Pyridine and Pyridine Derivatives

ULLMANN'S ENCYCLOPEDIA OF INDUSTRIAL CHEMISTRY

Shinkichi Shimizu, Koei Chemical Co. Ltd., Osaka 541, Japan
Nanao Watanabe, Koei Chemical Co. Ltd., Osaka 541, Japan
Toshiaki Kataoka, Koei Chemical Co. Ltd., Osaka 541, Japan
Takayuki Shoji, Koei Chemical Co. Ltd., Osaka 541, Japan
Nobuyuki Abe, Koei Chemical Co. Ltd., Osaka 541, Japan
Sinji Morishita, Koei Chemical Co. Ltd., Osaka 541, Japan
Hisao Ichimura, Koei Chemical Co. Ltd., Osaka 541, Japan

1. Introduction

Pyridine, C_5H_5N, is a six-membered heterocyclic compound containing one nitrogen atom. Pyridine and its homologues are commonly called pyridine bases. The first pyridine derivative, 2-methylpyridine (α-picoline; *pix*, Latin = pitch) was isolated from coal tar in 1846 by Anderson [1]. In 1851, Anderson obtained pyridine (*pyros*, Greek = fire) and dimethylpyridine (lutidine; *lutum*, Latin = dirt) from bone oil [2].

Ramsay synthesized pyridine in 1876 by passing a mixture of acetylene and hydrogen cyanide through a red-hot tube [3]. Typical syntheses of pyridine derivatives are based on the work of Hantzsch (1882) [4] and Chichibabin (1906) [5]. The method of the latter is especially suitable for mass production and it is still an important industrial process.

Compounds containing a pyridine ring, such as vitamin B_6 (pyridoxine) [6], nicotinamide [7], nicotinic acid, the coenzymes nicotinamide adeninedinucleotide (NAD) and reduced NAD (NADH), and many alkaloids, play important roles in metabolism. Pyridine bases are widely used in pharmaceuticals including nicotinamide and nicotinic acid. Similarly, pyridine derivatives are important insecticides and herbicides due to their high bioactivity. Further, they are used as adhesives for textiles and as chemicals, solvents, and catalysts.

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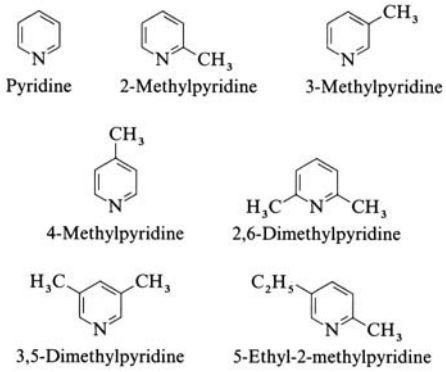
2. Pyridine and Alkylpyridines

Pyridine and alkylpyridines are produced commercially by synthesis as well as by isolation from natural sources such as coal tar. Commercially important compounds are pyridine, 2-methylpyridine, 3-methylpyridine, 4-methylpyridine, 2,6-dimethylpyridine, 3,5-dimethylpyridine, and 5-ethyl-2-methylpyridine.

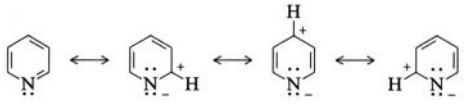


2.1. Properties

Pyridine is miscible in all proportions with water and most common organic solvents and has a boiling point 35 °C higher than benzene.

Physical data of pyridine and alkylpyridines are summarized in Table 1.

Since the pyridine ring has three double bonds, six π-electrons exist, which are sufficient for aromatic ring formation without involving the lone pair electrons of the nitrogen atom. Since the lone pair electrons remains free, quaternary salts retain the aromaticity. However, the nitrogen atom has a higher electronegativity than the carbon atoms and shows an electron-withdrawing effect. This is represented by the resonance hybrids:



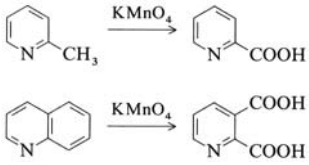
Therefore the electron densities at the 2- and 4-positions are low, and the ring is regarded as a π-electron-deficient aromatic ring. The weak basicity of pyridine and alkylpyridines is due to the lone pair of electrons on the ring nitrogen

Table 1. Physical properties of pyridine and alkylpyridines

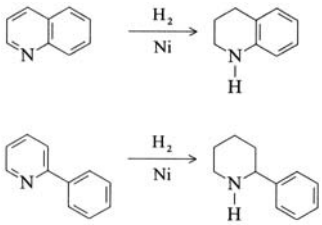
Compound	CAS registry no.	M_r	*mp*, °C	*bp*, °C	d_4^{20}	n_D^{20}	pK_a (H_2O, 25 °C)	Solubility in H_2O at 20 °C, g/100 g	Azeotrope with H_2O		Ignition temperature, °C	Explosion composition, %
									wt % H_2O	*bp*, °C		
Pyridine	[*110-86-1*]	79.10	−41.7	115.3	0.9819	1.5102	5.22	miscible	41.3	93.6	550	1.7 – 10.6
2-Methylpyridine	[*109-06-8*]	93.13	−66.7	129.4	0.9455	1.5010	5.96	miscible	48	93.5	535	1.4 – 8.6
3-Methylpyridine	[*108-99-6*]	93.13	− 18.2	144.1	0.9564	1.5043	5.63	miscible	63	97		1.3 – 8.7
4-Methylpyridine	[*108-89-4*]	93.13	3.6	145.4	0.9546	1.5058	5.98	miscible	63.5	97.35	500	1.3 – 8.7
2,6-Dimethylpyridine	[*108-48-5*]	107.16	− 6.1	144.5	0.9237	1.4977	6.72	27.2 (45.3 °C)	51.5	96.02		
3,5-Dimethylpyridine	[*591-22-0*]	107.16	− 6.5	171.9	0.944	1.5049	6.15	3.3				
5-Ethyl-2-methylpyridine	[*104-90-5*]	121.18	−70.3	178.3	0.9208	1.4974		1.2	72	98.4		

atom. The basicity of pyridine derivatives is increased by electron-donating substituents and decreased by electron-withdrawing substituents.

In oxidation and reduction reactions, the pyridine ring exhibits properties characteristic of π-electron-deficient aromatic rings: resistance to oxidation and facile reduction. In the oxidation of alkylpyridines with alkaline $KMnO_4$, the pyridine ring is not oxidized; instead the corresponding carboxylic acids are formed [8]. Furthermore in the oxidation of quinoline with alkaline $KMnO_4$, the main product is pyridine-2,3-dicarboxylic acid. This shows that the pyridine ring is more stable to oxidation than the benzene ring [9].



On reduction with hydrogen in the presence of catalyst, quinoline and 2-phenylpyridine are reduced preferentially at the pyridine ring [10].



Because of the low π-electron density at the ring carbon atoms, electrophilic reactions rarely occur on the pyridine ring, and they occur at the 3-position only under drastic conditions. Although nitration of pyridine bases is difficult [11], sulfonation occurs more readily [12].

Friedel – Crafts reactions and reactions catalyzed by $PdCl_2$ such as oxychlorination of benzene, which are useful for benzene derivatives, do not take place because of the coordination of the nitrogen atom to $AlCl_3$ or $PdCl_2$. Electron-donating substituents such as hydroxyl, amino, or alkyl groups attached to the pyridine ring facilitate electrophilic reactions because of the increased electron density in the ring.

In contrast, nucleophilic substitution reactions occur readily at the 2-, 4-, and 6-positions. Treatment of pyridine with sodium amide gives 2-aminopyridine (Chichibabin reaction) [13]. Reaction of pyridine bases with Grignard reagent, alkyllithium, or aryllithium gives 2-substituted pyridines [14]. Treatment of pyridine with methanol and hydrogen in the presence of a nickel catalyst gives 2-methylpyridine [15]. Substitution reactions of 2- or 4-halopyridines with nucleophiles, such as alkoxides, thiolates, amines, or carbanions, occur easily and provide important synthetic methods.

Radical reactions of pyridine – for example, the phenylation of pyridine with benzene diazonium chloride – give substituted products in the decreasing order 2- > 3- > 4- [16], and chlorination with chlorine above 270 °C or under UV irradiation gives a mixture of 2-, 4-, and 6-chloropyridines.

In the reaction of substituted groups in the pyridine ring, dealkylation and decarboxylation occur mainly at the 2-position [17], whereas hydroxymethylation of methyl groups with formaldehyde occurs at the 2- and 4-positions [18].

Like aliphatic tertiary amines, pyridine bases give *N*-oxides with hydrogen peroxide and peroxy acids, and form quaternary ammonium salts with alkyl halides.

2.2. Production

2.2.1. Separation from Tar

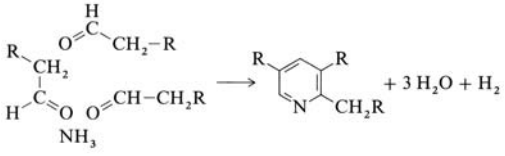
Pyridine bases are a constituent of tars. They were isolated from coal tar or coal gas before synthetic manufacturing processes became established. The amounts contained in coal tar and coal gas are small, and the pyridine bases isolated from them are a mixture of many components. Thus, with a few exceptions, isolation of pure pyridine bases was expensive. Today, almost all pyridine bases are produced by synthesis.

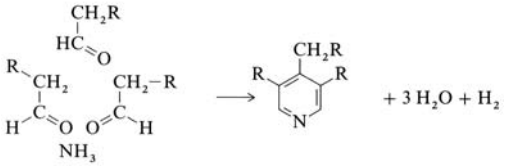
2.2.2. Synthesis from Aldehydes or Ketones with Ammonia

The reaction of aldehydes or ketones with ammonia is the most general synthetic reaction for the manufacture of pyridine bases and allows the

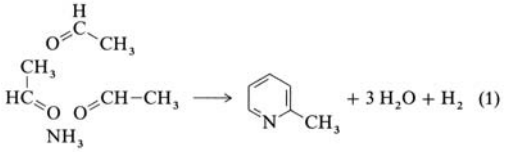
preparation of various pyridines. This reaction was first studied in detail by CHICHIBABIN in 1924 [19] and since then been studied extensively for industrial manufacturing because of cheap access to raw materials. The reaction is usually carried out at 350 – 550 °C and a space velocity of 500 – 1000 h^{-1} in the presence of a solid acid catalyst (e.g., silica – alumina).

Aldehydes react with ammonia as follows:

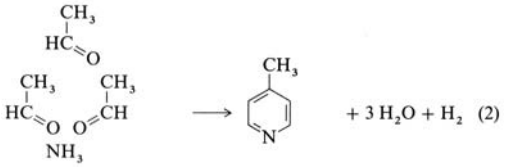




For example, acetaldehyde and ammonia give 2-methylpyridine (Eq. 1) and 4-methylpyridine (Eq. 2). Some examples of the synthesis are given in Table 2.

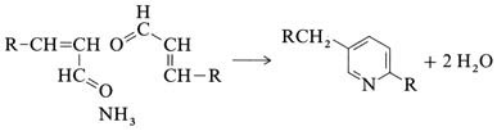


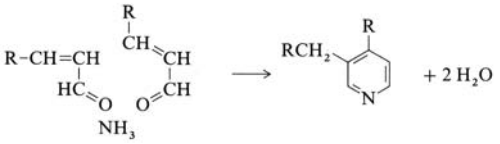
(1)



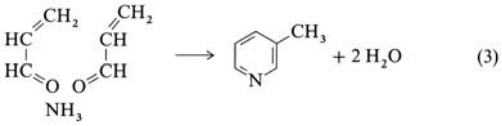
(2)

With α, β-unsaturated aldehydes the reaction occurs according to the following schemes:



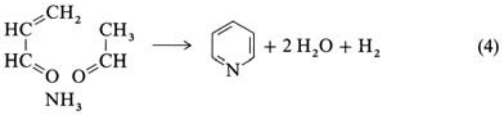


For example, acrolein and ammonia give 3-methylpyridine (Eq. 3); pyridine is simultaneously formed by demethylation. Examples of this synthesis are given in Table 3.



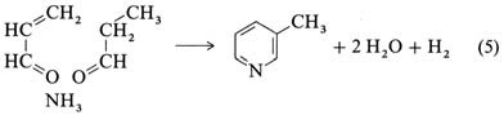
(3)

Acrolein and acetaldehyde react with ammonia mainly to form pyridine:



(4)

Acrolein and propionaldehyde react with ammonia to give primarily 3-methylpyridine (Eq. 5).



(5)

Acetaldehyde and formaldehyde react with ammonia to give mainly pyridine (Eq. 6): they appear to first form acrolein (Eq. 7), and then acrolein and formaldehyde react with ammonia to give pyridine. Simultaneously, 2-, 3-, and 4-methylpyridines are formed, as shown in Equations (1) – (4). This method is one of the most

Table 2. Synthesis of 2- and 4-methylpyridine from acetaldehyde and ammonia

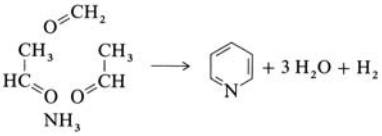
Company	Catalyst	Yield, %		Ref.
		2-Methylpyridine	4-Methylpyridine	
Koei Chemical	$Co_3Al_3(PO_4)_5^-$	45	9	[20]
Nippon Kayaku	Al_2O_3– SiO_2– $CdCl_2$	35	44	[21]

Table 3. Synthesis of 3-methylpyridine and pyridine from acrolein and ammonia

Company	Catalyst	Yield, %		Ref.
		Pyridine	3-Methylpyridine	
Degussa	Al_2O_3– MgF_2	25	49	[22]
ICI	SiO_2– Al_2O_3– H_2SiF_2	62	15	[23]
Nippon Kayaku	SiO_2 – Al_2O_3– CdF_2	26	56	[24]
Koei Chemical	SiO_2 – Al_2O_3– MnF_2	20	45	[25]
Daicel Chemical	SiO_2 – Al_2O_3	22	49	[26]

widely used for pyridine production. Table 4 lists some examples of this process, and Figure 1 illustrates the flow sheet of the plant.

