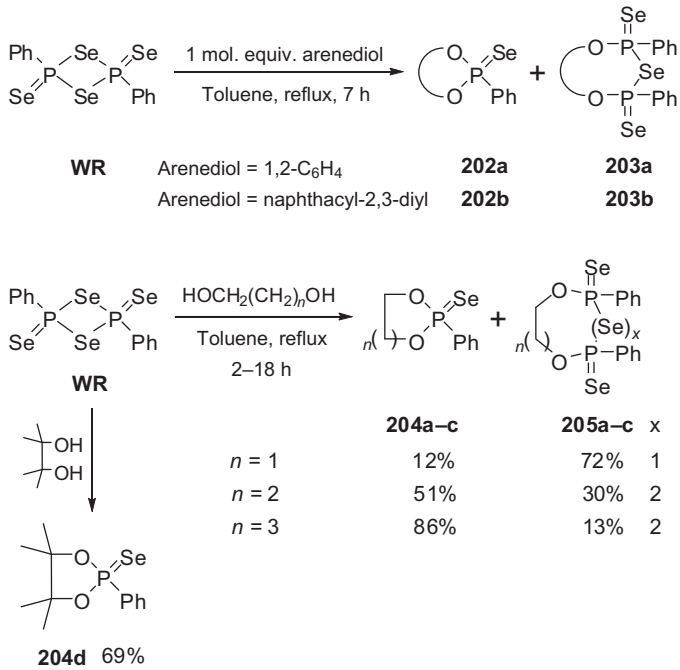


Figure 6.19.3.13

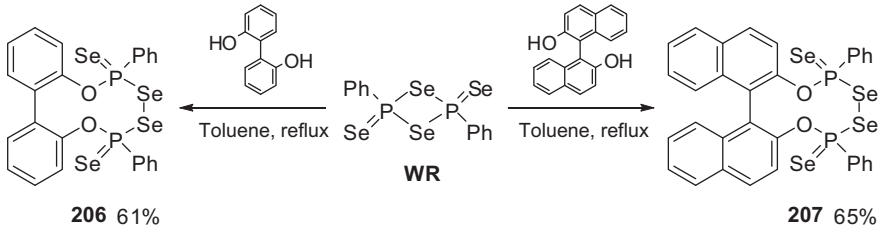


Figure 6.19.3.14

▶ *Heterocycles* (**206**) *and* (**207**) (*170*). A mixture of aromatic diol (1.0 mmol) and WR (0.54 g, 1.0 mmol) in toluene (20 ml) was heated under reflux for 15 h under nitrogen. Upon cooling to room temperature and solvent removal, the residue was chromatographed on silica gel, eluting with toluene, to afford white solids: **206** (61% yield). Mp 172–173 °C. δ_P (CD_2Cl_2) 67.2 ppm (s, $^1J_{P,Se}$ 507 and 826 Hz), δ_{Se} (CD_2Cl_2) 505.4 (dd, $^1J_{P,Se}$ 498 Hz, $^2J_{P,Se}$ 23.9 Hz) and 22.3 ppm (d, $^1J_{P,Se}$ 826 Hz); and **207** (65% yield). Mp 140–141 °C. δ_P (CD_2Cl_2) 65.8 ppm (s, $^1J_{P,Se}$ 502 and 822 Hz), δ_{Se} (CD_2Cl_2) 498.9 (dd, $^1J_{P,Se}$ 501 Hz, $^2J_{P,Se}$ 23 Hz) and 37.6 ppm (dd, $^1J_{P,Se}$ 820 Hz).

1,1′-Methylenedi-2-naphthol reacts with an equimolar amount of WR to provide the six-membered monophosphorus heterocycles (**208**) and (**209**) and the larger diphosphorus heterocycle (**210**) (Fig. 6.19.3.15) (*169*). Treating WR with 2 molar equivalents of 1,1′-methylenedi-2-naphthol under comparable conditions affords only two isolable products (**208**) and (**209**). It appears that compound (**209**) is the ring contraction product of heterocycle (**210**). Compound **208** might arise from decomposition of **210** owing to the relative lability of the methylene group linking the naphthalene units within the large ten-membered ring, driven by the stability of the formed six membered ring.

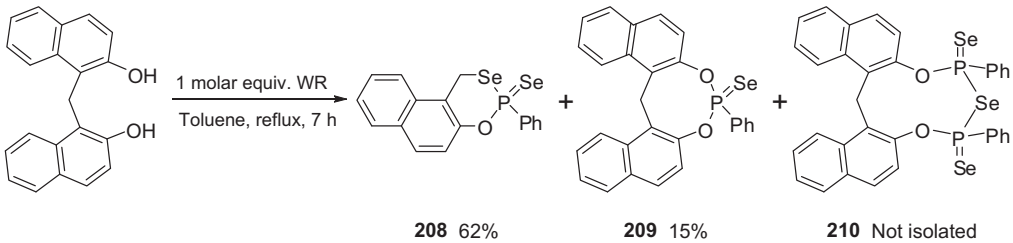


Figure 6.19.3.15

Heterocycles (**211a–c**) having a PhP(Se)SeSeP(Se)Ph bridge can be made in one pot by treating WR with diols $HO(CH_2)_nOH$ ($n = 2–6$, 8 or 10) and then *n*-butylamine to provide the bisdiselenophosphonic acid ammonium salts, followed by oxidation of these with iodine (Fig. 6.19.3.16) (*170*). The heterocycles are stable to air and moisture for several months and are soluble in common polar organic solvents.

Eight- to ten-membered rings (**211a–c**) (*170*). A mixture of WR (0.54 g, 1.0 mmol) and the appropriate alkanediol (1.0 mmol) in dry toluene (20 ml) was stirred at room temperature for 20 h.

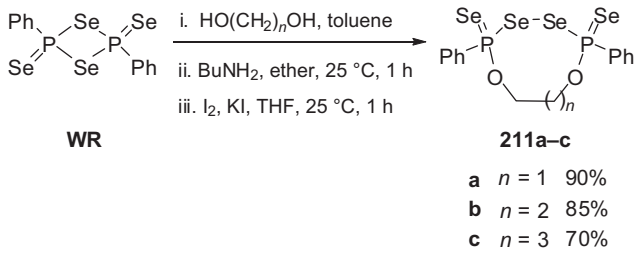


Figure 6.19.3.16

The red suspension changed to a green solution with a tiny amount of black selenium precipitating. The resulting mixture was filtered and concentrated to give a green paste that was dissolved in ether (20 ml) and butylamine (0.5 ml) was added dropwise with stirring. This resulted immediately in a brown suspension and then a grey suspension after 30 min. The grey solid di(butylammonium) *bis*(diselenophosphonate) was obtained by filtration and washed with ether. A portion of this phosphonate (0.5 mmol) was treated dropwise while stirring with a solution of potassium iodide and iodine (1.5 mmol) in THF (10 ml). A white precipitate formed immediately. The mixture was stirred at room temperature for 1 h to ensure complete reaction and then evaporated to dryness. The residue was dissolved in dichloromethane and filtered to give a yellow solution and a grey insoluble solid (polymeric side product). Column chromatography on silica gel, eluting with dichloromethane, gave the following products as crystals, obtained from dichloromethane solutions by diffusion of hexane: **211a** (90% yield). Mp 100 °C. δ_P (CD_2Cl_2) 66.8 (s, $^1J_{P,Se}$ 444 and 822 Hz), δ_{Se} (CD_2Cl_2) 490.7 (dd, $^1J_{P,Se}$ 433 Hz, $^2J_{P,Se}$ 24.7 Hz) and −74.6 ppm (d, $^1J_{P,Se}$ 822 Hz); **211b** (85% yield). Mp 162−163 °C. δ_P (CD_2Cl_2) 67.2 ppm (s, $^1J_{P,Se}$ 465 and 812 Hz), δ_{Se} (CD_2Cl_2) 441.2 (dd, $^1J_{P,Se}$ 465 Hz, $^2J_{P,Se}$ 21.5 Hz) and −61.2 ppm (dd, $^1J_{P,Se}$ 810 Hz); **211c** (70% yield). Mp 108 °C. δ_P (CD_2Cl_2) 68.3 ppm (s, $^1J_{P,Se}$ 460 and 808 Hz), δ_{Se} (CD_2Cl_2) 474.2 (dd, $^1J_{P,Se}$ 463 Hz, $^2J_{P,Se}$ 21.5 Hz) and −80.2 ppm (d, $^1J_{P,Se}$ 806 Hz).

Woollins' Reagent reacts with dibenzoylideneacetone to furnish in high yield 5-benzylidene-2,3-diphenyl-1,2-selenaphosphole-2-selenide (**212**) with a planar $C_3P(\mu\text{-Se})Se$ ring (*171*). A similar reaction of WR with a molar equivalent of 1,3-dibenzoylpropane gives in low yield 1,5,6-triphenyl-8-oxa-7-selena-6-phosphabicyclo[3.2.1]octane-6-selone (**213**) (Fig. 6.19.3.17) (*172*).

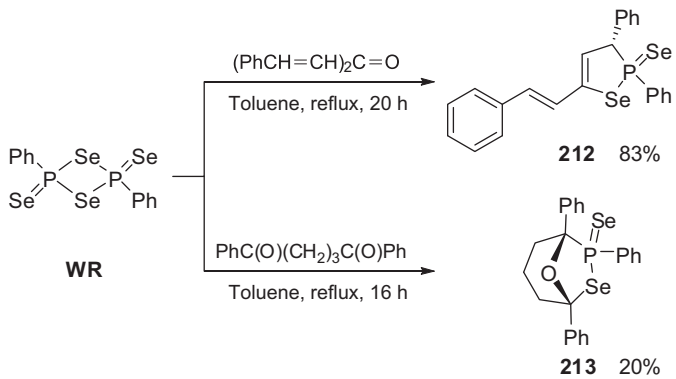


Figure 6.19.3.17

▶ *5-Benzylidene-2,3-diphenyl-1,2-selenaphosphole-2-selenide* (**212**) (*171*). A mixture of dibenzoylideneacetone (0.47 g, 2.0 mmol) and WR (0.54 g, 1.0 mmol) in anhydrous toluene (10 ml) was heated under reflux for 20 h. The red suspension disappeared and a red solution was formed along with a small amount of selenium. After cooling to room temperature the mixture was purified by column chromatography on silica gel, eluting with toluene, to give the title compound (83%). Colourless crystals were grown from dichloromethane with slow diffusion of *n*-hexane. δ_P ($CDCl_3$) 69.9 ppm (s, $J_{P,Se}$ 350 and 782 Hz), δ_{Se} ($CDCl_3$) 354.9 ppm (d, $J_{P,Se}$ 350 Hz) and −170.0 ppm (d, $J_{P,Se}$ 780 Hz).

▶ *1,5,6-Triphenyl-8-oxa-7-selena-6-phosphabicyclo[3.2.1]octane-6-selone* (**213**) (*172*). A red suspension of 1,3-dibenzoylpropane (0.25 g, 1 mmol) and WR (0.54 g, 1 mmol) in anhydrous toluene (10 ml) was heated under reflux for 16 h. A yellow suspension and a small amount of grey selenium formed. After cooling to room temperature the mixture was chromatographed on silica gel, eluting with 1:9 ethyl acetate—dichloromethane, to give the product (20%). Crystals were obtained from dichloromethane—hexane by a diffusion method. δ_P ($CDCl_3$) 79.2 ppm (s, $J_{P,Se}$ 430 and 776 Hz), δ_{Se} ($CDCl_3$) 34.6 (d, $J_{P,Se}$ 430 Hz) and −94.0 ppm (d, $J_{P,Se}$ 778 Hz).

