

SPECIALIST PERIODICAL REPORTS

# **The Alkaloids**

**VOLUME 11**

ROYAL SOCIETY OF CHEMISTRY

## Specialist Periodical Reports

For almost 60 years, The Royal Society of Chemistry and its predecessor, The Chemical Society, have published 'Reports' in which acknowledged experts have charted developments in chemistry.

In 1967 it was realised that the old-established '*Annual Reports*' could no longer encompass the whole of chemistry in a single volume, so the title was split into two (more recently, three) annual volumes, and, in addition the series '*Specialist Periodical Reports*' was created. The aim of the *Specialist Periodical Reports* was to provide systematic and detailed review coverage of progress in the major areas of chemical research. The Society has been extremely fortunate in obtaining the services of leading experts in their specialist fields, and the series provides a unique service for the active specialist chemist in the shape of regular critical in-depth accounts of progress in most areas of chemistry.

Inevitably, there are changes in the degree of activity in the various fields of chemistry; some subject areas flourish and expand, others contract. Some titles in the SPR series have remained unchanged, others have changed their emphasis and their titles, some have been combined with others under a new name, and some have been discontinued. In recent years several entirely new titles have appeared, which emphasises the Society's commitment to continue as a major provider of specialist tertiary literature.

For more general coverage of the highlights in chemistry, *Annual Reports* remains a 'must'. It is available in three volumes: (A) Inorganic Chemistry; (B) Organic Chemistry; and (C) Physical Chemistry. For further details about *Specialist Periodical Reports* and *Annual Reports*, write to:

The Marketing Department  
The Royal Society of Chemistry  
Burlington House  
Piccadilly  
London W1V 0BN

ISBN 0 85186 347-7

ISSN 0305-9707

Library of Congress Catalog No. 70-616637

The Alkaloids

---

Volume 11





A Specialist Periodical Report

---

# The Alkaloids

Volume 11

---

A Review of the Literature Published  
between July 1979 and June 1980

Senior Reporter

**M. F. Grundon** *School of Physical Sciences, New University of  
Ulster, Coleraine, Northern Ireland*

Reporters

**W. A. Ayer** *University of Alberta, Canada*

**K. W. Bentley** *University of Technology, Loughborough*

**A. S. Chawla** *University College, Cardiff*

**R. Dharanipragada** *University of West Virginia, U.S.A.*

**G. Fodor** *University of West Virginia, U.S.A.*

**D. M. Harrison** *New University of Ulster*

**R. B. Herbert** *University of Leeds*

**A. H. Jackson**, *University College, Cardiff*

**J. A. Lamberton** *C.S.I.R.O., Melbourne, Australia*

**J. R. Lewis** *University of Aberdeen*

**S. W. Page** *University of Georgia, U.S.A.*

**S. W. Pelletier** *University of Georgia, U.S.A.*

**A. R. Pinder** *Clemson University, South Carolina, U.S.A.*

**D. J. Robins** *Glasgow University*

**J. E. Saxton** *University of Leeds*

**M. Shamma** *Pennsylvania State University, U.S.A.*

The Royal Society of Chemistry  
Burlington House, London W1V 0BN

---

**British Library Cataloguing in Publication Data**

The alkaloids.—Vol. 11.—(Specialist periodical report/  
Royal Society of Chemistry)

1. Alkaloids – Periodicals

I. Royal Society of Chemistry

547.7'2'05 QD421.A1

ISBN 0-85186-347-7

ISSN 0305-9707

Copyright © 1981

The Royal Society of Chemistry

*All Rights Reserved*

*No part of this book may be reproduced or transmitted in any form  
or by any means – graphic, electronic, including photocopying, recording,  
taping, or information storage and retrieval systems – without  
written permission from The Royal Society of Chemistry*

Set in Times on Linotron and printed offset by  
J. W. Arrowsmith Ltd., Bristol, England

Made in Great Britain

# Foreword

---

The regular team of authors reviews the whole of the alkaloid literature for the year and a two-year coverage of *Erythrina* alkaloids is included.

Over seven-hundred references are concerned with the isolation and chemistry of alkaloids, and approximately one-third of these are devoted to synthesis and biosynthesis. It is perhaps in these areas that the most notable research is to be found. Although it is probably invidious to attempt the exercise, a personal selection of highlights would include new results on the biosynthesis of quinolizidine alkaloids (p. 4), the first synthesis of an eleven-membered macrocyclic pyrrolizidine diester (p. 49), the synthesis of *Poranthera* alkaloids (p. 68), and, in the indole field, the synthesis of tryptoquivalines G and L (p. 152), of a chiral intermediate in the construction of heteroyohimbine alkaloids (p. 167), and of a catharanthine intermediate, using palladium catalysts (p. 186).

September 1981

M. F. GRUNDON



# Contents

---

Chapter 1 Biosynthesis	1
<i>By R. B. Herbert</i>	
<b>1 Pyrrolidine, Pyridine, and Piperidine Alkaloids</b>	1
Hygrine	1
Nicotine	1
Pyrrolizidine Alkaloids	2
Lythraceae Alkaloids	3
Quinolizidine Alkaloids	4
Slaframine	7
Caerulomycin A	7
<b>2 Phenethylamine and Isoquinoline Alkaloids</b>	8
Normacromerine	8
Nornuciferine-I	10
Bisbenzylisoquinoline Alkaloids	11
Protoberberine and Related Alkaloids	12
<i>Erythrina</i> Alkaloids	14
<i>Cephalotaxus</i> Alkaloids	15
<b>3 Alkaloids Derived from Tryptophan</b>	17
Terpenoid Indole Alkaloids	17
Brevicolline	20
Echinulin	20
Roquefortine	22
Ergot Alkaloids	22
Streptonigrin	24
<b>4 Miscellaneous</b>	24
Phenazines	24
Actinomycin	26
Chloramphenicol	26
Sibiromycin, Anthramycin, and Tomaymycin	26
Gliotoxin	27
Mitomycins	28
Chapter 2 Pyrrolidine, Piperidine, and Pyridine Alkaloids	29
<i>By A. R. Pinder</i>	
<b>1 Pyrrolidine Alkaloids</b>	29
<i>Sceletium</i> Alkaloids	31
<i>Dendrobium</i> Alkaloids	31

<b>2 Piperidine Alkaloids</b>	31
Spiropiperidine Alkaloids	33
<b>3 Pyridine Alkaloids</b>	33
Alkaloids of the Celastraceae	33
 Chapter 3 Tropane Alkaloids	36
<i>By G. Fodor and R. Dharanipragada</i>	
<b>1 Occurrence and Structures of New Alkaloids</b>	36
<b>2 Synthesis and Chemical Transformations</b>	37
<b>3 Pharmacology: Structure–Activity Relationships</b>	41
<b>4 Analytical Aspects</b>	43
 Chapter 4 Pyrrolizidine Alkaloids	44
<i>By D. J. Robins</i>	
<b>1 Syntheses of the Necine Bases</b>	44
<b>2 Syntheses of the Necic Acids</b>	48
<b>3 Synthesis of a Macrocyclic Pyrrolizidine Diester</b>	49
<b>4 Alkaloids of the Apocynaceae</b>	50
<b>5 Alkaloids of the Boraginaceae</b>	51
<b>6 Alkaloids of the Compositae</b>	52
<b>7 Alkaloids of the Leguminosae</b>	53
<b>8 Alkaloids in the Lepidoptera</b>	54
<b>9 Pyrrolizidines in Micro-organisms</b>	55
<b>10 General Studies</b>	55
<b>11 Pharmacological and Biological Studies</b>	56
 Chapter 5 Indolizidine Alkaloids	59
<i>By J. A. Lambertson</i>	
<b>1 Swainsona Alkaloids</b>	59
<b>2 Cynanchum Alkaloids</b>	59
<b>3 Dendrobates Alkaloids</b>	59
<b>4 Syntheses</b>	60
<b>5 General Studies</b>	62

<b>Chapter 6</b>	<b>Quinolizidine Alkaloids</b>	<b>63</b>
	<i>By M. F. Grundon</i>	
<b>1</b>	<b>The Lupanine–Cytisine–Sparteine–Matrine Group</b>	<b>63</b>
	Occurrence	63
	Lupinine–Cytisine Group	63
	Sparteine Group	65
	Matrine Group	67
<b>2</b>	<b>Myrtine, Porantherilidine, and Porantheridine</b>	<b>68</b>
<b>3</b>	<b>9b-Azaphenalene Alkaloids</b>	<b>68</b>
<b>Chapter 7</b>	<b>Quinoline, Quinazoline, and Acridone Alkaloids</b>	<b>71</b>
	<i>By M. F. Grundon</i>	
<b>1</b>	<b>Quinoline Alkaloids</b>	<b>71</b>
	Non-hemiterpenoid Quinolines	71
	Furoquinoline Alkaloids	72
	3-Prenyl-quinolones and Related Tricyclic Alkaloids	73
<b>2</b>	<b>Quinazoline Alkaloids</b>	<b>75</b>
<b>3</b>	<b>Acridone Alkaloids</b>	<b>76</b>
<b>Chapter 8</b>	<b><math>\beta</math>-Phenylethylamines and the Isoquinoline Alkaloids</b>	<b>78</b>
	<i>By K. W. Bentley</i>	
<b>1</b>	<b><math>\beta</math>-Phenylethylamines</b>	<b>78</b>
<b>2</b>	<b>Isoquinolines</b>	<b>78</b>
<b>3</b>	<b>Benzylisoquinolines</b>	<b>79</b>
<b>4</b>	<b>Bisbenzylisoquinolines</b>	<b>82</b>
<b>5</b>	<b>Pavines and Isopavines</b>	<b>85</b>
<b>6</b>	<b>Berberines and Tetrahydroberberines</b>	<b>86</b>
<b>7</b>	<b>Secoberberines</b>	<b>94</b>
<b>8</b>	<b>Protopines</b>	<b>95</b>
<b>9</b>	<b>Phthalide-isoquinolines</b>	<b>95</b>
<b>10</b>	<b>Spiro-benzylisoquinolines</b>	<b>96</b>
<b>11</b>	<b>Rhoeadines</b>	<b>97</b>
<b>12</b>	<b>Emetine and Related Bases</b>	<b>98</b>
<b>13</b>	<b>Morphine Alkaloids</b>	<b>100</b>

<b>14 <math>\beta</math>-Phenylethylisoquinolines</b>	113
<b>15 Benzophenanthridines</b>	113
<b>16 Colchicine</b>	115
 Chapter 9 Aporphinoid Alkaloids <i>By M. Shamma</i>	117
<b>1 Introduction</b>	117
<b>2 Proaporphines</b>	117
<b>3 Aporphines</b>	118
<b>4 Aporphine Dimers</b>	127
<b>5 Oxoaporphines</b>	128
<b>6 4,5-Dioxoaporphines</b>	129
<b>7 Aristolactams</b>	129
<b>8 Phenanthrenes</b>	129
<b>9 Taspine</b>	129
<b>10 Tropoloisoquinolines</b>	130
 Chapter 10 Amaryllidaceae Alkaloids <i>By M. F. Grundon</i>	131
<b>1 Isolation and Structural Studies</b>	131
<b>2 Synthesis</b>	133
 Chapter 11 <i>Erythrina</i> and Related Alkaloids <i>By A. S. Chawla and A. H. Jackson</i>	137
<b>1 Isolation and Structure Determination</b>	137
<b>2 Synthesis</b>	139
 Chapter 12 Indole Alkaloids <i>By J. E. Saxton</i>	145
<b>1 Simple Alkaloids</b>	145
Non-tryptamines	145
Non-isoprenoid Tryptamines	147



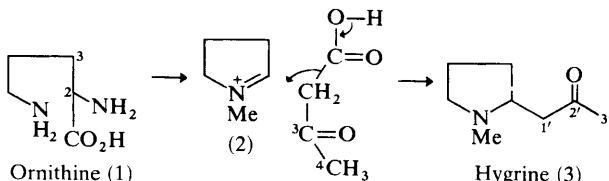
<b>2 Isoprenoid Tryptamine and Tryptophan Derivatives</b>	153
Mould Metabolites	154
Ergot Alkaloids	158
Monoterpenoid Alkaloids	160
<i>Aristolelia</i> Alkaloids	160
Corynantheine–Heteroyohimbine–Yohimbine Group, and Related Oxindoles	162
Sarpagine–Ajmaline–Picraline Group	170
Strychnine–Akuammicine–Ellipticine Group	174
Aspidospermine–Aspidofractine–Eburnamine Group	177
Catharanthine–Ibogamine–Cleavamine Group	183
<b>3 Bisindole Alkaloids</b>	187
<b>4 Biogenetically Related Quinoline Alkaloids</b>	197
<i>Cinchona</i> Group	197
Camptothecin Group	198
 Chapter 13 <i>Lycopodium</i> Alkaloids	199
<i>By W. A. Ayer</i>	
 Chapter 14 Diterpenoid Alkaloids	203
<i>By S. W. Pelletier and S. W. Page</i>	
<b>1 Introduction</b>	203
<b>2 C<sub>19</sub> Diterpenoid Alkaloids</b>	204
Alkaloids of <i>Delphinium cardiopetalum</i> DC (syn. <i>D. verdunense</i> Balbis)	204
Alkaloids of <i>Delphinium cashmirianum</i> Royle	204
Alkaloids of <i>Delphinium bicolor</i> Nutt.	206
Alkaloids from Plants in the Peoples Republic of China	206
The Structure of Nitro- <i>N</i> -nitrosoaconitinic Acid	206
<b>3 C<sub>20</sub> Diterpenoid Alkaloids</b>	207
The Structure of Atidine	207
Alkaloids of <i>Aconitum karakolicum</i>	208
Alkaloids of <i>Delphinium dictyocarpum</i> DC	209
Revision of the Structure of Cuauchichicine	209
The Mechanism of the Garryfoline–Cuauchichicine Rearrangement	211
Conversions of the Oxazolidine Rings in these Alkaloids	213
Michael Addition of Secondary Amines to Atisinone and other Exocyclic $\alpha\beta$ -Unsaturated Ketones	216
The von Braun Reaction with Dihydroatisine	216
Quantitation of Napelline	217

<b>4 <i>Daphniphyllum</i> Alkaloids</b>	217
Alkaloids of <i>Daphniphyllum gracile</i> Gage	217
<b>5 Synthetic Studies</b>	218
An Improved Synthesis of 13-Desoxydelphonine and Chasmanine	218
The Total Synthesis of Diacetyloxodenudatine	220
Synthetic Studies directed toward the Diterpenoid Alkaloids	222
<b>Chapter 15 Steroidal Alkaloids</b>	225
<i>By D. M. Harrison</i>	
<b>1 Alkaloids of the Apocynaceae</b>	225
<b>2 <i>Buxus</i> Alkaloids</b>	226
<b>3 Alkaloids of the Asclepiadaceae</b>	226
<b>4 <i>Solanum</i> Alkaloids</b>	227
<b>5 <i>Veratrum</i> and <i>Fritillaria</i> Alkaloids</b>	233
<b>6 Miscellaneous Steroidal Alkaloids</b>	237
<b>Chapter 16 Miscellaneous Alkaloids</b>	238
<i>By J. R. Lewis</i>	
<b>1 Muscarine Alkaloids</b>	238
<b>2 Imidazole Alkaloids</b>	238
<b>3 Peptide Alkaloids</b>	239
<b>4 Alkaloid-containing Plants and Unclassified Alkaloids</b>	243
<i>Fusarium moniliforme</i>	243
<i>Lycoperdon perlatum</i>	243
<i>Palythoa tuberculosa</i>	244
<i>Russula</i> species	244
<i>Zanthoxylum punctatum</i>	244
<b>Author Index</b>	245

References to earlier Reports in this series are included in the text. Two additional comprehensive reviews are also cited.<sup>1,2</sup>

### 1 Pyrrolidine, Pyridine, and Piperidine Alkaloids

**Hygrine.**—The alkaloid hygrine (3) is an intermediate in the formation of tropane bases. Biosynthesis is from acetic acid, plausibly *via* acetoacetic acid (*cf.* Vol. 10, p. 12), and from ornithine (1), very reasonably in the manner shown in Scheme 1.<sup>1,2</sup> Acetoacetate has been confirmed as an intact precursor for hygrine in experiments with [3-<sup>14</sup>C]- and [4-<sup>14</sup>C]-acetoacetic acid in *Nicandra physaloides*. Labelling in (3) was, respectively, of C-2' and C-3', which confirms the suspected orientation of acetoacetate in hygrine (see Scheme 1).<sup>3</sup>



Scheme 1

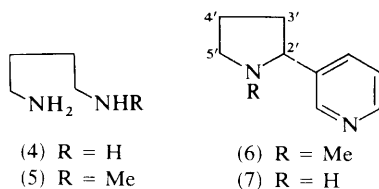
**Nicotine.**—The pyrrolidine ring of nicotine (6) derives from ornithine (1), label from, *e.g.*, C-2 appearing equally spread over C-2' and C-5'. This symmetrical incorporation of the precursor amino-acid is accounted for by the intermediacy of the symmetrical diamine putrescine (4), which is supported by other evidence too.<sup>1,2</sup> The symmetrical incorporation of ornithine into nicotine (6) and into nornicotine (7) has been confirmed by the results<sup>4</sup> of experiments with [2,3-<sup>13</sup>C<sub>2</sub>]ornithine [as (1)], thus reinforcing earlier <sup>14</sup>C and <sup>13</sup>C results (*cf.* Vol. 8, p. 5; Vol. 10, p. 14). Equal labelling of C-2', C-3' and of C-4', C-5' was observed.

<sup>1</sup> R. B. Herbert, in 'Comprehensive Organic Chemistry', ed. D. H. R. Barton and W. D. Ollis, Pergamon, Oxford, 1978, Vol. 5, p. 1045.

<sup>2</sup> R. B. Herbert, in 'Rodd's Chemistry of Carbon Compounds', 2nd edn, ed. S. Coffey, 1980, Vol. IVL, p. 291.

<sup>3</sup> B. A. McGaw and J. G. Woolley, *Tetrahedron Lett.*, 1979, 3135.

<sup>4</sup> E. Leete and M.-L. Yu, *Phytochemistry*, 1980, **19**, 1093.



The  $^{13}\text{C}$ -labelled ornithine was prepared so that individual molecules bore both labels. Consequently the  $^{13}\text{C}$  n.m.r. resonances appeared as doublets. Likewise, the  $^{13}\text{C}$  signals due to precursor label in the derived alkaloid appeared as (low-intensity) doublets on either side of the natural-abundance singlets, and were thus separate from them. This allowed an estimation of the extent to which label was incorporated into each site, even though that extent was low (0.05—0.07%). Clearly, this novel application of  $^{13}\text{C}$ -labelling will find use elsewhere, since incorporation of a precursor can be measured at high dilution (*ca* 4000 times).

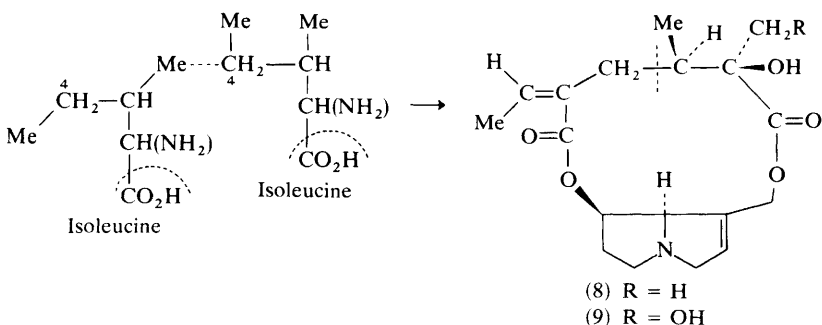
Enzymic and tracer evidence indicates strongly that the conversion of putrescine (4) into nicotine (6), in *Nicotiana tabacum*, involves first *N*-methylation, to give (5), and then oxidation, to give (2) as an intermediate. Enzymes responsible for these steps have been identified in *N. tabacum*, being called, respectively, putrescine *N*-methyltransferase and *N*-methylputrescine oxidase (*cf.* Vol. 4, p. 7). The levels of these two enzymes in four closely related genotypes of *N. tabacum* have been found to be proportional to the levels of nicotine (6), thus strongly supporting a role for such enzymes in normal nicotine biosynthesis.<sup>5</sup> A further enzyme, quinolinic acid phosphoribosyltransferase, has been identified as involved in nicotine biosynthesis, being responsive to demand for the nicotinic acid that is required for biosynthesis.

No differences were observed<sup>5</sup> in the enzymic oxidation of putrescine and *N*-methylputrescine by plant extracts of a cultivar of *N. tabacum* that had a high nicotine content and one with a high content of nornicotine (7). Thus a high nornicotine (7) content cannot be attributed to direct oxidation of putrescine, and this supports evidence which shows nornicotine (7) to be a demethylation product of nicotine.

**Pyrrolizidine Alkaloids.**—The necic acid component of senecionine (8) derives from two molecules of isoleucine, radioactivity from precursor amino-acid being equally incorporated into both halves of the necic acid fragment, as shown in Scheme 2 (*cf.* Vol. 9, p. 4). It has now been shown that biotransformation of isoleucine into the necic acid involves loss of half of a tritium label from C-4 in each of the two amino-acid fragments.<sup>6</sup> Removal of a proton is, therefore, stereospecific, and oxidation at C-4 does not proceed beyond the two-electron level; *i.e.*, a higher intermediate oxidation level, corresponding to a ketone, is excluded. Further results indicate that for each molecule of isoleucine it is the 4-*pro-S* proton [see (14)] which is lost.

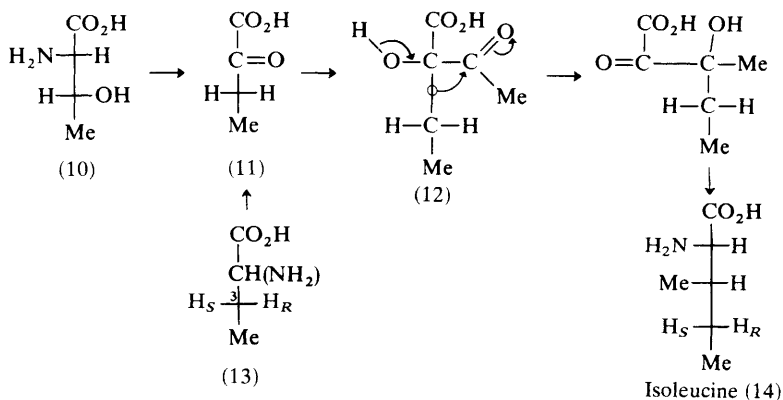
<sup>5</sup> J. W. Saunders and L. P. Bush, *Plant Physiol.*, 1979, **64**, 236.

<sup>6</sup> R. Cahill, D. H. G. Crout, M. B. Mitchell, and U. S. Müller, *J. Chem. Soc., Chem. Commun.*, 1980, 419.