A preheated gaseous mixture of acetaldehyde, 36 % formaldehyde, and ammonia is passed through the reactor (a) packed with the catalyst at 400 – 450 °C. The reaction mixture is separated from ammonia and hydrogen by a collector (b) and extracted with solvent, e.g., benzene (c). The solvent is removed from the extract (d) and pyridine and 3-methylpyridine are isolated in continuous distillation columns (e). The catalyst is periodically regenerated by air.



(6)

$$CH_3CHO + HCHO \longrightarrow CH_2{=}CHCHO + H_2O \qquad (7)$$

Propionaldehyde and formaldehyde react with ammonia to give 3,5-dimethylpyridine (Eq. 8) [31]; benzaldehyde and acetaldehyde

Table 4. Synthesis of pyridine and 3-methylpyridine from acetaldehyde and formaldehyde with ammonia

Company	Catalyst	Yield, %		Ref.
		Pyridine	3-Methylpyridine	
ICI	SiO_2– Al_2O_3– coke	38	25	[27]
Rütgerswerk	SiO_2– Al_2O_3– CdF_2	57	29	[28]
Nepera	ZSM-5*	54	28	[29]
Koei Chemical	Tl – ZSM-5	63	9	[30]

* Zeolite.

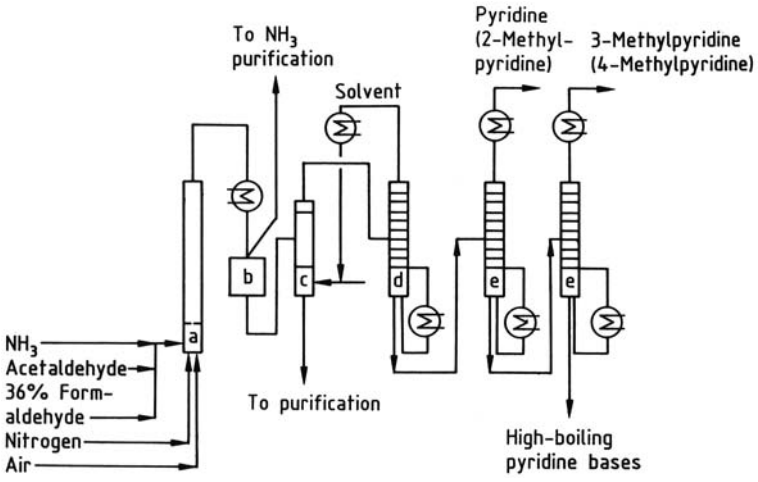
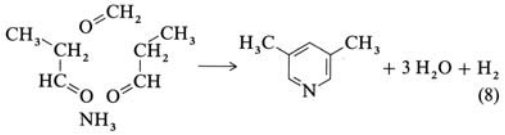
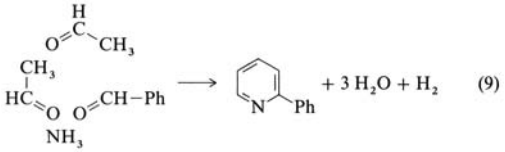
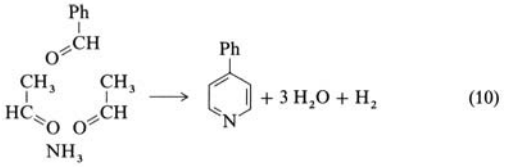


Figure 1. Flow sheet of pyridine and methylpyridine production from acetaldehyde and formaldehyde with ammonia
a) Reactor; b) Collector; c) Extraction; d) Solvent distillation; e) Distillation

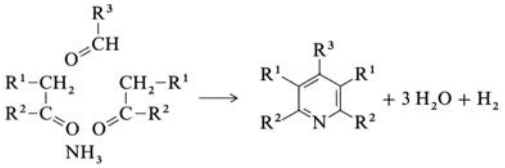
give 2-phenylpyridine [*1008-89-5*] (Eq. 9) and 4-phenylpyridine [*939-23-1*] (Eq. 10) [32].



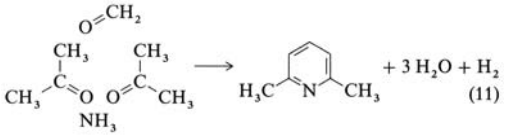




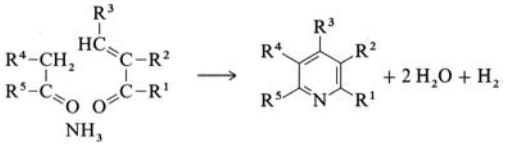
Ketones and aldehydes react with ammonia according to the following general scheme:



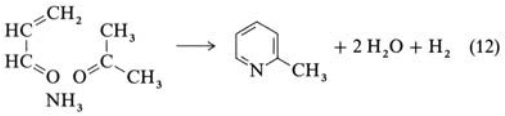
Typically, acetone [*67-64-1*] and formaldehyde with ammonia give 2,6-dimethylpyridine (Eq. 12) [33]:



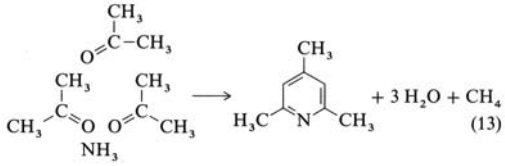
α, β-Unsaturated ketones or aldehydes react with ammonia according to the following scheme:

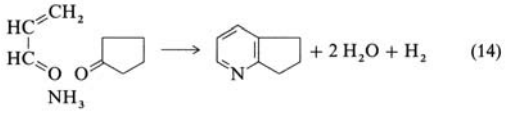


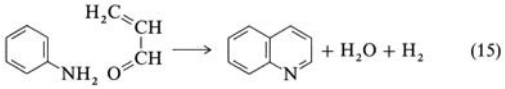
For example, acrolein and acetone react with ammonia to give 2-methylpyridine (Eq. 12) [34]:



As a variant, acetone with ammonia gives 2,4,6-trimethylpyridine [*108-75-8*] with simultaneous demethylation (Eq. 13) [35]. Cyclopentanone [*120-92-3*] and acrolein with ammonia give 2,3- cyclopentenopyridine [*533-37-9*] (Eq. 14) [36]. Using aniline instead of ammonia results in formation of quinoline (Eq. 15):





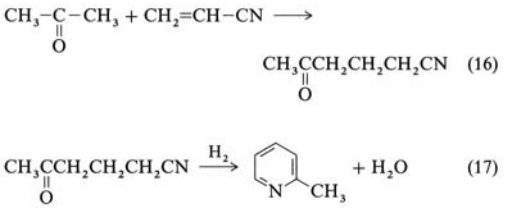


As shown above, various pyridines can be obtained by using different combinations of aldehydes, ketones, ammonia, and amines.

2.2.3. Synthesis from Acrylonitrile and Ketones

Synthesis from acrylonitrile and acetone gives 2-methylpyridine selectively, in contrast to the process using acetaldehyde and ammonia, which gives 4-methylpyridine as a byproduct. First, the reaction of acrylonitrile and acetone, catalyzed by a primary aliphatic amine such as isopropylamine and a weak acid such as benzoic acid [*65-85-0*], occurs in the liquid phase at 180 °C and 2.2 MPa to give 5-oxohexanenitrile [*10412-98-3*], with 91 % selectivity (Eq. 16). The acrylonitrile conversion is 86 % [37]. Then cyclization and dehydration of the initial product are carried out in the gas phase in the presence of hydrogen over a palladium, nickel, or cobalt- containing catalyst at ca. 240 °C to give 2-methylpyridine in 84 % yield (Eq. 17) [38]. 4-Methyl-5-oxohexa-

nenitrile [*10413-01-1*], formed from acrylonitrile and 2-butanone, gives 2,3-dimethylpyridine [*583-61-9*] in 89 % yield [38].

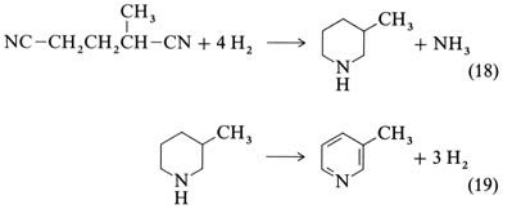


(16)

(17)

2.2.4. Synthesis from Dinitriles

In a vapor-phase reaction over a nickel- containing catalyst in the presence of hydrogen, 2-methylglutaronitrile [*4553-62-2*] gives 3-methylpiperidine [*626-56-2*], which then undergoes dehydrogenation over palladium – alumina to give 3-methylpyridine [39]:



(18)

(19)

A one-step gas-phase reaction over a palladium- containing catalyst is reported to give 3-methylpyridine in 50 % yield [40].

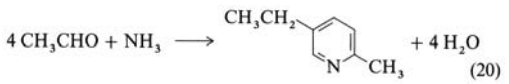
2.2.5. Dealkylation of Alkylpyridines

Alkylpyridines of low commercial value, obtained as byproducts of pyridine base synthesis, are occasionally converted into useful pyridine bases by dealkylation. The methods for dealkylation involve oxidative dealkylation by air over a vanadium oxide catalyst [23], steam dealkylation over a nickel catalyst [24], [25], and hydrodealkylation over a silver or platinum catalyst [44]. Examples are listed in Table 5.

2.2.6. Synthesis of 5-Ethyl-2-Methylpyridine from Paraldehyde and Ammonia

Reaction of paraldehyde with aqueous ammonia in the liquid phase is carried out at 200 –300 °C and 12 – 13 MPa in the presence of an ammonium salt (e.g., ammonium phosphate) to give 5-ethyl-2-methylpyridine (MEP) in about 70 % yield (Eq. 20) [45]. Figure 2 shows the reaction route, and Figure 3 illustrates the manufacture of MEP by the Montecatini – Edison process.

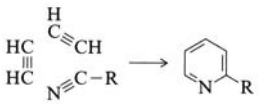
Paraldehyde, produced from acetaldehyde and sulfuric acid, is reacted with 30 – 40 % aqueous ammonia and acetic acid at 220 – 230 °C and 10 – 20 MPa. The reaction mixture is separated into two phases in a separator (c). Ammonia is recovered from the aqueous layer by a stripper (d). MEP, 2-methylpyridine, and 4-methylpyridine are isolated from the organic layer by distillation.



(20)

2.2.7. Synthesis from Nitriles and Acetylene

Liquid-phase reaction of nitriles with acetylene is carried out at 120 – 180 °C and 0.8 –2.5 MPa in the presence of an organocobalt catalyst and gives 2-substituted pyridines [46]:



For example, acetonitrile [*75-05-8*] and acetylene react in the presence of cobaltocene as

Table 5. Dealkylation of alkylpyridines

Starting material	Catalyst	Additives	Yield of pyridine, %	Ref.
3-Methylpyridine	V/Cr/Ag – Al_2O_3	air, H_2O	82	[41]
2-Methylpyridine	Ni – SiO_2	H_2, H_2O	93	[42]
2-Methylpyridine	Ni – ZrO_2	H_2O	50	[43]
Alkylpyridine	Ag	H_2	58	[44]

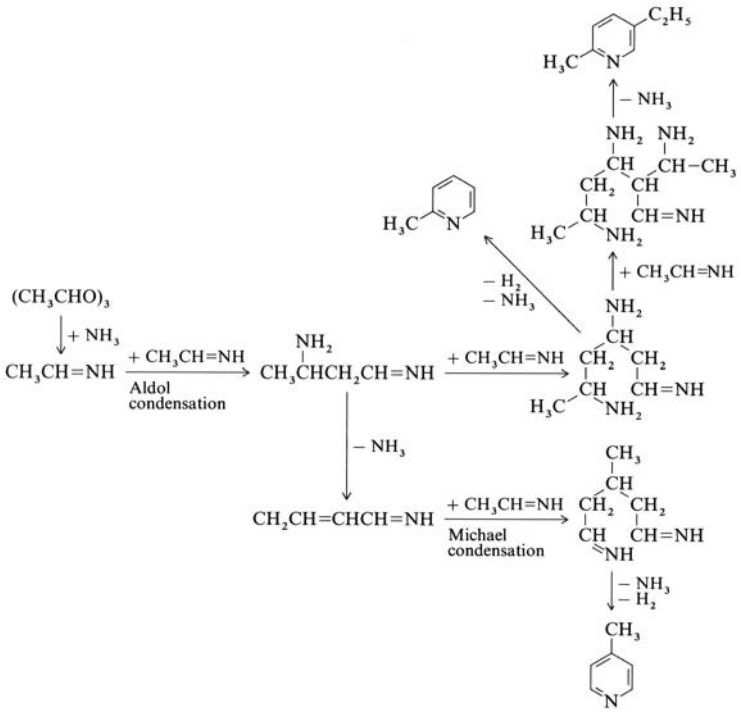


Figure 2. Mechanism of 5-ethyl-2-methylpyridine formation [45]

catalyst to give 2-methylpyridine in 76 % yield [47]. Acrylonitrile and acetylene react in the presence of cyclopentadienylcobalt – cycloocta-1,5-diene catalyst to give 2-vinylpyridine with 93 % selectivity [48].