The reaction of WR with secondary amines proceeds in dichloromethane or dibromomethane to give *bis*(*N,N*-dialkyl phenylphosphonamidodiselenoyl)methylenes (**214a—e**) (Fig. 6.19.3.18). The twelve-membered 1,2,4,5,7,8,10,11-octaselenacyclododecane (**215**) also forms (*173*). This C_4Se_8 ring is stable and does not eliminate selenium even when refluxed in toluene for over 24 h.

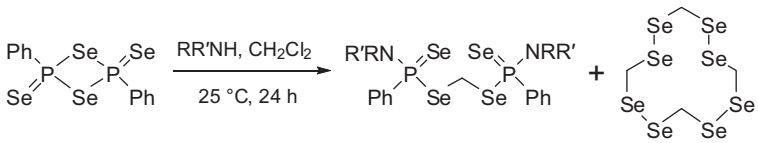


Figure 6.19.3.18

▶ *Bis(N,N-dialkyl phenylphosphonamidodiselenoyl)methylenes* (**214a—e**) *and 1,2,4,5,7,8,10,11-octaselenacyclododecane* (**215**) (*173*). A mixture of the appropriate dialkylamine (4.0 mmol) and WR (1.07 g, 2.0 mmol) in anhydrous dichloromethane (50 ml) or dibromomethane (10 ml) was stirred at room temperature for 24 h. The brown suspension disappeared and a greyish yellow suspension formed. Upon filtering to remove unreacted solid the filtrate was dried under vacuum, the residue was extracted

with dichloromethane (2 ml) and chromatographed on silica gel, eluting with 1: 1 hexane—dichloromethane, to give a mixture of **214a—e** and **215**. The latter compound, insoluble crystals, could be filtered off from a dichloromethane solution of these mixtures three days later. The filtrate was dried to give the pure methylene compounds.

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CHAPTER 7

Analysis of Organophosphorus Chemicals

James Riches
Detection Department, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, Wiltshire, SP4 0JQ, UK

7.1 INTRODUCTION

The most widely reported instrumental techniques for the analysis and characterisation of organophosphorus chemicals are mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, and infrared (IR) spectroscopy. Methods combining separation by gas chromatography (GC), liquid chromatography (LC) or capillary electrophoresis (CE) with selective detection, by MS, flame photometry or nitrogen–phosphorus detection are commonly applied to environmental samples. Trace analysis of organophosphorus chemicals, especially organophosphorus pesticides (OPPs), is driven by concerns over food safety and environmental contamination. Requirements for analytical method sensitivity for OPPs are set by legislation, making these compounds some of the most intensively studied. Other applications of organophosphorus chemicals, including their use as flame retardants and as additives in oil and gas exploration, have prompted the development of sensitive methods for environmental monitoring.

Defence against the use and proliferation of organophosphorus nerve agents has also resulted in the application of instrumental analysis techniques and innovations in related technologies such as sampling. The Chemical Weapons Convention (CWC) (*1*) prohibits the use of chemicals in war and stockpiling of chemical warfare agents (CWAs) and their precursors. Chemicals controlled under the CWC are listed in three schedules: Schedule 1 includes nerve agents belonging to three structural classes and some of their immediate precursor chemicals; Schedule 2 includes specific precursors to nerve agents and generic chemicals containing a P-alkyl group (C_1–C_3); and Schedule 3 includes some organophosphorus chemicals that can be used as, or converted to, precursor chemicals, and which also have legitimate industrial applications.

Most known organophosphorus chemicals can be analysed using commercial instrumentation that is available in bench-top format (NMR spectrometers are the exception). GC–MS remains the most widely applied technique because of its application to volatile chemicals and polar involatile chemicals following derivatisation. In recent years, the development of LC–MS including ultra performance LC (UPLC) and high-resolution MS, using time-of-flight and specialised ion trap analysers, has resulted in reduced analysis times, and improved selectivity and sensitivity of detection, particularly for polar and thermally labile analytes.

The main analytical techniques for organophosphorus chemicals are described following a description of the main classes of organophosphorus chemicals of environmental concern. Important reviews and recent references are cited, and because of the pace of development of analytical instrumentation, the majority of these are from the last decade. Generic analytical methods involving

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GC—MS, LC—MS and GC—flame photometric detection (FPD) are provided as starting points for the development of specific analytical methods.

7.2 SOME IMPORTANT ORGANOPHOSPHORUS CHEMICALS

7.2.1 Chemical warfare agents

The nerve agents tabun (**1**) and sarin (**2**) (Fig. 7.2.1.1) were discovered in Germany before World War II by Gerhard Schrader, a German chemist working on the development of pesticides to improve agricultural yields (*2*). Later, in 1944, soman (**3**), one of the most toxic phosphonofluoridates, was synthesised. These chemicals were found to be potent inhibitors of the enzyme acetylcholinesterase (AChE) and were too toxic to be used as pesticides. Their military potential was realised at an early stage by the German Ordnance Department and they were manufactured for military use, but fortunately not used during the war. In the same period, the Allies researched dialkyl phosphonofluoridates as possible warfare agents: diisopropyl phosphorofluoridate (**4**, DFP) was found to be one of the most toxic (*3*).

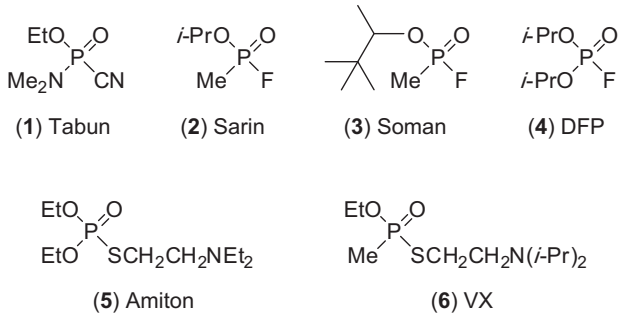


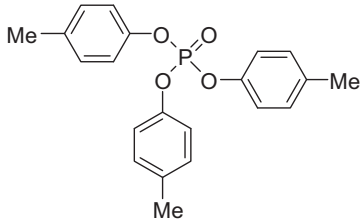
Figure 7.2.1.1 Some organophosphorus nerve agents.

Organophosphorus chemicals were widely used as pesticides after the war. The pesticide amiton (**5**) displayed high toxicity, too high to be used safely, and its modification led to the V series of nerve agents. These agents are of low volatility and highly toxic. The best known is *O*-ethyl *S*-(2-diisopropylaminoethyl) methylphosphonothiolate (**6**, VX). During the following decades, considerable quantities of toxic nerve agents were produced and stockpiled by the U.S. and former Soviet Union. In 1997, the CWC (*1*) was ratified and the process of dismantling facilities and destroying stockpiles of these chemicals began. This process is ongoing and some 60—70% of stockpiles have been destroyed. Nevertheless, the use of chemicals of this type remains an aspiration of terrorist organisations. This was exemplified in the 1990s with the use of sarin by the terrorist group Aum Shinrikyo in Japan (*4*). Furthermore, the development of related chemicals not covered by the CWC and the threat from the few countries that have not yet signed up to the CWC continue to drive the need for a defensive capability in this area.

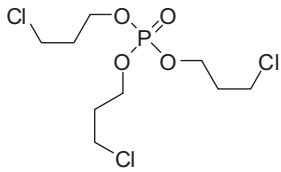
7.2.2 Flame retardants, plasticisers and industrial processing additives

Trialkyl phosphates (e.g. **7** and **8**, Fig. 7.2.2.1) are used as plasticisers, lubricating and hydraulic fluids, nuclear-processing additives, and flame retardants. Important flame retardants include

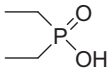
diethylphosphinic acid (**9**), dialkyl hydrogen phosphates (**10**), triaryl phosphates (**11**), and 6*H*-dibenzo [*c*,*e*][1,2]oxaphosphinine 6-oxide (**12**). The growth in their applications has triggered an increased awareness of their environmental impact. Sensitive analytical methods are required for their measurement and this has resulted in an emerging body of literature on successful analytical approaches (*5*,*6*).



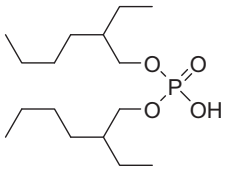
(**7**) Tri-*p*-cresyl phosphate



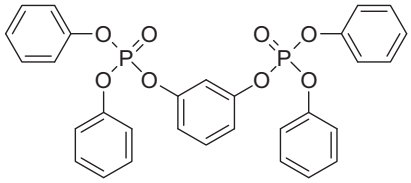
(**8**)Tris(3-chloropropyl) phosphate



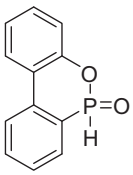
(**9**) Diethylphosphinic acid



(**10**) Di(2-ethylhexyl) hydrogen phosphate



(**11**) Resorcinol-*bis*(diphenyl) phosphate



(**12**) 6*H*-dibenzo[*c*,*e*][1,2]oxaphosphinine 6-oxide

Figure 7.2.2.1 Some phosphorus-containing flame retardants.

7.2.3 Pesticides and herbicides

OPPs span a large group of synthetic chemicals that can be broadly classified as esters, amides or thioester derivatives of phosphoric, phosphonic, phosphorothioic or phosphonothioic acids. Hundreds have been synthesised and screened for biological activity and many have been used commercially. Examples include dichlorvos (**13**), dimethoate (**14**), malathion (**15**), methamidophos (**16**), parathion-methyl (**17**) and chlorpyrifos (**18**) (Fig. 7.2.3.1). These chemicals act on the central nervous system of insects through the inhibition of AChE, which results in a build-up of toxic levels of

acetylcholine. Phosphorus-containing herbicides such as glyphosate (**19**) have been used to control broad-leaved weeds since their activity was discovered in the 1970s. Glyphosate inhibits an enzyme within the plant involved in the synthesis of the aromatic amino acids phenylalanine, tyrosine and tryptophan. Glyphosate has a low mammalian toxicity and is the most widely used herbicide: over 10,000 tonnes per year are applied annually in the U.S.A. This has resulted in the development of sensitive analytical methods for environmental monitoring of glyphosate and its metabolites and related products such as glufosinate (**20**). OPPs are often characterised by low solubility in water, a high water—oil partition coefficient, and a low vapour pressure. The herbicides, because of their different structure, are more polar and water soluble.