Scheme 2

Threonine (10) and 2-oxobutanoic acid (11) are sequential precursors for isoleucine (14), the isoleucine skeleton being derived from (11) by a 1,2-ethyl shift within (12). Further results<sup>6</sup> have been obtained for pyrrolizidine alkaloids with (13), which is a logical precursor for (11) by simple transamination. Both enantiomers of (13) were found to be comparably good precursors for the necic acid fragments of retrorsine (9), and it was found (but not rigorously proved) that biosynthesis was accompanied by loss of the 3-*pro-S* proton of (13) in each of the two isoleucine fragments. This, taken with the isoleucine results above, indicates that migration of the ethyl group within (12) proceeds with retention of configuration, which is in accord with predictions based on orbital-symmetry considerations.<sup>7</sup>



**Lythraceae Alkaloids.**—Results showing that lysine (15) is a precursor for decodine (22) and decinine (23) in *Decodon verticillatus*, which were published in preliminary form (*cf.* Vol. 1, p. 6), are now available in a full paper.<sup>8</sup> Label from either C-2 or C-6 of the amino-acid was found to be spread equally over C-5 and C-9 of the alkaloids, indicating that ring A derived from this amino-acid and that incorporation was *via* a symmetrical intermediate. Cadaverine (16),

<sup>7</sup> R. W. Alder, *Tetrahedron Lett.*, 1971, 193.

<sup>8</sup> R. N. Gupta, P. Horsewood, S. H. Koo, and I. D. Spenser, *Can. J. Chem.*, 1979, **57**, 1606.

formed by decarboxylation of (15), is a logical candidate for this symmetrical intermediate. In support,  $[1,5-^{14}\text{C}_2]$ cadaverine gave radioactive decodine (22).<sup>8</sup> Labelling was significantly and appropriately of C-5 and C-9. In the biosynthesis of other piperidine alkaloids,<sup>1,2</sup>  $\Delta^1$ -piperidine (17) is an intermediate after lysine and cadaverine. Material that was labelled on C-6 has been found also to be a precursor for decodine (22) with specific labelling of C-9, as expected.<sup>8</sup>

A key stage in the biosynthesis of piperidine alkaloids is reached with the formation of  $\Delta^1$ -piperidine. For the elaboration of diverse alkaloids, this intermediate undergoes condensation with a variety of nucleophiles, commonly a  $\beta$ -keto-acid. (A similar situation is found for pyrrolidine alkaloid biosynthesis; see, *e.g.*, Scheme 1).<sup>1,2</sup> Existing evidence on Lythraceae alkaloid biosynthesis, taken up again below, indicated that condensation occurred in this case between  $\Delta^1$ -piperidine (17) and acetoacetic acid to give pelletierine (26), further elaboration yielding alkaloids like (22). In the event, however, labelled pelletierine was found not to be a precursor for (22) or (23).<sup>8</sup> Negative evidence is always difficult to interpret, but is here made persuasive by the fact that other precursors that were fed concurrently were incorporated. Conclusive support for these results depended on others outlined below.

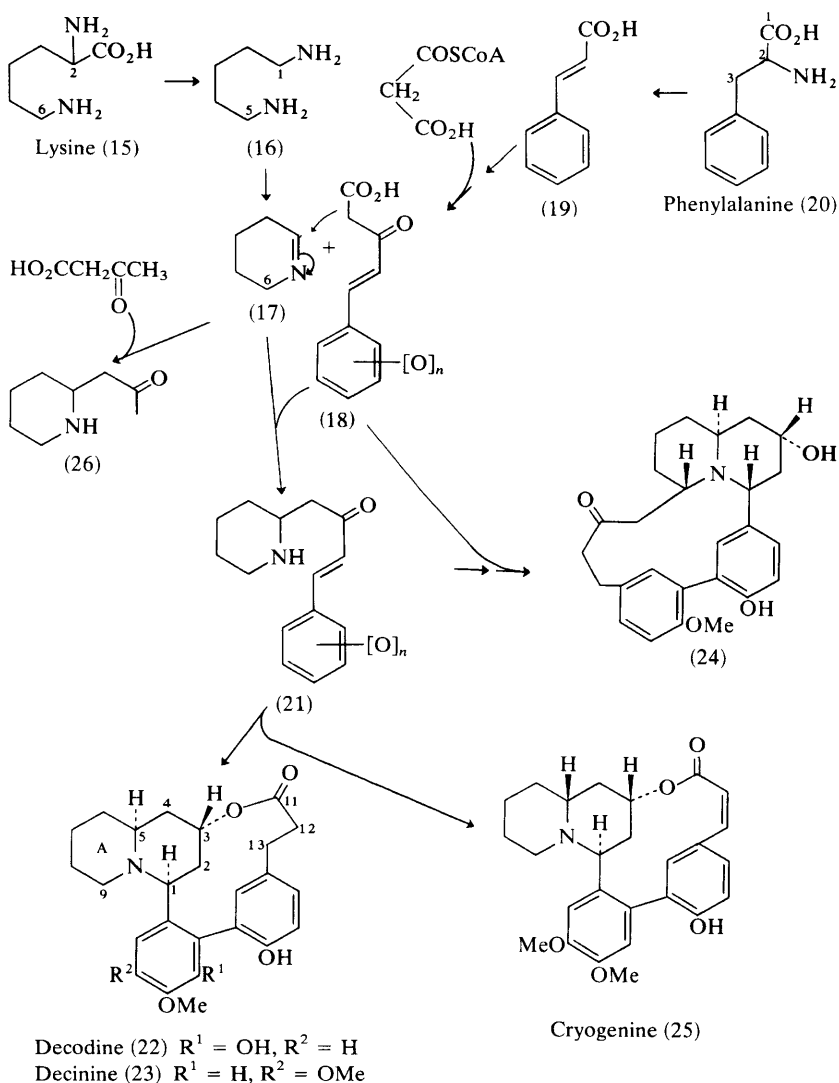
Both decodine (22) and cryogenine (25) (in another plant) were known (*cf.* Vol. 4, p. 13) to incorporate label from  $[3-^{14}\text{C}]$ phenylalanine [as (20)] into C-1 and C-13. Other results indicated that label from  $[1-^{14}\text{C}]$ phenylalanine was located at C-11 but not C-3. This is what strongly intimated that pelletierine (26) could be an alkaloid precursor, with its side-chain (rather than that of phenylalanine) providing C-4, C-3, and (possibly) C-2. Results of a complete set of feeding experiments with variously labelled samples of phenylalanine and accompanying careful degradation of (22) and (23) has shown that C-3 *does* derive from C-1 of phenylalanine, as well as confirming the derivation of the other atoms from this aromatic amino-acid.<sup>9</sup> The negative results that were obtained with pelletierine (26) fall into place.

The nature of the nucleophile which condenses with  $\Delta^1$ -piperidine (17) needs to be reconsidered. Very plausibly, this could be (18), which is formed as shown in Scheme 3 from phenylalanine (20) *via* cinnamic acid (19) and malonyl-CoA. A further unit of this type is found in alkaloids such as lythrumine (24). An outline biosynthetic route to Lythraceae alkaloids is given in Scheme 3.<sup>9</sup>

**Quinolizidine Alkaloids.**—Biosynthesis of quinolizidine alkaloids, *e.g.* sparteine (28), is from lysine (15) by way of cadaverine (16), as shown in Scheme 4. Three cadaverine units (as indicated by the thickened bonds) are required for the construction of alkaloids such as sparteine (28).<sup>10</sup> Although something has been discerned about the biosynthetic relationships of various quinolizidine alkaloids, the nature of early intermediates beyond cadaverine has remained quite elusive.<sup>10</sup> Exciting new results obtained with crude enzyme preparations from cell suspension cultures of *Lupinus polyphyllus* indicate why this is so.

<sup>9</sup> P. Horsewood, W. M. Golebiewski, J. T. Wrobel, I. D. Spenser, J. F. Cohen, and F. Comer, *Can. J. Chem.*, 1979, **57**, 1615.

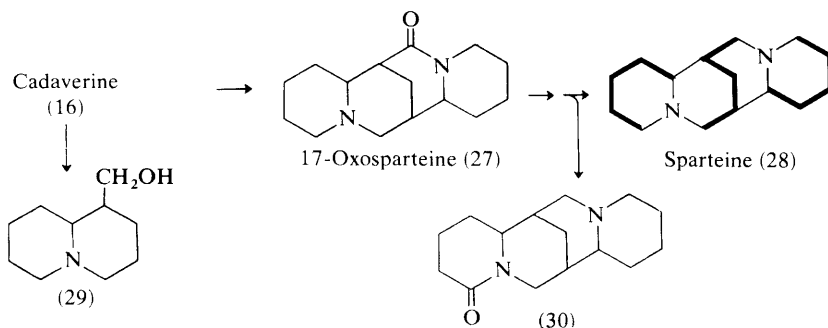
<sup>10</sup> R. B. Herbert, in ref. 1, p. 1065; in ref. 2, p. 326.



Scheme 3

The crude enzyme preparation was found to catalyse the conversion of cadaverine (16) mainly into 17-oxosparteine (27) in the presence of pyruvic acid. The pyruvic acid served as a receptor for the amino-groups of (16) in a transamination reaction, having manifestly a close relationship to alkaloid formation.<sup>11</sup> Diamine oxidase activity might have been expected to account for the

<sup>11</sup> M. Wink, T. Hartmann, and H.-M. Schiebel, *Z. Naturforsch., Teil C*, 1979, **34**, 704; M. Wink and T. Hartmann, *FEBS Lett.*, 1979, **101**, 343.



Scheme 4

transformation of cadaverine into alkaloid, but the use of an inhibitor for this enzyme, so far from resulting in a decrease in alkaloid formation, actually led to an increase. A diamine oxidase is thus not involved in alkaloid formation.

$\Delta^1$ -Piperidine (17) has been shown to be a precursor of quinolizidine alkaloids in whole plants (*cf.* Vol. 8, p. 3). However, neither it nor its self-condensation products could be detected as products in the enzymic reaction. [This conclusion is not completely unambiguous, albeit reasonably safe, because the products of the reaction of diamine oxidase, the first of which is (17), were simply compared with those of the alkaloid synthase reaction by g.l.c., and the products of the two reactions were found to be different].<sup>11</sup> It seems likely at this stage that (17) is not normally implicated in quinolizidine biosynthesis but can be substituted for an enzyme-generated intermediate *via* its open form (32) (see Scheme 5). Since no intermediates earlier than (27) could be detected, it is suggested that biosynthesis *in vitro* and *in vivo* proceeds by a series of enzyme-linked intermediates (see Scheme 5), none of which is desorbed from the enzyme or enzyme-complex until (27) is liberated. However, in some plants, biosynthesis must stop with the liberation of a compound (31), having the lupanine skeleton (29), to allow for the formation of alkaloids of this type.<sup>11</sup>

In some incubations, sparteine (28) was also formed, and it is suggested to derive from (27); sparteine (28) is known to be a precursor for other alkaloids in whole plants. Experiments with <sup>14</sup>CO<sub>2</sub> in whole plants suggest that sparteine (28) and lupanine (30), a closely related alkaloid, have a separate genesis, possibly with a dehydrosparteine [formed from (27)] as a common intermediate (*cf.* Vol. 2, p. 26). This is supported by unpublished observations with incubations of the crude alkaloid synthase.<sup>11</sup>

Quinolizidine alkaloids are associated with plant chloroplasts, which suggests that chloroplasts might be involved in alkaloid biosynthesis. This has been substantiated by further results obtained with chloroplasts from *L. polyphyllus*.<sup>12</sup>

Incubation of a crude chloroplast preparation with cadaverine yielded lupanine (30) as the main alkaloid. The production of 17-oxosparteine (27), at a lower level, was also observed. Instead of lupanine (30), chloroplasts that had been treated with digitonine synthesized sparteine (28) and a small quantity of another

<sup>12</sup> M. Wink, T. Hartmann, and L. Witte, *Z. Naturforsch., Teil C*, 1980, **35**, 93.



base corresponding to a dehydro-oxosparteine. Enzyme that had been solubilized from the chloroplasts produced 17-oxosparteine (27), which was also a lupanine precursor in chloroplasts. Correlation is thus given to the enzyme work discussed above. (Alkaloid synthesis in chloroplasts again does not involve a diamine oxidase). 17-Oxosparteine is therefore to be assigned a key role in alkaloid biosynthesis in plants (see Schemes 4 and 5). In addition, it is clear that intact membranes are important for the normal biosynthesis of quinolizidine alkaloids.

**Slaframine.**—Slaframine (37) is produced by the phytopathogen *Rhizoctonia leguminicola*. It has been known for some time that (37) derives in part from lysine *via* pipecolic acid (33), which is incorporated intact; the earliest bicyclic intermediate identified is (38) (*cf.* Vol. 5, p. 9 and ref. 2). New results have shown that the two skeletal carbons in (37), and also in the metabolite (36), not accounted for by pipecolic acid, derive from malonate (and acetate).<sup>13</sup> The labelling of (37) by, in particular, [2-<sup>2</sup>H<sub>2</sub>]acetate was deduced to be of C-2 on the basis of mass spectral evidence (which is not entirely convincing). The acyl-CoA derivative (34) has been suggested as an intermediate in the biosynthesis of (37) and also of (36). It is to be noted that condensation between malonyl-CoA and pipecolic acid (33) to give (34) must be simultaneous with decarboxylation of malonyl-CoA, since two deuterium atoms of acetate are retained at C-2 in (37) (later intermediates with a double-bond to C-2 are also excluded by these results).

The lactam (39), formed by cyclization of (34), is not a slaframine precursor, indicating that cyclization is of the derived aldehyde (35).<sup>14</sup> The earlier conclusion, *i.e.* that the alcohol corresponding to (38) is an intermediate in slaframine biosynthesis, has been confirmed.<sup>14</sup>

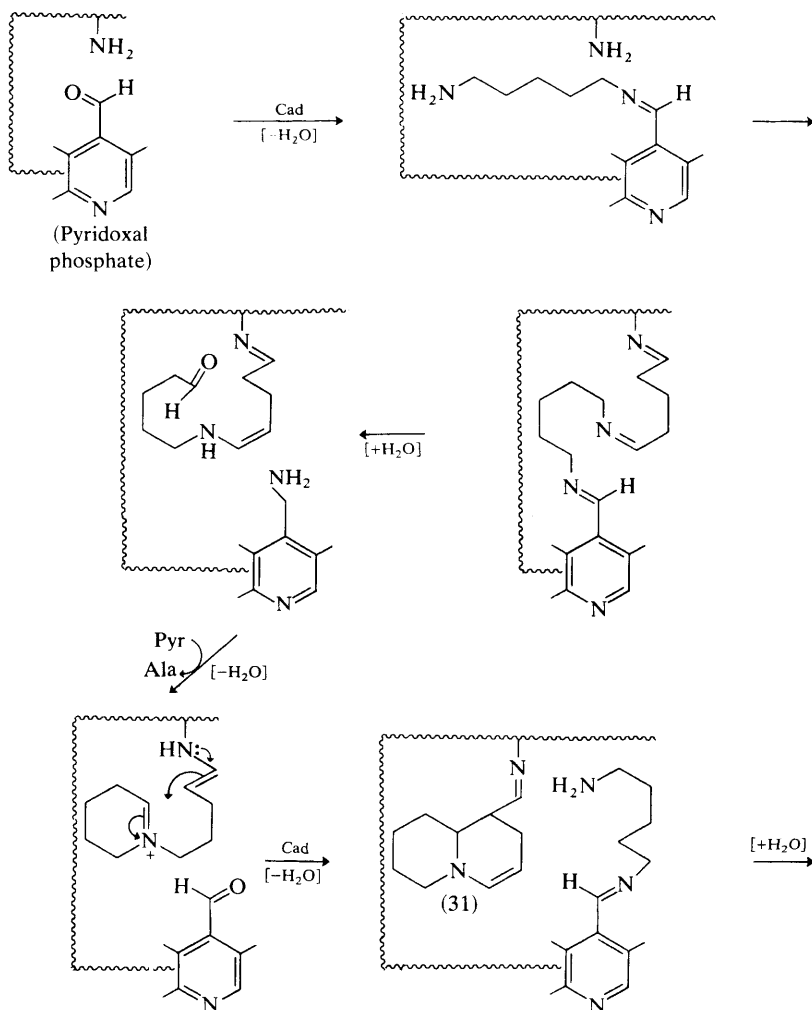
**Caerulomycin A.**—Caerulomycin A (40) is one of a unique group of metabolites from *Streptomyces caeruleus*. Study<sup>15</sup> of the biosynthesis of (40) has shown that it derives in part from lysine (15) and acetate. Labelling of the unsubstituted pyridyl ring in (40) by [1-<sup>13</sup>C]- and [1,2-<sup>13</sup>C<sub>2</sub>]-acetate was consistent with biosynthesis through lysine and an earlier symmetrical intermediate like (2*S*,6*S*)-2,6-diaminopimelic acid (41) (superposition of two equal amounts of unsymmetrical labelling). Lysine was a highly efficient precursor, and the conversion of (41) into lysine is irreversible, so lysine has been deduced to be a direct precursor for caerulomycin A. The pyridine ring in proferrosamine A (42) also derives from lysine, in this case *via* picolinic acid (43) (*cf.* Vol. 4, p. 9; Vol. 5, p. 11), and this compound may plausibly be an intermediate in the production of caerulomycin A too.

C-2 of the substituted pyridyl ring in (40) derives from lysine, and C-3 and C-4 from C-2 and C-1 of acetate, respectively, but the origin of the remainder is obscure (the *O*-methyl group derives from methionine). Sources likely to

<sup>13</sup> E. C. Clevestine, H. P. Broquist, and T. M. Harris, *Biochemistry*, 1979, **18**, 3659.

<sup>14</sup> E. C. Clevestine, P. Walter, T. M. Harris, and H. P. Broquist, *Biochemistry*, 1979, **18**, 3663.

<sup>15</sup> A. G. McInnes, D. G. Smith, J. A. Walter, L. C. Vining, and J. L. C. Wright, *Can. J. Chem.*, 1979, **57**, 3200.



Cad = cadaverine; Pyr = pyruvic acid; Ala = alanine

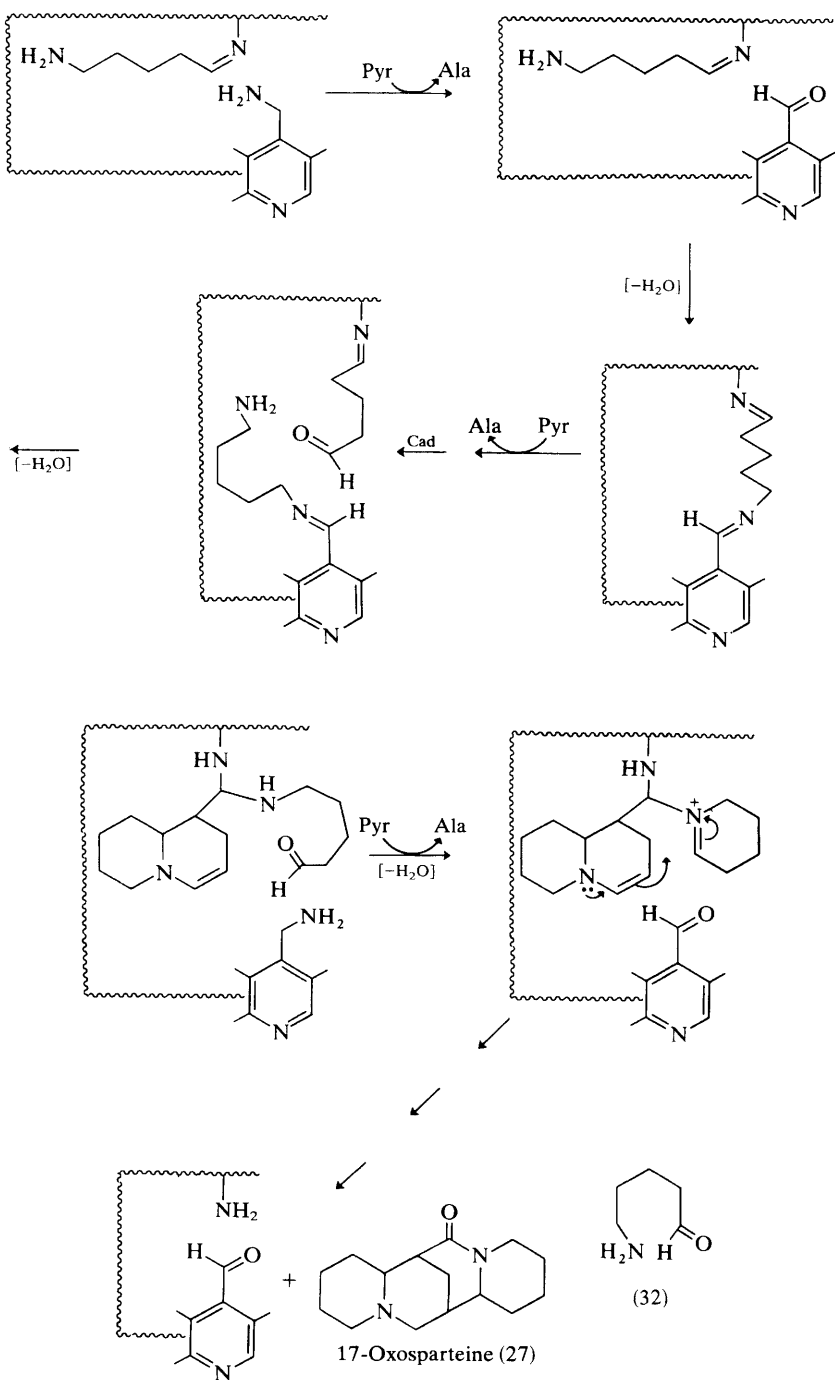
**Scheme 5**

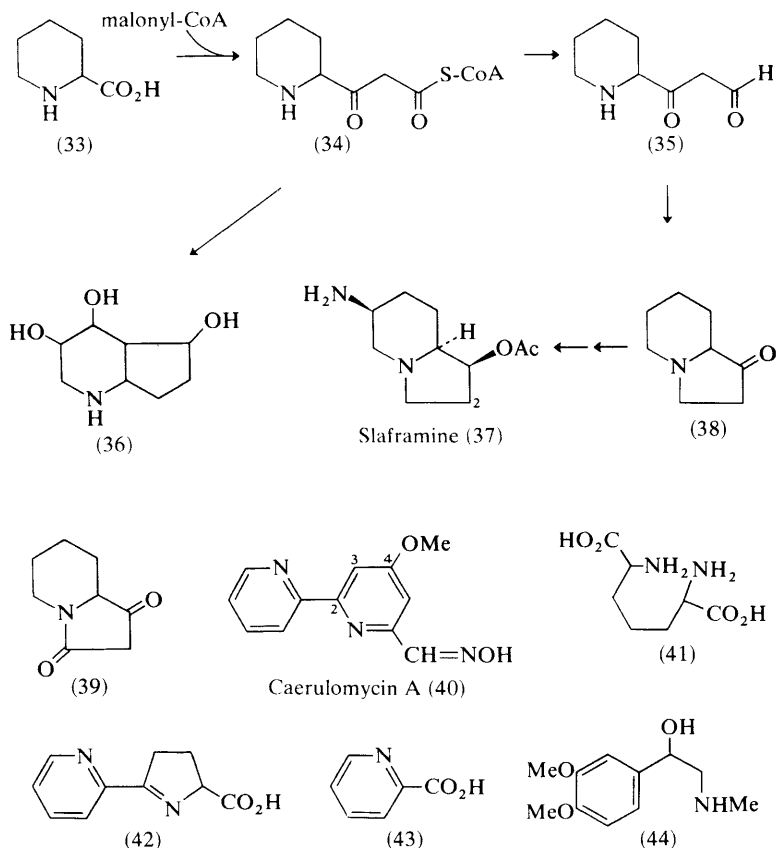
provide  $C_2$  and  $C_1$  units gave negative results; a source which will provide a  $C_3$  unit (dihydroxyacetone phosphate?) seems likely.