2.2.8. Other Synthetic Methods

Ethylene [*74-85-1*] and ammonia react in the presence of a palladium complex catalyst to give 2-methylpyridine and MEP [49]. Pyridine

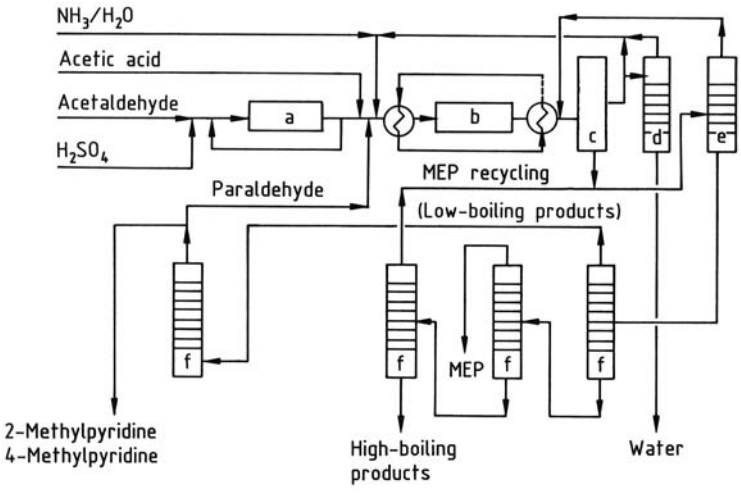


Figure 3. Flow sheet of 5-ethyl-2-methylpyridine (MEP) production by Montecatini – Edison process a) Paraldehyde production; b) Pyridine reactor; c) Separator; d) Stripper; e) Dewatering column; f) Fractionating columns

can be prepared from cyclopentadiene by ammoxidation [50], or from 2-pentenenitrile [*13284-42-9*] by cyclization and dehydrogenation [51]. Furfuryl alcohol or furfural reacts with ammonia in the gas phase to give pyridine [52]. 2-Methylpyridine is also prepared from aniline [53].

2.3. Quality Specifications, Storage, and Transportation

Specifications of pyridine vary according to country but are usually > 99.8 % purity by gas chromatographic analysis. Table 6 lists the standard specification for refined pyridine (ASTM) in the United States [54].

Pyridine bases should generally be stored under dark, cool conditions. They are transported in drums, tank cars, and bulk containers in accordance with the following regulations:

Road:	GGVS/ADR	Class 3, No. 15 b
Rail:	GGVE/RID	Class 3, No. 15
Sea:	GGVSee/IMDG	Class 3.2
Air:	IATA-DGR	Class 3
UN no.:	1282	

2.4. Uses

Pyridine is an excellent solvent, especially for dehydrochlorination reactions and extraction of antibiotics. Large amounts of pyridine are used as starting material for pharmaceuticals and agrochemicals: for example, herbicides such as diquat and paraquat, insecticides such as chlorpyrifos, and fungicides such as pyrithione (see Section 3.12).

Table 6. Standard specifications of refined pyridine (ASTM) [54]

Appearance	clear liquid, free of extraneous matter and sediment
Odor	pyridine, characteristic
$d^{15.56}$	0.985 – 0.990
Color	not darker than no. 20 on platinum – cobalt scale
Distillation range at atmospheric pressure	
Total distillation range	≤ 2 °C
Initial distillation temperature (first drop)	≥ 114.0 °C
End point (dry point)	≤ 117.0 °C
Water	≤ 0.20 wt %
Water solubility	clear solution, no turbidity or oil film

2-Methylpyridine. The major use of 2-methylpyridine is as a precursor of 2-vinylpyridine. The terpolymer of 2-vinylpyridine with butadiene and styrene is used as an adhesive for textile tire cord. 2-Methylpyridine is also used as a material for a variety of pharmaceuticals and agrochemicals: for example, chemicals such as nitrapyrin to prevent loss of ammonia from fertilizers, herbicides such as picloram, and coccidiostats such as amprolium (see Section 3.12).

3-Methylpyridine. A considerable amount of 3-methylpyridine is used as a starting material for pharmaceuticals and agrochemicals: for example, insecticides such as chlorpyrifos, feed additives such as nicotinic acid and nicotine carboxamide, and herbicides such as fluazifop-butyl (see Section 3.12).

4-Methylpyridine. The primary use of 4-methylpyridine is in the production of the antituberculosis agent isonicotinic hydrazide. Polymers containing 4-vinylpyridine, obtained from 4-methylpyridine, are used as anion exchangers (see Section 3.12).

Polyalkylpyridines. Large amounts of MEP are used as a starting material for nicotinic acid. 2,6-Dimethylpyridine is used for the antiarteriosclerotic pyridyl carbamate, while 3,5-dimethylpyridine is used for producing the antiulcer medication omeprazole (see Section 3.12).

2.5. Economic Aspects

The amounts of pyridine bases produced worldwide are estimated roughly as follows: pyridine, ca. 26 000 t/a (1989); 2-methylpyridine, ca. 8000 t/a (1989); 3-methylpyridine, ca. 9000 t/a (1989); 4-methylpyridine, ca. 1500 t/a (1989); and MEP, ca. 8000 t/a (1989). Table 7 lists the primary manufacturers of pyridine and alkylpyridines.

Table 7. Manufacturers of pyridine and alkylpyridines

Country	Company	Products
United States	Reilly Industry	pyridine; 2-, 3- and 4-methylpyridine; dimethylpyridine; trimethylpyridine
	Nepera Chemical Co.	pyridine; 2-, 3- and 4-methylpyridine
	Kopper Co.	coal-tar-derived pyridine
Japan	Koei Chemical Co.	pyridine; 2-, 3- and 4-methylpyridine; dimethylpyridine; trimethylpyridine
	Daicel Chemical	pyridine; 3-methylpyridine
	Nippon Steel	coal-tar-derived pyridine
Belgium	Reilly Industry	pyridine; 2-, 3- and 4-methylpyridine
Netherlands	DSM	2-methylpyridine
Switzerland	Lonza	2-methyl-5-ethylpyridine

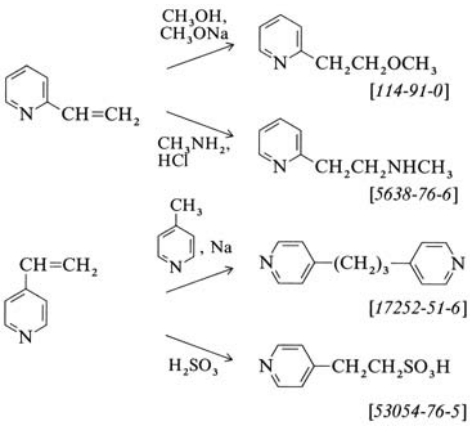
3. Pyridine Derivatives

3.1. Vinylpyridines

Vinylpyridines have the following general formula:

2-Vinylpyridine was first synthesized in 1887, and 4-vinylpyridine in 1920. However, not until 1950 did vinylpyridines begin to be used for various commercial purposes. Only 2- and 4-vinylpyridines are of industrial importance; Table 8 lists some physical properties.

Due to the electron-withdrawing effect of the ring nitrogen atom, 2- and 4-vinylpyridines act as electrophiles. Nucleophiles such as methoxide, cyanide, hydrogen sulfide, and others add to 2- and 4-vinylpyridine at the vinylic site to give addition products. The reactions shown below have been carried out on a commercial scale [55–57]:



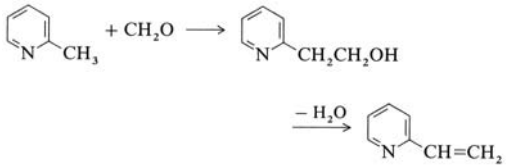
In addition to these Michael-type reactions, vinylpyridines are reduced at the side chain to give ethylpyridines [58]. Addition of chlorine to the vinyl group leads to (1,2-dichloroethyl)-pyridines [59].

Vinylpyridines are readily polymerized or copolymerized with styrene, butadiene, isobutylene, methyl methacrylate, and other compounds in the presence of radical, cationic, and anionic initiators. The homopolymer is soluble in organic solvents such as methanol and acetone, whereas cross-linked copolymers are insoluble in organic solvents.

Table 8. Physical properties of vinylpyridines

	2-Vinylpyridine	4-Vinylpyridine
CAS registry no.	[*100-69-6*]	[*100-43-6*]
Density (20 °C), g/cm^3	0.977	0.988
bp, °C (20 kPa)	110	120
(4 kPa)	70	
(2 kPa)		65
n_D^{20}	1.5509	1.5525
Solubility in water (20 °C), g/L	27.5	29
Viscosity (20 °C), mPa · s	1.17	
pK_a	4.98	5.5

Preparation. Industrially, 2- and 4-vinylpyridines are manufactured by treatment of 2- or 4-methylpyridine with aqueous formaldehyde, followed by dehydration of the resulting intermediate alcohol [60]:



For the manufacture of 2-vinylpyridine, the reaction is carried out at 150 – 200 °C in an autoclave. The conversion must be kept relatively low with short reaction time to suppress the formation of byproducts. After removal of unreacted 2-methylpyridine by distillation, concentrated aqueous sodium hydroxide is added to the residue and the resultant mixture is distilled under reduced pressure. During distillation, the dehydration of 2-(2-pyridyl)ethanol occurs to give 2-vinylpyridine as a distillate, which can be purified further by fractional distillation under reduced pressure in the presence of an inhibitor such as 4-*tert*-butylcatecohol. 4-Vinylpyridine is manufactured by a similar method.

Uses. Among vinylpyridines, only 2-vinylpyridine is in large demand, as much as 3000 t annually. The polymer of 2-methyl-5-vinylpyridine [*140-76-1*] was formerly used as a coating material for medicine tablets; today, it is not used at all. Although 4-vinylpyridine has been used for various purposes, its total annual demand is presumed to be only several hundred tons.

Most of the 2-vinylpyridine is used in the production of a latex terpolymer of 2-vinylpyridine, styrene, and butadiene, used as a tire-cord binder.

The cross-linked resin made from 4-vinylpyridine and divinylbenzene has been used to remove poisonous hexavalent chromium ions from wastewater [61] by formation of complexes with the nitrogen atoms of the pendant pyridine rings. Similarly, this type of resin can be used to remove or recover phenol from wastewater [62]. Furthermore, the poly(4-vinylpyridines) are used as ion-exchange membranes and electrodes for reversible cells.

The addition product of methanol to 2-vinylpyridine, 2-(2-methoxyethyl)pyridine is a veterinary anthelmintic (methypidine) [63]. 4,4′-(1,3-Propanediyl)bispiperidine, made from 4-vinylpyridine, is used as a raw material for polyamide resins [64], and 2-(4-pyridyl)ethylsulfonic acid from 4-vinylpyridine is a coagulation accelerator for the gelatin layer of photographic plates [65].

3.2. Bipyridines

Bipyridines have become increasingly important as intermediates for herbicides since the 1960s. A significant part of pyridine is used for the manufacture of bipyridines (i.e., 2,2′- and 4,4′-bipyridine). The herbicides diquat [*85-00-7*] and paraquat (dichloride [*1910-42-5*]; bis(methylsulfate) [*2074-50-2*]) are produced by quaternization of 2,2′- and 4,4′-bipyridines, respectively. Their physical properties are listed in Table 9.

2,2′-Bipyridine is synthesized by the dimerization of pyridine in the presence of an oxidizing agent or catalyst, such as iron(III) chloride, iodine, or nickel – aluminum, or by the reaction of 2-bromopyridine with copper. For industrial production, Raney nickel is used, and the amount of catalyst employed is an indicator of the economy of the process. In Table 10, the historical development of the process is demonstrated in terms of the decrease in amount of catalyst employed.

Production of 4,4′-Bipyridine. As early as 1870, pyridine was known to react with sodium to give 4,4′-bipyridine after oxidation of the initial product [72]. The reduction of pyridine with zinc powder and acetic acid followed by oxidation was also known. Many patents have been applied for concerning the improvement of this procedure with respect to reaction temperature, choice of solvent, and isolation of the product. The ICI process, which seems at present to be the best, is described below [73].

Sodium is dissolved in liquid ammonia at −45 °C, and the solution is successively diluted

Table 9. Physical properties of bipyridines (M_r 156.18)

Compound	CAS registry no.	*mp*, °C	*bp*, °C	Solubility in water
2,2′-Bipyridine	[*366-18-7*]	70.1	272 – 273	sparingly soluble
2,3′-Bipyridine	[*581-50-0*]		295 – 296	practically insoluble
2,4′-Bipyridine	[*581-47-5*]	61.1 – 61.5	280 – 282	practically insoluble
3,3′-Bipyridine	[*581-46-4*]	68	291 – 292	readily soluble
3,4′-Bipyridine	[*4394-11-0*]	61	297	soluble in hot water
4,4′-Bipyridine	[*553-26-4*]	114	304.8	soluble in hot water

Table 10. Amount of Raney nickel employed in synthesis of 2,2′-bipyridine

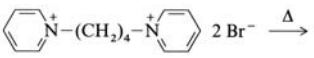
Method	Raney nickel, g/100 g 2,2′-bipyridine
[66]	595
[67]	143
[68]	25
[69]	17
[70]	14
[71]	8

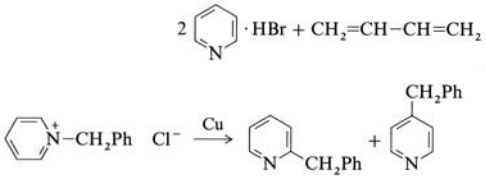
with pyridine and *N,N*-dimethylformamide. The resulting mixture is poured into *N,N*-dimethylformamide at −25 °C, while air is passed through the solution. The mixture is then warmed to room temperature, and ammonia is allowed to evaporate. After work-up, 4,4′-bipyridine is obtained in 84 % yield.