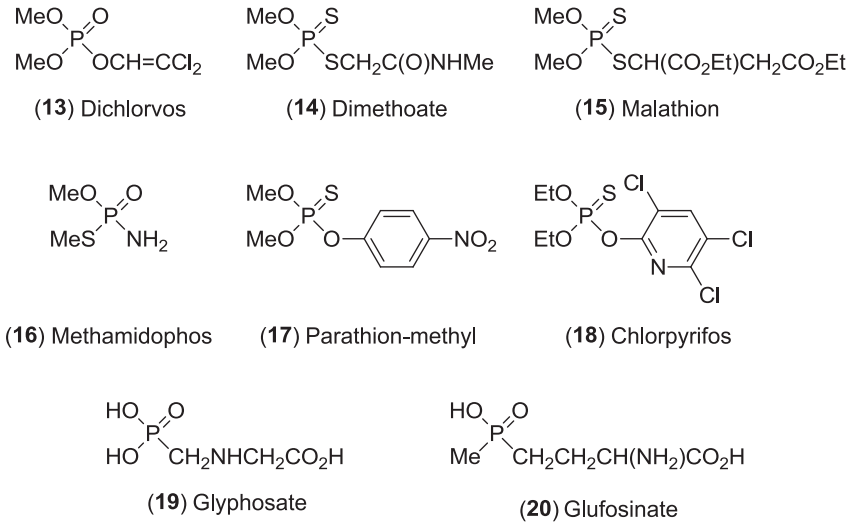
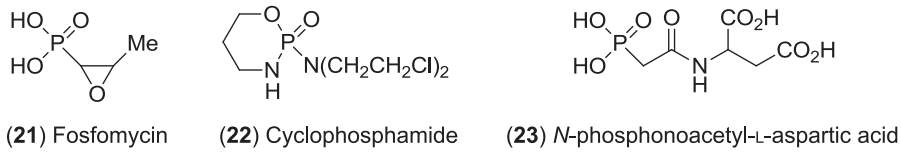


Figure 7.2.3.1 Some organophosphorus pesticides.

Widespread concern over chronic health effects in humans from pesticide residues in food has prompted the control and regulation of pesticide use in developed countries. Despite the availability of alternative pesticides, application of OPPs remains significant in such countries and is growing in developing countries; it is estimated that OPPs comprise 40% of the global market in pesticides. A huge body of literature describes the analysis of OPP residues in food and environmental samples, and almost every conceivable analytical method has been used. Recent trends, such as improvements in analytical sensitivity and the development of multiclass methods, are driven by regulations imposing strict limits on pesticide residues in food and a desire to monitor a range of pesticides and pollutants simultaneously. Many such pollutants are polar chemicals that are not amenable to GC—MS analysis (7); however standard GC—MS methods are still widely reported. The analysis of herbicides is more challenging as they are polar, involatile, water soluble and amphoteric, and consequently the preferred technique is LC—MS (see Section 7.3.2).

7.2.4 Pharmaceuticals and medicines

Phosphorus compounds were largely ignored in drug discovery until the natural product fosfomycin (**21**) (Fig. 7.2.4.1) was recognised as an important antibiotic in 1969. Since then, other medically important compounds have been developed, including the anticancer drug cyclophosphamide (**22**). Many phosphonic acids such as *N*-phosphonoacetyl-L-aspartic acid (**23**) have been synthesised and tested for chemotherapeutic activity. Other organophosphorus compounds that have been used clinically are described in Chapter 1.

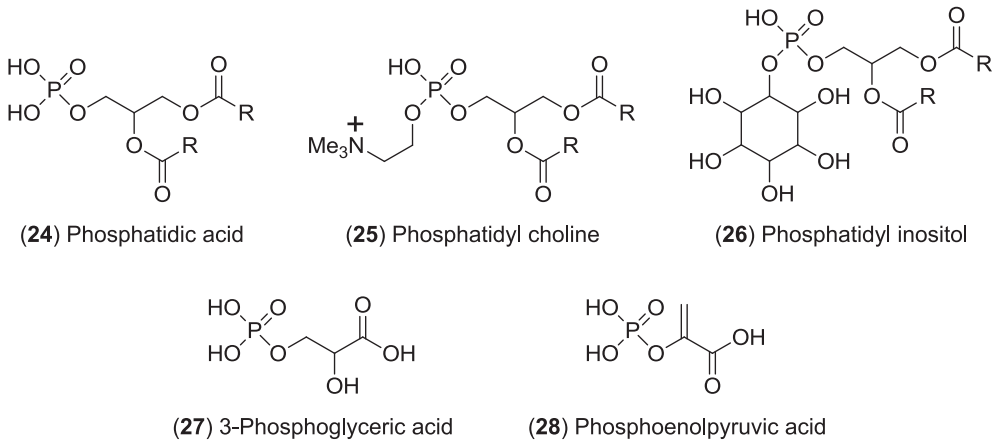


(**21**) Fosfomycin (**22**) Cyclophosphamide (**23**) *N*-phosphonoacetyl-L-aspartic acid

Figure 7.2.4.1 Some organophosphorus drugs.

7.2.5 Phosphorus compounds of biological importance

Dialkyl hydrogen phosphates are fundamental components of the backbones of ribonucleic acid and deoxyribonucleic acid. Membrane phospholipids are constructed from glycerol and include phosphoglycerides where the 2- and 3- positions of glycerol are esterified to form phosphatidic acid (**24**) (Fig. 7.2.5.1). Biologically important molecules formed from phosphatidic acid include phosphatidyl choline (**25**) and phosphatidyl inositol (**26**). Phosphoric acid derivatives are important in glucose metabolism (glycolysis). Among the intermediates involved are 3-phosphoglyceric acid (**27**) and phosphoenolpyruvic acid (**28**).



(**24**) Phosphatidic acid (**25**) Phosphatidyl choline (**26**) Phosphatidyl inositol

(**27**) 3-Phosphoglyceric acid (**28**) Phosphoenolpyruvic acid

Figure 7.2.5.1 Some natural organophosphorus products.

7.3 ANALYTICAL TECHNIQUES FOR THE ANALYSIS OF ORGANOPHOSPHORUS CHEMICALS

A wide range of analytical techniques has been used for the analysis of organophosphorus chemicals; however GC—MS, LC—MS, and NMR spectroscopy are the most common. Their application to the analysis of some of the organophosphorus chemicals discussed already is described next. For major techniques such as GC—MS, the theory and concepts of operation are assumed, but for specialist detection options, such as inductively coupled plasma-MS (ICP-MS) and FPD, the theory behind these techniques is summarised.

7.3.1 Gas chromatography—mass spectrometry

GC—MS remains one of the preferred and most widely reported techniques for the characterisation of environmental samples and mixtures from synthetic processes. Extensive libraries of mass spectra are available commercially for use in identification and include most commercially available organophosphorus chemicals. The latest version of the National Institute of Standards and Technology library contains spectra for several hundred organophosphorus chemicals and the GC—MS database collated by the Organisation for the Prohibition of Chemical Weapons (OPCW) contains spectra for over 2000 organophosphorus chemicals controlled by the CWC. Improvements in GC—MS technology have occurred steadily and include the use of electronic pressure control and improved overall design, making it easier to switch between different analysis modes. Essentially though, the format, design and footprint of GC—MS systems have changed little since the 1980s.

Fast GC using narrow bore columns and hydrogen carrier gas has not found mainstream use and only modest improvements in quadrupole mass analyser sensitivity have been made. The main developments have been the inclusion of time-of-flight mass analysers in the GC—MS instruments (*8—10*), an approximate ten-fold increase in sensitivity in the full-scan mode, and two-dimensional GC (*11—13*). Research-grade tandem MS instruments based on quadrupole or ion-trap analysers have developed considerably: these instruments are now available in bench-top format, are more affordable than before, and are being used increasingly to establish selective and sensitive analytical methods. Demanding legislation for measuring pesticide residues in food has led to important developments in technology and criteria for trace identification (*14*). A generic GC—MS method suitable for analysing volatile organophosphorus compounds is described in Table 7.3.1.1.

The chromatographic properties of organophosphorus chemicals can present difficulties during analysis. Tailing of peaks for some of the nerve agents and for dialkyl alkylphosphonates obtained using 100% polydimethyl siloxane and 5% diphenyl—95% dimethyl polysiloxane stationary phases are sometimes observed. Improved performance can often be achieved using 14% cyanopropyl phenyl and 86% dimethyl polysiloxane (also known as 1701) columns.

7.3.1.1 GC—MS analysis of specific organophosphorus chemicals

Halogenated phosphorus compounds. Methylphosphonic dichloride $MeP(O)Cl_2$ (DC) and its difluoride $MeP(O)F_2$ (DF) feature in Schedule 2 (2B.4) and Schedule 1 (1B.9) respectively of the chemicals

Table 7.3.1.1 A generic GC–MS method for volatile organophosphorus compounds

Parameter	Setting	Notes
GC parameters		
Column	25–30 m, 0.20–0.25 mm i.d. (0.25–0.33 μm film thickness), 95% methyl–5% phenyl polysiloxane low bleed column (various manufacturers)	Columns of a wide range of polarities have been applied to the analysis of organophosphorus chemicals. The chromatographic properties of volatile phosphonates and phosphates are not always ideal on standard low-polarity columns and midpolarity columns can improve performance.
Injection mode	Splitless	Retention index data valid only in splitless injection mode. Cool on-column injection can be applied to thermally labile compounds. Examples include RO(Me)P(O)OP(O)(Me)OR impurities in the synthesis of organophosphorus nerve agents, and the pesticide tetraethyl pyrophosphate. These compounds can undergo significant thermal degradation under standard chromatographic conditions. Sulfur-containing compounds can also be prone to thermal degradation and consideration should be given to this in method development.
Injection volume	1 μl	
Splitless time	Up to 1 min	
Injector temperature	200–280 °C	Careful consideration should be given to the analysis of thermally labile compounds (see injection mode above).
Carrier gas	Helium	Constant-pressure or constant-flow mode. Hydrogen can be used but very few examples appear in the literature (*15*).
Septum purge flow	2–4 ml/min	
Temperature programme	40 °C (1 min) to 280 °C at a rate of 10 °C/min (hold for 5–10 min)	Subtle modifications can improve the separation of specific compounds.
MS parameters		
Solvent delay	3 min	Solvent dependent.
Mass range	m/z 40–550	
Scan rate	>1 scan/s	
Electron energy	70 eV	Lower energy can be used to identify molecular ions.
Source temperature		Refer to manufacturer's instructions.

controlled under the CWC (*1*). They are precursors to alkyl methylphosphonofluoridate nerve agents. The high volatility and reactivity of DC and DF to water, which produces MeP(O)(Cl)OH and MeP(O)(F)OH respectively, render gas chromatographic analysis difficult, although qualitative assessments can be made. DC hydrolyses ultimately to $MeP(O)(OH)_2$, and DF to MeP(O)(F)(OH) and hydrofluoric acid. Mixtures of DC and DF have been characterised by IR spectroscopy and their hydrolysis products by LC—MS (see Section 7.3.2).

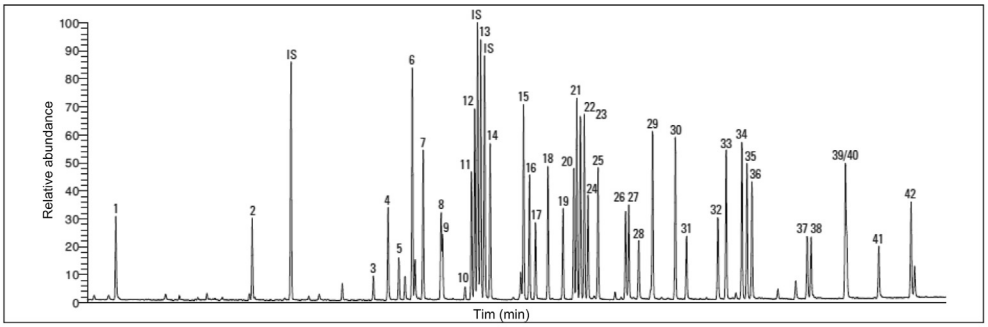
Alkyl methylphosphonofluoridates RO(Me)P(O)F have been studied by GC—MS because of their high toxicity and development as CWAs. The alkyl methylphosphonochloridates RO(Me)P(O)Cl are also toxic, but less so, and can be converted to the corresponding phosphonofluoridates. Two chloridates feature in the CWC Schedules (chlorosarin and chlorosoman in Schedule 1B.11 and 1B.12 respectively) as precursors to the nerve agents sarin and soman. They can be analysed by GC—MS (*16*,*17*). Methods are well established and have been applied to trace analysis of nerve agent residues in real environmental samples (*18*). The GC—MS method in Table 7.3.1.1 is ideal for these compounds.