## 2 Phenethylamine and Isoquinoline Alkaloids

**Normacromerine.**—Normacromerine (44) has previously been shown to derive from tyrosine and tyramine (*cf.* Vol. 9, p. 7; Vol. 10, p. 15). New results have shown that *N*-methyltyramine is an efficient and specific precursor too.<sup>16</sup>

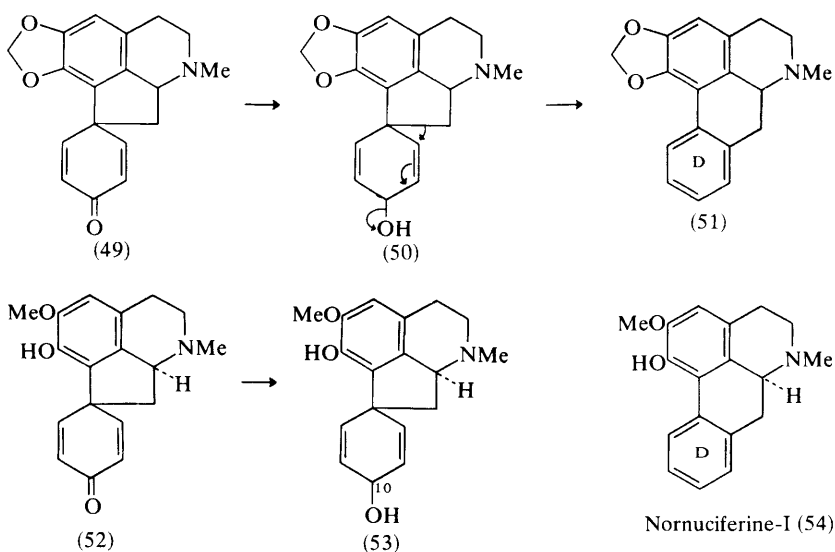
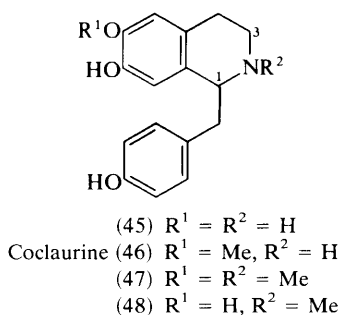
<sup>16</sup> W. J. Keller, *Phytochemistry*, 1980, **19**, 413.





**Nornuciferine-I.**—Nornuciferine-I (54) is one example of an aporphine alkaloid amongst many. A key step in the biosynthesis of aporphines is ring-closure within a benzyloquinoline [as (46)] by an oxidative coupling reaction which involves the phenolic functions on the two rings.<sup>1,2</sup> Roemerine (51) is like (54) in having ring D devoid of oxygen. Loss of oxygen occurs during roemerine biosynthesis by rearrangement of the dienol (50). This intermediate derives from *N*-methylcoclaurine (47) by way of (49). A similar biogenesis can be expected for (54), and this has turned out to be the case.<sup>17</sup> Tyrosine, norcoclaurine (45), coclaurine (46), and *N*-methylcoclaurine (47) were satisfactorily incorporated into (54) in *Croton sparsiflorus* [(48) was a very poor precursor, showing that *N*-methylation does not precede *O*-methylation]. The specificity of the incorporation of *N*-methylcoclaurine (label on C-3) was established by degradation (*N*-methyl label also retained), and it was also shown that the (*S*)-isomer of (47), with the same stereochemistry as (54), was a much better precursor for

<sup>17</sup> D. S. Bhakuni, S. Jain, and R. Chaturvedi, *Tetrahedron*, 1979, **35**, 2323.

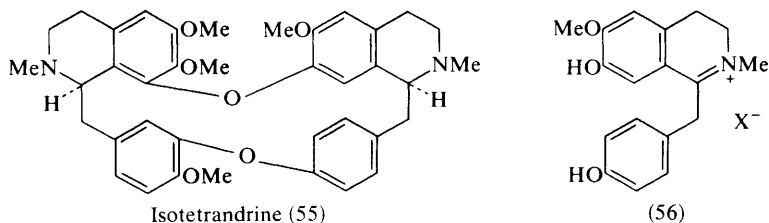


(54) than its enantiomer. In accord with roemerine biosynthesis, *N*-methylcrot-sparine (52) and (53) were also found to be precursors for (54), one of the C-10 epimeric alcohols (53) being used with significantly greater efficiency than the other. The detail of nornuciferine-I biosynthesis is completed by the observation that (47) and (52) are natural constituents of *C. sparsiflorus*. (For work on the biosynthesis of other alkaloids in this plant, see Vol. 6, p. 19).

**Bisbenzylisoquinoline Alkaloids.**—The skeleton of coclaurine (46) is one which serves as a common starting point for the biosynthesis of several bisbenzylisoquinoline alkaloids (*cf.* Vol. 10, p. 16). Coclaurine (46) and *N*-methylcoclaurine (47) have recently been found to be precursors also for isotetrandrine (55).<sup>18</sup> (*R,S*)-[*N*-methyl-<sup>14</sup>C,1-<sup>3</sup>H]-*N*-methylcoclaurine [as (47)] gave (55) without change in isotope ratio, so tritium at C-1 is not lost during biotransformation of (47) into (55). Therefore the (*R*)- and (*S*)-isomers of (47) are not

<sup>18</sup> D. S. Bhakuni, A. N. Singh, and S. Jain, *Tetrahedron*, 1980, **36**, 2149.

interconverted during biosynthesis. [This could in principle have occurred *via* (56), which is an efficient precursor for (55). Since, however, proton loss from C-1 in (47) does not occur, (56) cannot be a normal intermediate in biosynthesis. Similar conclusions have been reached for the biosynthesis of the other bisbenzylisoquinoline alkaloids.]



It was further noted<sup>18</sup> that (*R*)- and (*S*)-*N*-methylcoclaurine separately gave rise to the halves of (55) with the same absolute configuration (*cf.* Vol. 10, p. 16).

**Protoberberine and Related Alkaloids.**—The benzylisoquinoline skeleton [as (64)], which appears in diversely modified form in various alkaloids [see, *e.g.*, (66)—(71)], is formed from two molecules of tyrosine; label from this amino-acid often appears equally divided over the two halves of the alkaloid examined,<sup>1,2,19</sup> but dopa (60), like dopamine (59), is incorporated only into the isoquinoline moiety (*cf.* Vol. 6, pp. 17, 26; Vol. 7, p. 10; Vol. 9, p. 8).

The incorporation of dopa (60) has been further studied by examining its utilization in the formation of berberine (66) and hydrastine (67) in *Hydrastis canadensis*, corydaline (68) and protopine (70) in *Corydalis solida*, and ochotensimine (71) and protopine (70) in *C. ochotensis*.<sup>20</sup> [2-<sup>14</sup>C]Dopa [as (60)] was again found to label only the isoquinoline moiety of these alkaloids (label is shown by ●).

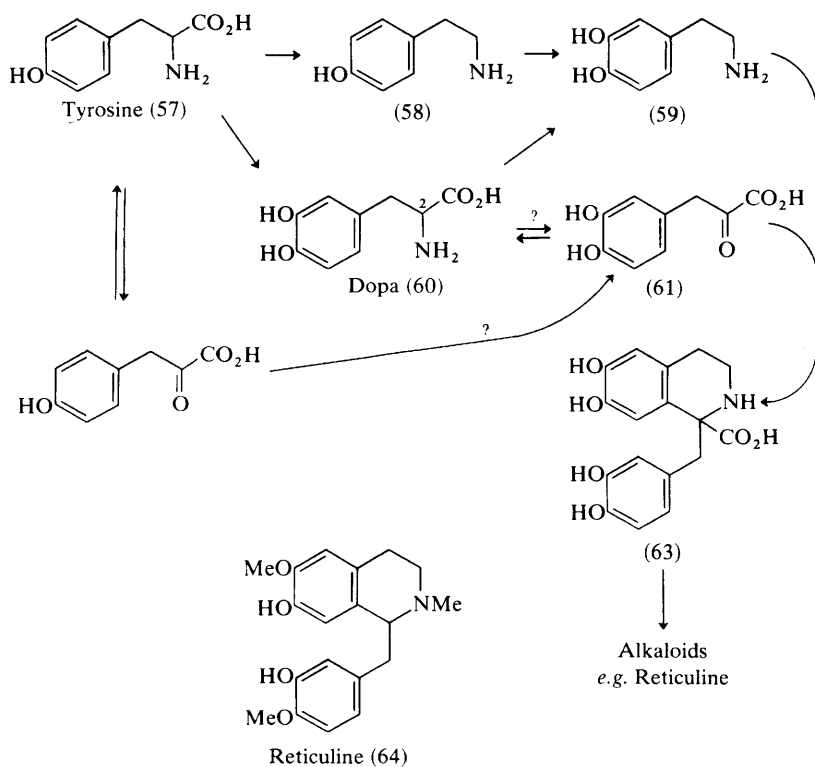
Perhaps the simplest explanation at this stage for the results obtained with dopa is that material which is *fed* to plants is poorly transported to the appropriate transaminating enzyme that is normally involved in alkaloid biosynthesis. The early pathway to benzylisoquinoline alkaloids that has so far been deduced is illustrated in Scheme 6. The compound (65) is not involved in the biosynthesis of reticuline. For details of the later stages in the biosynthesis of (66)—(71), see refs. 1 and 2.

Both tyrosine and methionine are precursors for corydaline (68) and ochotensimine (71) (*cf.* Vol. 6, p. 23). Formation of ochotensimine (71) from L-[methyl-<sup>3</sup>H,<sup>14</sup>C]methionine with high retention of tritium has been confirmed.<sup>20</sup>

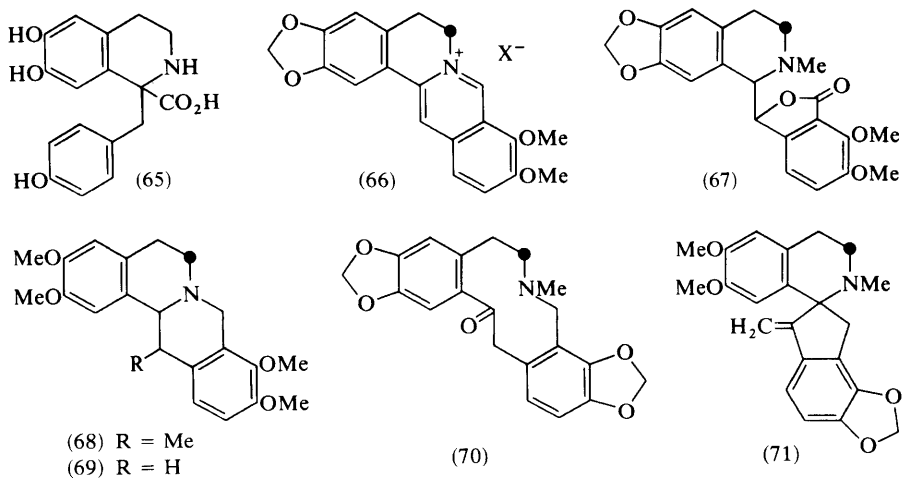
The berberine relative (72) has been found to be a precursor of corydaline (68), acting to provide the hypothetical intermediate (73) for introduction of the *C*-methyl group. Curiously, the likely precursor, *i.e.* (69), for both (72) and (73) was not incorporated.<sup>20</sup>

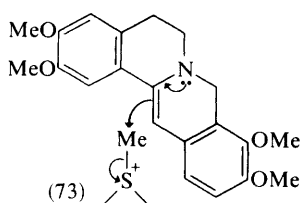
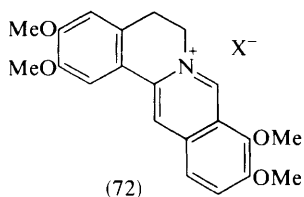
<sup>19</sup> H. R. Schütte, in 'Biosynthese der Alkaloide', ed. K. Mothes and H. R. Schütte, VEB Deutscher Verlag der Wissenschaften, Berlin, 1969, p. 367.

<sup>20</sup> H. L. Holland, P. W. Jeffs, T. M. Capps, and D. B. MacLean, *Can. J. Chem.*, 1979, **57**, 1588.



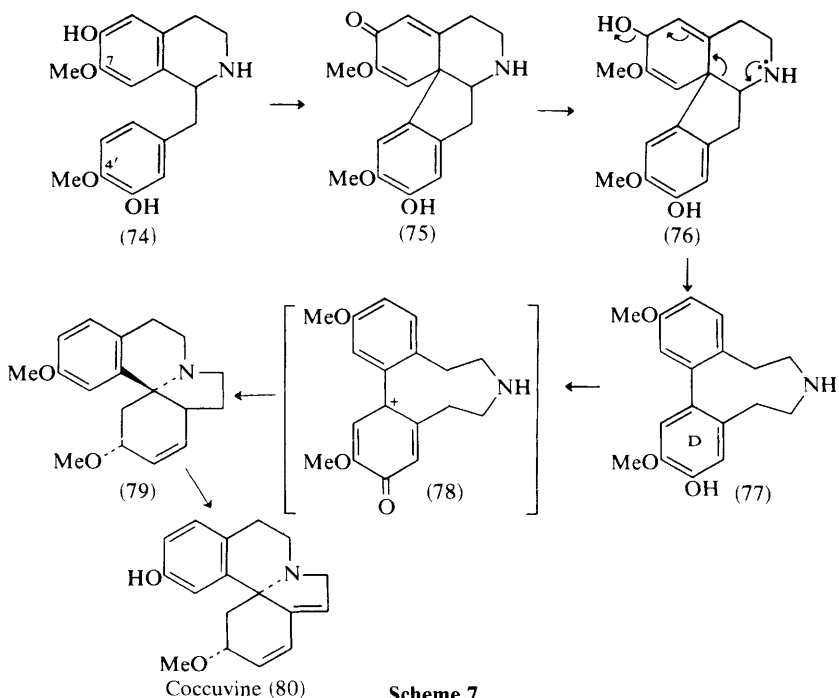
Scheme 6





Horseradish peroxidase, it has been observed, will oxidatively decarboxylate amino-acids such as (63).<sup>21</sup>

**Erythrina Alkaloids.**—*N*-Norprotosinomenine (74) is known to be a key precursor for *Erythrina* alkaloids (*cf.* Vol. 8, p. 10; Vol. 9, p. 16; *ref.* 2), and its unique role compared to isomeric isoquinolines has been confirmed for coccuvine (80) in *Cocculus laurifolius*.<sup>22</sup> The incorporation of *N*-norprotosinomenine (74) [the (+)-(*S*)-isomer is preferred] was with loss of the *O*-methyl group at C-7 and complete retention of the 4'-*O*-methyl group, measured relative to a secure internal tritium marker. The results for coccuvine (80) show that no symmetrical intermediate is involved, unlike, *e.g.*, for erythraline. Consequently the same biosynthetic route is not followed. Plausibly this route could be (74) → (75) → (76) → (77) (Scheme 7). The unsymmetrical intermediate



<sup>21</sup> I. G. C. Coutts, M. R. Hamblin, E. J. Tinley, and J. M. Bobbitt, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2744.

<sup>22</sup> D. S. Bhakuni and S. Jain, *Tetrahedron*, 1980, **36**, 2153.

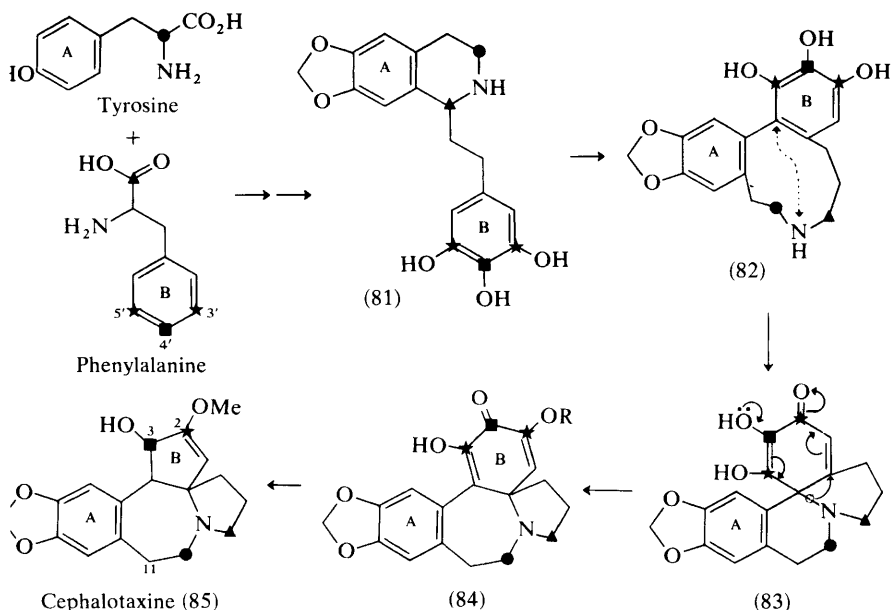


(77) could then cyclize in an oxidative reaction involving ring C and the nitrogen atom, *e.g. via* what is formally (78).

Study of the biosynthetic interrelationships of alkaloids in *C. laurifolius* has shown that, up to and beyond (80), the reactions involved are demethylation as well as dehydrogenation and oxygenation.<sup>22</sup>

**Cephalotaxus Alkaloids.**—The interesting results relating to the incorporation of phenylalanine and tyrosine into cephalotaxine (85) in *Cephalotaxus harringtonia*, previously published in preliminary form (*cf.* Vol. 8, p. 12), are now available in a full paper.<sup>23</sup> New results are concerned with the incorporation of ring-labelled phenylalanine and with the later stages of biosynthesis. A <sup>14</sup>C label at C-4' of phenylalanine appeared without loss (measured relative to a tritium label in the side-chain) at C-3, whereas a <sup>14</sup>C label at C-3' ( $\equiv$  C-5') appeared, with a 50% loss, at C-2. This, together with results obtained with other labelled samples of phenylalanine and tyrosine, is consistent with the pathway shown in Scheme 8. Ring-closure within (82) must take the course shown because of the results obtained; alternative modes of cyclization would have given distinctly different labelling results.

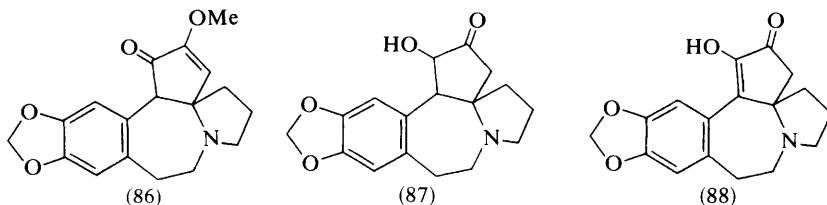
The biosynthetic pathway suggested for cephalotaxine (Scheme 8) includes intermediates which are homologous with those for *Erythrina* alkaloids (see above). It depends in part on the fact that homo-*Erythrina* alkaloids co-occur naturally with those having the cephalotaxine skeleton.



Scheme 8

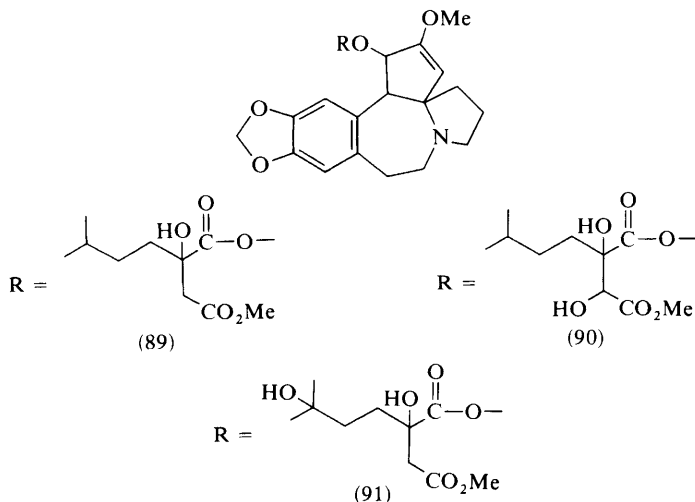
<sup>23</sup> R. J. Parry, M. N. T. Chang, J. M. Schwab, and B. M. Foxman, *J. Am. Chem. Soc.*, 1980, **102**, 1099.

Further experiments have been carried out in which (85)—(88) were tested as precursors for each other.<sup>23</sup> It appears that (85) and (86) are interconvertible and that (87) and (88) are formed after (85), *i.e.*, the *O*-methyl group in (85) is retained from an early stage of biosynthesis; (88) is readily reduced to (87) *in vivo*.



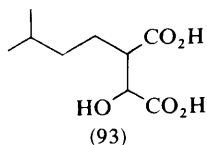
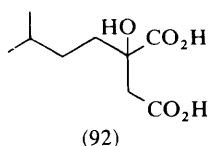
Alkaloid distribution in *C. harringtonia* in relation to age has been noted. Physiological stress (pruning) was found to cause hydrolysis of cephalotaxine esters. Environmental factors also caused hydrolysis and, in addition, oxidation of cephalotaxine (85) to 11-hydroxycephalotaxine and of two other alkaloids to epoxy-derivatives.<sup>24</sup>

Esters of cephalotaxine (85) that are found in *Cephalotaxus* species are exemplified by deoxyharringtonine (89), isoharringtonine (90), and harringtonine (91). The acyl portion (92) of deoxyharringtonine (89) derives from the amino-acid leucine. The results published previously in preliminary form (*cf.* Vol. 8, p. 13) are now available in full.<sup>25</sup> Additional information is that (92) serves as a specific precursor for the acyl portions of (91) and (90) and that (93) is not involved in the biosynthesis of the latter. Results of an examination of (89) as a possibly intact precursor for (91) were inconclusive.<sup>25</sup>



<sup>24</sup> N. E. Delfel, *Phytochemistry*, 1980, **19**, 403.

<sup>25</sup> A. Glitterman, R. J. Parry, R. F. Dufresne, D. D. Sternbach, and M. D. Cabelli, *J. Am. Chem. Soc.*, 1980, **102**, 2074.



### 3 Alkaloids Derived from Tryptophan

**Terpenoid Indole Alkaloids.**—Important recent work has defined strictosidine (97) as a key intermediate in the biosynthesis of terpenoid indole alkaloids with both  $3\alpha$ - and  $3\beta$ -configurations. Some of this work, published earlier in preliminary form (*cf.* Vol. 9, p. 18), is now available in a full paper.<sup>26</sup> In addition to those alkaloids examined earlier, strychnine, gelsemine, vincadifformine, isoreserpiline, aricine, isoreserpinine, and ajmaline have been shown to derive from strictosidine (data are also included for ajmalicine, for catharanthine, and for vindoline which had been reported earlier).