Other variants are described in [74–77].

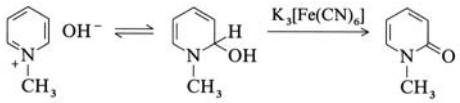
3.3. Quaternary Pyridinium Salts

Properties. Pyridine and some of its derivatives are readily converted to quaternary salts by alkylating agents such as alkyl halides. Quaternary salts can be regarded as being formed by the neutralization of strong bases (i.e., pyridinium hydroxides) with strong acids (e.g., hydrogen halides). Therefore, these salts are practically neutral when dissolved in water. Although stable under normal conditions, they are degraded into pyridine hydrohalides and alkenes on intense heating [78], or they undergo the Ladenburg rearrangement in the presence of copper as a catalyst [79]:

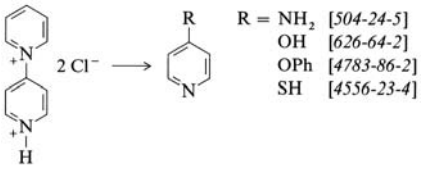




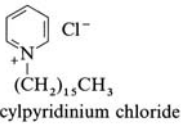
The pyridine ring of these salts is susceptible to nucleophilic attack as a result of the quaterniza-tion of the nitrogen atom. The reaction of 1-methylpyridinium salts with alkaline ferricyanide gives *N*-methylpyridone via oxidation of a pseudobase, which is considered to exist at low concentration in equilibrium with the pyridinium hydroxide [80], [81]:



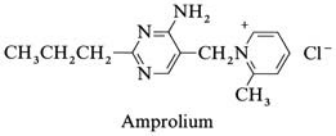
1-Pyridylpyridinium dichloride [*5421-92-1*], obtained from pyridine and thionyl chloride or chlorine, is particularly useful as a synthetic intermediate [82], [83]. It affords 4-amino- and 4-hydroxypyridine on ammonolysis and hydrolysis, respectively. Treatment with phenol and sodium phenoxide gives 4-phenoxypyridine, and reaction with hydrogen sulfide in pyridine gives 4-mercaptopyridine [84–87].



Uses. The major use of quaternary pyridinium salts is in the manufacture of the herbicides paraquat and diquat. These compounds are produced by the quaternization of 4,4′-bipyridyl and 2,2′-bipyridyl with methyl chloride and dibromoethane, respectively. Higher alkylpyridinium salts are used in the textile industry as dye auxiliaries and spin bath additives (antistatic agents and softeners). The higher alkylpyridinium salts also exhibit antimicrobial activity. Hexadecylpyridinium chloride [*123-03-5*] is a topical antiseptic, and amprolium [*121-25-5*], a quaternary salt of 2-methylpyridine, is a veterinary coccidiostat.



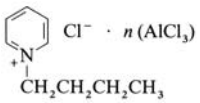
Hexadecylpyridinium chloride



Amprolium

Of the many quaternary salts, 1-butylpyridinium bromide [*1124-64-7*] and other lower

1-alkyl homologues are of interest. Although each component is solid at ambient temperature, the mixture of these salts with aluminum chloride leads to melts that can exist as liquids below room temperature in fairly wide proportions.

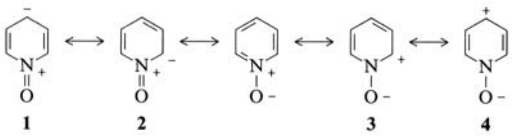


The molten salt with $n = 2$ exhibits a specific conductivity of ca. 7 mS/cm at 25 °C [88]. The utilization of these molten salts for battery electrolytes [89] and electroplating baths for aluminum has been proposed [90]. These binary salts are reportedly excellent solvents and catalysts for Friedel – Crafts reactions [91] and for the formylation of toluene by carbon monoxide [92].

3.4. Pyridine *N*-Oxides

Properties. Some physical properties of pyridine *N*-oxides are listed in Table 11.

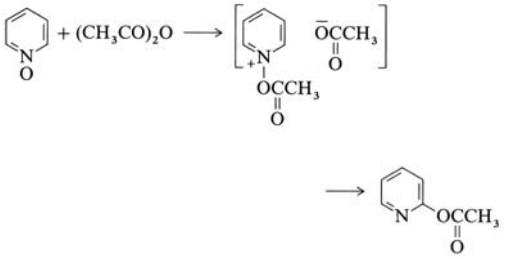
Resonance structures of pyridine *N*-oxide are as follows:



The *N*-oxide group in pyridine *N*-oxide has both electron-withdrawing and electron-donating effects. Consequently, pyridine *N*-oxide reacts with both electrophiles and nucleophiles, resulting in a more versatile reactivity of the pyridine ring compared to pyridine itself.

Nitration of pyridine *N*-oxide is a typical electrophilic reaction of the *N*-oxide. Pyridine *N*-oxide is nitrated under relatively mild conditions due to the contribution of structures **1** and **2**, giving 4-nitropyridine *N*-oxide in good yield [93], [94], in contrast to the nitration of pyridine, which requires drastic conditions and gives 3-nitropyridine only in poor yield. The nitro group of 4-nitropyridine *N*-oxide can be reduced to an amino group or displaced by various nucleophiles such as halides and alkoxides to give many useful 4-substituted pyridines. The oxygen of pyridine *N*-oxides can usually be removed by phosphorus trichloride.

Owing to the contribution of resonance structures **3** and **4**, the oxygen atom of the *N*-oxide group readily undergoes protonation, acylation, allylation, etc. Reaction with nucleophiles proceeds via quaternized intermediates, an example being the formation of 2-acetoxypyridine [*3847-19-6*] from the reaction of pyridine *N*-oxide with acetic anhydride [95]:



Trimethylsilyl cyanide, formed in situ from trimethylsilyl chloride and sodium cyanide, reacts with pyridine *N*-oxide to give almost exclusively 2-pyridinecarbonitrile [*100-70-9*] in 80 % yield [96]. Although the chlorination of pyridine *N*-oxide with sulfuryl chloride gives a mixture of 2- [*109-09-1*] and 4- chloropyridines [*626-61-9*] [97], treatment of 3-methylpyridine *N*-oxide with phosphoryl chloride in the presence of diisopropylamine yields predominantly 2- chloro-5-methylpyridine [*18368-64-4*] [98]. In the chlorination of 3-pyridinecarbonitrile *N*-oxide and

Table 11. Physical properties of pyridine N-oxides

Compound	CAS registry no.	*mp*, °C	*bp*, °C (kPa)	pK_a
Pyridine *N*-oxide	[*694-59-7*]	67	122 – 124 (0.67)	0.79 (24 °C)
2-Methylpyridine *N*-oxide	[*931-19-1*]		123 – 124 (2.0)	
3-Methylpyridine *N*-oxide	[*1003-73-2*]	37 – 38	146 – 149 (2.0)	1.08 (25°C)
4-Methylpyridine *N*-oxide	[*1003-67-4*]	186 – 188		1.29 (25°C)
Nicotinic acid *N*-oxide	[*2398-81-4*]	258		
3-Pyridinecarbonitrile *N*-oxide	[*14906-64-0*]	178		

nicotinic acid *N*-oxide, 2- chloro-3-pyridinecarbonitrile [*6602-54-6*] [99] and 2- chloronicotinic acid [*2942-59-8*] [100] are obtained as the main products.

The *N*-oxide of 2-methylpyridine reacts with acetic anhydride at the methyl group to give 2-acetoxymethylpyridine [*1007-49-4*] [101], which on hydrolysis leads to 2-pyridylmethanol [*586-98-1*].

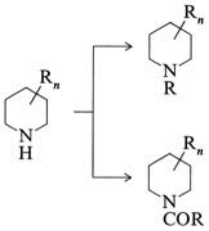
Preparation. Pyridine *N*-oxide can be prepared by treatment of pyridine with 30 % hydrogen peroxide in acetic acid [102]. A similar and easier method is also known [103], in which molybdenum trioxide is used as catalyst and water as solvent. Pyridine *N*-oxide and its alkyl derivatives are isolated by distillation after complete decomposition of unreacted peroxides.

Uses. Pyridine *N*-oxides are important as synthetic intermediates in the manufacture of pharmaceuticals and agrochemicals. The anti-ulcer agent omeprazole [*73590-58-6*] is produced from 2,3,5-trimethylpyridine *N*-oxide [*74409-42-0*]. Niflumic acid [*4394-00-7*] and pranoprofen [*52549-17-4*] are analgesics and anti-inflammatories, which are manufactured from nicotinic acid *N*-oxide, obtained either by *N*-oxidation of nicotinic acid or by hydrolysis of 3-pyridinecarbonitrile *N*-oxide. Zinc pyrithione [*13463-41-7*], the zinc salt of 2-pyridinethiol *N*-oxide [*1121-31-9*], is a fungicide derived from 2- chloropyridine *N*-oxide [*2402-95-1*].

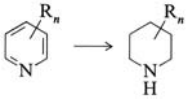
3.5. Piperidines (see also → Amines, Aliphatic)

Physical properties of common piperidines are listed in Table 12.

Piperidines react with alkyl halides and acid anhydrides to give *N*-alkylpiperidines and amides, respectively.



Piperidine and most of its derivatives are easily produced by hydrogenation of the corresponding pyridine derivatives at elevated temperature and pressure over nickel, palladium, or ruthenium catalysts [104–108].



A major use of piperidine is in the production of dithiuram tetrasulfide [*120-54-7*], which is used as a vulcanization accelerator in the rubber industry. Other uses of piperidine are in the production of vasodilators such as dipyridamole and minoxidil, diuretics such as etozolin, and fungicides such as piperalin. Piperidine is also used as a solvent. 2-Methylpiperidine is used for

Table 12. Physical properties of piperidines

Compound	CAS registry no.	M_r	*bp*, °C (kPa)	*mp*, °C	n_D^{20}	d_4^{20}	Flash point, °C
Piperidine	[*110-89-4*]	85.15	106		1.4525	0.861	4
2-Methylpiperidine	[*109-05-7*]	99.18	119		1.4459	0.844	8
3-Methylpiperidine	[*626-56-2*]	99.18	125		1.4470	0.845	17
4-Methylpiperidine	[*626-58-4*]	99.18	124		1.4458	0.838	7
cis-2,6-Dimethylpiperidine	[*766-17-6*]	113.20	126		1.4394	0.840	11
2-Piperidinecarboxylic acid	[*4043-87-2*]	129.16		282			
3-Piperidinecarboxylic acid	[*498-95-3*]	129.16		261			
4-Piperidinecarboxylic acid	[*498-94-2*]	129.16		> 300			
4-Piperidinol	[*5382-16-1*]	101.15	108 – 114 (1.3)				107
4-Benzylpiperidine	[*31252-42-3*]	175.28	279	6 – 7	1.5370	0.997	
2-Piperidylmethanol	[*3433-37-2*]	115.18		68 – 70			
2-(2-Piperidyl)ethanol	[*1484-84-0*]	129.20	234	38 – 40		1.010	102
1-Methylpiperidine	[*626-67-5*]	99.18	106 – 107		1.4378	0.816	3
1-Methyl-2-piperidylmethanol	[*20845-34-5*]	129.20	79 – 80 (0.9)		1.4823	0.984	81

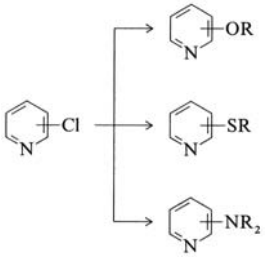
the herbicide piperophos, and *cis*-2,6-dimethylpiperidine for the antiarrhythmic pirmenol. 4-Benzylpyridine is quaternized and hydrogenated to give a 4-benzylpiperidine derivative that is used as a cerebral vasodilator (ifenprodil tartrate).

3.6. Halopyridines

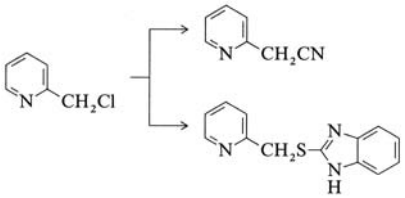
Physical properties of common halopyridines are listed in Table 13.

The 2- and 4- chloropyridines react with various nucleophiles to give alkyl ether [109], alkyl thioether [110], and alkylamine derivatives [111]. Furthermore, pyridylation of phenylacetonitrile can be achieved by using strong base [112].

Because of its relatively low reactivity, 3-chloropyridine does not undergo nucleophilic attack easily.



Haloalkylpyridines are useful intermediates for pyridylacetonitriles [113] or benzimidazolylthiomethylpyridines [114], [115].