Nitrogen-containing compounds. The nerve agent tabun (Fig. 7.2.1.1) and relatives can be analysed by GC—MS (*19*,*20*). These compounds hydrolyse in aqueous media but survive long enough to be measured under electrospray ionisation (ESI) conditions (*21*) using a generic LC—MS method described later. Common impurities and degradation products (phosphoramidates) are also amenable to GC—MS analysis (*22*).

Dialkyl alkylphosphonates. Dialkyl alkylphosphonates have been used as fire retardants and industrial additives, and GC—MS methods have been developed in relation to their control as precursors to CWAs and their presence as impurities and degradation products of CWAs. They are produced deliberately by conversion of alkyl alkylphosphonic acids to their methyl esters by the reagent diazomethane (*23*) for GC—MS and GC—FPD analyses. The chromatographic properties of the dialkyl alkylphosphonates using standard columns for nonpolar compounds can be quite poor. More polar phases, for example DB-1701, often yield improved results. Cyclic compounds have also been studied using GC—MS, although they resist hydrolysis and can be analysed also by LC—MS (*24*).

Organophosphorus pesticides. Recent literature covering modern sample preparation and analysis techniques for OPPs in water (*25*) demonstrates that GC—MS analysis is still the most often reported method, although for more complex systems, such as pesticide residues in food, LC—MS is now preferred. The U.S. Environmental Protection Agency method 8141B (*26*) is a protocol for the separation of 42 OPPs from aqueous and solid samples. Detection options include flame photometric and nitrogen—phosphorus detection, but adequate sensitivity can also be obtained by GC—MS using standard quadrupole analyser technology (*27*). An example of the separation of OPPs using this method appears in Fig. 7.3.1.1.1. The analytical run time was 45 minutes.

Some OPPs are thermally labile, highly polar, or otherwise unsuitable for GC—MS analysis. Examples include methamidophos, acephate and azinphos-methyl. These are generally analysed by LC—MS, which is also suitable for many of the analytes depicted in Fig. 7.3.1.1.1. To achieve the lowest possible detection limits by GC—MS, two stages of MS and sample clean-up



Compound name	Peak no	Compound name	Peak no	Compound name	Peak no
Dichlorvos	1	Internal standard	IS	Crotoxyphos	28
Mevinphos	2	Disulfoton	14	Tetrachlorvinphos	29
Internal standard	IS	Dichlofenthion	I5	Tokuthion	39
Demeton-S	3	Chlorpyrifos-metil	16	Tribuphos(DEF)	31
Ethoprop	4	Parathion-metil	17	Fensulfothion	32
Naled	5	Fenchlorphos	18	Ethion	33
Sulfotep	6	Fenitrothion	19	Sulprophos	34
Phorate	7	Malathion	20	Famphur	35
Dimethoate	8	Aspon	21	Carbofenothion	36
Demeton-O	9	Chlorpyrifos-etil	22	Phosmet	37
Dioxation	10	Fenthion	23	EPN	38
Terbuphos	11	Parathion-etil	24	Leptophos	39
Fonofos	12	Trichloronate	25	Azinphos-metil	40
Internal standard	IS	Chlorfenvinphos	26	Azinphos-etil	41
Diazinon	13	Merphos	27	Coumaphos	42

Figure 7.3.1.1.1 Chromatogram from GC—MS analysis of 42 organophosphorus pesticides. (For a colour version of this figure, the reader is referred to the online version of this book.) *(Source: Reproduced with permission from Thermo Fischer Scientific Ltd. (27).)*

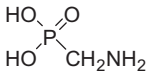
are often used. GC—MS—MS using bench-top triple quadrupole MS analysers are preferred (*28—30*).

Industrial additives and flame retardants. Trialkyl phosphates, used as industrial additives and flame retardants, can be analysed by GC—MS and LC—MS. The initial work on their analysis mostly employed GC—MS (*31—34*). GC—MS has been used to analyse water samples for trialkyl phosphate flame retardants as the electron capture negative ion mode lacks sensitivity for halogenated trialkyl phosphates, including tris(2-chloroethyl) phosphate, tris(2-chloro-1-methylethyl) phosphate and tris(2-chloro-1-(chloromethyl)ethyl) phosphate (*35*). More recently, enabled by improvements in LC separation and requirements for multiresidue methods, LC—MS has been used to analyse these compounds.

7.3.1.2 GC—MS following derivatisation

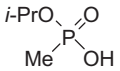
Small polar acidic organophosphorus compounds cannot usually be analysed by GC—MS without derivatisation. Some examples of these, which are often environmental hydrolysis products or

metabolites, are given in Fig. 7.3.1.2.1. Many reagents have been developed for analytical derivatisations: they are used to convert target molecules to more volatile and/or less polar compounds or confer special properties to the derivative, for example, enhanced detectability (addition of ultraviolet (UV) chromophore) or sensitivity. Strategies for organophosphorus acids include methylation using diazomethane (*23*) and trimethylphenylammonium hydroxide or trimethylsulphonium hydroxide (*36*), silylation (*37*,*38*) or acylation (*39*–*42*). The amino group of herbicide hydrolysis products can be treated with chloroformate reagents (*43*,*44*). Advantages and disadvantages of strategies for derivatising nerve-agent degradation products have been reviewed (*45*).



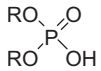
Aminomethylphosphonic acid

Degradation product of the herbicide glyphosate



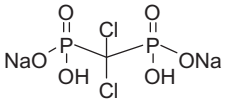
Isopropyl methylphosphonic acid

Degradation product and urinary metabolite of the nerve agent sarin



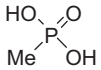
Dialkyl hydrogen phosphates

Degradation products and metabolites of pesticides



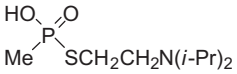
Clodronate disodium

An example of the bisphosphonate class of pharmaceuticals



Methylphosphonic acid

Final degradation product of G and V nerve agents and natural source of CH_4



N,N-diisopropylaminoethyl methylphosphonothioic acid

Toxic hydrolysis product of nerve agent VX

Figure 7.3.1.2.1 Polar compounds not amenable to direct analysis by GC–MS.

The availability of bench-top LC–MS instrumentation has increased LC–MS-based analysis in recent years, although in some cases GC–MS methods are preferred when demanding lower limits of detection are required.

7.3.1.3 GC–MS using chemical ionisation (CI)

The majority of GC–MS instruments have rapidly interchangeable electron impact (EI) and chemical ionisation (CI) sources. Various reagent gases have been used to promote ionisation in CI experiments including methane, isobutane (which results in less fragmentation) and ammonia. Methane has a low proton affinity and can result in unwanted formation of protonated molecules from a wide range of

background chemicals including hydrocarbons. In such matrices, isobutane or ammonia, which have higher proton affinities, are preferred as reagent gases. Applications of CI are varied; the technique is particularly suited to establishing the molecular weight of compounds and is therefore useful for identification and screening applications; e.g. to characterise reaction mixtures or screen for compounds that do not produce molecular ions or highly characteristic EI mass spectra (for example, *O*-alkyl *S*-2-dialkylaminoethyl alkylphosphonothiolates) (*46*). All three reagent gases have been used successfully to analyse organophosphorus nerve agents and their impurities and degradation products (*46*,*47*).

Another widespread application of CI has been trace analysis, where analytical derivatives containing electron-capturing groups have enabled the development of negative-ion chemical ionisation (NICI) methods with low detection limits for degradation products and metabolites of nerve agents (*39*,*40*), metabolites of OPPs (*41*,*42*) and herbicides (*43*,*44*).

Conditions for CI experiments are instrument/ionisation source-dependent but generally GC–MS methods can be identical, or closely similar, to those of EI experiments. Subtle differences include increasing the mass range to cover the range of adduct ions; for example $(M + C_2H_5)^+$ and $(M + C_3H_5)^+$ ions often form when using methane reagent gas. Instructions for setting up CI experiments for maximum sensitivity are provided by instrument manufacturers. Test chemicals such as octafluoronaphthalene or decafluorobenzophenone are used to optimise performance in CI mode (particularly NICI) because of their favourable electron-capturing properties.

7.3.2 Liquid chromatography–mass spectrometry

The technique of LC–MS has developed rapidly since its commercialisation in the late 1980s. Improvements in LC and mass analysers have resulted in methods that can be used for nontargeted screening of up to 500 pesticides, including organophosphorus ones, at parts per billion (ppb) concentrations in less than 3 minutes (*49*). High-resolution measurements are now made on bench-top instruments using Orbitrap™ (*49*,*50*) or time-of-flight mass analysers (*51*). The quadrupole analyser remains useful for targeted analysis of OPPs, particularly in triple quadrupole format, because of its high selectivity and sensitivity.

Advances in LC pump design, separation techniques and column particle technology have occurred. The introduction of UPLC (*52*,*53*) has reduced analysis times considerably. Hydrophilic interaction LC (HILIC) (*54*–*56*) and mixed mode LC (*57*) have improved retention of small highly polar molecules and simultaneous separation of charged/noncharged acidic and basic analytes. Many commercial separation possibilities beyond those offered by standard reverse phase chemistry now exist.

Modern ionisation techniques such as ESI and atmospheric pressure chemical ionisation (APCI) are applicable to many organophosphorus chemicals. Commercial atmospheric pressure photo ionisation sources are worth considering for molecules containing aromatic groups and for other specialist applications. Note that ionisation techniques and conditions require compound-specific optimisation. Ionisation efficiency can vary considerably across a compound class when using gradient separations, as it is affected by the mobile phase composition.

LC—MS is particularly applicable to chemicals that are not amenable to analysis by GC—MS without time-consuming derivatisation. LC—MS-compatible organophosphorus chemicals include the acidic species in Fig. 7.3.1.2.1, urinary metabolites and environmental degradation products of some pesticides; alkyl alkylphosphonic acids R′O(R)P(O)OH and alkylphosphonic acids $RP(O)(OH)_2$ (urinary metabolites and environmental degradation products of nerve agents and some flame retardants). Some polar and thermally labile OPPs are much more amenable to LC—MS than to GC—MS. The range of column technologies is vast; however standard reversed phase stationary phases (octadecylsilyl, C18) are still widely used. A generic LC—MS method for the analysis of polar and nonpolar organophosphorus compounds appears in Table 7.3.2.1.