Strictosidine (97) is formed by condensation of tryptamine (95) with secologanin (96), as shown in Scheme 9. The enzyme which catalyses the condensation has been isolated, purified, and characterized.<sup>27</sup> Subsequent transformation of strictosidine (97) involves first the loss of the glucose moiety. Two strictosidine-specific glucosidases have been isolated and characterized.<sup>28</sup>

Cathenamine (100) has been identified as an early intermediate in terpenoid indole alkaloid biosynthesis (*cf.* Vol. 8, p. 27). It has also been isolated from *Guettarda eximia*. Another alkaloid, 4,21-dehydrogeissoschizine (99), has now been isolated from this plant; it is readily converted into (100) in alkaline solution.<sup>29</sup> On incubation with an enzyme preparation from *Catharanthus roseus* cell cultures in the presence of NADPH at pH 7, (99) was converted into ajmalicine (102), 19-*epi*-ajmalicine (103), and tetrahydroalstonine (104), which are the normal products with this enzyme preparation. In the absence of NADPH, cathenamine (100) accumulated.<sup>30</sup> The reaction to give (100) proceeded linearly with time, and was dependent on the concentration of protein and substrate. No conversion occurred in the absence of enzyme.

Further experimental results have proved (99) to be an obligatory intermediate in alkaloid biosynthesis.<sup>30</sup> Inactive material diluted radioactivity from [ $1\text{-}^{14}\text{C}$ ]tryptamine into (102)—(104), and (99) could be isolated in a radioactive form from incubations with [ $1\text{-}^{14}\text{C}$ ]tryptamine and secologanin (96).

Under NADPH-regenerating conditions, (99) was converted into geissoschizine (101), which has been shown not to be a direct alkaloid precursor (for further discussion, see below).

In the presence of deuterium oxide, the conversion of (95) plus (96) into (102)—(104) is accompanied by the incorporation of two deuterium atoms, one

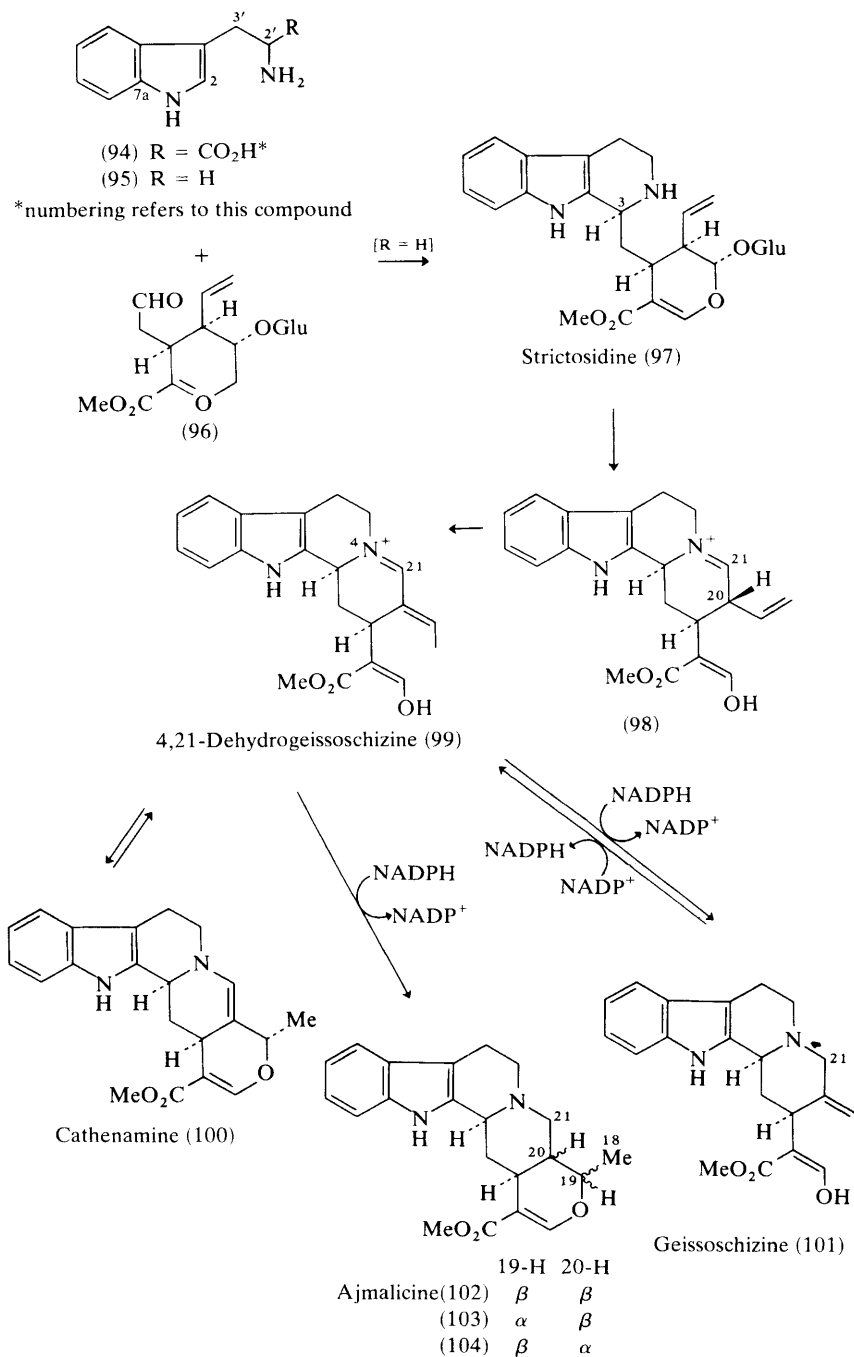
<sup>26</sup> N. Nagakura, M. Rueffer, and M. H. Zenk, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2308.

<sup>27</sup> J. F. Treimer and M. H. Zenk, *Eur. J. Biochem.*, 1979, **101**, 225; for earlier work on this enzyme, see Vol. 9 of these Reports, p. 18.

<sup>28</sup> T. Hemscheidt and M. H. Zenk, *FEBS Lett.*, 1980, **110**, 187.

<sup>29</sup> C. Kan-Fan and H.-P. Husson, *J. Chem. Soc., Chem. Commun.*, 1979, 1015.

<sup>30</sup> M. Rueffer, C. Kan-Fan, H.-P. Husson, J. Stöckigt, and M. H. Zenk, *J. Chem. Soc., Chem. Commun.*, 1979, 1016.



Scheme 9

each onto C-18 and C-20.<sup>31</sup> On the other hand, (99) affords monodeuteriated alkaloids. Thus, under the conditions used, isomerization of (99) to (98) or its 20,21-isomer does not occur. Furthermore, the incorporation of only one deuterium atom into the alkaloids (102)—(104) provides further evidence that (99) is the immediate precursor for (100).

It is suggested in conclusion that (99) occupies a crucial position at the branch-point in the biosynthesis of *Corynanthe*, *Iboga*, and *Aspidosperma* alkaloids.<sup>30</sup>

Further evidence<sup>32</sup> has been obtained which strongly supports the conclusion (*cf.* Vol. 10, p. 19) that geissoschizine (101) is at a shunt in the biosynthesis of the three tissue-culture alkaloids (102)—(104). Incubation of (101) with the enzyme preparation plus NADP<sup>+</sup> and NADPH in D<sub>2</sub>O afforded a sample of (103) that contained one deuterium atom per molecule. Geissoschizine (101) must thus be involved in biosynthesis after (98). With NADPD as co-factor, a sample of (103) was isolated that contained a single deuterium atom, located at C-21, in each molecule. Moreover, geissoschizine with deuterium that was stereochemically  $\alpha$  at C-21 gave (103) that was devoid of label. These two results support biosynthesis *via* (99).

A cell-free extract of *C. roseus* tissue cultures has been found to convert geissoschizine (101) into one of the C-16 isomers of isositsikirine. The absolute configuration of this product has been shown to be as in (105); the same isomer is produced in intact *C. roseus* plants. Isositsikirine (105) was produced not only from (101) by the cell-free preparation but also from (95) and (96); all three conversions were NADPH-dependent.<sup>33</sup>

For (essentially) the first time recently, strains of *C. roseus* cultures have been obtained which will synthesize *Strychnos*, *Iboga*, and *Aspidosperma* alkaloids.<sup>34</sup> This opens up the exciting possibility of studying the biosynthesis of those alkaloids lying beyond the *Corynanthe* type, such as (102), by using enzyme preparations from tissue cultures, which have proved so powerful for the early stages of biosynthesis (see above).

The biosynthesis of terpenoid indole alkaloids from tryptophan has long been known.<sup>1,2</sup> In new experiments with DL-[2-<sup>14</sup>C,2',3'-<sup>13</sup>C<sub>2</sub>]tryptophan [as (94)], this has been confirmed for vindoline (106).<sup>35</sup> Incorporation measured by assay for radioactivity and by n.m.r. spectroscopy was the same, thus indicating an intact incorporation (with loss, of course, of the carboxy-group) (for discussion of the particular application of <sup>13</sup>C labelling used here, see pp. 1–2).

Vinblastine (108) has been shown to derive from catharanthine (107) and vindoline (106) by way of anhydrovinblastine (109) (*cf.* Vol. 10, p. 19). Recently, 20'-deoxyeuosidine (110) has been shown to be a precursor for (108).<sup>36</sup> The relationship of the two precursors (109) and (110) to normal vinblastine biosynthesis is not yet clear.

<sup>31</sup> J. Stöckigt and P. Heinsteins, to be published; quoted in ref. 30.

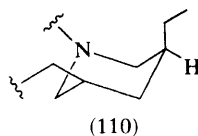
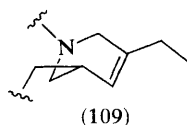
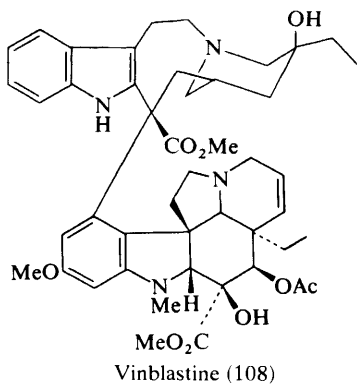
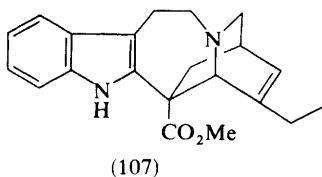
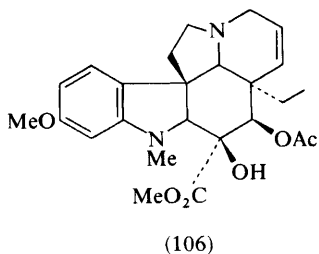
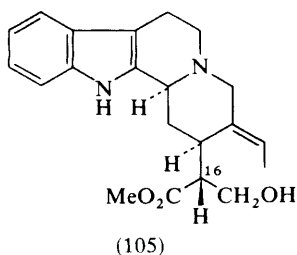
<sup>32</sup> J. Stöckigt, G. Hölfe, and A. Pfützner, *Tetrahedron Lett.*, 1980, **21**, 1925.

<sup>33</sup> T. Hirata, S.-L. Lee and A. I. Scott, *J. Chem. Soc., Chem. Commun.*, 1979, 1081.

<sup>34</sup> A. I. Scott, H. Mizukami, T. Hirata, and S.-L. Lee, *Phytochemistry*, 1980, **19**, 488; J. P. Kutney, L. S. L. Choi, P. Kolodziejczyk, S. K. Sleight, K. L. Stuart, B. R. Worth, W. G. W. Kurz, K. B. Chatson, and F. Constabel, *Heterocycles*, 1980, **14**, 765.

<sup>35</sup> E. Leete, *J. Nat. Products (Lloydia)*, 1980, **43**, 130.

<sup>36</sup> F. Guérillon, N. V. Bac, Y. Langlois, and P. Potier, *J. Chem. Soc., Chem. Commun.*, 1980, 452.



A scheme of possible biosynthesis has been proposed for the *Aristolelia* indole alkaloids, which include a regular monoterpenoid unit.<sup>37</sup>

**Brevicolline.**—The  $\beta$ -carboline part of the plant alkaloid brevicolline (114) has been shown to derive from tryptophan (94) and pyruvic acid.<sup>37</sup> Putrescine (4) and related compounds provide the pyrrolidine ring.<sup>38</sup> A key intermediate in brevicolline biosynthesis is likely to be (113), derived by oxidative decarboxylation of (111), which in turn is formed through the condensation of (94) with pyruvic acid; condensation of (113) and (112) (formed from putrescine) would lead to (114). This has been supported by successfully mimicking the biogenetic sequence, starting with the chemical oxidative decarboxylation of (111).<sup>39</sup>

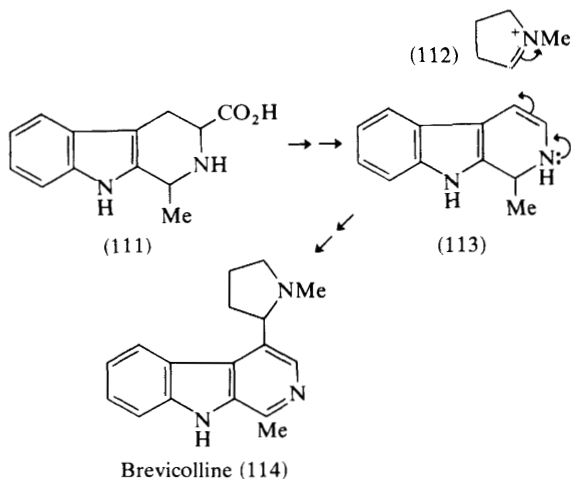
**Echinulin.**—Detailed work<sup>40</sup> has been carried out in the biosynthesis of echinulin (115). This fungal metabolite arises from tryptophan and alanine through the

<sup>37</sup> I. R. C. Bick, M. A. Hai, and N. W. Preston, *Heterocycles*, 1979, **12**, 1563.

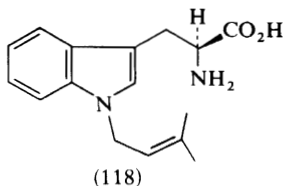
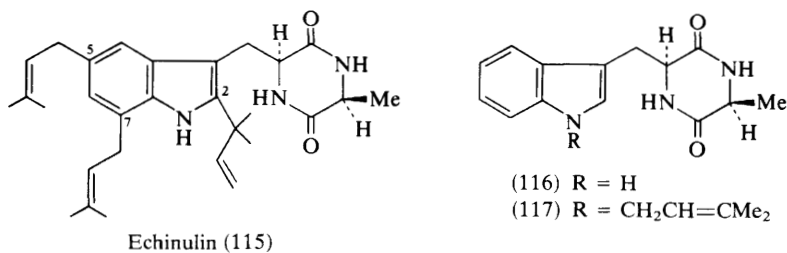
<sup>38</sup> M. Ya. Lovkova, G. V. Lazurjevski, and N. I. Klimentjev, in Proceedings of the 11th IUPAC International Symposium on Chemistry of Natural Products, Golden Sands, Bulgaria, 1978, Vol. 1, p. 159; I. Kompis, E. Grossman, I. V. Terentjeva, and G. V. Lazurjevski, *Khim. Prir. Soedin.*, 1969, 39.

<sup>39</sup> E. Leete, *J. Chem. Soc., Chem. Commun.*, 1979, 821.

<sup>40</sup> R. B. Herbert, in ref. 2, p. 343 and in previous volumes of these Reports, viz. in Vol. 10, p. 24 and Vol. 9, p. 24; see also refs. cited in ref. 41.



cyclic dipeptide (116). The isoprene unit at C-2 on the indole nucleus is the first to be introduced. It is a reasonable hypothesis that this group may arrive at C-2 *via* the indolic nitrogen atom. However, neither (117) nor (118) was significantly incorporated into echinulin (115) when other known precursors (mevalonate and tryptophan) were.<sup>41</sup>

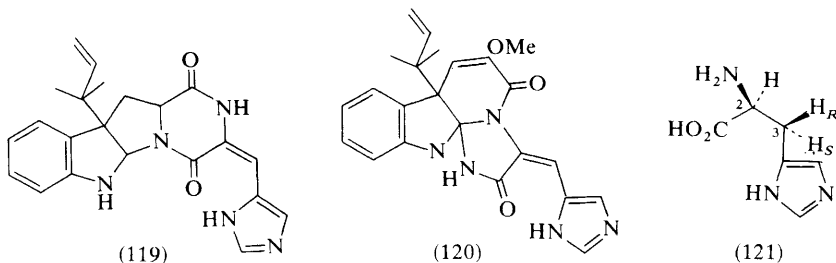


Introduction of the isoprenyl groups at C-5 and C-7 in echinulin (115) has been shown, by the results of [5(*R*)-<sup>3</sup>H]- and [5(*S*)-<sup>3</sup>H]-mevalonate incorporations, to proceed with normal inversion of configuration at C-5 (mevalonate numbering) in the intermediate dimethylallyl pyrophosphate. The pattern of incorporation of [1,2-<sup>13</sup>C<sub>2</sub>]acetate indicates that the stereochemistry at the double-bonds is the same as that of dimethylallyl pyrophosphate.<sup>42</sup>

<sup>41</sup> M. F. Grundon, M. R. Hamblin, D. M. Harrison, J. N. D. Logue, M. Maguire, and J. A. McGrath, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1294.

<sup>42</sup> J. K. Allen, K. D. Barrow, and A. J. Jones, *J. Chem. Soc., Chem. Commun.*, 1979, 280.

**Roquefortine.**—Histidine (121) is a part precursor for roquefortine (119) (*cf.* Vol. 10, p. 25). Its incorporation involves desaturation with loss of the proton at C-2 and one of the protons at C-3. Experimental results with (2*S*,3*S*)- and (2*S*,3*R*)-[3-<sup>3</sup>H]histidine [as (121)] show that, in the biosynthesis of both roquefortine (119) and oxaline (120), the 3-*pro-S* proton is lost stereospecifically.<sup>43</sup> Dehydrogenation to generate these double-bonds of (*E*) configuration thus proceeds in a *syn* sense. Desaturation with the same *syn* stereochemistry has been observed in the biosynthesis of other diketopiperazine metabolites, *e.g.* mycelianamide and cryptoechinulin A, which both have (*Z*) double-bonds (*cf.* Vol. 7, p. 19; Vol. 8, p. 35).



Metabolites of the ergoline type [as (128)], as well as those of type (119), have been isolated from *Penicillium roqueforti*. The incorporation has been observed of radioactive samples of tryptophan and mevalonate into both series of metabolites, and of histidine into those of type (119).<sup>44</sup> Diversion from tryptophan into the two independent biosynthetic pathways is initiated on the one hand by the formation of (122) and on the other by reaction with histidine to give a diketopiperazine precursor for metabolites such as (119). Which route is followed is temperature-dependent.

**Ergot Alkaloids.**—4-( $\gamma\gamma$ -Dimethylallyl)tryptophan (122) is the first intermediate beyond tryptophan in ergot alkaloid biosynthesis. Chanoclavine-I (127) is the first tricyclic base (*cf.* Vol. 10, p. 26, and *ref.* 2). Recently, (124; labels as shown) has been found to be a very efficient and intact precursor for elymoclavine (128).<sup>45</sup> The high level of incorporation indicates that (123) is a probable intermediate situated between (122) and (127). The decarboxylation product (125) was not utilized for biosynthesis, so, although decarboxylation of (123) is required for the conversion of (123) into (127), either it is intimately associated with ring-closure or an imine that is related to (126) is involved.

It has been found that elymoclavine (128) inhibits dimethylallyltryptophan synthetase, and the mechanism is one of feedback inhibition.<sup>46</sup>

Clavicipitic acid (129) (naturally occurring as a mixture of C-10 epimers) has been identified as a metabolite which is at a shunt from the main line of

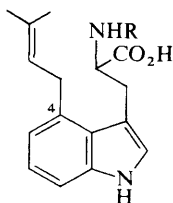
<sup>43</sup> R. Vleggaar and P. L. Wessels, *J. Chem. Soc., Chem. Commun.*, 1979, 160.

<sup>44</sup> S. Ohmoto, T. Ohashi, and M. Abe, *Agric. Biol. Chem.*, 1979, **43**, 2035.

<sup>45</sup> H. Otsuka, J. A. Anderson, and H. G. Floss, *J. Chem. Soc., Chem. Commun.*, 1979, 660.

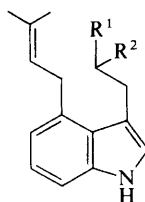
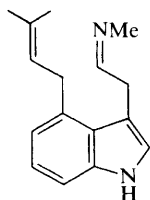
<sup>46</sup> L.-J. Cheng, J. E. Robbers, and H. G. Floss, *J. Nat. Products (Lloydia)*, 1980, **43**, 329.



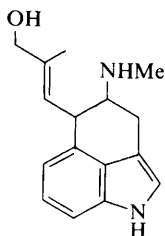


(122) R = H

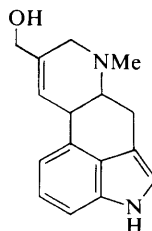
(123) R = Me

(124) R<sup>1</sup> = <sup>15</sup>NHC<sup>2</sup>H<sub>3</sub>, R<sup>2</sup> = CO<sub>2</sub>H(125) R<sup>1</sup> = NHMe, R<sup>2</sup> = H

(126)



(127)



(128)

ergot alkaloid biosynthesis (*cf.* Vol. 8, p. 27). New results support this.<sup>47</sup> Clavicipitic acid (129) was deduced (on the basis of a relatively poor incorporation) not to be a precursor for elymoclavine (128).

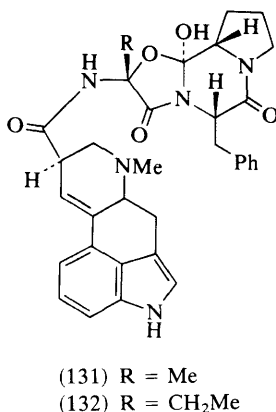
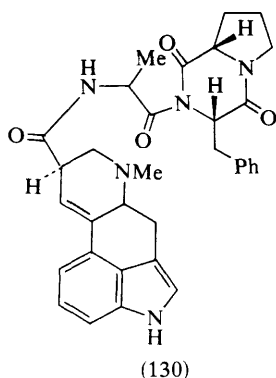
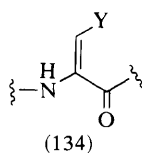
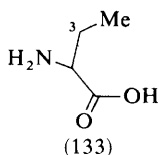
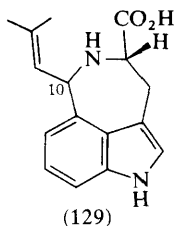
Clavicipitic acid (129) was found to be formed from the intact skeleton of tryptophan and from mevalonate. Tritium at C-5 in samples of labelled mevalonate was retained at an abnormally high level (at C-10) of (129). The reason for this is not clear.