Halogenation of pyridines generally gives a mixture of chlorinated pyridines. For instance, direct chlorination of pyridine with molecular chlorine can be achieved above 270 °C to give 2-chloropyridine and 2,6-dichloropyridine [116–118].

In the chlorination of methylpyridines, reaction occurs first at the side chain and then at a ring position. Liquid-phase chlorination generally leads to chloromethylpyridines [119].

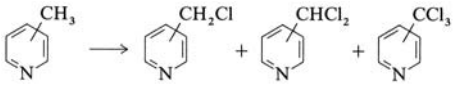
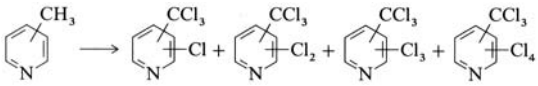


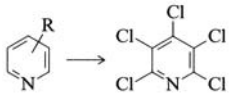
Table 13. Physical properties of halopyridines

Compound	CAS registry no.	M_r	*bp*, °C (kPa)	*mp*, °C	n_D^{20}	d_4^{20}	Flash point, °C
2-Chloropyridine	[*109-09-1*]	113.55	166 (95)	– 46.5	1.5320	1.200	65
3-Chloropyridine	[*626-60-8*]	113.55	148		1.5330	1.194	65
4-Chloropyridine hydrochloride	[*7379-35-3*]	150.01		210			
2-Bromopyridine	[*109-04-6*]	158.00	192 – 194		1.5720	1.657	54
3-Bromopyridine	[*626-55-1*]	158.00	173		1.5700	1.640	51
4-Bromopyridine hydrochloride	[*19524-06-2*]	194–46		270			
2-Fluoropyridine	[*372-48-5*]	97.09	126 (100)		1.4660	1.128	28
2-Chloro-3-methylpyridine	[*18368-76-8*]	127.57	192 – 193 (100)				
2-Chloro-6-methylpyridine	[*23468-31-7*]	127.57	184/100		1.5270	1.167	73
2,3-Dichloropyridine	[*2402-77-9*]	147.99	203 – 204	65 – 67			
2,5-Dichloropyridine	[*16110-09-1*]	147.99	193 – 194	59 – 62			
2,6-Dichloropyridine	[*2402-78-0*]	147.99	211 – 212	86 – 89			
3,5-Dichloropyridine	[*2457-47-8*]	147.99	178 – 179	65 – 67			
2-Chloromethylpyridine hydrochloride	[*6959-47-3*]	164.04		125 – 129			
3-Chloromethylpyridine hydrochloride	[*6959-48-4*]	164.04		137 – 143			
4-Chloromethylpyridine hydrochloride	[*1822-51-1*]	164.04		166 – 173			
2,3,5,6-Tetrachloropyridine	[*2402-79-1*]	216.88	251 – 252	91 – 92			
Pentachloropyridine	[*2176-62-7*]	251.33	279 – 280	124 – 126			
2-Chloro-5-trifluoromethylpyridine	[*52334-81-3*]	181.54	152 – 153	30 – 32			
2-Chloro-3-pyridinecarboxylic acid	[*2942-59-8*]	157.56		175			
6-Chloro-3-pyridinecarboxylic acid	[*5326-23-8*]	157.56		190			

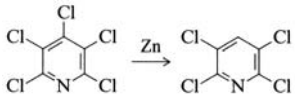
In contrast, gas-phase chlorination tends to give a mixture of trichloromethylchloropyridines [120–122]:



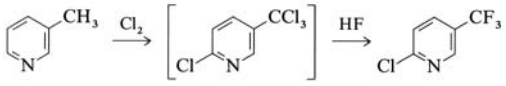
Exhaustive chlorination of pyridines gives pentachloropyridine [123], [124]:



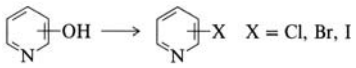
Pentachloropyridine can be reduced by zinc metal to 2,3,5,6-tetrachloropyridine because of enhanced reactivity at the 4-position [125], [126].



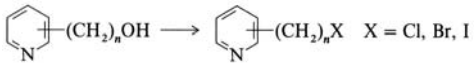
5-Trifluoromethyl-2-chloropyridine is produced directly from 3-methylpyridine by the combined action of chlorine and hydrogen fluoride [127]:



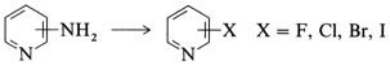
The preparation of 2- and 4-chloropyridines from pyridinols is achieved by the use of halogenating reagents such as phosphoryl chloride [128–130].



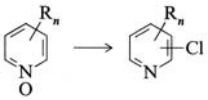
Pyridyl alcohols react with thionyl chloride or phosphorus halide reagents, such as phosphoryl chloride, phosphorus trihalide, or phosphorus pentahalide, to give the corresponding haloalkylpyridines [114], [115], [131].



Diazotization of aminopyridines in the presence of halide ions is used for the preparation of halopyridines [132–135].



Chlorination of pyridine *N*-oxides leads to halopyridines; usually, 2- and 4-isomers are formed by the action of phosphorus halide reagents [98–100] (see Section 3.4):



In industry, vapor-phase chlorination products are important intermediates for pharmaceuticals and agrochemicals.

A major use of 2-chloropyridine is the production of pyrithione, which is used widely as a fungicide. Another use is in the production of insecticides such as pyripropoxyfen. Pyridylation products of phenylacetonitrile lead to antihistamines such as chloropheniramine and antiarrhythmics such as disopyramide. Reaction of 4-chloropyridine with mercaptoacetic acid gives pyridylmercaptoacetic acid, which is a precursor for cephalosporin antibiotics (e.g., cephapirin sodium salt). 2,6-Dichloropyridine is used for quinoline antibiotics such as enoxacin.

2-Chloro-6-trichloromethylpyridine is used to prepare nitrapyrin, which prevents the loss of ammonia from fertilizers. 2,5-Dichloro-6-trichloromethylpyridine is converted to the herbicide clopyralid. 2,3,4,5-Tetrachloro-6-trichloromethylpyridine is a precursor of the herbicide picloram. 2,3,5,6-Tetrachloropyridine is used for producing the insecticide chlorpyrifos, and 2-chloro-5-trifluoromethylpyridine for the herbicide fluazifop-butyl.

Uses of liquid-phase chlorination products are limited at present. Major uses of 2-chloropyridine-3-carboxylic acid are for the production of herbicides such as diflufenican and anti-inflammatory agents such as niflumic acid and pranoprofen.

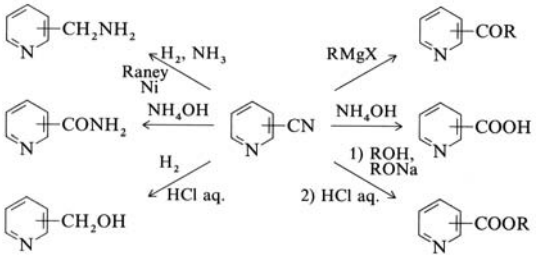
3.7. Pyridinecarbonitriles, Carboxylic Acids, and Carboxamides

The 3-carbonitrile, 3-carboxylic acid, and 3-carboxamide are important from both a physiological and an industrial point of view.

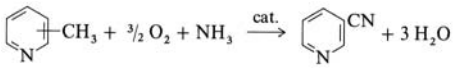
3-Pyridinecarboxylic acid and 3-pyridinecarboxamide are known as niacin. Niacin is widely distributed in plants and animals. It forms coenzymes, nicotinamide – adenine dinucleotide (NAD) and nicotinamide – adenine dinucleotide phosphate (NADP), which participate in oxidation – reduction cycles in living cells. Since 3-pyridinecarboxylic acid is obtained by oxidation of nicotine with nitric acid, it is commonly called nicotinic acid. 3-Pyridinecarbonitrile and 3-pyridinecarboxamide are referred to as nicotinonitrile and nicotinamide. The prefix isonicotin- is often used to denote the 4-position of pyridinecarbonitrile, - carboxylic acid, and - carboxamide.

Physical data for pyridinecarbonitriles, pyridinecarboxylic acids, and pyridinecarboxamides are listed in Table 14.

Pyridinecarbonitriles. Pyridinecarbonitriles are important intermediates for a variety of pyridine derivatives [136–141]:



Pyridinecarbonitriles are usually manufactured by catalytic vapor-phase ammoxidation of alkylpyridines :



Generally, 1 to 20 mol of ammonia and 2 to 20 mol of oxygen are used per mole of alkylpyridine. Reaction temperatures range between 280 and 500 °C. Catalysts containing vanadium oxide are commonly used. Examples of the process are given in Table 15, and a flow sheet is illustrated in Figure 4.

3-Methylpyridine is ammoxidized to 3- cyanopyridine in the reactor (a). The reaction gas is quenched with water in the absorber (b), and the condensed mixture is extracted with a solvent in the extraction column (c). 3-Cyanopyridine is separated from the solvent and 3-methylpyridine by three-stage distillation.

3-Pyridinecarbonitrile is used for the production of 3-pyridinecarboxamide (vitamin complex), and 4-pyridinecarbonitrile for antituberculosis agents such as isoniazid [148].

Pyridinecarboxylic Acids. Pyridinecarboxylic acids behave like ordinary carboxylic acids. Some important reactions are shown below [149], [150]:

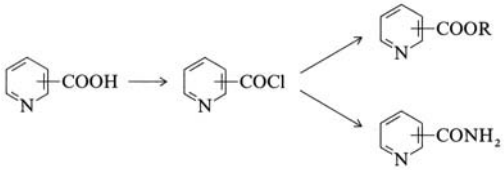


Table 14. Physical data of pyridinecarbonitriles, pyridinecarboxamides, and pyridinecarboxylic acids

Compound	CAS registry no.	M_r	*mp*, °C	*bp*, °C (kPa)
Nitriles				
2-Pyridinecarbonitrile	[*100-70-9*]	104.11	26	216 – 226
3-Pyridinecarbonitrile	[*100-54-9*]	104.11	51	198 – 202
4-Pyridinecarbonitrile	[*100-48-1*]	104.11	76 – 78	190 – 226
6-Methyl-2-pyridinecarbonitrile	[*1620-75-3*]	118.15	71 – 71.5	112 – 114 (2.0)
2,6-Pyridinedicarbonitrile	[*1452-77-3*]	129.12	104 – 105	143 (2.67)
Amides				
2-Pyridinecarboxamide	[*2893-33-6*]	122.13	126 – 127	
3-Pyridinecarboxamide	[*98-92-0*]	122.13	128 – 131	
4-Pyridinecarboxamide	[*1453-82-3*]	122.13	155 – 156	
Acids				
2-Pyridinecarboxylic acid	[*98-98-6*]	123.11	137 – 138	
3-Pyridinecarboxylic acid	[*59-67-6*]	123.11	236	
4-Pyridinecarboxylic acid	[*55-22-1*]	123.11	317	
2,3-Pyridinedicarboxylic acid	[*89-00-9*]	167.12	229 – 230	
2,4-Pyridinedicarboxylic acid	[*499-80-9*]	167.12	242 – 243	
2,6-Pyridinedicarboxylic acid	[*499-83-2*]	167.12	228	

Table 15. Synthesis of pyridinecarbonitriles

Company	Catalyst	Starting material	Conversion, %	Yield, %	Ref.
Lonza	V_2O_5	2-methylpyridine	62.7	44.2	[142]
	V_2O_5	3-methylpyridine	89.3	83.5	
	V_2O_5	4-methylpyridine	98.4	81.3	
Degussa	Sb_2O_5– V_2O_5– TiO_2 – montmorillonite – SiO_2	3-methylpyridine	94	90	[143]
Yuki Gousei	MoO_3– V_2O_5	3-methylpyridine	96.4	83.0	[144]
	MoO_3– Cr_2O_3– Al_2O_3	4-methylpyridine	97.3	82.3	
Takeda Chemical	V_2O_5– Sb_2O_5– Cr_2O_3– TiO_2	3-methylpyridine	100	98.6	[145]
Koei Chemical	V_2O_5 – P_2O_5– SiO_2	2-methylpyridine	97.6	79.3	[146]
	V_2O_5– P_2O_5– SiO_2	3-methylpyridine	96.1	82.3	
	V_2O_5– P_2O_5	4-methylpyridine	99.5	94.0	
Nippon Shokubai	V_2O_5– Sb_2O_5– TiO_2– SiO_2– SiC	2-methylpyridine		73	[147]
	V_2O_5– Sb_2O_5– TiO_2 – SiO_2– SiC	3-methylpyridine		85	
	V_2O_5– Sb_2O_5– TiO_2 – SiO_2– SiC	4-methylpyridine		97	

Two basic methods are used for the production of pyridinecarboxylic acids: hydrolysis of pyridinecarbonitriles and nitric acid oxidation of alkylpyridines.

Pyridinecarbonitriles are hydrolyzed to pyridinecarboxamides under basic conditions at 0 – 100 °C; subsequent hydrolysis to pyridinecarboxylic acids is carried out under more severe conditions [151], [152].

Nitric acid oxidation of alkylpyridines (e.g., 5-ethyl-2-methylpyridine to 3-pyridinecarboxylic acid) has been developed commercially by Lonza.