Table 7.3.2.1 A generic LC—MS method based on reversed-phase separation

Parameter	Setting	Notes
LC parameters		
Column	150 by 2.0 mm C18 (3 or 5 μm particle size)	Smaller particle size columns and UPLC conditions are increasingly being used for LC separations
Mobile-phase gradient	**APCI** A: 20 mM ammonium formate in water B: 20 mM ammonium formate in methanol	These mobile-phase compositions are applicable to both positive- and negative-ion mode analysis; their modification can alter selectivity.
	ESI A: 0.1% formic acid in water B: 0.1% formic in acetonitrile	Ammonium acetate can be used instead of ammonium formate.
Mobile-phase flow rate	200 μl/min	Higher flow rates are used under UPLC conditions
Mobile-phase gradient	5% B (0—5 min) to 90% B (15 min). Hold at 90% B (5 min)	Longer hold times at 90% B can be used to elute late-eluting compounds e.g. trialkyl phosphates (alkyl > C_4). An equilibration time (2 min) for the starting mobile-phase composition is essential.
MS parameters		
Source conditions	**APCI** Vaporiser temperature = 400 °C Corona current = 4—6 μA **ESI** ESI voltage = 3—5 kV	
Source Collision induced dissociation (CID)	5—25 V	Higher voltages will result in in-source fragmentation.
Mass range	m/z 40—400	
Scan rate	1 scan/s	Set by automatic gain control in ion trap instruments.
Sheath, sweep and auxiliary gas	Nitrogen	Flows are dependent on manufacturer's recommendations.

7.3.2.1 LC–MS analysis of specific organophosphorus chemicals

Organophosphorus nerve agents. Alkyl alkylphosphonofluoridates RO(R′)P(O)F hydrolyse quite readily in water but survive long enough to be analysed in aqueous samples using the ESI conditions given in Table 7.3.2.1. Ionisation produces the protonated molecule (MH^+). A common fragment ion for fluoridates in the CWC Schedules is *m/z* 99 from loss of an alkyl moiety from the alkoxy group with proton transfer; for example $(MH^+-C_3H_6)^+$ for sarin (*58*,*59*). LC–MS is particularly useful for studying amiton (*60*) and V class nerve agents (*61–63*).

Dialkyl alkylphosphonates. Dialkyl alkylphosphonates $(RO)_2P(O)R'$ are impurities and degradation products often present in samples of nerve agents such as sarin. They are sufficiently soluble in water to be extracted from environmental samples and water-immiscible organic material and ionise successfully under APCI and ESI conditions. Specific methods for their analysis have not been developed but the generic method in Table 7.3.2.1 is applicable. Dialkyl alkylphosphonates are easily distinguished from alkyl alkylphosphonic acids RO(R′)P(O)OH (nerve agent hydrolysis products) by a lack of response in the negative-ion mode (*64*).

Nerve agent hydrolysis products. LC–MS is useful for detecting alkyl alkylphosphonic acids RO(R′)P(O)OH and alkylphosphonic acids $R'P(O)(OH)_2$ using electrospray (ESI) and APCI sources (*65–67*). It is also useful for detecting the degradation products of VX (*68*). The lowest detection limits are obtained in negative-ion modes. Detection limits are modest (5–10 μg/ml in water in full-scan positive-ion mode) for the polar hydrophilic alkylphosphonic acids, which are poorly retained on the standard reversed-phase columns. Lower limits of detection are achievable using tandem MS in negative-ion modes. Highly sensitive methods using HILIC and tandem MS (LC–MS–MS) have been developed for specialist applications such as urine analysis (*69*,*70*). HILIC columns retain alkylphosphonic acids better than standard C18 reversed-phase columns. In our laboratory, we have applied mixed mode anion exchange reversed phase columns to separate methylphosphonofluoridic acid MeP(O)(F)OH from methylphosphonic acid $MeP(O)(OH)_2$ with significant retention of both analytes. Peak shape and sensitivity depend upon the buffer concentration and mobile phase composition, and the analysis requires more development than methods based on reversed phase separation. An example separation of $MeP(O)(OH)_2$ and MeP(O)(F)OH is shown in Fig. 7.3.2.1.1. The more hydrophobic alkyl alkylphosphonic acids such as pinacolyl methylphosphonic acid (the first hydrolysis product on the nerve agent soman) elute late under these conditions.

Organophosphorus pesticides. OPPs have been replaced by chemicals of lower environmental impact over the last 20 years. Despite this, regulatory requirements still demand monitoring and control of OPP residues in food and therefore considerable research on 'multiresidue methods' to detect a diversity of pesticides has been conducted. Recent developments in LC and MS methodologies have improved the speed and sensitivity of the analysis. UPLC and high-resolution MS are now capable of screening for a wide range of pesticide residues in food (up to 300 pesticides in less than 5 minutes with low ppb detection limits) (*49*). A multiresidue method (116 pesticides) based on UPLC and tandem MS using a triple quadrupole mass spectrometer has been reported (*71*). The lowest limits of detection

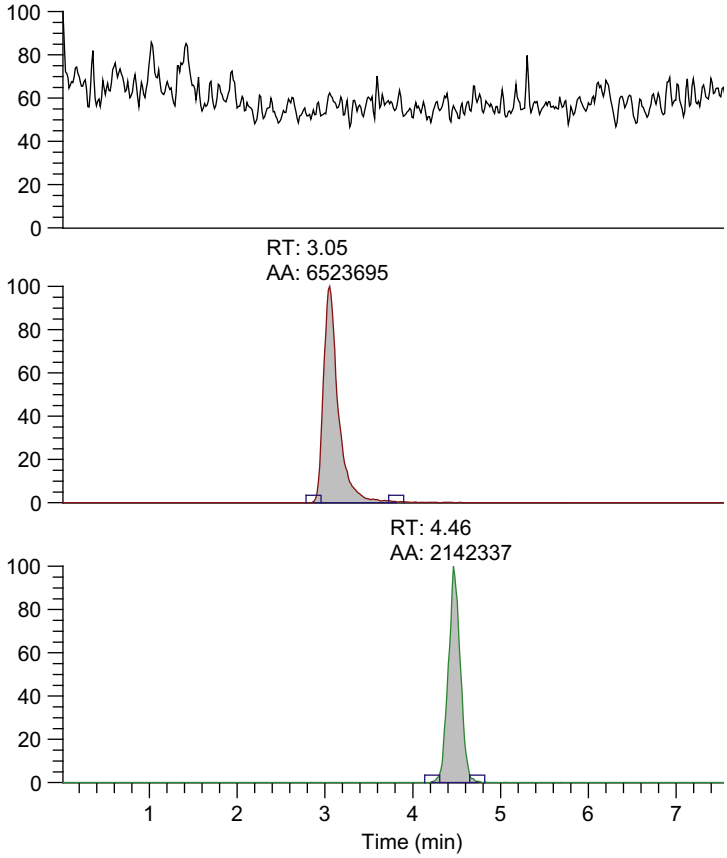


Figure 7.3.2.1.1 Separation of nerve-agent precursor hydrolysis products methylphosphonic acid (*middle trace*) and methylphosphonofluoridic acid (*bottom trace*) using a mixed mode LC column. (For a colour version of this figure, the reader is referred to the online version of this book.)

for targeted pesticide analysis are currently achieved using LC—MS—MS with triple quadrupole mass spectrometers (72,73).

Metabolites of OPPs. Another development driven by water quality assurance and food safety is the analysis and identification of pesticide metabolites. OPPs hydrolyse in the body to the species shown in Fig. 7.3.2.1.2. Thiono (P═S) compounds are usually oxidised in the body to the more toxic oxono (P═O) metabolites. About 75% of registered OP insecticides are metabolised to such products. These highly polar metabolites are difficult to quantify by GC—MS methods because of difficulties in reproducing derivatisation procedures and the complexity of the matrices (usually urine or blood). Advances in separation technologies and the availability of bench-top high-resolution mass spectrometers, such as those based on time of flight, and Orbitrap™ mass spectrometers, have improved the speed and precision of such analyses, which can be used to estimate the exposure of the general population to pesticides. Sometimes, a more specific metabolite released during

binding of the pesticide to AChE can be used for biomonitoring (e.g. *p*-nitrophenol can be used for parathion-methyl). However, many assessments of OPP exposure rely on the analysis of dialkyl hydrogen phosphates in urine (*74*) by GC—MS (*75*,*76*) and LC—MS (*77*). LC—MS methods are preferred because of reduced sample preparation time (no derivatisation), speed of analysis and high sensitivity. Separation of dialkyl hydrogen phosphates using standard reversed phase columns can sometimes be difficult, and HILIC has been used to improve separation and minimise ion-suppression effects (*78*).

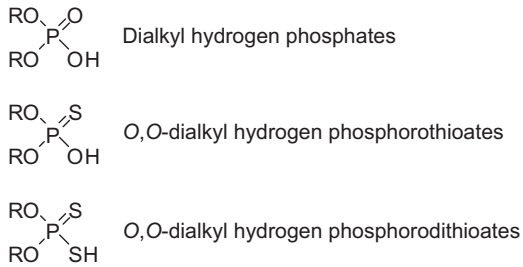


Figure 7.3.2.1.2 Types of OPP urinary metabolites.

Dialkyl hydrogen phosphates are also metabolites of emerging organophosphorus flame retardants (*5*) whose health effects and environmental persistence are an increasing cause for concern.

Phosphorus-containing herbicides. The analysis of broad-spectrum herbicides, including glyphosate (Fig. 7.2.3.1) and its metabolite aminomethylphosphonic acid (Fig. 7.3.1.2.1), is challenging. Concern over their persistence and toxicity in the environment has resulted in the development of sensitive analytical methods. Their polar and amphoteric nature means that even LC—MS-based methods require derivatisation to achieve adequate sensitivity (*79*), although advances in separation technologies have enabled sensitive methods based on a direct analysis by LC—MS (*80*,*81*). Such analytes are also suited to inductively coupled plasma MS (ICP-MS) detection and CE-based techniques that are discussed later.

Bisphosphonate drugs. Analysis of bisphosphonate drugs (Fig. 7.3.1.2.1 and Chapter 1) is particularly challenging. They are highly polar, multiply charged in solution and lack a UV chromophore. GC following derivatisation is one option (*82*) but direct analysis by LC is preferred because of the sample matrices involved (biomedical samples such as blood and urine). Bisphosphonates elute using standard reversed-phase LC near the column dead volume and are difficult to separate. Derivatisation (methylation) is therefore recommended prior to LC—MS analysis (*83*). Ion chromatography (*84*) and CE (*85*) are suitable separation techniques. MS is the conventional detection technique and has included ICP-MS (*86*) and ESI (*87*). Analysis in negative-ion mode would normally be preferred for this class of compound (anionic species),

however poor retention by reversed-phase separation using standard chromatographic solvents provides only modest sensitivity (*88*,*89*).

Industrial additives and flame retardants. Diethylphosphinic acid $Et_2P(O)OH$ (Fig. 7.2.2.1) has been used as a flame retardant (*5*) and as a candidate replacement for brominated flame retardants. A good choice of analytical method for this compound would be the generic LC—MS method given in Table 7.3.2.1. Similar to the situation for alkylphosphonic acids, HILIC or mixed-mode LC phases may offer specialised solutions. LC—MS is increasingly being applied to the analysis of trialkyl phosphate flame retardants and additives (*6*,*90*,*91*). Detection limits generally compare with the ones obtained using GC—MS, although LC—MS—MS may offer enhanced detection limits in some cases (owing to the difficulty of producing molecular ions from some branched trialkyl phosphates). Non-halogenated, chlorinated and brominated organophosphate flame retardants in herring gulls eggs at very low concentrations have been analysed by LC—MS—MS (*92*). LC—MS can also have disadvantages such as the formation of sodium adducts in some environmental samples (soil/sediment extracts). Reviews describe the range of sample preparation and extraction methods used for environmental applications (*5*,*6*).