A unique cyclol structure is contained within most of the peptidic ergot alkaloids, *e.g.* ergotamine (131). It is believed, that this structural feature is introduced at a late stage of biosynthesis, possibly at the stage corresponding to (130), through formation of an  $\alpha$ -hydroxy- $\alpha$ -amino-acid fragment. The mechanism of this hydroxylation has been probed<sup>48</sup> initially by making use of the observation that 2-aminobutyric acid will substitute for alanine in biosynthesis with the generation of ergostine (132) in cultures that do not normally produce it (*cf.* Vol. 10, p. 26). (*R,S*)-[3-<sup>13</sup>C,3-<sup>2</sup>H<sub>2</sub>]-2-Aminobutyric acid [as (133)] gave (132), mass spectral analysis of which showed the molecule to have very largely retained the three isotopes of the precursor in the 2-aminobutyric acid portion. (A check with a mixture of labelled and unlabelled precursor confirmed that deuterium was not retained as a result of intermolecular recycling of a hydrogen atom that was removed during introduction of the hydroxy-group). Thus intermediates of the type (134) are not implicated in cyclol formation.

The labelling of paspalin (138) and its congeners (136) and (137) by [<sup>13</sup>C]acetate, together with the natural occurrence of (135), has indicated that the

<sup>47</sup> J. E. Robbers, H. Otsuka, H. G. Floss, E. V. Arnold, and J. Clardy, *J. Org. Chem.*, 1980, **45**, 1117.

<sup>48</sup> C. M. Belzecki, F. R. Quigley, H. G. Floss, N. Crespi-Perellino, and A. Guicciardi, *J. Org. Chem.*, 1980, **45**, 2215.



biosynthetic route to (136)—(138) is that shown in Scheme 10.<sup>49</sup> Two metabolites from *Aspergillus flavus* appear to be deviations from this pathway.<sup>50</sup>

**Streptonigrin.**—Details of a study of the biosynthesis of streptonigrin (139) that had earlier been published in preliminary form (*cf.* Vol. 9, p. 24; Vol. 10, p. 23) are now available in full papers.<sup>51,52</sup> In essence, the new results are that labelled anthranilic acid was not incorporated into streptonigrin (139),<sup>51</sup> that L- rather than D-tryptophan was a precursor, and that label from C-7a in tryptophan (94) appeared, it was deduced, at C-8' in (139).<sup>52</sup> The exclusive labelling of C-8' by tryptophan indicates that rings A and B do not derive from this amino-acid. These rings do not derive from phenylalanine and tyrosine, and negative results have been obtained with shikimic acid due, at the least, to poor cellular uptake.<sup>51</sup>

#### 4 Miscellaneous

**Phenazines.**—Results on the biosynthesis of microbial phenazines from shikimic acid (previously published in preliminary form; *cf.* Vol. 5, p. 44 and Vol. 7, p. 27) are now available in full papers.<sup>53</sup> Additional results are that 2,3-dihydro-3-hydroxyanthranilic acid (140) was not a precursor for iodinin (141), nor was

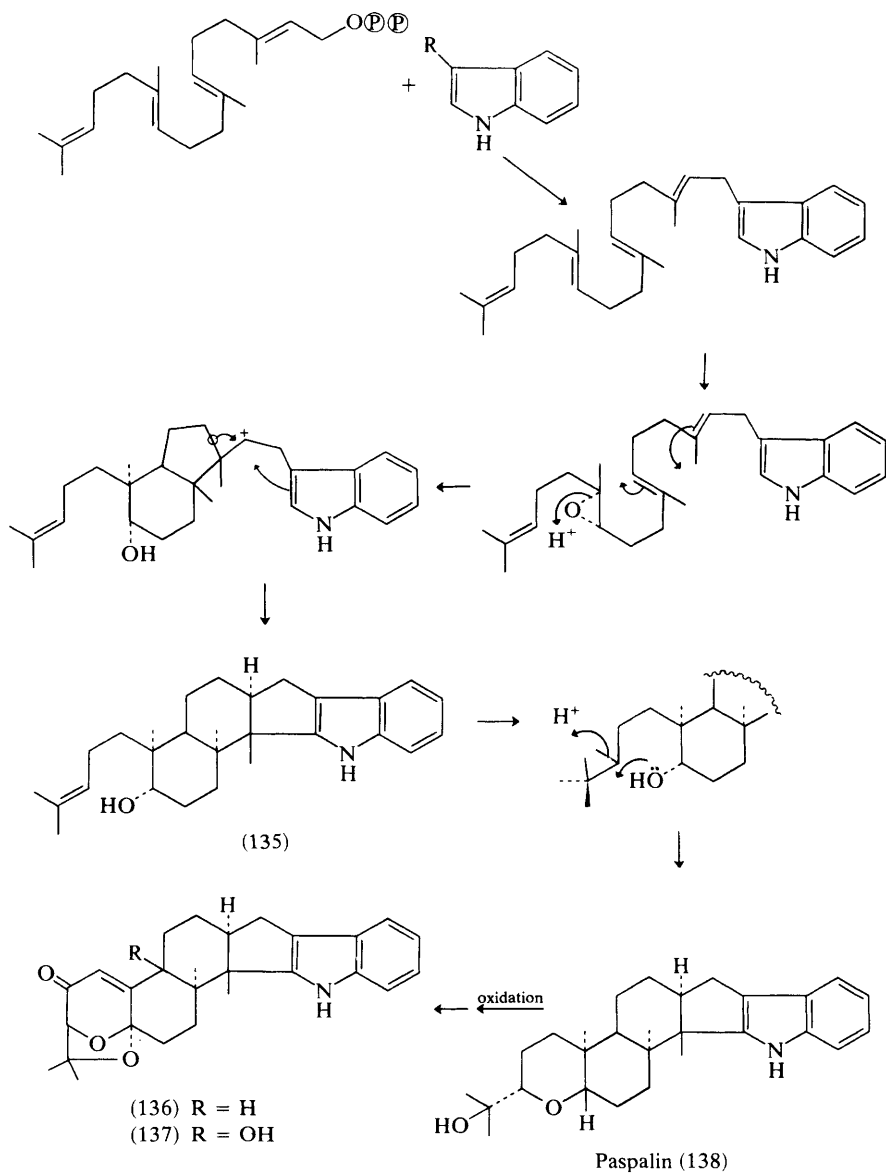
<sup>49</sup> W. Acklin, F. Weibel, and D. Arigoni, *Chimia*, 1977, **31**, 63.

<sup>50</sup> R. T. Gallagher, J. Clardy, and B. J. Wilson, *Tetrahedron Lett.*, 1980, **21**, 239; R. T. Gallagher, T. McCabe, K. Hirotsu, J. Clardy, J. Nicholson, and B. J. White, *ibid.*, p. 243.

<sup>51</sup> S. J. Gould and C. C. Chang, *J. Am. Chem. Soc.*, 1980, **102**, 1702.

<sup>52</sup> S. J. Gould, C. C. Chang, D. S. Darling, J. D. Roberts, and M. Squillacote, *J. Am. Chem. Soc.*, 1980, **102**, 1707.

<sup>53</sup> R. B. Herbert, F. G. Holliman, P. N. Ibberson, and J. B. Sheridan, *J. Chem. Soc., Perkin Trans. I*, 1979, 2411; T. Etherington, R. B. Herbert, F. G. Holliman, and J. B. Sheridan, *ibid.*, p. 2416.

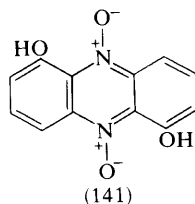
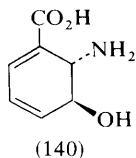
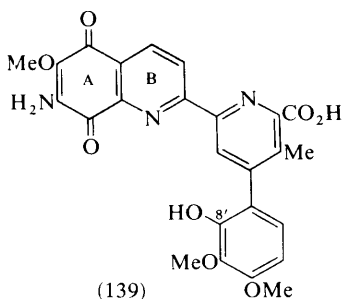


Scheme 10

anthranilic acid, in confirmation of earlier results. In a study with mutants of *Pseudomonas aeruginosa*,<sup>54</sup> earlier conclusions<sup>55</sup> about biosynthetic relationships

<sup>54</sup> G. S. Byng, D. C. Eustace, and R. A. Jensen, *J. Bacteriol.*, 1979, **138**, 846.

<sup>55</sup> M. E. Flood, R. B. Herbert, and F. G. Hooliman, *J. Chem. Soc., Perkin Trans. 1*, 1972, 622; G. S. Hansford, F. G. Holliman, and R. B. Herbert, *ibid.*, p. 103; R. B. Herbert, in Vol. 3 of these Reports, p. 36.



between some phenazines have been supported. *m*-Aminobenzoic acid, which was found not to be a precursor for iodinin,<sup>56</sup> was found<sup>54</sup> to be an inhibitor for *N*-methylation in phenazine biosynthesis.

**Actinomycin.**—Kynurenine and 3-hydroxykynurenine are actinomycin precursors in *Streptomyces antibioticus* (*cf.* Vol. 6, p. 42). Recently, kynureninase and hydroxykynureninase activity has been identified in *S. parvulus* cultures and the latter activity was found to show correlation with actinomycin formation.<sup>57</sup>

**Chloramphenicol.**—A synthetase which converts chorismic acid into *p*-aminophenylalanine (an intermediate in chloramphenicol biosynthesis) has been partly characterized; it requires an aminotransferase and pyridoxal phosphate for activity.<sup>58</sup>

**Sibiromycin, Anthramycin, and Tomaymycin.**—Sibiromycin (143) is closely similar to anthramycin and 11-demethyltomaymycin in structure. Its biosynthesis turns out to be similar too (see Scheme 11); the amino-sugar unit derives from glucose<sup>59</sup> [*cf.* Vol. 5, p. 40; Vol. 6, p. 41; Vol. 7, p. 25; and Vol. 8, p. 24 for the biosynthesis of the other two metabolites]. The acid (142) is an intermediate along the path to (143) from tryptophan (94),<sup>60</sup> and for sibiromycin, the necessary subsequent hydroxylation of (142) has been shown to occur with an expected 'NIH' shift [migration of tritium from C-5 in (142) to C-6 in (143)].<sup>59</sup>

The utilization of tyrosine in the biosynthesis of demethyltomaymycin, anthramycin, sibiromycin, and the lincomycins involves closely similar fragmentation of the tyrosine skeleton. In a series of experiments with tyrosine samples that were separately labelled with deuterium or tritium it was possible to trace the fate of each hydrogen atom.<sup>61</sup> In particular, it appears, by way of conclusion, that cleavage of the aromatic ring occurs [as shown in (144)] before formation of the pyrrolidine ring. In neither tomaymycin nor anthramycin formation is a proton lost from C-3' of tyrosine [as (144)]. In the case of (143) the pyrrolidine ring has a double-bond between C-1 and C-11a. Its introduction

<sup>56</sup> P. R. Buckland, R. B. Herbert, and F. G. Holliman, unpublished work.

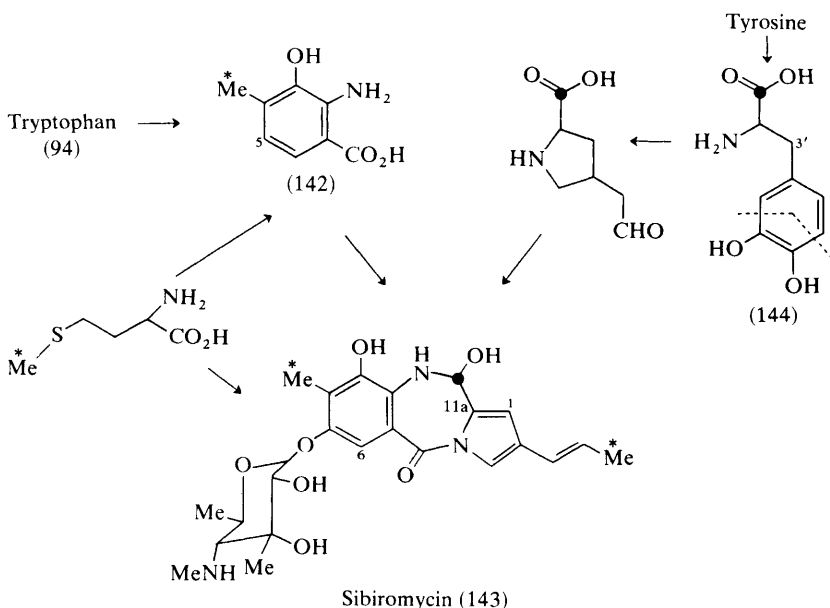
<sup>57</sup> T. Troost, M. J. M. Hitchcock, and E. Katz, *Biochim. Biophys. Acta*, 1980, **612**, 97.

<sup>58</sup> M. M. Francis and D. W. Westlake, *Can. J. Microbiol.*, 1979, **25**, 1408.

<sup>59</sup> L. H. Hurley, W. L. Lasswell, R. K. Malhotra, and N. V. Das, *Biochemistry*, 1979, **18**, 4225.

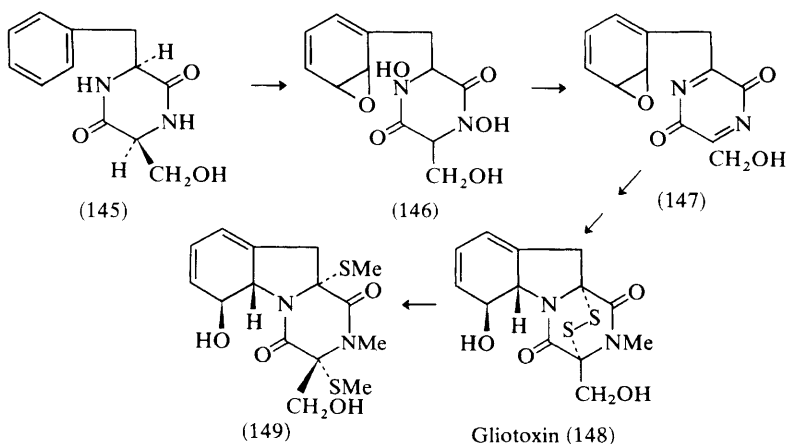
<sup>60</sup> L. H. Hurley and C. Gairola, *Antimicrob. Agents Chemother.*, 1979, **15**, 42.

<sup>61</sup> L. H. Hurley, W. L. Lasswell, J. M. Ostrander, and R. Parry, *Biochemistry*, 1979, **18**, 4230.



involves the loss of the 3'-*pro-S* proton in tyrosine. Additionally, it was found that the L-isomer of tyrosine is much preferred as a precursor over its antipode, and that nitrogen is partially retained from tyrosine. A detailed working hypothesis for the formation of these antibiotics has been proposed.<sup>61</sup>

**Gliotoxin.**—Examination of the biosynthesis of gliotoxin (148) in *Gliocladium deliquescens* has shown that a new metabolite (149) is formed, apparently irreversibly, from (148).<sup>62</sup>

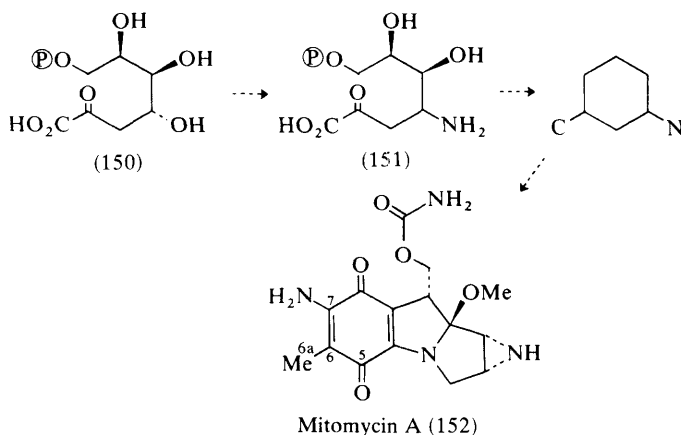


<sup>62</sup> G. W. Kirkby, D. J. Robins, M. A. Sefton, and R. R. Talekar, *J. Chem. Soc., Perkin Trans. 1*, 1980, 119.

The mechanism of entry of sulphur in gliotoxin formation is an intriguing puzzle. A route involving a *NN*-dihydroxy-diketopiperazine (146) derived from (145) (*cf.* Vol. 10, p. 27), followed by (147), is lent support by the results of chemical experiments.<sup>63</sup> By contrast, ring-closure involving sulphur in the biosynthesis of penicillins is likely to involve a radical mechanism.<sup>64</sup>

**Mitomycins.**—Support for the derivation of mitomycin (152) from a point along the shikimate pathway comes from the pattern of incorporation of glucose and, particularly, that of incorporation of pyruvic acid. Pyruvic acid was deduced to provide C-5,<sup>65</sup> C-6, and C-6a (*cf.* Vol. 6, p. 45), with C-5 corresponding to C-3 in pyruvic acid. Moreover, D-[4-<sup>14</sup>C]erythrose labelled C-7 in (152).<sup>65</sup>

Neither shikimic acid<sup>66</sup> nor its methyl ester, nor dehydroquinic acid,<sup>65</sup> were precursors of mitomycin, so it is likely that deviation to mitomycin biosynthesis occurs from DAHP (150) *via*, it has been suggested,<sup>65</sup> (151), as shown in Scheme 12.



**Scheme 12**

<sup>63</sup> J. D. M. Herscheid, R. J. F. Nivard, M. W. Tijhuis, and H. C. J. Ottenheijm, *J. Org. Chem.*, 1980, **45**, 1885.

<sup>64</sup> J. E. Baldwin and T. S. Wan, *J. Chem. Soc., Chem. Commun.*, 1979, 249.

<sup>65</sup> U. Hornemann, J. H. Eggert, and D. P. Honor, *J. Chem. Soc., Chem. Commun.*, 1980, 11.

<sup>66</sup> G. S. Bezanson and L. C. Vining, *Can. J. Biochem.*, 1971, **49**, 911; U. Hornemann and J. C. Cloyd, *J. Chem. Soc., Chem. Commun.*, 1971, 301.

# 2

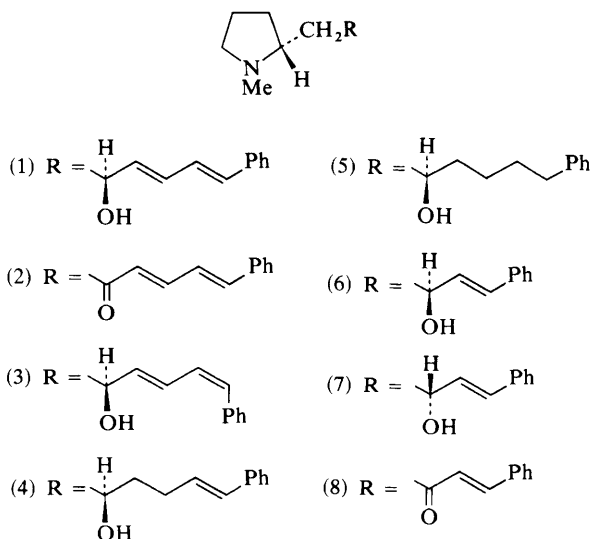
## Pyrrolidine, Piperidine, and Pyridine Alkaloids

BY A. R. PINDER

A new monograph on alkaloid chemistry has been published; parts of it are devoted to pyrrolidine, piperidine, and pyridine alkaloids.<sup>1</sup> A review on the synthesis of alkaloids *via* nitrones has appeared,<sup>2</sup> and another on the photochemistry of alkaloids, which includes a section on alkaloids of this group.<sup>3</sup>

### 1 Pyrrolidine Alkaloids

The leaves and stems of the Queensland tree *Darlingia darlingiana* have yielded eight pyrrolidine bases: darlingianine (1), dehydrodarlingianine (2), isodarlingianine (3), dihydrodarlingianine (4), tetrahydrodarlingianine (5), darlinine (6), epidarlinine (7), and dehydrodarlinine (8). Their structures have been arrived at largely by spectral measurements, and in some cases confirmed by synthesis and inter-relationships.<sup>4</sup>



<sup>1</sup> D. R. Dalton, 'The Alkaloids. The Fundamental Chemistry', Marcel Dekker, New York and Basel, 1979, Parts 2, 3, and 4.

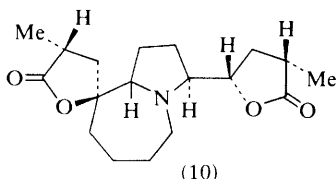
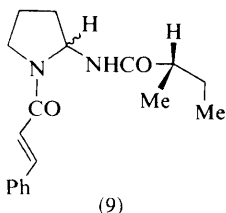
<sup>2</sup> J. J. Tufariello, *Acc. Chem. Res.*, 1979, **12**, 396.

<sup>3</sup> S. P. Singh, V. I. Stenberg, and S. S. Parmar, *Chem. Rev.*, 1980, **80**, 269.

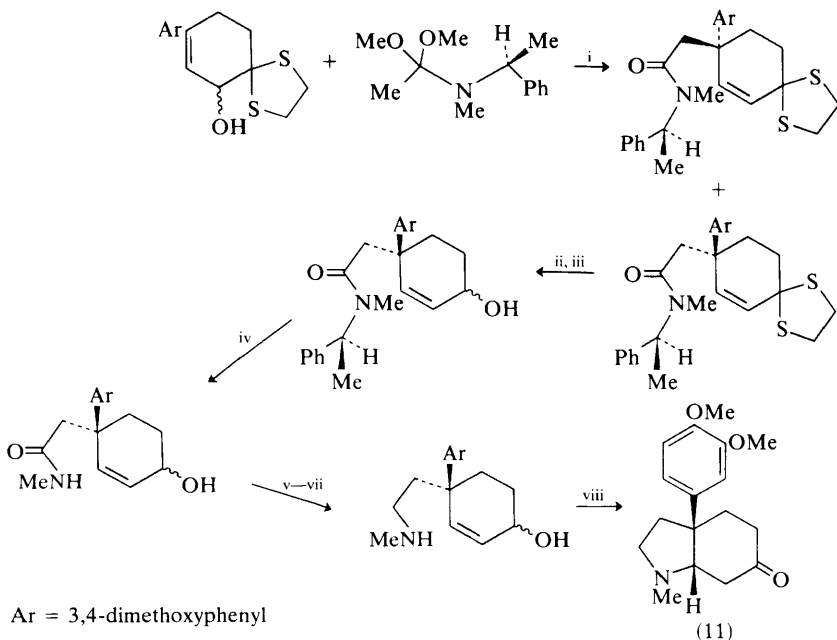
<sup>4</sup> I. R. C. Bick, J. W. Gillard, and H.-M. Leow, *Aust. J. Chem.*, 1979, **32**, 2523.

The principal component of the secretion of the poison gland of the European thief ant (*Solenopsis fugax*) is *trans*-2-n-butyl-5-n-heptylpyrrolidine, identified by mass spectrometry and synthesis.<sup>5</sup> The reductive amination of 1,4-diketones with sodium cyanoborohydride and ammonium acetate has yielded various 2,5-dialkyl-pyrrolidines that occur in the poison glands of ants of *Monomorium* spp.<sup>6</sup>

The leaves of *Aglaria roxburghiana* contain roxburghilin, a bis-amide that has been shown to be *N*-cinnamoyl-2-(2-methylbutanoylamino)pyrrolidine (9)



by chemical and spectroscopic study. The corresponding dihydro-derivative has been synthesized from L-proline.<sup>7</sup>



Reagents: i, heat in toluene; ii,  $\text{HgCl}_2$ ,  $\text{HgO}$ ,  $\text{MeOH}$ ,  $\text{H}_2\text{O}$ ; iii,  $\text{NaBH}_4$ ; iv,  $\text{Na}$ , liq.  $\text{NH}_3$ , THF; v, DHP,  $\text{H}^+$ ; vi,  $\text{LiAlH}_4$ , THF; vii,  $\text{H}^+$ ,  $\text{H}_2\text{O}$ ; viii,  $\text{MnO}_2$

**Scheme 1**

<sup>5</sup> M. S. Blum, T. H. Jones, B. Hölldobler, H. M. Fales, and T. Jaouni, *Naturwiss.*, 1980, **67**, 144.