The flow diagram of the process is shown in Figure 5 [153]. 5-Ethyl-2-methylpyridine (MEP) is mixed with nitric acid and fed to a tubular reactor (b). The reaction to form 3-pyridine carboxylic acid nitrate is carried out at 180 – 370 °C and 2 – 50 MPa. Nitrogen oxides gases are recovered by the absorber (d) and recycled. After removal of water (e), crystallization of the nitrate (f), and neutralization with

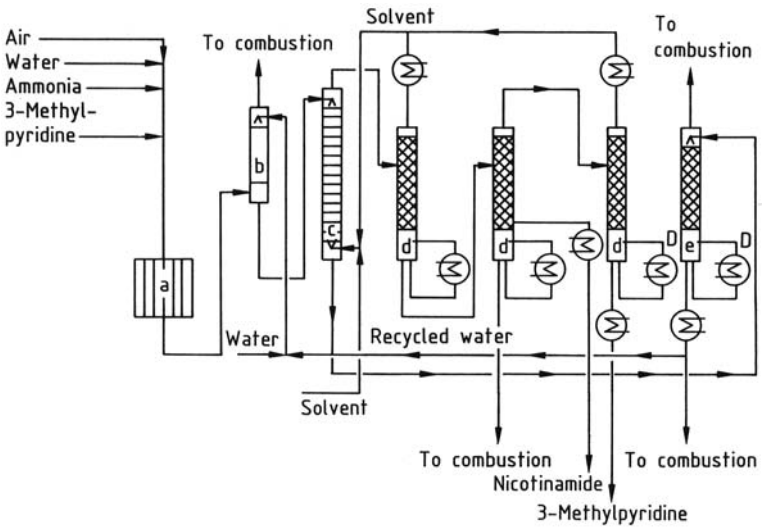


Figure 4. Ammoxidation of 3-methylpyridine a) Multitubular reactor; b) Absorber; c) Extraction column; d) Fractionating columns; e) Treatment of process water

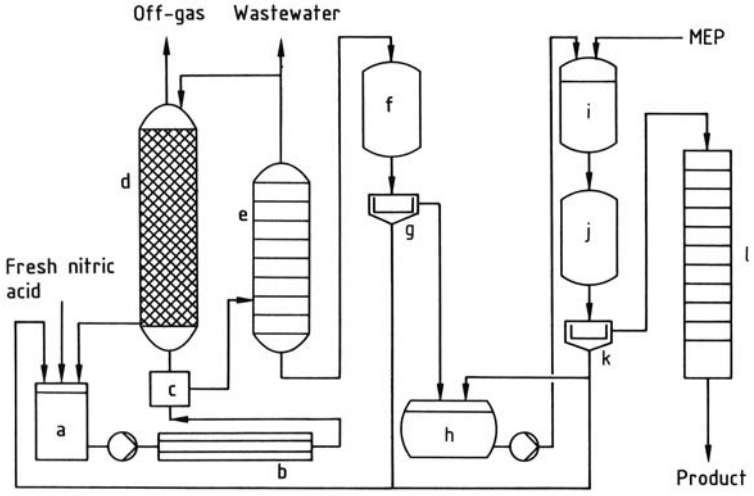
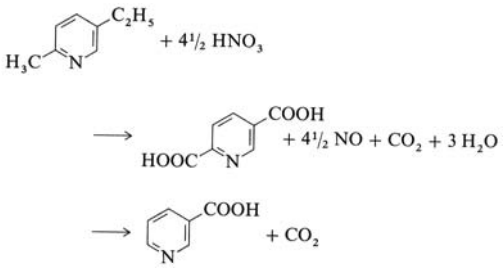


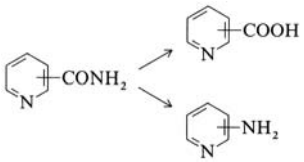
Figure 5. Lonza process for 3-pyridinecarboxylic acid a) Mixing; b) Reactor; c) Pressure relief; d) Absorption column; e) Distillation column; f) Crystallization; g) Separator; h) Dissolution; i) Neutralization; j) Crystallization; k) Separator; l) Dryer

MEP (i), the free acid is crystallized (j) and dried. Unreacted nitric acid from the separators (g, k) is recycled to the reactor.



3-Pyridinecarboxylic acid has been used mainly as vitamin B_3 or vitamin PP for treating pellagra. Furthermore, it is used as an intermediate for the vasodilator nicorandil. Other uses are for plant growth regulators (inabenfide); antihistamines (terfenadine); and antidepressants (nialamide). 2-Piperidinecarboxylic acid, derived from 2-pyridinecarboxylic acid, is used as intermediate for local anesthetics such as mepivacaine hydrochloride and bupivacaine hydrochloride. 2,3-Pyridinedicarboxylic acid is used as an intermediate for the herbicide imazapyr.

Pyridinecarboxamides. Pyridinecarboxamides are used for the production of pyridinecarboxylic acids [152] and aminopyridines [154].



Pyridinecarboxamides are prepared by hydrolysis of pyridinecarbonitriles [155].

3-Pyridinecarboxamide and 3-pyridinecarboxylic acid are important as vitamin B_3 [156]. 4-Pyridinecarboxamide is used for producing antibiotics (e.g., cefsulodin sodium) [157].

3.8. Aminopyridines

Table 16 lists commercially available aminopyridines and their physical properties.

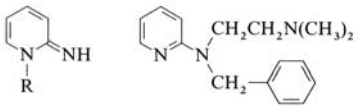
3.8.1. 2-Aminopyridine

2-Aminopyridine [*504-29-0*] exists as tautomeric amino and imino forms. The amino form predominates over the imino form, and their ratio is generally 1000: 1.

Table 16. Physical properties of aminopyridines

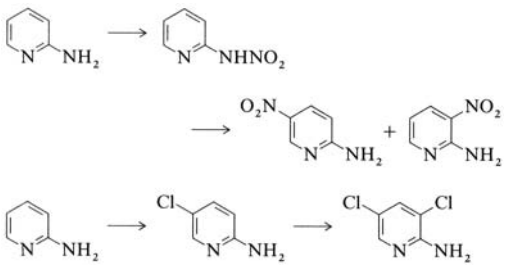
Compound	CAS registry no.	M_r	*mp*, °C	*bp*, °C (kPa)
2-Aminopyridine	[*504-29-0*]	94.12	59 – 60	210
3-Aminopyridine	[*462-08-8*]	94.12	64 – 65	260
4-Aminopyridine	[*504-24-5*]	94.12	159	273
2-Amino-6-methylpyridine	[*1824-81-3*]	108.14	40	208 – 209
2,6-Diaminopyridine	[*141-86-6*]	109.13	121 – 122	170 (4.0)
N,N-Dimethyl-4-pyridinamine	[*1122-58-3*]	122.17	112 – 113	145 – 150 (4.0)

2-Aminopyridine generally reacts with alkylating agents at the ring nitrogen to give derivatives of type **5**. In the presence of sodium amide or sodium methoxide, however, it reacts with alkylating agents at the exocyclic nitrogen. Such reactions are used to produce antihistamines of type **6**.

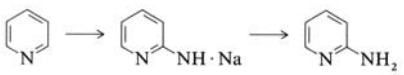


5 **6**

Electrophilic reactions such as halogenation and nitration occur at the positions *para* and *ortho* to the amino group [158–160]:



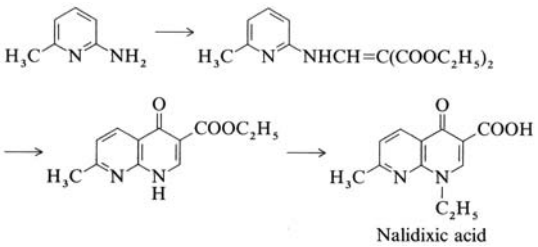
The most important method for the manufacture of 2-aminopyridine is the reaction of pyridine with sodium amide (Chichibabin amination). Upon hydrolysis of the intermediate sodium salt, 2-aminopyridine is obtained in high yield [161–164]:



The major uses of 2-aminopyridine are as an intermediate for pharmaceuticals such as sulfapyridine [*144-83-2*], tripelennamine [*91-81-6*], piroxicam [*36322-90-4*], and tenoxicam [*59804-37-4*], as well as a variety of agrochemicals.

3.8.2. Other Aminopyridines

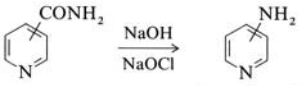
2-Amino-6-Methylpyridine. 2-Amino-6-methylpyridine [*1824-81-3*] is produced from 2-methylpyridine and sodium amide. It is converted to nalidixic acid [*389-08-2*], an antibacterial agent [165].



Nalidixic acid

2,6-Diaminopyridine. Amination of pyridine or 2-aminopyridine under severe conditions gives 2,6-diaminopyridine [*141-86-6*], the coupling of which with benzenediazonium salts gives the antiseptic phenazopyridine [*136-40-3*] [166]. 2,6-Diaminopyridine is also utilized for the production of polyamides.

3-Aminopyridine and 4-Aminopyridine. 3-Aminopyridine [*462-08-8*] and 4-aminopyridine [*504-24-5*] are produced from the corresponding pyridinecarboxamides and sodium hypochlorite in alkaline solution (Hofmann reaction).

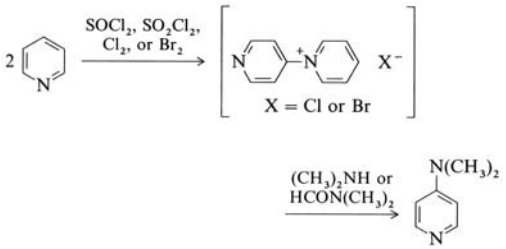


(3- or 4-position)

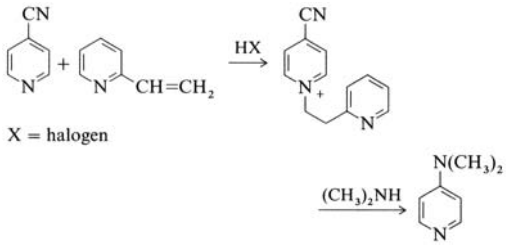
These aminopyridines are used as intermediates for pharmaceuticals such as pinacidil [*85371-64-8*] and for agrochemicals.

***N,N*-Dimethyl-4-Pyridinamine** [*1122-58-3*] is widely employed as a supernucleophilic catalyst for many organic reactions. Two processes are used for its production:

1. *N*-(4-Pyridyl)pyridinium halide, prepared from pyridine and halogenating agents, is reacted with dimethylamine or *N,N*-dimethylformamide to give *N,N*-dimethyl-4-pyridinamine [167–170].



2. 1-[2-(2-Pyridyl)ethyl]-4- cyanopyridinium chloride, prepared from 4-pyridinecarbonitrile, 2-vinylpyridine, and hydrogen halide, gives *N,N*-dimethyl-4-pyridinamine by a reaction similar to that described above [171].

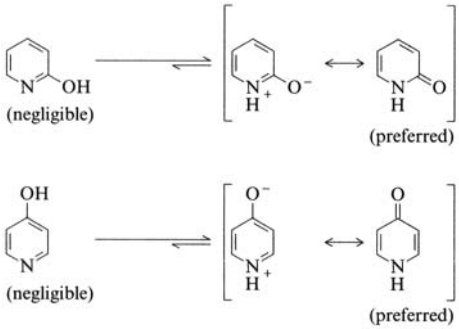


The major uses are as a catalyst for acylation, alkylation, halogenation, cyanation, and silylation, and as an accelerator in the manufacture of polyurethanes.

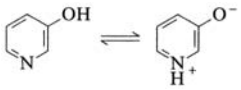
3.9. Pyridinols

Physical properties of typical pyridinols are listed in Table 17.

Tautomerization of pyridinols is discussed in [172]; both 2- and 4-pyridiols prefer the ketonic pyridone tautomer to the hydroxylic tautomer.



In contrast, 3-pyridinol is a phenolic compound because the ketonic tautomer does not exist.



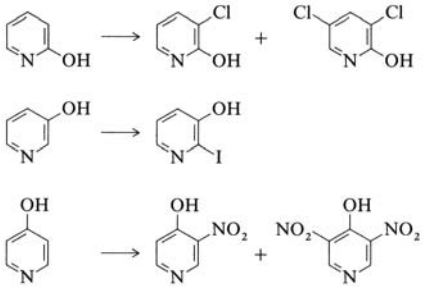
Chlorination of 2- and 4-pyridinols with phosphorus halides gives halopyridines [126–128].

Electrophilic substitution of pyridinols is facile because of the electron-donating nature of the

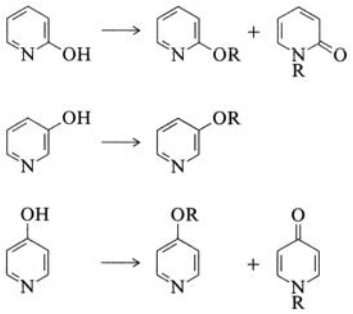
Table 17. Physical properties of pyridinols

Compound	CAS registry no.	M_r	*bp*, °C (kPa)	*mp*, °C
2-Pyridinol	[*142-08-5*]	95.10	280 – 281	105 – 107
3-Pyridinol	[*109-00-2*]	95.10	151 – 153 (0.4)	126 – 129
4-Pyridinol	[*626-64-2*]	95.10	230 – 235 (1.6)	146 – 149
6-Methyl-2-pyridinol	[*3279-76-3*]	109.13		158 – 160
6-Methyl-3-pyridinol	[*1121-78-4*]	109.13		168 – 170
5-Chloro-2-pyridinol	[*4214-79-3*]	129.55		163 – 165
2-Nitro-3-pyridinol	[*15128-82-2*]	140.10		69 – 71

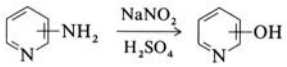
hydroxyl group. Reaction occurs at positions *ortho* or *para* to the hydroxyl group, similar to phenols [173–176].