7.3.3 Gas chromatography

GC with selective detection (flame photometric, nitrogen—phosphorus, or atomic emission detection), is used to analyse organophosphorus chemicals in environmental samples, food and drink. The main detection options are now discussed.

7.3.3.1 Flame photometry

The flame photometric detector was invented in the late 1950s for measuring aromatic hydrocarbons in coal gas. The detector relies on light emission from a hydrogen-rich flame. A narrow band-pass filter is used to select light from the chemical element of interest for detection in a photomultiplier tube. Flame photometry has been used for selective and sensitive detection of compounds containing phosphorus and/or sulfur based on a narrow band pass filter at 532 nm for phosphorus-containing compounds and 332 nm for those containing sulfur. The detector is available from several manufacturers in dual format incorporating the two filter and photomultiplier combinations to enable phosphorus and sulfur compounds to be detected simultaneously. This is an ideal format for screening for OPPs and military nerve agents; several examples of which contain both phosphorus and sulfur. The flame photometric detector can detect OPPs at low ppb concentrations (phosphorus detection). The detector response is linear over two to three orders of magnitude. In sulfur mode, the response is exponential (doubling the sulfur concentration approximately quadruples the signal). General conditions for a GC-based method with FPD are listed in Table 7.3.3.1.1.

A powerful technique for environmental screening, employing flame photometry in parallel with MS, uses a microfluidic splitter to divide the flow between the two detectors. This technique conveniently identifies phosphorus and sulfur-containing chemicals in complex environmental samples and allows their mass spectra to be isolated from background material. An

Table 7.3.3.1.1 A generic GC–FPD method

Parameter	Setting	Notes
GC parameters		
Column	15–20 m, 0.33 mm i.d. (0.33 μm film thickness) 1701 phase	25–30 m, 0.20–0.25 mm i.d. (0.25–0.33 μm film thickness), 95% methyl–5% phenyl polysiloxane low bleed column (various manufacturers) used for experiments employing simultaneous FPD and MS detection. The 1701 phase column is applicable to a wide range of organophosphorus chemicals.
Injection mode	Splitless	Large-volume injection (LVI) can be used for enhanced sensitivity. Retention index data valid only in splitless mode.
Injection volume	1 μl	Higher for LVI.
Temperature	250–280 °C	The response of some analytes relevant to the CWC, for example symmetrical pyrophosphonates of structure RO(R′)P(O)OP(O)(R′)OR, is temperature-dependent and lower temperatures or on-column injection should be used.
Carrier gas	Helium	Constant-pressure or constant-flow mode.
Septum purge flow	2–4 ml/min	
Temperature programme	40 °C (1 min) to 280 °C at a rate of 10 °C/min (hold for 5–10 min)	Subtle modifications can improve separation of specific compounds.
FPD parameters		
Detector gas conditions	**Phosphorus mode (532 nm filter)** Hydrogen = 75 ml/min Air = 100 ml/min Nitrogen = 60 ml/min **Sulfur mode (393 nm filter)** Hydrogen = 50 ml/min Air = 60 ml/min Nitrogen = 60 ml/min	Response in sulfur mode is quadratic in nature. Limited dynamic range for quantitative work (three orders of magnitude).
Detector temperature	250 °C	

example of the analysis of a soil extract contaminated with the nerve agent VX and fuel based hydrocarbons is shown in Fig. 7.3.3.1.1. The phosphorus and sulfur containing peaks can be clearly isolated to aid the MS identification process. FPD continues to be used for the targeted detection of phosphorus-containing chemicals as demonstrated by recent publications describing the analysis

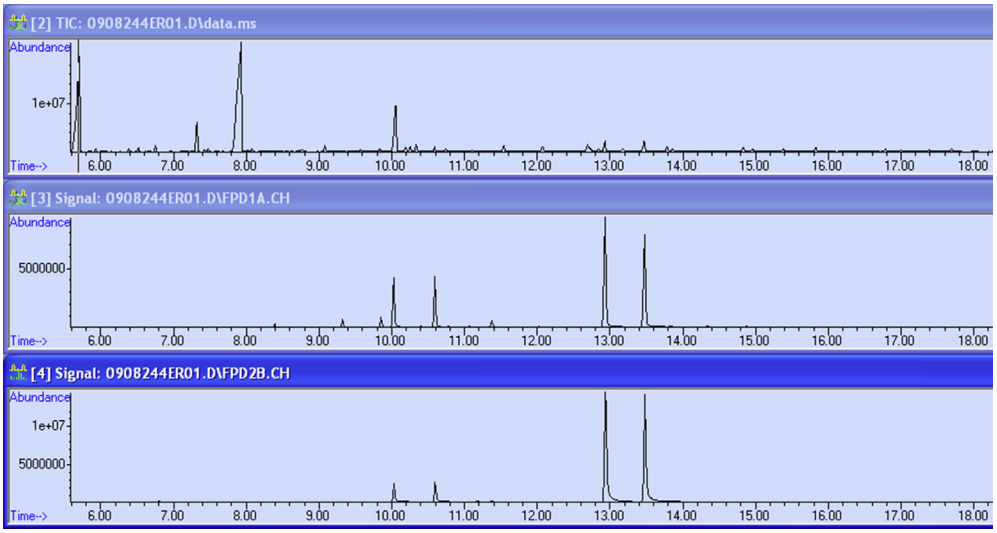


Figure 7.3.3.1.1 Simultaneous GC—MS (*upper trace*) and dual FPD (sulfur (*middle trace*) and phosphorus (*lower trace*)) analysis of V class nerve agents in a complex hydrocarbon matrix. (For a colour version of this figure, the reader is referred to the online version of this book.)

of pesticides in water (*93*), agricultural products (*94*) and food (*95*,*96*), as well as flame retardants in air (*97*) and sediments (*98*).

7.3.3.2 Nitrogen—phosphorus detection

The nitrogen—phosphorus detector (NPD), or thermionic detector, consists of a heated catalytic bead sensitive to phosphorus and nitrogen-containing chemicals. The bead emits electrons by thermionic emission. These electrons are collected under a potential of a few volts by an anode and provide a background current. A solute containing nitrogen or phosphorus elutes from the chromatography column and the partially combusted nitrogen and phosphorus materials are absorbed by the bead. The adsorbed material reduces the work function of its surface and the emission of electrons and the current collected at the electrode increases. The detector is more sensitive to phosphorus than nitrogen and signals from each element are not differentiated. Advantages include high sensitivity and selectivity, particularly to phosphorus-containing chemicals for which low ppb concentrations can be measured; and disadvantages include the vulnerability of the detector to poisoning by halogenated solvents and silicon-containing chemicals. The NPD continues to be used for screening and targeted detection of organophosphorus chemicals as demonstrated by recent publications on the analysis of OPPs in air (*99*) and food (*100*—*102*), and the analysis of organophosphorus petroleum additives (*103*) and flame retardants in air (*104*,*105*).

7.3.3.3 Atomic emission detector

The atomic emission detector (AED) is particularly suited to the analysis of heteroatoms such as phosphorus and sulfur. Molecules eluted during GC are atomised to excited states in a microwave

plasma. Relaxation to the ground state results in the emission of light at wavelengths characteristic of the component elements, which is detected by a spectrometer. Application of AED to phosphorus-containing compounds has reduced in recent years possibly due to the more widespread use of ICP-MS. The AED has been used to analyse pesticides in food (*106–108*) and water (*109,110*), nerve agent chemicals (*111*) and flame retardants (*32*).

7.3.4 IR spectroscopy

IR spectroscopy was the favoured technique for the identification and characterisation of functional groups in organophosphorus compounds until the advent of NMR spectroscopy. Nowadays, IR spectroscopy is used to a lesser extent, although low-cost bench-top portable Fourier transform IR spectrometers have found application in quantitative analysis for monitoring reactions and identifying unknowns. Literature on the interpretation of IR spectra is extensive (*112–114*). Detailed correlations of IR absorption frequencies for different functional groups attached to phosphorus atoms have been made by L. C. Thomas (*115,116*) and remain the most comprehensive. The phosphoryl group (P═O) is characterised by a medium-strong absorption band between 1087 and 1415/cm. This is wide but the shape of the band is characteristic and easily recognised. The range is narrower for the families of compounds in Table 7.3.4.1 (*115,116*).

If hydroxyl groups bound to phosphorus are present, the P═O vibration frequency lowers due to hydrogen bonding and the band becomes much broader; this is due to the variation in the extent of hydrogen bonding between the OH group and the P═O (or P═S) group. The P═O vibration frequency increases as the electronegativity of the substituents on the phosphorus atom increases. IR spectroscopy has been used to show that the equilibrium between dialkyl *H*-phosphonates $(RO)_2P(O)H$ and dialkyl phosphites $(RO)_2POH$ favours the former tautomer (confirmed presence of P═O and P–H, and absence of P–OH) (*115,116*).

The P–OH group is easily recognised as the P–O and O–H stretching vibrations are highly characteristic. Dialkyl phosphinic acids $R_2P(O)OH$ give five absorption bands in the regions 2525–2725, 2080–2350, 1600–1740, 917–1040 and 450–540/cm. The relative intensity of the bands can be a useful guide to the type of phosphorus acid. For example for dialkyl hydrogen phosphates $(RO)_2P(O)OH$, the 2600/cm band is the strongest, whereas for dialkyl hydrogen

Table 7.3.4.1 Infrared absorption frequency ranges for P═O vibrations in various compounds

Structure	Frequency range (/cm)	Structure	Frequency range (/cm)
$R_2P(O)OH$[a]	1087–1205	$R_3P{=}O$	1143–1204
$RO(R')P(O)OH$[a]	1170–1225	$(RO)_3P{=}O$	1252–1314
$(RO)_2P(O)H$	1210–1261	$R_2P(O)OP(O)R_2$[c]	1206–1239
$RP(O)(OH)_2$	1150–1220	$RO(R')P(O)OP(O)(R')OR$	1253–1266
$ROP(O)(OH)_2$[b]	1250	$(RO)_2P(O)OP(O)(OR)_2$	1282–1307
$(RO)_2P(O)R'$[a]	1225–1282	$(RO)_2P(O)OP(OR)_2$	1260–1282

[a]R = H, alkyl or aryl. Frequency ranges measured for more than 10 compounds, except, [b]for one compound, and [c]for eight compounds.

phosphinites $R_2P(O)OH$, the 1700/cm band is invariably the strongest. The three bands are of roughly equal intensity in phosphonic acids.

In P═S compounds diffuse bands occur in the regions 3000–3100 and 2200–2360/cm, and the P–O vibration is found in the region 909–932/cm, as opposed to 914–1040/cm for the phosphinic acids.

Affordable IR portable devices based on attenuated total reflectance IR spectroscopy are now available and bench-top GC–IR instruments have been developed. Detection limits are modest compared to MS-based techniques but can aid structural identifications. For example, pairs of dialkyl iso- and *n*-propylphosphonates, alkyl iso- and *n*-propylphosphonochloridates and alkyl iso- and *n*-propylphosphonofluoridates have been analysed by LC–ion trap tandem MS and GC–Fourier transform IR spectroscopy (*117*). The *P*-propyl isomers could be differentiated reliably by collision-induced dissociation of selected fragment ions and by their IR P═O stretching and C–H deformation frequencies.