<sup>6</sup> T. H. Jones, J. B. Franko, M. S. Blum, and H. M. Fales, *Tetrahedron Lett.*, 1980, **21**, 789.

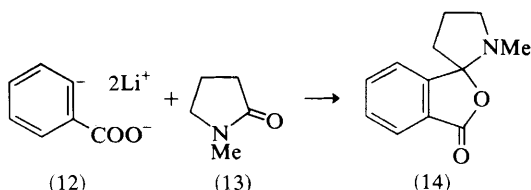
<sup>7</sup> K. K. Purushothaman, A. Sarada, J. D. Connolly, and J. A. Akininji, *J. Chem. Soc., Perkin Trans. I*, 1979, 3171.



Croomine is a major alkaloid of the roots and rhizomes of *Croomia heterosepala*. Its structure (10) has been settled by its chemical reactions and spectroscopic properties, and confirmed by X-ray diffraction analysis of its methiodide. On mild oxidation (dehydrogenation) with silver oxide, the alkaloid affords the corresponding pyrrole.<sup>8</sup>

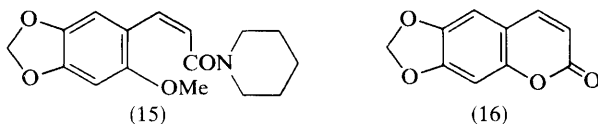
**Sceletium Alkaloids.**—Another synthesis of ( $\pm$ )-mesembrine has been described,<sup>9</sup> and also the first total synthesis of (–)-mesembranone (11),<sup>10</sup> summarized in Scheme 1.

**Dendrobium Alkaloids.**—A third synthesis of shihunine, the principal base of several *Dendrobium* spp., has been reported. It involves allowing the dilithioanion (12) to react with 1-methyl-2-pyrrolidone (13), to yield ( $\pm$ )-shihunine (14) in 23% yield.<sup>11</sup> Full experimental details pertaining to a synthesis of ( $\pm$ )-dendrobine, reported briefly earlier, have been described.<sup>12</sup>



## 2 Piperidine Alkaloids

A pepper alkaloid, isolated earlier<sup>13</sup> from *Piper peepuloides* and assigned the *trans* configuration, has now been shown, on spectral evidence and by synthesis of both isomers, to be the *cis*-piperidide (15). The synthesis of the latter was achieved by a novel ring-cleavage of the coumarin (16) with sodium hydride-methyl iodide, leading to a mixture of the geometrical isomers of 2-methoxy-4,5-methylenedioxybenzoic acid (*cis:trans* = 4:1). Conversion into the piperidide by the usual route, followed by careful fractional crystallization, afforded the pure *cis*-amide (15).<sup>14</sup> Other synthetic endeavours in the area of pepper alkaloids have been described.<sup>15</sup> Piperine is one of several amides occurring in *P. attenuatum*.<sup>16</sup>



<sup>8</sup> T. Noro, S. Fukushima, A. Ueno, T. Miyase, Y. Iitaka, and Y. Saiki, *Chem. Pharm. Bull.*, 1979, **27**, 1495.

<sup>9</sup> S. F. Martin, T. A. Puckette, and J. A. Colapret, *J. Org. Chem.*, 1979, **44**, 3391.

<sup>10</sup> H. F. Strauss and A. Wiechers, *Tetrahedron Lett.*, 1979, 4495.

<sup>11</sup> G. B. Bodem and E. Leete, *J. Org. Chem.*, 1979, **44**, 4696.

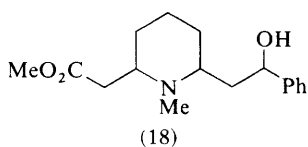
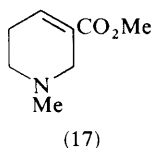
<sup>12</sup> W. R. Roush, *J. Am. Chem. Soc.*, 1980, **102**, 1390.

<sup>13</sup> O. P. Gupta, S. C. Gupta, K. L. Dhar, and C. K. Atal, *Phytochemistry*, 1978, **17**, 601.

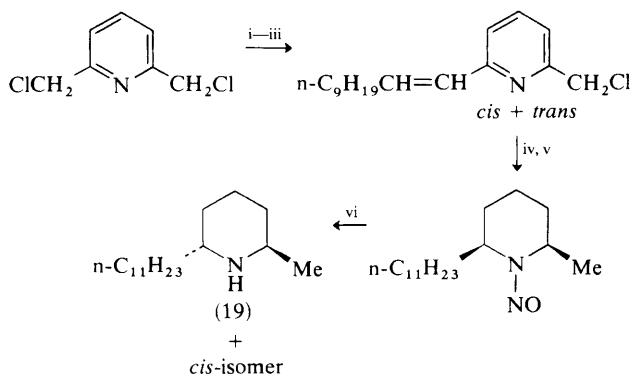
<sup>14</sup> C. K. Sehgal, P. L. Kachroo, R. L. Sharma, S. C. Taneja, K. L. Dhar, and C. K. Atal, *Phytochemistry*, 1979, **18**, 1865.

<sup>15</sup> O. P. Vig, V. K. Handa, I. R. Trehan, and S. Singh, *Indian J. Chem., Sect. B*, 1979, **17**, 427, 521.

<sup>16</sup> S. Dasgupta and A. B. Ray, *Indian J. Chem., Sect. B*, 1979, **17**, 538.



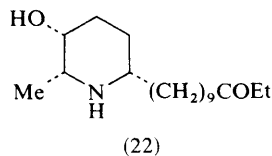
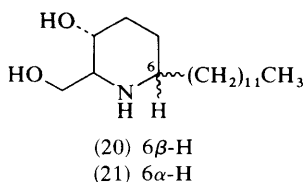
A synthesis of arecoline (17) from acetaldehyde has been described.<sup>17</sup> Sederine (18) is a minor base occurring in *Sedum acre*; its structure has been settled by spectral and chemical study, but its stereochemistry has yet to be established.<sup>18</sup> A new total synthesis of racemic solenopsin A (19) (fire-ant venom) has been published; the pathway is outlined in Scheme 2.<sup>19</sup>



Reagents: i,  $\text{Ph}_3\text{P}$ ,  $\text{PhH}$ ; ii,  $\text{NaH}$ ; iii,  $n$ -decanal; iv,  $\text{Ni}$ ,  $\text{Pt}$ ,  $\text{H}_2$ ; v, isoamyl nitrite; vi,  $\text{KOBu}^t$ ,  $\text{DMSO}$ , at  $90$ – $100^\circ\text{C}$ , then  $\text{Ni}$ ,  $\text{H}_2$ , and separation by preparative g.l.c.

**Scheme 2**

Stereoselective total syntheses of (–)-deoxoprosopinine (20) and (–)-deoxoprosophylline (21), derived respectively from the natural bases prosopinine and prosophylline, have been described; the route adopted should be applicable to other related piperidine bases.<sup>20</sup> Prosafrinine (22), a piperidine alkaloid of *Prosopis africana*, has been synthesized stereoselectively, along with pseudocarpamic acid (23), as racemic varieties.<sup>21</sup> Additional stereoselective syntheses of (±)-carpamic and (±)-azimic acids have been described.<sup>22</sup>



<sup>17</sup> I. A. Kozello, V. I. Khmelevskii, A. Ya. Gasheva, and G. N. Birbaeva, *Khim.-Farm. Zh.*, 1979, **13**, 61.

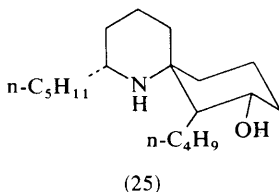
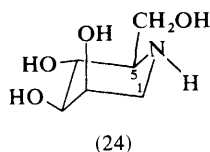
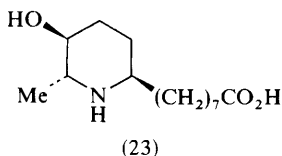
<sup>18</sup> C. Hootel , J. P. Etienne, and B. Colau, *Bull. Soc. Chim. Belg.*, 1979, **88**, 111.

<sup>19</sup> K. Fuji, K. Ichikawa, and E. Fujita, *Chem. Pharm. Bull.*, 1979, **27**, 3183.

<sup>20</sup> Y. Saitoh, Y. Moriyama, T. Takahashi, and Q. Khuong-Huu, *Tetrahedron Lett.*, 1980, **21**, 75.

<sup>21</sup> M. Natsume and M. Ogawa, *Heterocycles*, 1980, **14**, 615.

<sup>22</sup> M. Natsume and M. Ogawa, *Heterocycles*, 1980, **14**, 169.

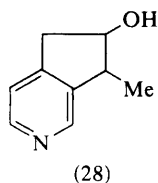
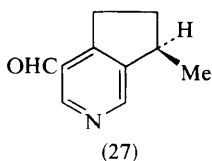
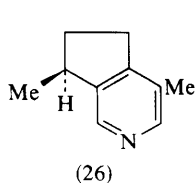


1,5-Dideoxy-1,5-imino-D-mannitol (24) has been isolated from seeds of the legumes *Lonchocarpus sericeus* and *L. costaricensis*. Its structure has been elucidated mainly by mass and n.m.r. spectral analysis, and its absolute configuration by the benzoate chirality method.<sup>23</sup>

**Spiropiperidine Alkaloids.**—Full details of a preliminarily reported synthesis of (±)-perhydrohistrionicotoxin (25) have been provided.<sup>24</sup>

### 3 Pyridine Alkaloids

Actinidine (26) has been isolated from the roots and rhizomes of *Valeriana officinalis* L.<sup>25</sup> Boschniakine (27) has been found in the seeds of *Plantago sempervirens*; its absolute configuration has been established by optical rotatory dispersion comparisons with other monoterpene bases.<sup>26</sup> Venoterpine (28) has been found in *Striga hermonteca*; the stereochemistry is as yet uncertain.<sup>27</sup>



**Alkaloids of the Celastraceae.**—The structures of eleven new alkaloids of this family, all related to nicotinic acid, have been elucidated, largely by interconversions and degradations and by spectral study and analysis.<sup>28—30</sup>

<sup>23</sup> L. E. Fellows, E. A. Bell, D. G. Lynn, F. Pilikiewicz, I. Miura, and K. Nakanishi, *J. Chem. Soc., Chem. Commun.*, 1979, 977.

<sup>24</sup> H. E. Schoemaker and W. N. Speckamp, *Tetrahedron*, 1980, **36**, 951.

<sup>25</sup> M.-M. Janot, J. Guilhem, O. Contz, G. Venera, and E. Cionga, *Ann. Pharm. Fr.*, 1979, **37**, 413.

<sup>26</sup> H. Ripperger, *Pharmazie*, 1979, **34**, 577.

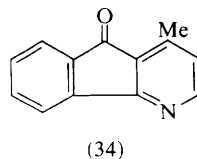
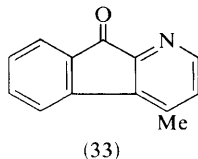
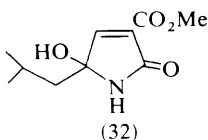
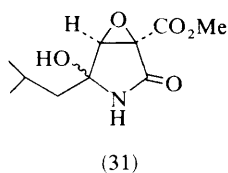
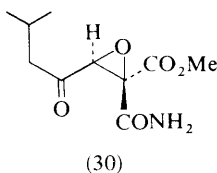
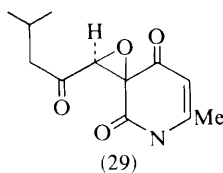
<sup>27</sup> M. Baoua, J.-M. Bessiere, B. Pucci, and J.-P. Rigaud, *Phytochemistry*, 1980, **19**, 718.

<sup>28</sup> R. L. Baxter, L. Crombie, D. J. Simmonds, and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2972.

<sup>29</sup> L. Crombie, W. M. L. Crombie, D. A. Whiting, and K. Szendrei, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2976.

<sup>30</sup> R. L. Baxter, W. M. L. Crombie, L. Crombie, D. J. Simmonds, D. A. Whiting, and K. Szendrei, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2982.

The relative configuration of flavipucine (29) has been determined by a chemical procedure; the result is in harmony with an X-ray diffraction analysis of the racemic base reported earlier. Ozonolysis of the ( $\pm$ )-alkaloid afforded the crystalline amido-ester (30), which, in contact with silica gel, cyclized to the carbinolamides (31). This cyclization requires that the isovaleryl and amide functions in (30) be *cis*. The former compound was synthesized by the base-catalysed reaction of isobutylyglyoxal with 2-(methoxycarbonyl)acetamide to give, after treatment with acetic anhydride, the carbinol (32). Epoxidation (by  $\text{H}_2\text{O}_2$  and  $\text{OH}^-$ ) of this compound generated (31) and (30), the latter being secured by fractional crystallization from ether.<sup>31</sup> Some analogues of flavipucine have been synthesized and tested biologically.<sup>32</sup>



The structure of onychine, an alkaloid of *Onychopetalum amazonicum* that has hitherto been formulated as (33), must be revised to (34). Both structures have been synthesized; the former was found to be different from onychine and the latter identical with it.<sup>33</sup> Three stereospecific syntheses of sesbanine (35) have been reported. In one, 4-(methoxycarbonyl)nicotinic acid is the starting point (Scheme 3).<sup>34</sup> The other two both start from 4-methylnicotinonitrile, one<sup>35</sup> leading to ( $\pm$ )-sesbanine and the other to the (+)-enantiomer.<sup>36</sup> 10-Deoxysesbanine has also been synthesized, by a route which appears applicable to the alkaloid itself.<sup>37</sup>

The interest in alkaloids of the nicotine group continues. Convenient syntheses of *N*-CD<sub>3</sub>-labelled nicotine and nicotine analogues have been described.<sup>38</sup> The <sup>13</sup>C n.m.r. spin-lattice relaxation times of nicotine have been analysed in terms of anisotropic rotational diffusion constants. The results agree best with a dihedral angle of H(2'')-C(2'')-C(3)-C(2) of ca 0°. <sup>39</sup> 'Dithiodinicotyrine', obtained

<sup>31</sup> N. N. Girotra and N. L. Wendler, *Tetrahedron Lett.*, 1979, 4793.

<sup>32</sup> N. N. Girotra, A. A. Patchett, S. B. Zimmerman, D. L. Achimov, and N. L. Wendler, *J. Med. Chem.*, 1980, **23**, 209.

<sup>33</sup> J. Koyama, T. Sugita, Y. Suzuta, and H. Irie, *Heterocycles*, 1979, **12**, 1017.

<sup>34</sup> J. C. Bottaro and G. A. Berchtold, *J. Org. Chem.*, 1980, **45**, 1176.

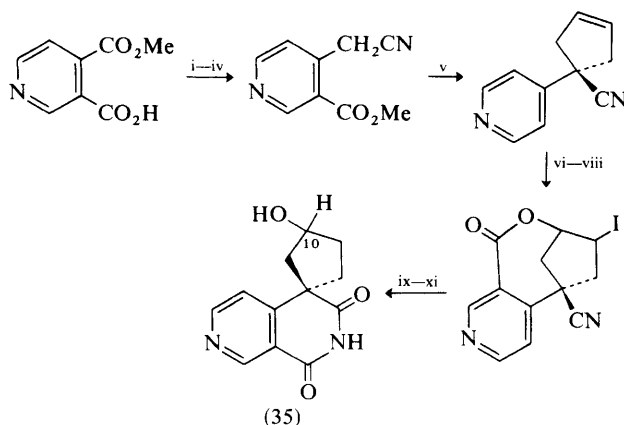
<sup>35</sup> A. S. Kende and T. P. Demuth, *Tetrahedron Lett.*, 1980, **21**, 715.

<sup>36</sup> K. Tomioka and K. Koga, *Tetrahedron Lett.*, 1980, **21**, 2321.

<sup>37</sup> M. J. Wanner, G.-J. Koomen, and U. K. Pandit, *Heterocycles*, 1980, **14**, 643.

<sup>38</sup> J. I. Seeman, H. V. Secor, and G. Forrest, *J. Labelled Compd. Radiopharm.*, 1979, **16**, 387.

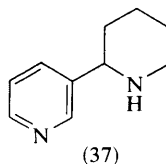
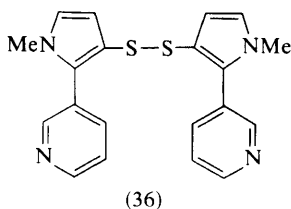
<sup>39</sup> T. P. Pitner, J. F. Whidby, and W. B. Edwards, *J. Am. Chem. Soc.*, 1980, **102**, 5149.



Reagents: i,  $\text{LiAlH}_4$ , THF; ii,  $\text{PCl}_5$ ,  $\text{CH}_2\text{Cl}_2$ ; iii, MeOH; iv, NaCN, Aliquat 336,  $\text{CH}_2\text{Cl}_2$ ; v, (Z)-1,4-dichloro-2-butene, NaH, THF; vi, NaOH,  $\text{H}_2\text{O}$ , THF; vii,  $\text{I}_2$ , KI,  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ; viii,  $\text{Bu}^n_3\text{SnH}$ , AIBN, benzene; ix,  $\text{NH}_3$ , MeOH; x, NaH,  $\text{Pr}^i\text{OH}$ ; xi,  $\text{H}_3\text{O}^+$

Scheme 3

by heating nicotine with sulphur, has been proved to be bis-[1-methyl-2-(3-pyridyl)-3-pyrrolyl] disulphide (36) by spectral study, chemical reactions, and X-ray diffraction analysis.<sup>40</sup> Some transformations of the pyridine ring<sup>41</sup> and of the pyrrolidine ring<sup>42</sup> of nicotine have been described, and the formation of quinolizines and indolizines from nicotine derivatives and acetylenic esters has been investigated.<sup>43</sup> Several *N*-nornicotines have been synthesized for use as haptens in immunoassay studies.<sup>44</sup> The mechanism of the oxidation of nicotine to 3-nitro-5-(3'-pyridyl)pyrazole by nitric acid has been investigated: the yield was increased by addition of sodium nitrite, and decreased by addition of urea. The oxidation of [ $1'$ - $^{15}\text{N}$ ]nicotine afforded a pyrazole that was labelled solely at N-1. A mechanism consistent with these observations has been proposed.<sup>45</sup>



The tobacco alkaloid anabasine (37) has been synthesized from 3-pyridyl-lithium (prepared from 3-bromopyridine and *t*-butyl-lithium) by reaction with  $\Delta^1$ -piperidine at  $-120^\circ\text{C}$ .<sup>46</sup>

<sup>40</sup> R. M. Acheson, M. J. Ferris, S. R. Critchley, and D. J. Watkin, *J. Chem. Soc., Perkin Trans. 1*, 1980, 326.

<sup>41</sup> R. M. Acheson, M. J. Ferris, and N. M. Sinclair, *J. Chem. Res.*, 1979 (S), 333; (M), 3901.

<sup>42</sup> R. M. Acheson, M. J. Ferris, and N. M. Sinclair, *J. Chem. Soc., Perkin Trans. 1*, 1980, 579.

<sup>43</sup> R. M. Acheson, M. J. Ferris, and N. M. Sinclair, *J. Chem. Soc., Perkin Trans. 1*, 1980, 78.

<sup>44</sup> A. Castonguay and H. V. Vunakis, *J. Org. Chem.*, 1979, **44**, 4332.

<sup>45</sup> E. Leete and H. V. Isaacson, *J. Indian Chem. Soc.*, 1978, **55**, 1125.

<sup>46</sup> F. E. Scully, Jr., *J. Org. Chem.*, 1980, **45**, 1515.

### 1 Occurrence and Structures of New Alkaloids

Three new alkaloids have been isolated<sup>1</sup> from the root-bark of *Erythroxylum dekindtii* besides the already known methylecgonidine, valeroidine, poroidine, isoporoidine, and tropine. A decoction of this bark is used in West Africa as a febrifuge.<sup>2</sup>

The constituents were separated by column chromatography followed by t.l.c. and recrystallization of the picrate of the principal alkaloid (1). Spectral data were consistent with a saturated C<sub>5</sub> carboxylic ester of 3 $\alpha$ -tropanol and were confirmed by the hydrolysis of the compound to tropine and isovaleric acid. A second base, C<sub>16</sub>H<sub>21</sub>NO<sub>2</sub>, was obtained from the mother liquors of the recrystallization, and was identified by its mass spectrum and by comparison with synthetic tropan-3 $\alpha$ -yl phenylacetate (2). A third base was isolated from the chloroform eluate and purified by paper chromatography. The base showed a blue fluorescence when irradiated at 254 nm and had a mass spectrum that was typical of a monohydroxylated tropane. Fragmentation of the molecular ion C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub><sup>+</sup> indicated the esterifying acid to be C<sub>5</sub>H<sub>4</sub>O<sub>3</sub>. The i.r. spectrum contains no hydroxyl absorption, but an olefinic band at 1583 cm<sup>-1</sup>. The proton resonance spectrum gave the AMX pattern of a 2-furoate [ $\delta$  6.47 (dd;  $J$  = 3.6 and 0.8 Hz), 7.16 (dd;  $J$  = 3.6 and 0.8 Hz), and 7.60 (dd;  $J$  = 1.8 Hz)] in addition to the 3 $\alpha$ -tropanyl protons. Structure (3) was confirmed by inference from a partial synthesis of 3 $\beta$ -tropanyl 2-furoate and of the two epimeric 3-furoates, all of which gave physical data widely different from those of the natural product. Base (3) caused mydriasis in the rabbit and had 1/200th of the activity of atropine in its effect on the isolated guinea-pig ileum. This is the first occurrence of a 2-furoic acid group in a tropane alkaloid.

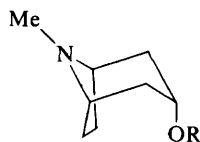
A biogenetically interesting new group of 'secotropane' alkaloids have been discovered<sup>3</sup> this year in *Physalis peruviana*. (+)-Physoperuvine, the first representative of this class, was described four years ago in a preliminary paper<sup>4</sup> as 3-(methylamino)cycloheptanone (4), based exclusively on <sup>1</sup>H n.m.r. and mass spectral evidence. Now chemical and configurational evidence has been added to the previous data for (4) and for two other representatives of the same class,

<sup>1</sup> M. A. I. Al-Yahya, W. C. Evans, and R. J. Grout, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2130.

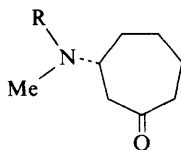
<sup>2</sup> M. T. Campos Neves and A. da S. Campos Neves, *Garcia de Orla*, 1966, **14**, 97.

<sup>3</sup> M. Sahai and A. B. Ray, *J. Org. Chem.*, 1980, **45**, 3265.

<sup>4</sup> A. B. Ray, M. Sahai, and P. D. Sethi, *Chem. Ind. (London)*, 1976, 454.