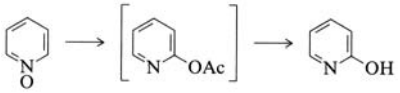
When 2- and 4-pyridinols are alkylated with alkyl halides, they give a mixture of the *O*- and *N*-alkylated products [177], but 3-pyridinol gives only the *O*-alkylated product [178].



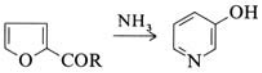
Diazotization of aminopyridines is used for the production of pyridinols [179–182].



2-Pyridinol is also obtained from pyridine *N*-oxide by reaction with acid anhydrides and subsequent hydrolysis [183], [184].



2-Alkyl-3-pyridinols are reported to be formed from alkanoylfurans and ammonia under pressure [185–187].

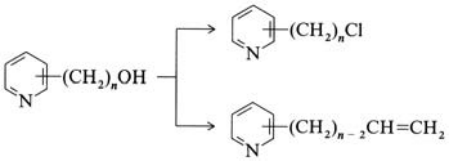


2-Pyridinol is a synthetic intermediate for the tranquilizer amphenidone. 3-Pyridinol is used for synthesizing the cholinesterase inhibitors pyridostigmine bromide and distigmine bromide. 4-Pyridinol is a precursor of the X-ray contrast agent propyliodone. It is hydrogenated to give 4-piperidinol, which is used to produce the psychotropic agent pericyazine.

3.10. Pyridyl Alcohols

Physical properties of common pyridyl alcohols are listed in Table 18.

Reactivities of pyridyl alcohols are similar to ordinary alcohols; for example, chloroalkylpyridines are formed by the action of thionyl chloride or phosphorus halide reagents [130], [131], and dehydration gives alkenylpyridines.



Pyridylmethanols. The simple pyridylmethanols are produced by catalytic hydrogenation of pyridinecarbonitriles in acidic media [188].

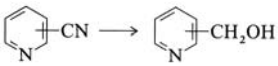
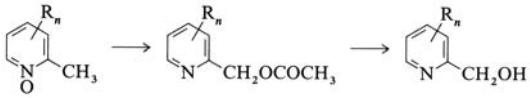


Table 18. Physical properties of pyridyl alcohols

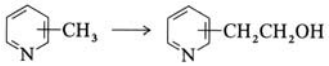
Compound	CAS registry no.	M_r	*bp*, °C (kPa)	*mp*, °C	n_D^{20}	d_4^{20}	Flash point, °C
2-Pyridylmethanol	[*586-98-1*]	109.13	112 – 113 (0.5)		1.5440	1.131	110
3-Pyridylmethanol	[*100-55-0*]	109.13	154 (2.9)		1.5460	1.124	130
4-Pyridylmethanol	[*586-95-8*]	109.13	107 – 110 (0.1)	57 – 59			112
2,6-Pyridyldimethanol	[*1195-59-1*]	139.15	185 (2.0)	114 – 116			
2-(2-Pyridyl)ethanol	[*103-74-2*]	123.16	114 – 116 (1.2)		1.5370	1.093	92
2-(4-Pyridyl)ethanol	[*5344-27-4*]	123.16	262				160

Substituted 2-pyridylmethanols can be produced from 2-methylpyridine *N*-oxides by the action of acetic anhydride, followed by hydrolysis [130], [131], [189].



2-Pyridylmethanol is used in the preparation of the anti-inflammatory ibuprofen piconol. 3-Pyridylmethanol is used as an intermediate for the vasodilator nicotinic alcohol. 2,6-Pyridyldimethanol is carbamated to give the antiarteriosclerotic agent pyridinol carbamate.

Pyridylethanols. Condensation of 2- or 4-methylpyridines with formaldehyde or other aliphatic aldehydes gives the corresponding pyridylethanols due to the high acidity of the methyl group in the 2- or 4-position [18], [190–193].

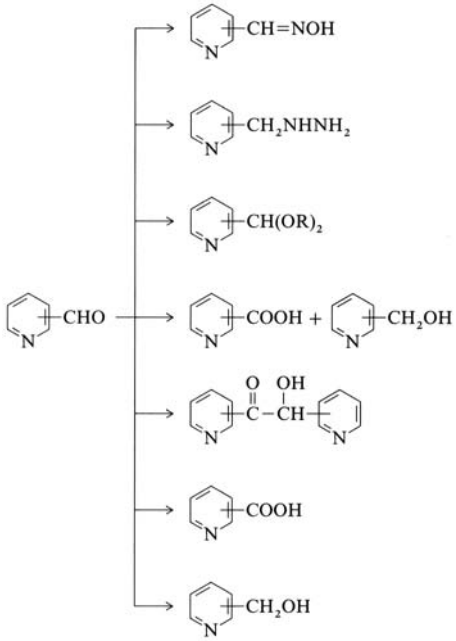


Pyridylethanols are used mainly for the manufacture of vinylpyridines (see Section 3.1). Other uses of 2-(2-pyridyl)ethanol are in the production of a psychotropic agent thioridazine and the antispasmodic tiquizium bromide.

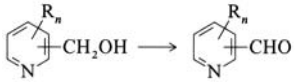
3.11. Pyridinecarbaldehydes

Physical properties of typical pyridinecarbaldehydes are listed in Table 19.

Reactions of pyridinecarbaldehydes are similar to those of aromatic aldehydes: benzoin condensation [194], oxidation to pyridinecarboxylic acids [195], reduction to pyridylmethanols [196], oximation [197], and hydrazone formation [198].



Pyridinecarbaldehydes are prepared from pyridylmethanols by oxidation with manganese dioxide [199].



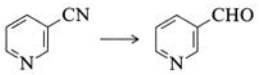
The oxidation of methylpyridines with selenium dioxide gives pyridinecarbaldehydes [200], which are also obtained by vapor-phase oxidation of methylpyridines over avanadium – molybdenum – titanium oxide catalyst [201].

The catalytic partial reduction of 3-pyridinecarbonitrile with hydrogen over a palladium catalyst in acidic media gives 3-pyridinecarbal-

Table 19. Physical properties of pyridylcarbaldehydes

Compound	CAS registry no.	M_r	*bp*, °C (kPa)	*mp*, °C	n_D^{20}	d_4^{20}	Flash point, °C
2-Pyridinecarbaldehyde	[*1121-60-4*]	107.11	181		1.5370	1.126	54
3-Pyridinecarbaldehyde	[*500-22-1*]	107.11	95 – 97 (0.9)		1.5490	1.135	60
4-Pyridinecarbaldehyde	[*872-85-5*]	107.11	77 – 78 (1.6)		1.5440	1.122	54
2-Pyridine aldoxime	[*873-69-8*]	122.13		110 – 112			
3-Pyridine aldoxime	[*1193-92-6*]	122.13		150 – 153			
4-Pyridine aldoxime	[*696-54-8*]	122.13		130 – 133			

dehyde [202].



Quaternary salts of pyridinecarbaldehyde oximes, particularly pralidoxime methiodide, are used as antidotes for poisoning by organophosphate acetylcholinesterase inhibitors. Another use of 2-pyridinecarbaldehyde is in the production of bisacodyl, a laxative.

3.12. Pharmaceuticals and Agrochemicals

Typical pharmaceuticals and agrochemicals derived from pyridine are listed in Table 20.

4. Toxicology

4.1. Acute Toxicity

The acute toxicity of pyridine and its common derivatives is listed in Table 21.

Pyridine has a narcotic action. Toxic doses cause weakness, ataxia, unconsciousness, and salivation. In humans, pyridine is readily absorbed through the lungs, gastrointestinal tract, and skin. In 1893 a human fatality resulted from the accidental ingestion of half a cupful of commercial pyridine [203]. OSHA states that a vapor concentration of 3600 ppm in air is immediately dangerous to life and health [204]. The LDLo (oral) in humans is 500 mg/kg [205].

The acute toxicity of monoalkylpyridines is similar to that of pyridine, but some dimethyl- and trimethylpyridines are several times more toxic than pyridine. 2-Methylpyridine is one of the most important commercially produced alkylpyridines; its toxicity and safety data are summarized in [206].

Of aminopyridines, the toxicity of 4-aminopyridine has been thoroughly investigated because of its high toxicity and its use as a bird repellent. The acute toxicity of 4-aminopyridine has been determined for 41 species of birds and mammals. The oral LD_{50} values are generally < 10 mg/kg [207], and the LDLo (oral) in humans is 0.59 mg/kg. Most of the pharmacological effects of 4-aminopyridine can be attributed to its neurotoxicity [208].

The calculated fatal dose of 2-aminopyridine for a man of 70-kg weight is ca. 5 g [209]. A fatal accident involving 2-aminopyridine was described as follows: an employee died 1.5 h after spilling 2-aminopyridine on his clothes during its distillation and continuing to work. Aminopyridines are toxic if inhaled, swallowed, or absorbed through skin [209].

The acute toxicity of 13 chlorinated pyridines has been investigated [210], including monochloro to pentachloro derivatives. In the comparison of relative toxicity to mice by intraperitoneal injection, 2,6-dichloropyridine shows the highest toxicity ($LD_{50} = 115$ mg/kg) and 2,5-dichloropyridine the lowest ($LD_{50} = 1690$ mg/kg).

The toxicity of 2-chloropyridine to rabbits after dermal application ($LD_{50} = 64$ mg/kg) and by intraperitoneal injection ($LD_{50} = 48$ mg/kg) indicates that 2-chloropyridine is readily absorbed through the skin.

3-Acetylpyridine causes central neurotoxic effects upon intraperitoneal injection of 70–80 mg/kg in rats [211]. The zinc salt of 1-hydroxypyridine-2-thione (HPT), known as zinc pyrithione (ZnPT), is used as an antidandruff agent. The oral LD_{50} of HPT in mice is 533 mg/kg. The metal complexes (Zn, Cd) are more toxic than HPT itself. Percutaneous and eye toxicity is also discussed in [212].

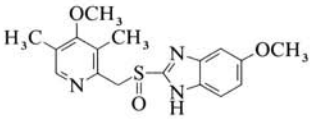
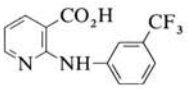
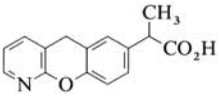
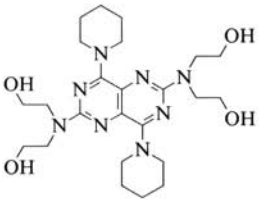
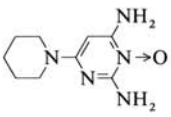
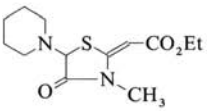
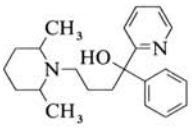
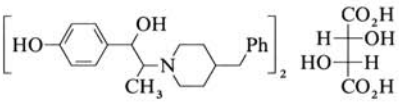
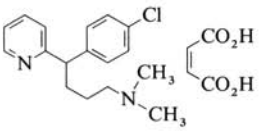
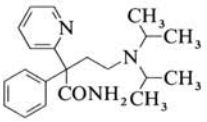
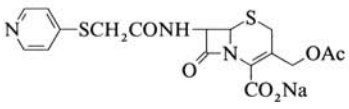
Paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride), which consumes the largest amount of pyridine as starting material, exhibits very high toxicity. The oral LDLo in humans is 43 mg/kg. Nicotine is one of the well-known pyridine derivatives from natural sources, and its toxicity has been investigated in detail. The LDLo in humans is 0.882 mg/kg. Reports on the toxicity of paraquat and nicotine can be found in [213].

Vinylpyridines irritate the skin intensely, and contact with the vapor or liquid generally causes inflammation or blisters. They also show high toxicity by inhalation.