7.3.5 Ultraviolet and visible spectroscopy

No common functional groups in four-coordinate pentavalent phosphorus compounds act as chromophores when irradiated with UV or visible (Vis) light. UV–Vis spectroscopy is therefore limited to studies involving absorption by organic substituents such those in aryl-containing organophosphorus compounds (*118*). UV spectroscopy has a role in the monitoring of biologically important phosphates, for example adenosine triphosphate, which absorbs strongly at 259 nm (*119*).

7.3.6 Nuclear magnetic resonance spectroscopy

Phosphorus has only one naturally occurring isotope and only one spin state, which makes ^{31}P NMR spectra simple and highly informative. The nucleus is however, of low sensitivity in comparison with the proton (6.3%). Most phosphorus-containing compounds have chemical shifts spread over a range of just 500 ppm and common functional groups are observed at characteristic positions. Phosphorus NMR spectroscopy is quantitative in its response, allowing components of complex mixtures to be quantified. A good introduction to the basics of ^{31}P NMR spectroscopy is provided in *A Guide to Organophosphorus Chemistry* (*120*). Invaluable reference information appears in the *Handbook of Phosphorus-31 NMR Nuclear Magnetic Resonance Data* (*121*). Commercial libraries of ^{31}P NMR data are also available that include chemical shifts for over 20,000 compounds. Older literature is also worth consulting (*122–126*).

Proton NMR spectroscopy is used routinely for characterising organophosphorus compounds and experimental conditions have become standardised. Chemical shifts can be influenced by the solvent and this must be specified. Ref. (*120*) is a good introduction to the subject and a useful compendium of relevant literature. Chemical shifts and phosphorus-proton coupling constants for organophosphorus compounds have been collated (*127*). In four-coordinate pentavalent phosphorus compounds, the complexity of proton NMR spectra can increase for alkyl groups higher than methyl because of the diastereotopic character resulting from an alkoxy or amino group attached to a phosphorus atom bearing three different substituents (*128*). A good example is diethyl methylphosphonate (*129*). The two protons of the methylene portion of each of the ethyl groups are chemically nonequivalent

(diastereotopic). These protons can couple with each other to give more complicated spectra than expected. This phenomenon is encountered quite regularly in the spectra of organophosphorus compounds. Long-range effects through space rather than through bonds can be observed in spectra of the cyclic phosphorus compounds whose groups are in fixed positions; this effect can be used to distinguish between *cis* and *trans* isomers. ^{31}P NMR data for OPPs (*130*), ^{31}P–^{19}F NMR data for phosphorus–fluorine compounds (*131*), and the application of two-dimensional ^{1}H–^{31}P inverse NMR spectroscopy to the detection of trace amounts of organophosphorus compounds related to the CWC (*132*), have been described.

^{13}C NMR spectroscopy is now used routinely to characterise organophosphorus compounds (*120*). Commercial spectral libraries contain many organophosphorus compounds. A review on NMR techniques for toxic organophosphorus compound profiling (*133*) provides useful information on the analysis of organophosphorus chemicals in biomedical and environmental samples. Although the sensitivity of NMR techniques is lower than MS or photometric detection, OPPs can be detected at low ppm concentrations in water (*134*,*135*). NMR spectroscopy in the study of pesticides has been reviewed (*136*) and the persistence of chlorpyrifos on soil ascertained (*137*). Carbon NMR spectroscopy has been used to assess the efficacy of decontamination of CWAs (*138–142*). It can measure intact and polar degradation products simultaneously in contrast to other techniques such as GC–MS and LC–MS where this is not always possible.

NMR spectroscopy has helped address the mechanism of enzyme inhibition by nerve agents and the structure of phosphonylated enzymes (*143*). It has proved invaluable in studies related to the toxicity of pesticide stereoisomers: studies report higher toxicity for one of the stereoisomers of isoparathion-methyl (*144*) and profenofos (*145*) respectively. NMR spectroscopy is also useful for screening for organophosphorus compounds in unknown samples (*133*). In combination with other techniques such as GC–MS and LC–MS, it has been used in the verification of CWAs (*146*,*147*) and in Proficiency Tests organised by the OPCW (*148*,*149*).

7.3.7 Inductively coupled plasma-based techniques

ICP sources were developed initially for optical emission spectroscopy in the 1960s. Plasma is generated by application of a radio-frequency discharge to an aerosolised sample; it can sustain temperatures of 6000–7000 K and is very reproducible. The spontaneous emission of photons from excited atoms and ions produced in the plasma are measured using a spectrometer (*150*). The technique can detect upwards of 70 elements including phosphorus. The commercial success of the ICP source was soon applied to MS-based detection, and ICP–MS became a mainstream technique in the 1980s. The combination of sample introduction techniques including GC, LC and electrophoresis has been reviewed (*151*). ICP-MS has been used to monitor and understand biological processes (*152–154*). An advantage of ICP-MS is its compound-independent response to phosphorus, although tandem MS experiments are required to identify target analytes. Medium resolution using a sector field mass spectrometer to remove polyatomic interferences to phosphorus can enhance detection limits to sub ng/g levels (*154*).

LC–ICP-MS has great potential for environmental analysis because it provides low detection limits and simple chromatograms (*155*). It has been used to analyse glyphosate and glufosinate and their

metabolites in water (*156–158*), pesticides (*159*), CWA degradation products (LC reversed-phase ion pairing separation (*160*) and GC separation following derivatisation (*161*)) and flame retardants (*162*,*163*).

7.3.8 Capillary electrophoresis

CE, or capillary zone electrophoresis (CZE), separates ionic species by charge, frictional forces and hydrodynamic radius (*164*). Electrically charged analytes move in a conductive liquid under the influence of an electric field. The instrumentation is simple with the main components being a sample vial, source and destination vials, a capillary, electrodes, a high-voltage power supply, a detector, and a data output and handling device. Migration of analytes is initiated by an electric field applied between the source and destination vials and supplied to the electrodes by the power supply. The analytes separate as they migrate due to their electrophoretic mobility and are detected near the outlet of the capillary. The data are displayed in an electropherogram that reports detector response as a function of time. For uncharged analytes adding a surfactant to the electrolyte can facilitate separation (micellar electrokinetic chromatography). A related technique, capillary gel electrophoresis, can separate polymeric charged molecules through size exclusion.

CE is well suited to the study of polar molecules in aqueous samples including blood and urine extracts. The high separation efficiency, speed and low sample consumption are three of its unique features. Various detection methods can be employed including indirect UV (*165*), conductivity (*166*), FPD (*167*) and MS (*168*). Sensitive CE methods for alkylphosphonic acids and their monoesters, and other degradation products of CWAs, have been reviewed (*169*). Limits of detection for alkylphosphonic acids and alkyl alkylphosphonic acids in water are between 48 and 86 μg/ml. The efficiency of extraction of these acids from soil has also been studied using mass spectrometric detection (*170*). Good lower limits of detection (12.5–60 mg/l) were observed for the alkyl alkylphosphonic acids, however poor ionisation efficiency for methylphosphonic acid $MeP(O)(OH)_2$ resulted in a higher lower limit of detection (300 mg/l). Poor ionisation efficiency also results in modest detection limits for this analyte in LC–MS experiments, particularly ones based on standard reversed-phase separation (where the analyte elutes in a high proportion of aqueous mobile phase). Few publications discuss analysis of biomedical samples. OPPs have been analysed by CE (*171–173*). Phosphorothioate oligodeoxynucleotides, a class of antisense oligonucleotides being developed as therapeutic agents, have been studied by both capillary gel electrophoresis (*174*,*175*) and CZE (*176*).

7.3.9 Mass spectrometry of organophosphorus compounds

General reference sources to the mass spectra of organophosphorus compounds are available (*177–179*). EI mass spectra of nerve agents have been reported (*16*,*180–182*). Mass spectral studies have been published to help identify these and related compounds for verification purposes. These are summarized in this section. Many of the fragmentation and rearrangement reactions will apply to related pesticides and industrially important organophosphorus compounds.

Alkyl methylphosphonofluoridates do not produce abundant molecular ions (these are often absent from the mass spectra). Cleavage reactions commonly occur at the C—C bond next to a heteroatom. An example fragmentation of isopropyl methylphosphonofluoridate (sarin) appears in Fig. 7.3.9.1. Ion *m/z* 125 is the second most abundant in the mass spectrum. *O*-Methyl ester analogues of sarin are exceptional and give a molecular ion; cleavage and loss of a methyl radical is not possible in this particular case.

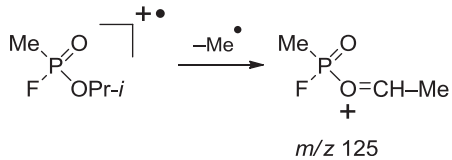


Figure 7.3.9.1 EI fragmentation of sarin by loss of a methyl radical.

A common rearrangement of alkyl methylphosphonofluoridates and dialkyl methylphosphonates involves the migration of two hydrogen atoms. The example in Fig. 7.3.9.2 shows sarin losing a propenyl radical to give a base peak ion of *m/z* 99.

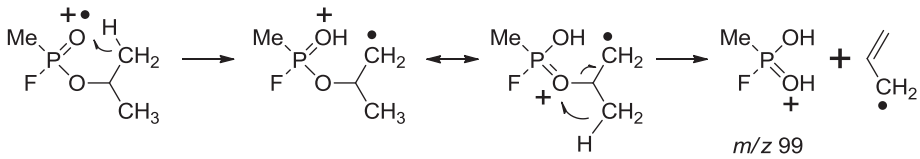


Figure 7.3.9.2 EI fragmentation of sarin with loss of a propenyl radical.

McLafferty rearrangement involving transfer of a hydrogen atom and loss of an alkene from the *O*-alkyl group is rarely observed in the mass spectra of alkyl alkylphosphonofluoridates. The ions of highest mass present depend on the size and branching of the *O*-alkyl group. Observations from several publications of the fragmentation of the nerve agent soman appear in Fig. 7.3.9.3.

Algorithms for the alkyl alkylphosphonofluoridates have been calculated (*181*). The CI spectra of these nerve agents are relatively simple and fragmentation occurs by cleavage of the carbon—heteroatom bonds. Carbon—carbon bond cleavage occurs less under CI conditions as the protonated molecules formed have less excess internal energy.

Another well-studied class is the *O*-alkyl *S*-2-(dialkylaminoethyl) alkylphosphonothiolates or V agents. Their spectra do not contain molecular ions because of the low energy pathway resulting from fragmentation of the sulfur-containing side chain. The base peak is the immonium ion $(CH_2{=}NR_2)^+$ from cleavage of the C—C bond adjacent to the nitrogen atom. Depending on the alkyl substituent, $(CH_2{=}NHR)^+$ and $(CH_2{=}CH_2NR_2)^+$ may be present at lower abundance. Higher mass phosphorus-containing ions are rare but provide useful information when present. Typical fragmentations of V agents appear in Fig. 7.3.9.4.