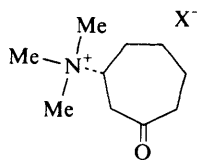
(1) R = COCH<sub>2</sub>CHMe<sub>2</sub>(2) R = COCH<sub>2</sub>Ph

(3) R = 2-furoyl



(4) R = H

(5) R = Me



(6)

*i.e.* (±)-physoperuvine [(±)-(4)] and (+)-*NN*-dimethylphysoperuvinium salt (6), that have recently been isolated.<sup>3</sup> The i.r. spectrum of (+)-physoperuvine showed bands (3300, NH; 1698 cm<sup>-1</sup>, C=O) that are characteristic of β-aminoketones. Base (4) gives a monobenzoyl derivative, which is indicative of a secondary amine, while the carbonyl group was proven to be present by the formation of an oxime. Four protons were easily exchanged by deuterium, resulting in the disappearance of the signals of the methylene protons around δ 2.46 in the n.m.r. spectrum. This indicates the presence of an α,α'-unsubstituted keto-group in physoperuvine. The resemblance of the <sup>13</sup>C n.m.r. spectrum to that of tropinone strongly supports the postulate of the β-amino-ketone character of this alkaloid. The final proof came from the synthesis of (±)-*NN*-dimethylphysoperuvinium iodide. Michael addition of dimethylamine to 2-cyclohepten-1-one gave (±)-*N*-methylphysoperuvine (5), and this, by quaternization with methyl iodide, afforded (±)-(6).

The absolute configuration of (+)-physoperuvine, and of its *N*-benzoyl derivative, was determined by the positive Cotton effect around 290 nm, in the region exactly as reported<sup>5</sup> for (*R*)-(+)-3-methylcycloheptanone. The racemic form accompanies the optically active one in the plant; they were separated by column chromatography. Since tropane alkaloids form *in vivo* from ornithine *via* Δ-pyrroline,<sup>6</sup> the biogenetic role of secotropanes is likely to be that of products of degradation rather than of intermediates in the formation of the tropane bases.

## 2 Synthesis and Chemical Transformations

The first partial synthesis<sup>7,8</sup> of anatoxin-a (12) (a neurotoxin from algae) has been reported, starting with (–)-cocaine.

New total syntheses<sup>9</sup> of azabicyclo[4.2.1]nonanone (10) have now been elaborated. The first synthesis started with 5-azidocyclo-oct-1-ene (7). Reduction and *N*-methylation (*via* the urethane), followed by treatment of the secondary amine with hypobromous acid and with base, gave a mixture of 9-methyl-9-azabicyclo[4.2.1]nonan-2α-ol (8) and its 2β-isomer (9), contaminated with some azabicyclo[3.3.1]nonane analogue; *cf.* (18). The second synthesis starts with the monoepoxide from cyclo-octa-1,5-diene (11). Treatment with methylamine and

<sup>5</sup> C. Djerassi, B. F. Burrows, C. G. Overberger, T. Takekoshi, C. D. Gutsche, and C. T. Chang, *J. Am. Chem. Soc.*, 1963, **85**, 949.

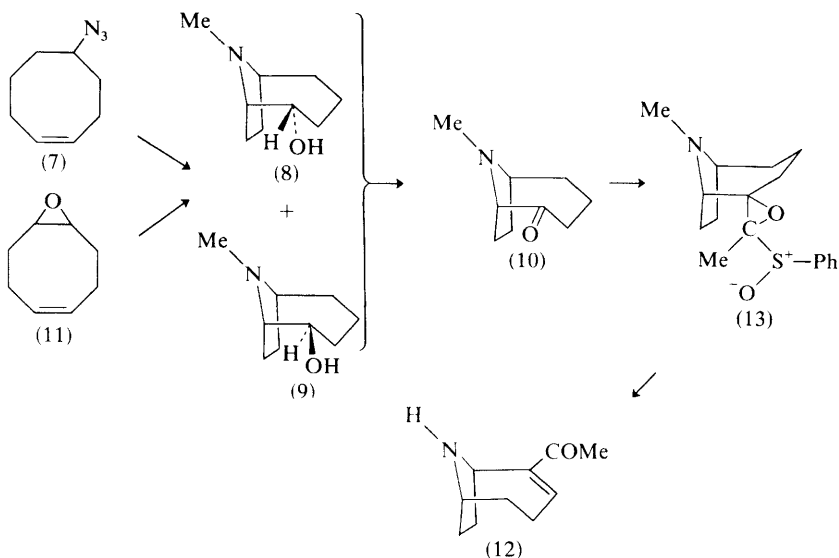
<sup>6</sup> E. Leete, in 'Encyclopedia of Plant Physiology, New Series, Vol. 8, Secondary Plant Products', Springer, Berlin, 1980, pp. 67–71.

<sup>7</sup> See these Reports, Vol. 7, p. 50.

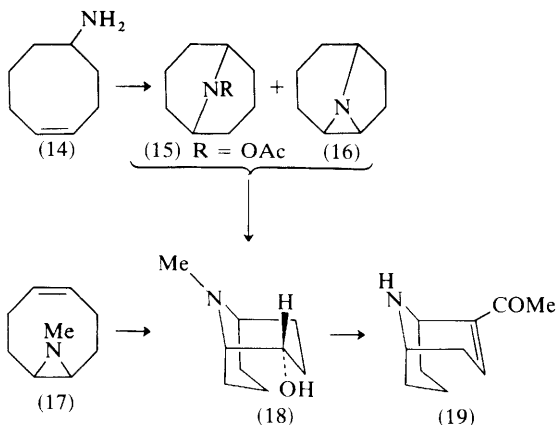
<sup>8</sup> H. F. Campbell, O. E. Edwards, and R. J. Kolt, *Can. J. Chem.*, 1977, **55**, 1372.

<sup>9</sup> H. F. Campbell, O. E. Edwards, J. W. Elder, and R. J. Kolt, *Pol. J. Chem.*, 1979, **53**, 27.

subsequently with mercuric acetate, and ultimately demercuration with borohydride, gave mainly the bicyclo[4.2.1]nonanols (8) and (9). The ketone (10) was prepared from the mixture of epimeric alcohols by Jones oxidation. Conversion of the ketones (8) into the desired natural product succeeded by using the carbanion of  $\alpha$ -chloroethyl phenyl sulphoxide, and proceeded *via* the epoxy-sulphoxide (13) and thermal rearrangement of the latter and finally by *N*-demethylation with ethyl azodicarboxylate and hydrolysis to (12). The authors



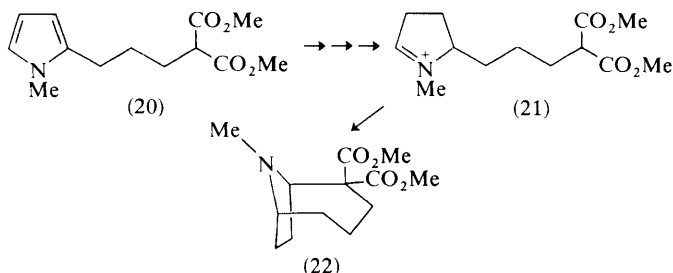
have suggested a new, concerted mechanism involving a cyclic transition state in the thermolysis of the epoxy-sulphoxide. Isoanatoxin-a (19) was synthesized similarly. Oxidation of 5-aminocyclo-octene (14) with lead tetra-acetate gave a mixture of an acetoxamine (15) and an aziridine (16). Treatment with diethyl pyrocarbonate, followed by partial hydrolysis and then reaction with  $\text{LiAlH}_4$ ,



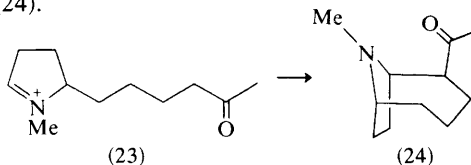


gave the *N*-methyl derivative (18). A variant of this method involved preparation of an *N*-methylaziridine (17). Oxidation by mercuric acetate and reductive demercuration then gave *N*-methyl-azabicyclo[3.3.1]nonan-2 $\alpha$ -ol (18), which was converted into isoanatoxin-a by the method used to prepare compound (12).

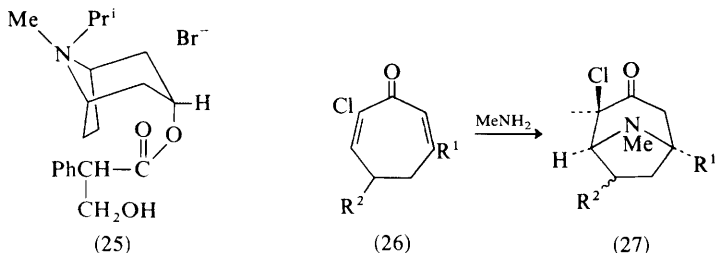
Independently, another group had elaborated<sup>10</sup> an alternative method to anatoxin-a *via* intramolecular cyclization of iminium salts. 1-Methylpyrrole-2-aldehyde was converted into the (1-methyl-2-pyrrolyl)propylmalonic ester (20) by a conventional route. Another carboxyl group was introduced at the 5-position of the pyrrole ring (*via* the trichloroacetylpyrrole) and the product was then hydrogenated to the pyrrolidinecarboxylate over Rh/alumina. Decarbonylation gave the iminium salt (21) quantitatively. Subsequent cyclization gave rise to the dimethyl homotropane-2,2-dicarboxylate (22) in basic medium, by extracting



the product from the equilibrium mixture immediately after its formation. Better results were achieved by using a single electron-withdrawing group, as is present in the 2-(5-oxohexyl)-1-methyl- $\Delta^5$ -pyrrolenium salt (23); upon cyclization and then *N*-demethylation, this afforded a 15% yield of the bicyclic ketone 'dihydroanatoxin-a' (24).



*N*<sub>a</sub>-Isopropylatropinium bromide (25) (ipratropium bromide) has been obtained<sup>11</sup> by a Robinson-type total synthesis from succinic aldehyde, isopropylamine, and acetonedicarboxylic acid, followed by reduction of the carbonyl

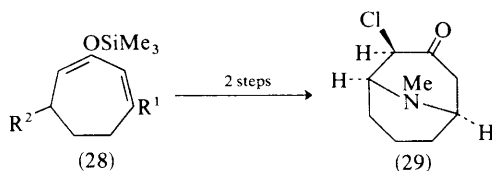


<sup>10</sup> H. A. Bates and H. Rapoport, *J. Am. Chem. Soc.*, 1979, **101**, 1259.

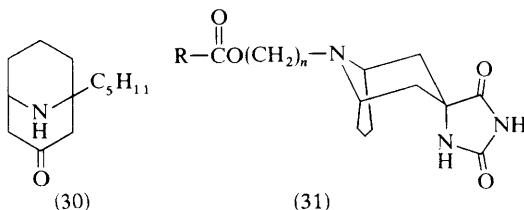
<sup>11</sup> K. L. Rominger, *Scand. J. Respir. Dis., Suppl.*, 1979, **103**, 116; concerning the assignment of *N*-stereoisomers, see G. Fodor, J. Toth, and I. Vincze, *J. Chem. Soc.*, 1955, 3504.

group, esterification of the  $3\beta$ -hydroxyl group of *N*-isopropyl-nortropine with  $\alpha$ -formyl-phenylacetic acid methyl ester, and reduction of the formyl group to hydroxymethyl of a tropic ester. Quaternization with methyl bromide gave ipratropium bromide (25), which is a product that has considerable pharmacodynamic properties (in contrast with its  $N_b$ -epimer).

A regiospecific synthesis of a  $2\beta$ -chlorotropan-3-one (27) has been elaborated<sup>12</sup> from a 2-chlorocyclohepta-2,6-dienone (26) by bis-conjugate addition of a primary amine. Reductive dehalogenation can give a tropanone. Addition of dichlorocarbene to 2-cycloheptenone trimethylsilyl enol ether (28) gave, upon rearrangement, 2-chlorocyclo-octa-2,7-dienone; by a similar bis-conjugate addition of methylamine, this led to 2-chloropseudopelletierine (29).



Homologues of tropane and granatane can be prepared by starting with alkyl derivatives of cyclohexenone and heptanone, respectively. Full details<sup>13</sup> of the synthesis<sup>7</sup> of adaline (30), a homotropane, using the nitron route,<sup>14</sup> have now been given.



The synthesis of *N*-( $\omega$ -hydroxyalkyl)norgranatanones and their conversion into 3-spiro-5-hydantoin derivatives (31) have been described.<sup>15</sup>

The quantitative racemization of hyoscyamine to atropine was achieved<sup>16</sup> by refluxing the methanolic or butanolic solution (catalysed by a base) or, even better, by refluxing in diethylamine. The partial racemization, *i.e.* epimerization at C-2, of (–)-cocaine to (+)-pseudococaine was effected by strong bases in methanol followed by re-benzoylation of C-3 in pseudoeconine methyl ester. This interconversion<sup>17</sup> allows the detection of small amounts of cocaine in forensic medicine.

The thermal and catalytic decomposition of *N*-methylatropinium nitrite has been studied kinetically.<sup>18</sup>

<sup>12</sup> T. L. MacDonald and R. Dolan, *J. Org. Chem.*, 1979, **44**, 4973.

<sup>13</sup> B. Witkop and E. Gossinger, *Monatsh. Chem.*, 1980, **111**, 803.

<sup>14</sup> See these Reports, Vol. 9, p. 49.

<sup>15</sup> G. G. Trigo, C. Avendano, P. Ballesteros, and A. Sastre, *J. Heterocycl. Chem.*, 1980, **17**, 103.

<sup>16</sup> T. Singh, K. L. Handa, and P. R. Rao, *J. Inst. Chem., Calcutta*, 1978, **50**, 267.

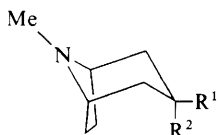
<sup>17</sup> J. A. Siegel and R. A. Cormier, *J. Forensic Sci.*, 1980, **25**, 359.

<sup>18</sup> M. Adamska, *Herba Polonica*, 1979, **25**, 7.

The conformations of the atropinium and scopolaminium ions have been studied<sup>19</sup> by  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. In the 270 MHz  $^1\text{H}$  n.m.r. spectrum, the  $J$  values in the tropic ester moiety show a 60:40 ratio for the population of conformers A:B and a complete absence of conformer C. The conformation of the two tropanium ions proved to be a distorted chair<sup>20</sup> in the piperidine ring (based on H-2–H-3 coupling constants). Quite surprisingly, however, the proton pairs H-1 and H-5 on the one hand and H-2 and H-4 on the other are non-equivalent. The conformations of both the scopolaminium ion and of the atropinium ion are identical in the crystal lattice and in solution, while the configuration of the *N*-methyl group is axial at  $\text{N}_a$  in the atropinium ion and equatorial at  $\text{N}_b$  in scopolaminium bromide.<sup>20</sup> The method used for confirming conformations was a comparison of observed and calculated ring-current shielding contributions for the nuclei of the tropane ring.

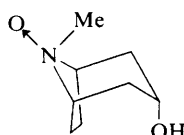
Nortropacocaine hydrochloride showed<sup>21</sup> markedly different 270 MHz  $^1\text{H}$  n.m.r. spectra in  $\text{D}_2\text{O}$  and  $\text{CDCl}_3$ . However, analysis of coupling constants between vicinal protons indicated the slightly distorted chair conformation to be favoured even in hydrophobic media. The spectral differences were ascribed to a decreased deshielding of the protonated nitrogen on the protons of the neighbouring bicyclic ring.

Photolysis of both  $3\alpha$ -tropanol (32) and the  $3\beta$ -isomer (33) in methanolic solution (using Methylene Blue as a sensitizer) gave nortropanols and *N*-formyl-nortropanols.<sup>22</sup>  $3\alpha$ -Tropanol gave the *N*-oxide (34) as a third photo-product. Scopoline (35) was photolysed to the ether of *N*-(hydroxymethyl)norscopoline (36) besides *N*-formylnorscopoline. A photochemical study on cocaines has previously been reviewed<sup>23</sup> in these Reports.

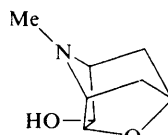


(32)  $\text{R}^1 = \text{H}, \text{R}^2 = \text{OH}$

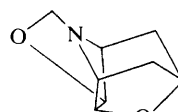
(33)  $\text{R}^1 = \text{OH}, \text{R}^2 = \text{H}$



(34)



(35)



(36)

### 3 Pharmacology: Structure–Activity Relationships

The effect of atropine upon chromosomal abnormalities<sup>24</sup> has been studied. A significant dose-dependent reduction of heart rate and blood pressure has been observed.<sup>25</sup> A possible effectiveness of atropine on Prinzmetal's variant form of

<sup>19</sup> J. Feeney, E. A. Piper, and R. Foster, *Adv. Pharmacol. Ther. Proc. Congr. Pharmacol.*, 1978, **3**, 281.

<sup>20</sup> N. Mandava and G. Fodor, *Can. J. Chem.*, 1968, **46**, 2761; C. H. MacGillavry, S. Skolnik, and J. Laan, *Acta Crystallogr.*, 1967, **23**, 423; C. H. MacGillavry and G. Fodor, *J. Chem. Soc.*, 1964, 597; C. S. Huber, G. Fodor, and N. Mandava, *Can. J. Chem.*, 1971, **49**, 3258.

<sup>21</sup> A. Makriyannis and G. J. Hite, *J. Pharm. Sci.*, 1979, **68**, 788.

<sup>22</sup> S. P. Singh, V. I. Stenberg, and S. S. Parmar, *Chem. Rev.*, 1980, **80**, pp. 274–275.

<sup>23</sup> See these Reports, Vol. 10, p. 46.

<sup>24</sup> A. K. Saha and S. C. Chattopadhyay, *CIS, Chromosome Inf. Serv.*, 1977, **22**, 3 (*Chem. Abstr.*, 1980, **93**, 14 763).

<sup>25</sup> A. Merrick, W. M. Hadley, and T. L. Holeslaw, *Res. Commun. Chem. Pathol. Pharmacol.*, 1979, **25**, 13.

angina pectoris has been reported.<sup>26</sup> Atropine, alone or in combination with phenobarbitone, gives partial or complete protection against the toxic effects of malathion.<sup>27</sup> Changes in atropine concentrations in plasma have been followed by radioimmunoassay.<sup>28</sup> The behavioural effects of atropine have been tested.<sup>29</sup> The configurational dependence<sup>30</sup> of analgesic activity in 3 $\alpha$ - and 3 $\beta$ -4-anilidopiperidines is analogous to that of 3 $\alpha$ - and 3 $\beta$ -tropanyl esters. However, the boat form of the piperidine ring was postulated to exist,<sup>30</sup> in contrast to a 270 MHz <sup>1</sup>H n.m.r. study on tropanes stating that no boat form was found, in any tropanes in the ground state. Structure-activity relationships of selected 3-oxotropanium ethers have been studied.<sup>31</sup>

Quaternary *N*-(xanthinylalkyl)nortropines have been claimed<sup>32</sup> to have spasmolytic (particularly bronchospasmolytic) effects without the side-effects of atropine.

A large number of pharmacological studies have been undertaken with cocaine, in animals and in humans.

Behavioural antecedents of a cocaine-induced stereotype<sup>33</sup> and rate dependency of behavioral effects<sup>34</sup> have been studied. Studies of the physiological effects on Man of intravenous administration of cocaine<sup>35</sup> and of the discriminative response of humans to cocaine<sup>36</sup> have given new results.

The locomotor and toxic effects of cocaine are reduced when the subject is pre-treated with monoaminergic inhibitors;<sup>37</sup> 2 $\beta$ -methoxycarbonyl-3-phenyltropane is ten times more potent<sup>38</sup> than cocaine in its behavioural effects. *N*-Allyl-, *N*-dimethylallyl-, and *N*-cyclopropylmethyl-norcocaines proved less potent than cocaine in their effect on the inhibition of uptake of [<sup>3</sup>H]serotonin and in causing behavioural modifications.<sup>39,40</sup> Daily electrostimulation of the left amygdal, *i.e.* kindling, is greatly influenced by treatment with cocaine.<sup>41</sup> A metabolic-neurochemical approach<sup>42</sup> to behavioural effects of cocaine in rats has been considered. The action and interactions of cocaine on self-stimulation behaviour of rats have been studied.<sup>43</sup> The metabolism<sup>44</sup> of norcocaine and of *N*-hydroxynorcocaine gives the corresponding norecgonine derivatives;

<sup>26</sup> M. Sakanashi, T. Furukawa, and Y. Horio, *Jpn. Heart J.*, 1979, **20**, 75 (*Chem. Abstr.*, 1979, **91**, 117 350).

<sup>27</sup> B. S. Paul, R. C. Gupta, and J. K. Malik, *Indian J. Exp. Biol.*, 1979, **17**, 1069.

<sup>28</sup> L. E. Berghem, U. Bergman, B. Schildt, and B. Soerbo, *Br. J. Anaesth.*, 1980, **72**, 597.

<sup>29</sup> P. B. Dews and G. R. Wenger, *Neurobehav. Toxicol.*, 1979, **1**, suppl. 1, p. 119.

<sup>30</sup> T. N. Riley and J. R. Bagley, *J. Med. Chem.*, 1979, **22**, 1167.

<sup>31</sup> R. B. Patel, *Diss. Abstr. Int. B*, 1979, **40**, 1184.

<sup>32</sup> Austrian P. 352 300 (1979) (*Chem. Abstr.*, 1980, **92**, 42 212).

<sup>33</sup> J. P. Collins, H. Lesse, and L. A. Dagan, *Pharmacol. Biochem. Behav.*, 1979, **11**, 683.

<sup>34</sup> L. D. Byrd, *Eur. J. Pharmacol.*, 1979, **56**, 355.

<sup>35</sup> M. W. Fischman, C. R. Schuster, and N. A. Krasgenor, *Adv. Behav. Biol.*, 1979, **21**, 647.

<sup>36</sup> T. Yanagida and K. Andu, *Rinsho Yakuri*, 1979, **10**, 25 (*Chem. Abstr.*, 1979, **91**, 375).

<sup>37</sup> A. M. Lallimant, *C. R. Soc. Biol.*, 1979, **173**, 600.

<sup>38</sup> R. D. Spealman and R. T. Kelleher, *Catecholamines: Basic Clin. Front Proc. 4th Intl. Catecholamine Symp.*, 1979, **2**, 1977.

<sup>39</sup> E. S. Lazer, N. D. Aggarwal, G. J. Hite, K. A. Nieforth, R. T. Kelleher, R. D. Spealman, C. R. Schuster, and W. Wolvertton, *J. Pharm. Sci.*, 1978, **67**, 1656.

<sup>40</sup> E. S. Lazer, *Diss. Abstr. Int. B*, 1979, **40**, 265.

<sup>41</sup> M. M. Kilber, E. H. Everett, and M. E. Easler, *Exp. Neurol.*, 1979, **64**, 306 (*Chem. Abstr.*, 1979, **91**, 68 514).

<sup>42</sup> B. T. Ho, D. L. Taylor, V. S. Estevez, L. F. Englert, and M. O. McKenna, *Adv. Behav. Biol.*, 1977, **21**, 229.

<sup>43</sup> C. S. Aulakh, B. Ghosh, and S. N. Pradhan, *Psychopharmacology (Berlin)*, 1979, **63**, 75.