4.2. Subacute and Chronic Toxicity

Few long-term studies can be found on the toxicity of pyridine to animals. Six rats were fed a basal diet containing 0.1 % pyridine. Five rats died during the 14th to 32nd days. The livers and

Table 20. Pharmaceuticals and agrochemicals derived from pyridine

Compound	Common name	Developer	Use
Pharmaceuticals			
	omeprazole [*73590-58-6*]	Astra	antiulcer
	niflumic acid [*4394-00-7*]	Heydon	anti-inflammatory
	pranoprofen [*52549-17-4*]	Yoshitomi	anti-inflammatory
	dipyridamole [*58-32-2*]	Thomae	vasodilator
	minoxidil [*38304-91-5*]	Upjohn	vasodilator
	etozolin [*73-09-6*]	Warner-Lambert	diuretic
	pirmenol [*61477-94-9*]	Parke, Davis	antiarrhythmic
	ifenprodil tartrate [*23210-56-2*]	Funai	cardiovascular
	chloropheniramine maleate [*2438-32-6*]	Schering	antihistamine
	disopyramide [*3737-09-5*]	Roussel Uclaf	antiarrhythmic
	cephapirin sodium [*24356-60-3*]	Bristol-Myers	antibiotic

(*Continued*)

Table 20 (*Continued*)

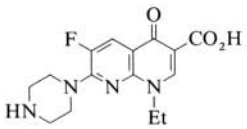
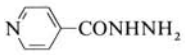
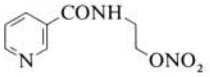
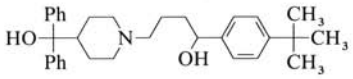
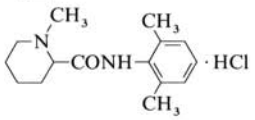
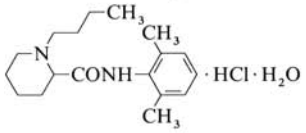
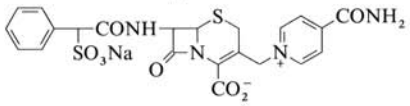
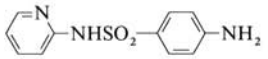
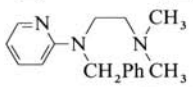
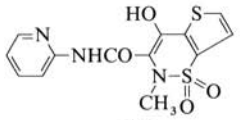
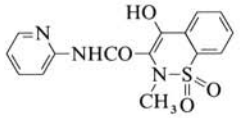
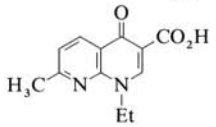
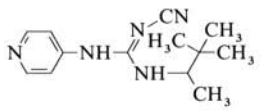
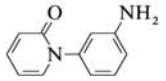
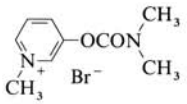
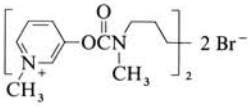
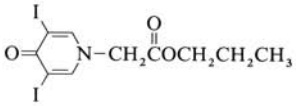
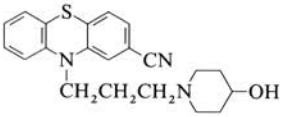
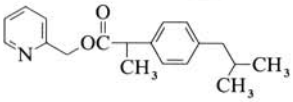
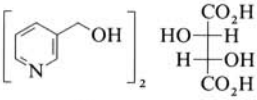
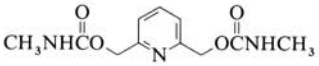
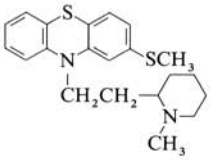
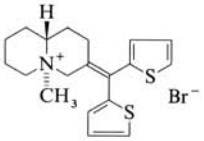
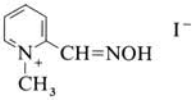
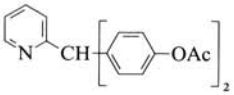
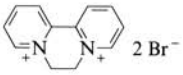
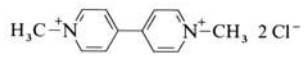
	enoxacin [*74011-58-8*]	Dainippon	antibiotic
	isoniazid [*54-85-3*]	Bayer	antituberculous
	nicorandil [*65141-46-0*]	Tyugai	vasodilator
	terfenadine [*50679-08-8*]	Merrell Dow	antihistamine
	nialamide [*51-12-7*]	Pfizer	monoamine oxidase
	mepivacaine hydrochloride [*1722-62-9*]	Astra	local anesthetic
	bupivacaine hydrochloride [*14252-80-3*]	Astra	local anesthetic
	cefsulodin sodium [*52152-93-9*]	Takeda	antibiotic
	sulfapyridine [*144-83-2*]	Visuvia	chemotherapeutic
	tripelennamine [*91-81-6*]	Ciba-Geigy	antihistamine
	tenoxicam [*59804-37-4*]	Roche	anti-inflammatory
	piroxicam [*36322-90-4*]	Pfizer	anti-inflammatory
	nalidixic acid [*389-08-2*]	Winthrop	chemotherapeutic
	pinacidil [*85371-64-8*]	Leo Denmark	antihypertensive
	amphenidone [*134-37-2*]	Wallace & Tiernan	tranquilizer

Table 20 (*Continued*)

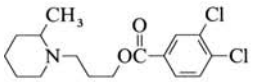
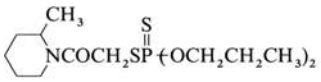
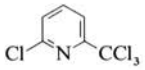
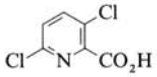
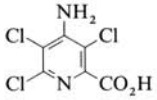
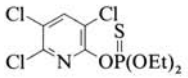
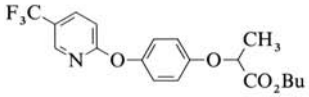
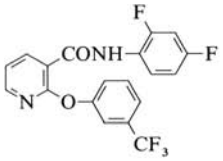
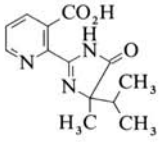
	pyridostigmine bromide [*101-26-8*]	Roche	autonomic anticholinesterase
	distigmine bromide [*15876-67-2*]	Chemie Linz	autonomic anticholinesterase
	propyliodone [*587-61-1*]	Glaxo	X-ray contrast
	pericyazine [*2622-26-6*]	Rhône-Poulenc	psychotropic
	ibuprofen piconol [*112017-99-9*]	Hisamitu/Torii	anti-inflammatory
	nicotinyl tartrate [*100-55-0*]	Roche	vasodilator
	pyridinol carbamate [*1882-26-4*]	Banyu	antiarteriosclerotic
	thioridazine [*50-52-2*]	Sandoz	psychotropic
	tiquizium bromide [*71731-58-3*]	Hokuriku	antispasmodic
	pralidoxime iodide [*51-15-0*]	Wyeth-Ayerst	antidote
	bisacodyl [*603-50-9*]	Thomae	laxative

Agrochemicals

	diquat dibromide [*85-00-7*]	ICI	herbicide
	paraquat dichloride [*1910-42-5*]	ICI	herbicide

(*Continued*)

Table 20 (*Continued*)

	piperalin [*3478-94-2*]	Eli Lilly	fungicide
	piperophos [*24151-93-7*]	Ciba-Geigy	herbicide
	nitrapyrin [*1929-82-4*]	Dow	prevents loss of fertilizer
	clopyralid [*1702-17-6*]	Dow	herbicide
	picloram [*1918-02-1*]	Dow	herbicide
	chlorpyrifos [*2921-88-2*]	Dow	insecticide
	fluazifop-butyl [*69806-50-4*]	Ishihara	herbicide
	diflufenican [*83164-33-4*]	May & Baker	herbicide
	inabenfide [*82211-24-3*]	Tyugai	growth regulator
	imazapyr [*81334-34-1*]	ACC	herbicide

Others

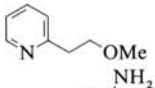
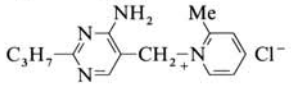
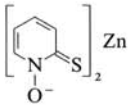
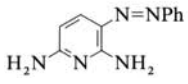
	metyridine [*114-91-0*]	ICI	anthelmintic
	amprolium [*121-25-5*]	Merck	coccidiostat
	zinc pyrithione [*13463-41-7*]	Olin	fungicide
	phenazopyridine [*136-40-3*]	Gödecke	antiseptic

Table 21. Acute toxicity of pyridine and derivatives*

Compound	CAS registry no.	LD_{50} (oral), mg/kg	LCLo (inhalation), ppm/h	LD_{50} (i.p.), mg/kg	LD_{50} (i.v.), mg/kg
Pyridine	[*110-86-1*]	R: 891	R (LC_{50}) : 9010/1	R: 866	
Pyridine HCl	[*628-13-7*]	R (LDLo): 1600		R: 800	
2-Methylpyridine	[*109-06-8*]	R: 790	R: 4000/4	M: 529	
3-Methylpyridine	[*108-99-6*]	R: 400	R: 8700/2	M: 596	M: 298
4-Methylpyridine	[*108-89-4*]	R: 1290	R: 100/4	M: 335	
2,4-Dimethylpyridine	[*108-47-4*]	R: 200			
2,6-Dimethylpyridine	[*108-48-5*]	R: 400	R: 7500/1		
2-Methyl-5-ethylpyridine	[*104-90-5*]	R: 368	R: 1000/4		
2,4,6-Trimethylpyridine	[*108-75-8*]	R: 400	R: 2500/2		
2-Chloropyridine	[*109-09-1*]	M: 110	R: 100/4	M: 130	
2,3-Dichloropyridine	[*2402-77-9*]			M: 135	
2,5-Dichloropyridine	[*16110-09-1*]			M: 1690	
2,6-Dichloropyridine	[*2402-78-0*]	M: 176		M: 115	
Pentachloropyridine	[*2176-62-7*]			M: 235	
2-Chloro-6-(trichloromethyl)-pyridine	[*1929-82-4*]	R: 940, M: 710			
2-Chloromethylpyridine HCl	[*6959-47-3*]	R: 316, M: 316			
3-Chloromethylpyridine	[*6959-48-4*]	R: 316, M: 316			
2-Aminopyridine	[*504-29-0*]	R: 200	Hum (TCLo): 5/5	M: 28	R: 29
3-Aminopyridine	[*462-08-8*]	Q: 178		M: 28	M: 24
4-Aminopyridine	[*504-24-5*]	R: 21, Hum (LDLo): 0.59		R: 6.5	
2,3-Diaminopyridine	[*452-58-4*]			M: 25	
2,6-Diaminopyridine	[*141-86-6*]			M: 100	M: 56
4-Dimethylaminopyridine	[*1122-58-3*]	M (LDLo): 470			M: 56
2-Aminomethylpyridine	[*3731-51-9*]	Q: 750			M: 340
2-Vinylpyridine	[*100-69-6*]	R: 100	R: 5500/1.5		
4-Vinylpyridine	[*100-43-6*]	R: 100	R: 2000/2		
3-Cyanopyridine	[*100-54-9*]	R: 1185		M (LD_{25}): 800	
Picolinic acid	[*98-98-6*]	Q: 562		M: 360	M: 487
Nicotinic acid	[*59-67-6*]	R: 7000		M: 358	M: 5000
Isonicotinic acid	[*55-22-1*]	R: 5000, M: 3123			M: 5000
Methyl nicotinate	[*93-60-7*]			M (LDLo): 2000	
Ethyl isonicotinate	[*1570-45-2*]				M: 56
Nicotinamide	[*98-92-0*]	R: 3500		M: 2050	R: 2200
Isonicotinic acid hydrazide	[*54-85-3*]	R: 1250		M: 100	M: 149
Pyridine 1-oxide	[*694-59-7*]	Q: 1000		M: 1425	M: 180
2-Pyridinemethanol	[*586-98-1*]	Q: 1000			M: 1000
2-Acetylpyridine	[*1122-62-9*]	R: 2280			
2-Benzoylpyridine	[*91-02-1*]			M: 475	
Nicotinaldehyde	[*500-22-1*]			M: 720	
2-Pyridinaldoxime	[*873-69-8*]			M: 200	
2-Hydroxypyridine	[*142-08-5*]			M: 410	M: 750
2-Pyridinethione	[*2637-34-5*]	M: 533		M: 250	M: 250
2,2′-Bipyridine	[*366-18-7*]	R: 100		M: 200	
Diquat dibromide	[*2764-72-9*]	R: 215			
4,4′-Bipyridine	[*553-26-4*]	R: 172			
Paraquat dichloride	[*1910-42-5*]	R: 57, Hum (LDLo): 43		R: 26	R: 21
4-Phenylpyridine	[*939-23-1*]				M: 89
Hexadecylpyridinium chloride	[*6004-24-6*]	R: 200		M (LDLo): 3	
4-Nitropyridine *N*-oxide	[*1124-33-0*]	R: 107			
Nicotine	[*54-11-5*]	R: 50, Hum (LDLo): 0.88			
Niflumic acid	[*4394-00-7*]	R: 250, M: 375		M: 196	M: 152
Piperidine	[*110-89-4*]	R: 400, M: 30	R: 4000/4	M: 50	

*R = rat; M = mouse; Q = quail; Hum = human.

kidneys revealed acute lesions and some of the livers exhibited pronounced cirrhosis [214].

When humans are exposed to pyridine vapor, the toxicity affects mainly the central nervous system and the gastrointestinal tract. Symptoms are headache, dizziness, nausea, insomnia, anorexia, and weakness of the limbs. As examples, the cases of a chemist who had worked with

pyridine for six months and of a man who had worked with it for 13 years are reported in [215]. Formerly, pyridine was used as an anticonvulsant, and an epileptic who received 1.8 – 2.5 mL/d of pyridine for one month died as a result of liver and kidney damage [216].

In 1983 LANGSTON first reported that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes acute symptoms of parkinsonism [217]; more than 1000 papers have been published, mainly in the United States, in the following years [218].

4.3. Mutagenicity and Ecotoxicity

Mutagenic pyridine derivatives include 2,2′-bipyridine, 4-nitropyridine *N*-oxide derivatives, chloropyridine derivatives,chloromethylpyridine derivatives, 2,6-diaminopyridine, 4-phenylpyridine, 2-hydroxy-3-nitropyridine, isonicotinic acid hydrazide, and 2-pyridine aldoxime.

Of these compounds, chloromethylpyridine derivatives [219] and 4-nitropyridine *N*-oxide derivatives [220] have been investigated with respect to their carcinogenicity.

Pyridine has a characteristic disagreeable, nauseating odor, detectable at < 1 ppm. The odor threshold is 0.021 ppm [221]. TLV and MAK values (in ppm) in several countries are as follows:

Australia	5
Germany	5
Italy	2
Japan	5
CIS	1.7
United States	5

The acute toxicity of pyridine for *Daphnia magna* is 240 mg/L, and the 24-h LC_{50} is 170 mg/L for newborns and 944 mg/L for adults. Reported acute toxic concentrations in fish vary widely and range from 26 to 1300 mg/L [204].

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