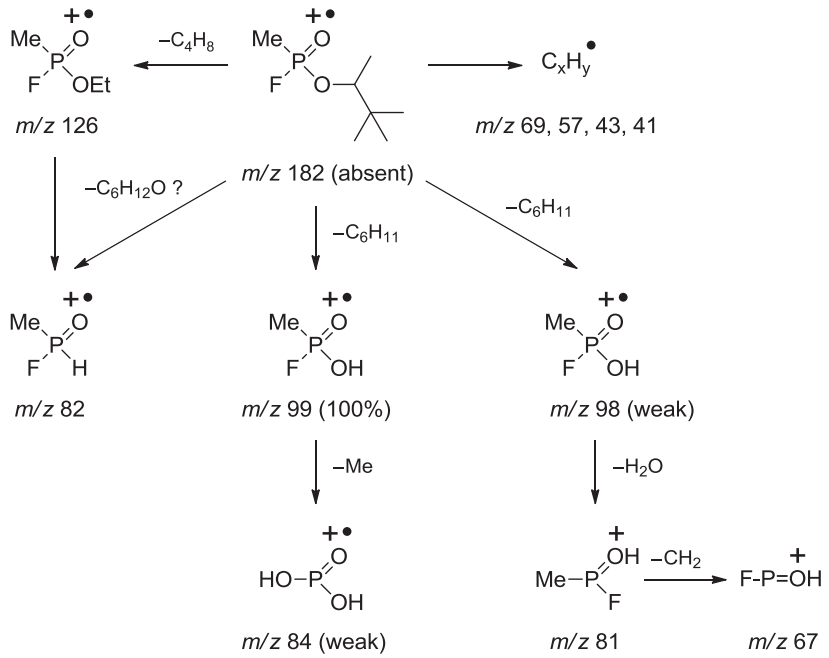


Figure 7.3.9.3 EI fragmentation pathways for soman.

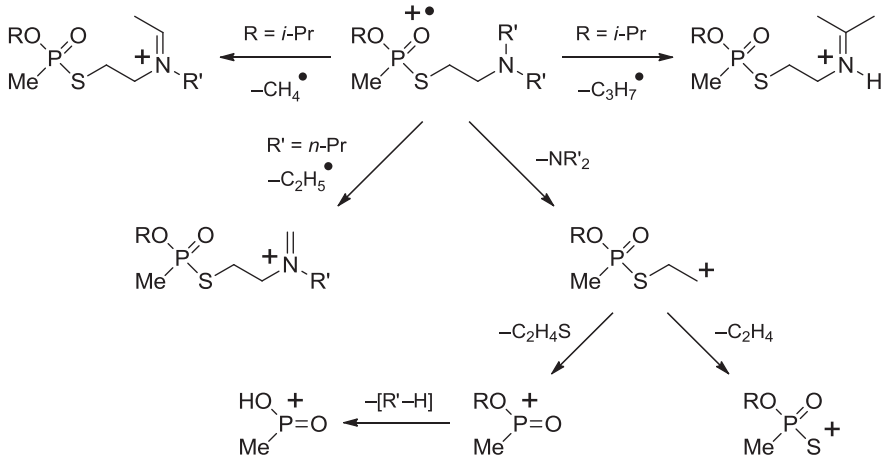


Figure. 7.3.9.4 EI fragmentation pathways for V agents.

Another important class of nerve agent is the *O*-alkyl *N*,*N*-dialkylphosphoramidocyanidates whose spectra contain a moderately abundant molecular ion (whose abundance decreases as the alkyl substituent becomes larger). Fragmentation patterns vary considerably depending upon the nature of the *O*- and *N*-alkyl substituents. The main fragmentations of *O*-ethyl *N*,*N*-dimethyl phosphoramidocyanidate (tabun) appear in Fig. 7.3.9.5.

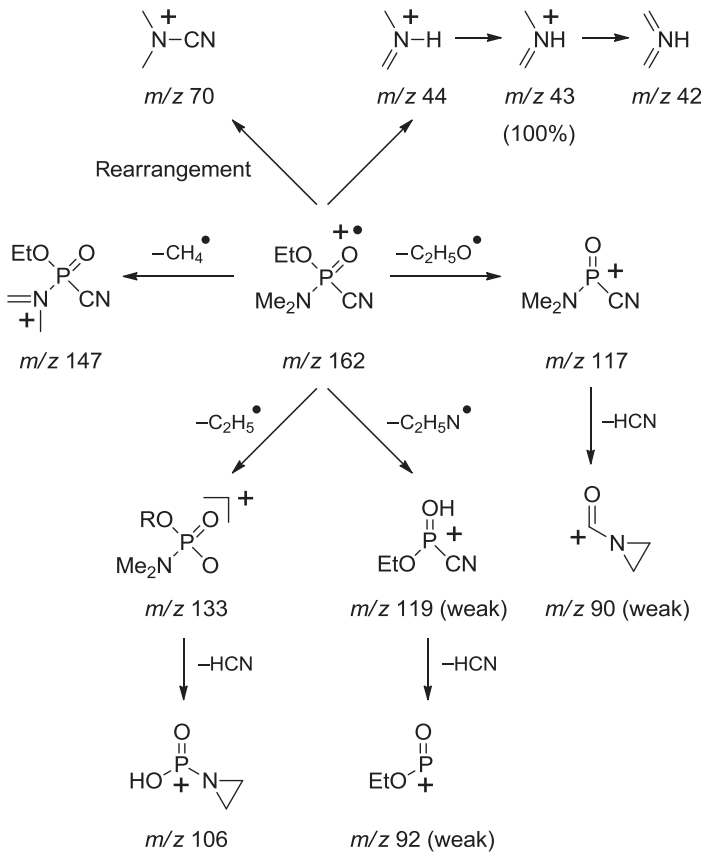


Figure 7.3.9.5 EI fragmentation pathways for tabun.

Dialkyl *H*-phosphonates $(RO)_2P(O)H$ exhibit small or negligible molecular ions in their mass spectra (*182*,*183*). Hydrogen rearrangements which are characteristic of all esters of phosphorus acids are common. The base peak for dimethyl *H*-phosphonate $(MeO)_2P(O)H$ results from loss of CH_2O or H followed by CH_2O giving $(MeOP(OH)H)^+$. The ion *m/z* 83 $((HO)_3PH)^+$ is the base peak for many dialkyl *H*-phosphonates. Degradation of the alkyl chain is only significant if it is branched.

The dialkyl alkylphosphonates $(RO)_2P(O)R'$ have been studied in detail as they are controlled under the CWC and used as fire retardants (*177*). McLafferty rearrangement is possible only when R is greater than ethyl. Except for the methyl substituted compounds, the dialkyl alkylphosphonates behave similarly to alkyl alkylphosphonofluoridates and lose an alkenyl radical to give $(RO(HO)P(O)R')^+$. If both R groups are larger than methyl then further reaction occurs to give $((HO)_3PR')^+$. This fragmentation gives base peaks characteristic of the P-alkyl substituent useful for screening purposes at *m/z* 97 (methyl), *m/z* 111 (ethyl) and *m/z* 125 (propyl). These ions lose water to give *m/z* 79, 93 and 107 (*184*). Some of the more important fragmentations of dialkyl alkylphosphonates appear in Fig. 7.3.9.6.

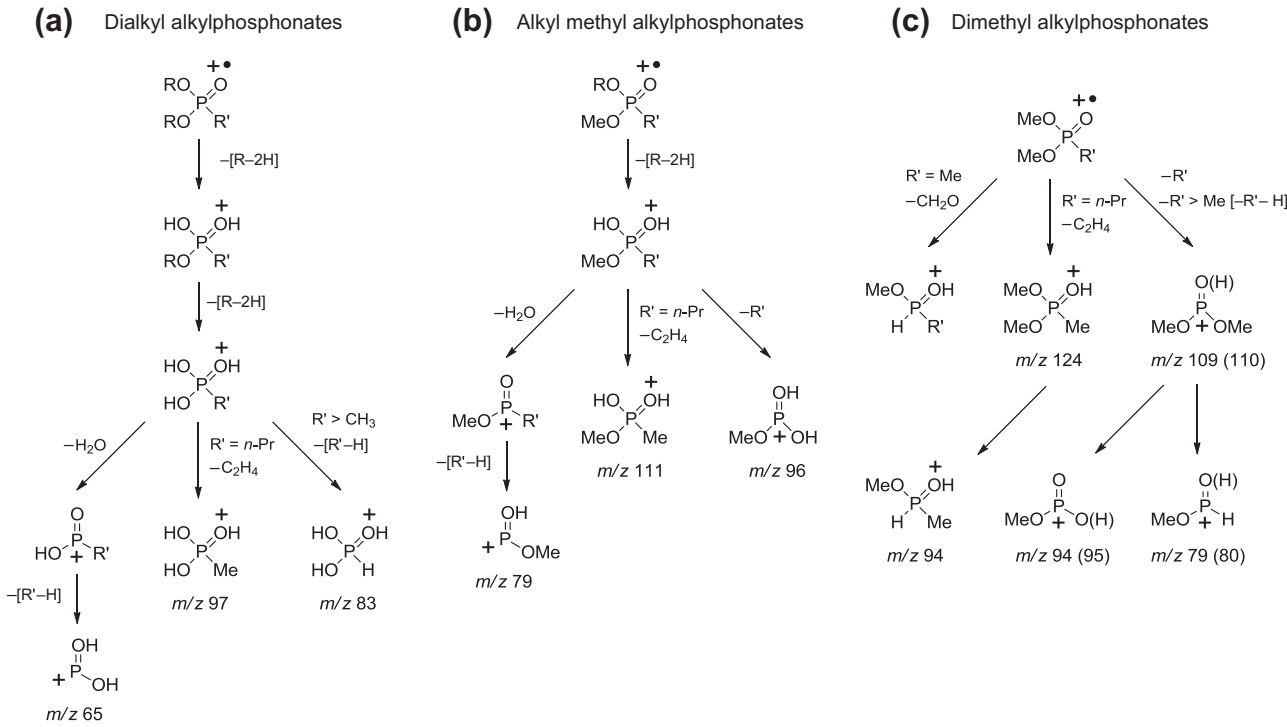


Figure 7.3.9.6 EI fragmentations of (a) dialkyl alkylphosphonates, (b) alkyl methyl alkylphosphonates, and (c) dimethyl alkylphosphonates.

Methane CI mass spectra of dialkyl alkylphosphonates contain a strong peak for the protonated molecule and fragments from loss of alkene from the alkoxy group. Ammonia CI spectra show less fragmentation. Spectra of dialkyl alkenylphosphonates are similar to those of dialkyl alkylphosphonates (*185*).

Triaryl phosphates are thermally stable and are used as lubricant additives and flame retardants. Symmetrical alkyl- and mixed alkyl/aryl-substituted phosphates can undergo thermal degradation prior to mass spectral fragmentation (*177*). Aryl-substituted phosphates are stable under EI conditions and tend to give rise to more intense molecular ions than alkyl-substituted phosphates. The most prominent ions in the spectra of trialkyl phosphates are from a series of rearrangement reactions (*186*) that produce an intense ion at m/z 99.

The fragmentation and reactions of various organophosphorus compounds have been studied by ESI MS. These include isomeric *O*-alkyl *S*-(2-dialkylaminoethyl) methylphosphonothiolates (V agents) (*187*), the pesticide diazinon and its oxygen analogue diazoxon (*188*), isotopically labelled dimethyl methyl phosphono and trimethyl phosphoro thiolates and thionates (*189*), and protonated dimethyl ethylphosphonate (*190*).

7.4 CONCLUDING COMMENTS

This survey suggests the analysis of organophosphorus compounds in different matrices will remain important. Advances in analytical technology are expected to offer great opportunities for scientists seeking to solve novel analytical problems in organophosphorus chemistry.

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