<sup>44</sup> A. L. Misra, R. B. Poutani, and N. L. Vadlamani, *Xenobiotica*, 1979, **9**, 189.

thiocaine *N*-oxide is oxidized and hydrolysed to ecgonine *N*-oxide besides cocaine and benzoylecgonine.

Chronic administration of cocaine influences behaviour<sup>45</sup> and levels of cyclic AMP in the cerebrospinal fluid<sup>4</sup> of rhesus monkeys.

(*S*)-(-)-Scopolamine (hyoscyne) is 50 to 100 times more active than the (*R*)-(+)-enantiomer in abolishing oxotremorine-induced tremor and in stimulating spontaneous locomotor activity.<sup>46</sup> The effect of scopolamine on human mental activities has been extensively studied, particularly on memory function of chess players,<sup>47</sup> on state-dependent memory processes,<sup>48,49</sup> on maze-learning performance,<sup>50</sup> on the higher nervous activity in Man<sup>51</sup> (alone or combined with physostigmine), and on induced muscarinic sensitivity,<sup>52</sup> *i.e.* changes in sleep.

Scopolamine causes<sup>53</sup> an increase of 49–53% in the pain threshold in rabbits and has slight anti-inflammatory properties.<sup>54</sup> Quaternary salts, *e.g.* *N*-methylscopolaminium bromide<sup>55</sup> and *N*-ethyl-norscopolaminium bromide,<sup>56</sup> show bronchospasmolytic activity.

#### 4 Analytical Aspects

A new method for the rapid separation of alkaloids, *inter alia* atropine, has been elaborated, using chromatography on paper that is impregnated with zirconium oxide.<sup>57</sup> Cation-exchange h.p.l.c. analysis of tropane alkaloids has been developed,<sup>58</sup> followed by post-column derivatization using the fluorimetric ion-pair technique.<sup>58,59</sup> Gas chromatography of tropanes has been reviewed.<sup>60</sup>

Proton<sup>61</sup> and carbon-13<sup>62</sup> n.m.r. spectroscopy have recently been used extensively for the analysis of tropane alkaloids. The non-equivalence of H-6 and H-7 on the one hand and of H-2 and H-4 on the other in atropine and scopolamine is due to the non-symmetrical shielding by the tropic acid moiety. The configuration of *N*-substituents, *e.g.* *N*-oxides, has been determined by studying the deshielding of the 6- and 7 $\beta$ -hydrogens. All of these results should be useful for the identification of new tropane alkaloids and other related systems in the future.

<sup>45</sup> R. M. Post, C. C. Craig, K. M. Squillace, and J. F. Tallman, *Commun. Phys.*, 1979, **3**, 143.

<sup>46</sup> N. Rosic and M. Milosevic, *Jugosl. Physiol. Pharmacol. Acta*, 1979, **15**, 125 (*Chem. Abstr.*, 1980, **92**, 121 848).

<sup>47</sup> R. Liljequist and M. J. Mattila, *Med. Biol.*, 1979, **57**, 402.

<sup>48</sup> R. C. Petersen, *Psychopharmacology (Berlin)*, 1979, **64**, 309.

<sup>49</sup> S. P. Mewaldt and M. M. Ghoneim, *Pharmacol. Biochem. Behav.*, 1979, **10**, 205.

<sup>50</sup> D. D. Rasmussen and J. D. Dudar, *Experientia*, 1979, **35**, 1069.

<sup>51</sup> J. Hrbek, S. Komenda, A. Siroka, J. Macakova, K. Dostalova, and J. Navratil, *Acta Univ. Palacki. Olomuc., Fac. Med.*, 1978, **85**, 281 (*Chem. Abstr.*, 1980, **92**, 69 703).

<sup>52</sup> N. Sitaram, A. M. Moore, and J. C. Christian, *Psychiatry Res.*, 1979, **1**, 9.

<sup>53</sup> C. F. Bian, S. H. Xing, S. J. Jin, and J. F. Dang, *Yao Hsueh Hsueh Pao*, 1979, **14**, 397 (*Chem. Abstr.*, 1980, **92**, 34 168).

<sup>54</sup> B. Balestrieri, L. Capasso, S. Masiello, S. Castaldo, and F. Capasso, *Clin. Ter.*, 1980, **92**, 127 (*Chem. Abstr.*, 1980, **93**, 125 722).

<sup>55</sup> M. A. Wasserman and R. L. Griffith, *J. Pharmacol. Exp. Ther.*, 1979, **211**, 159.

<sup>56</sup> K. Zeile, R. Banholzer, G. Walther, W. Schulz, and H. Wick, *Ger. P.* 1 795 818 (*Chem. Abstr.*, 1980, **92**, 164 147).

<sup>57</sup> N. V. R. Rao and N. J. Singh, *Curr. Sci.*, 1980, **49**, 193.

<sup>58</sup> J. M. Huen and J. P. Thevenin, *HRC CC, J. High Resolut. Chromatogr. Chromatogr. Commun.*, 1979, **2**, 154.

<sup>59</sup> J. C. Gfeller, G. Frey, J. M. Huen and J. P. Thevenin, *J. Chromatogr.*, 1979, **172**, 141.

<sup>60</sup> R. E. Sanforo and J. E. Zaremba, *Chromatogr. Sci.*, 1979, **9**, 1191.

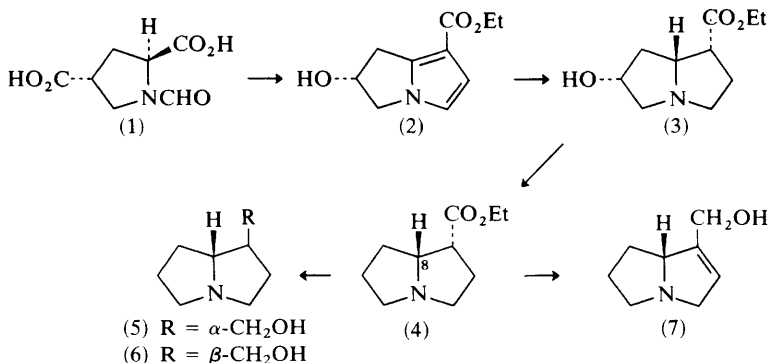
<sup>61</sup> T. A. Crabb, *Annu. Rep. NMR Spectrosc.*, 1978, **8**, 85–90.

<sup>62</sup> A. M. Taha and G. Rucker, *Egypt. J. Pharm. Sci.*, 1977, **18**, 59 (publ. 1979).

The occurrence and systematic importance of pyrrolizidine alkaloids in angiosperms have been reviewed.<sup>1</sup>

### 1 Syntheses of the Necine Bases

The number of synthetic routes to the natural 1-hydroxymethyl-pyrrolizidines continues to increase. Robins and Sakdarat have achieved the first synthesis of these necines in optically active form, using natural (-)-4-hydroxy-L-proline as a chiral template.<sup>2</sup> The dihydropyrrolizine ester (2) was prepared by regiospecific 1,3-dipolar cycloaddition of ethyl propiolate to the *N,O*-diformyl derivative (1) of (-)-4-hydroxy-L-proline, followed by deformylation (Scheme 1). Addition



Scheme 1

of hydrogen to the less sterically hindered  $\beta$ -face of (2) gave a single optically active ester (3). Having controlled the formation of the two new chiral centres, the hydroxyl group in (3) was removed by replacement with chlorine followed by catalytic hydrogenation to give the (+)-ester (4). This 8 $\beta$ -ester was converted, by known steps, into (+)-isoretronecanol (5) [50% yield from (1)], (+)-laburnine (6),<sup>3</sup> and (+)-supinidine (7),<sup>4</sup> with optical purities >80% in each case. In

<sup>1</sup> C. C. J. Culvenor, *Bot. Notiser*, 1978, **131**, 473.

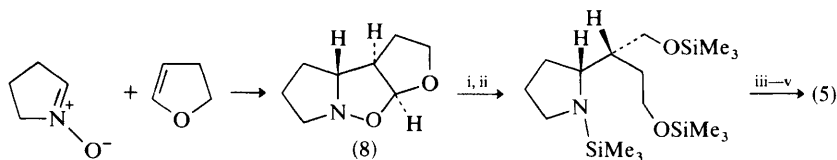
<sup>2</sup> D. J. Robins and S. Sakdarat, *J. Chem. Soc., Chem. Commun.*, 1979, 1181.

<sup>3</sup> M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, 1974, **39**, 731.

<sup>4</sup> D. J. Robins and S. Sakdarat, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1734.

order to establish the synthesis of the corresponding  $8\alpha$ -bases, the hydroxy-ester (2) was converted into its tosylate derivative, which was treated with formate anion to give (after deformylation) the enantiomer of (2). Thus all six naturally occurring 1-hydroxymethyl-pyrrolizidines can be prepared, in optically active form, in reasonable yield.

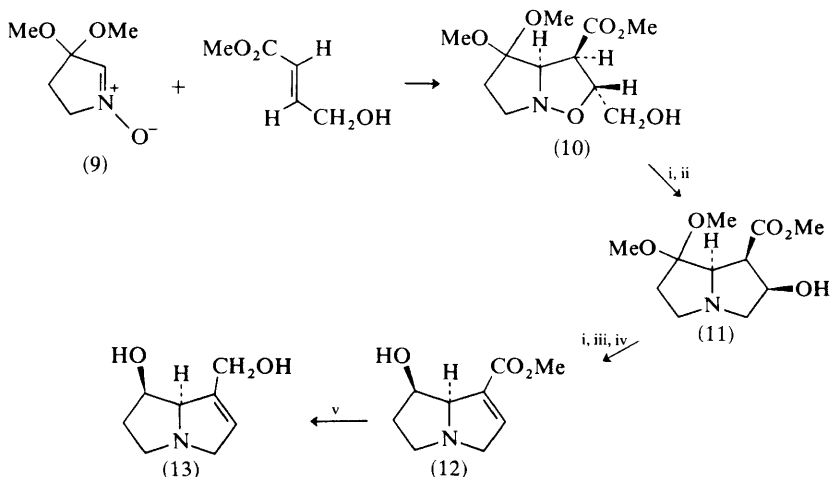
Tufariello has reviewed his strategy for the synthesis of alkaloids (including necine bases) using the 1,3-dipolar cycloaddition of nitrones to alkenes.<sup>5</sup> This work began with the synthesis of ( $\pm$ )-supinidine (7) from 1-pyrroline 1-oxide (see these Reports, Vol. 2, Ch. 4). A related approach has been used by Iwashita *et al.* in their synthesis of ( $\pm$ )-isoretronecanol (5).<sup>6</sup> The stereochemistry of the *exo*-product (8), formed by regiospecific 1,3-dipolar cycloaddition of 1-pyrroline 1-oxide to dihydrofuran (Scheme 2), was confirmed by its conversion into



Reagents: i,  $\text{LiAlH}_4$ ; ii,  $\text{Me}_3\text{SiNEt}_2$ ; iii,  $\text{Me}_3\text{SiI}$ ; iv,  $\text{PhCH}_2\text{NMe}_3^+\text{F}^-$ ; v,  $\text{H}_2\text{O}$

**Scheme 2**

( $\pm$ )-isoretronecanol (5). The scope of this route has now been extended by Tufariello and Lee by the use of substituted nitrones, and a synthesis of ( $\pm$ )-retronecine (13) has been developed.<sup>7</sup> This constitutes only the second reported



Reagents: i,  $\text{MeSO}_2\text{Cl}$ ,  $\text{Et}_3\text{N}$ ; ii,  $\text{H}_2$ -Pd/C; iii,  $\text{HCl}$ ; iv,  $\text{NaBH}_4$ ; v, *alane*

**Scheme 3**

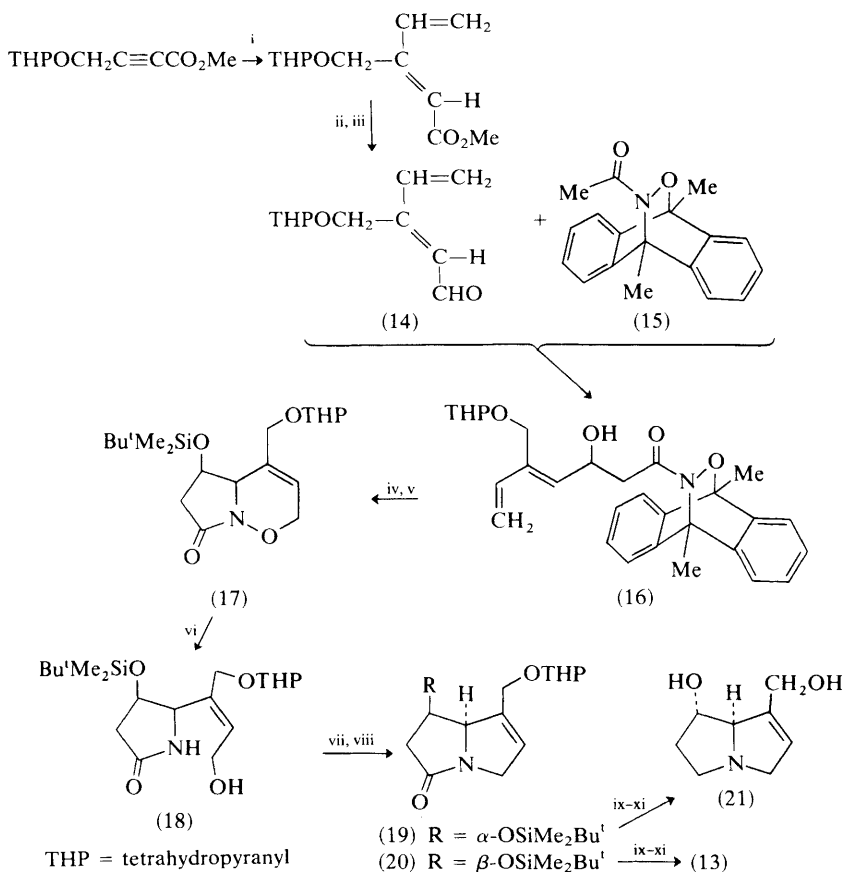
<sup>5</sup> J. J. Tufariello, *Acc. Chem. Res.*, 1979, **12**, 396.

<sup>6</sup> T. Iwashita, T. Kusumi, and H. Kakisawa, *Chem. Lett.*, 1980, 1337.

<sup>7</sup> J. J. Tufariello and G. E. Lee, *J. Am. Chem. Soc.*, 1980, **102**, 373.

synthesis of retronecine (*cf.* ref. 8). Regiospecific addition of the protected  $\alpha$ -keto-nitrone (9) to methyl  $\gamma$ -hydroxycrotonate gave the isoxazolidine (10) (Scheme 3). The pyrrolizidine nucleus (11) was generated by hydrogenolysis of the mesylate of (10). Dehydration of the mesylate of (11), followed by deprotection of the ketal and reduction, afforded the hydroxy-ester (12), which was reduced to (±)-retronecine (13).

Another route to (±)-retronecine, together with its C-7 epimer (±)-heliotridine (21), has been described by Keck and Nickell.<sup>9</sup> This synthesis depends upon the transfer of an acylnitroso moiety, generated from the Diels-Alder adduct (15) with dimethylanthalracene.<sup>10</sup> Addition of the lithium enolate of this adduct to the unstable dienal (14), formed as shown in Scheme 4, gave an alcohol (16).



Reagents: i, Lithium divinylcuprate; ii, Bu<sub>2</sub>AlH; iii, MnO<sub>2</sub>; iv, Bu<sup>t</sup>Me<sub>2</sub>SiCl; v, heat; vi, Na/Hg; vii, MeSO<sub>2</sub>Cl, Et<sub>3</sub>N; viii, LiNPr<sub>2</sub>; ix, MeOH, H<sup>+</sup>; x, Bu<sub>4</sub>N<sup>+</sup> F<sup>-</sup>; xi, LiAlH<sub>4</sub>

Scheme 4

<sup>8</sup> T. A. Geissman and A. C. Waiss, *J. Org. Chem.*, 1962, **27**, 139.

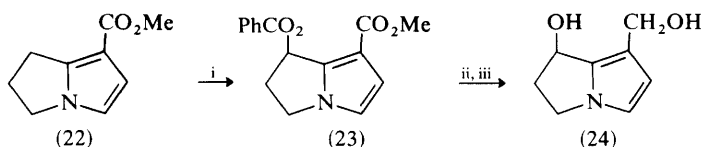
<sup>9</sup> G. E. Keck and D. G. Nickell, *J. Am. Chem. Soc.*, 1980, **102**, 3632.

<sup>10</sup> G. W. Kirby, *Chem. Soc. Rev.*, 1977, **6**, 1.



Thermolysis of the protected alcohol led to intramolecular transfer of the acylnitroso dienophile to yield the oxazine derivative (17). Cleavage of the N—O bond of (17) gave a lactam (18); this was cyclized, to yield the diastereoisomeric dihydropyrrolizinones (19) and (20), which were separated by medium-pressure liquid chromatography. Removal of the protecting groups in (19), followed by reduction of the carbonyl group, gave ( $\pm$ )-heliotridine (21). Analogous treatment of the epimer (20) afforded ( $\pm$ )-retronecine (13).

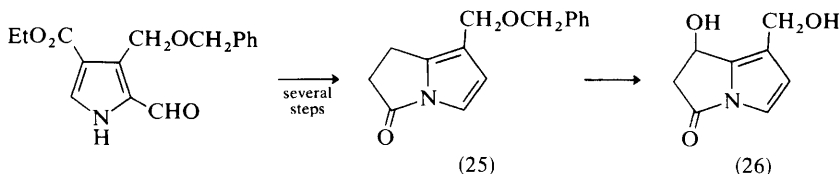
Dihydropyrrolizine esters such as (22) are readily available by 1,3-dipolar cycloaddition of *N*-formyl-L-proline to methyl propiolate.<sup>3</sup> Bohlmann and co-workers have developed a useful method for the direct introduction of an oxygen function into the allylic position on the non-substituted ring.<sup>11</sup> Thus treatment of the ester (22) with a peroxy-ester gave a 42% yield of the diester (23), which afforded ( $\pm$ )-dehydroheliotridine (24) in 57% yield on reduction (Scheme 5).



Reagents: i,  $\text{PhCO}_3\text{Bu}^+$ ; ii,  $\text{H}^+$ ; iii,  $\text{Bu}_2\text{AlH}$

Scheme 5

In an extension of the approach, the dihydropyrrolizinone (26) was prepared in similar yield from the bicyclic lactam (25) (Scheme 6). Both (+)- and (–)-forms of (26) are present as part of macrocyclic diesters in *Senecio* species (cf. Vol. 10, p. 54).



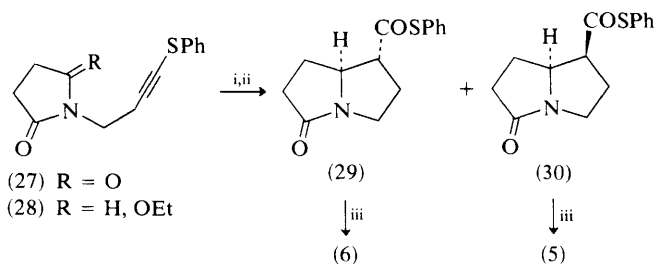
Scheme 6

A new route to ( $\pm$ )-trachelanthamidine (6) and ( $\pm$ )-isoretronecanol (5) has been reported by Nossin and Speckamp.<sup>12</sup> Cyclization of the ethoxy-lactam (28), which is formed on reduction of the imide (27), led to ring-closure with the acetylene to give, after hydrolysis, a 4:1 mixture of the epimers (29) and (30) (Scheme 7). The preferential formation of the five-membered ring is considered to be due to stabilization of an exocyclic vinyl cationic intermediate by the phenylthio group. Reduction of the separated diastereoisomers (29) and (30) yielded ( $\pm$ )-trachelanthamidine (6) and ( $\pm$ )-isoretronecanol (5), respectively.

The iminium salt (32), produced by decarbonylation of an  $\alpha$ -amino-acid, is the key intermediate in the generation of the pyrrolizidine nucleus in the strategy

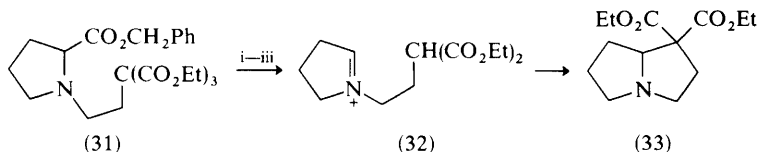
<sup>11</sup> F. Bohlmann, W. Klose, and K. Nickisch, *Tetrahedron Lett.*, 1979, 3699.

<sup>12</sup> P. M. M. Nossin and W. N. Speckamp, *Tetrahedron Lett.*, 1979, 4411.



Scheme 7

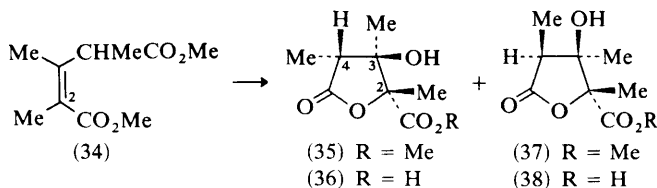
developed by Rapoport and co-workers.<sup>13</sup> Alkylation of L-proline benzyl ester gave a tetra-ester (31), which was then reduced, selectively decarboxylated, and decarbonylated to give the iminium ion (32); this yielded the pyrrolizidine diester (33) on cyclization at pH 6 (Scheme 8). There is an obvious extension of this route to the synthesis of the natural 1-hydroxymethyl-pyrrolizidines.



Scheme 8

## 2 Syntheses of the Necic Acids

Monocrotalic acid (36) was previously shown to have the (2*R*, 3*R*, 4*R*) absolute configuration.<sup>14</sup> All eight stereoisomers of monocrotalic acid have been synthesized by Matsumoto and co-workers.<sup>15</sup> *cis*-Hydroxylation of the ( $\pm$ )-(*Z*)-alkene (34) with potassium permanganate gave the epimeric ( $\pm$ )- $\gamma$ -lactones (35) and (37) in the ratio 5:1 (Scheme 9). The major product (35) was separated and



Scheme 9

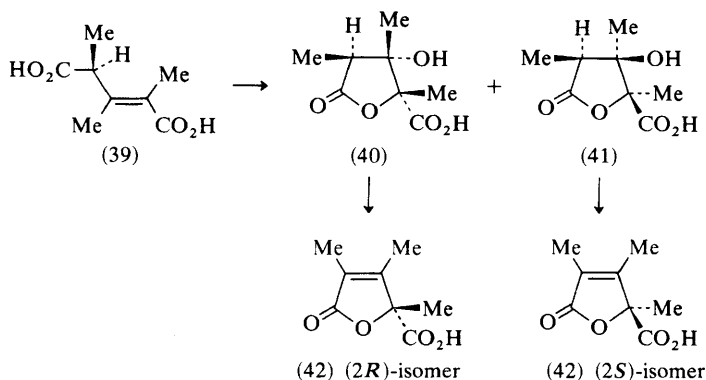
hydrolysed to yield a racemic acid. Resolution of this acid with brucine afforded the (–)-acid (36), which was identical with natural (–)-monocrotalic acid. Analogous treatment of the minor product (37) led to the isolation of the

<sup>13</sup> I. G. Csendes, Y. Y. Lee, H. C. Padgett, and H. Rapoport, *J. Org. Chem.*, 1979, **44**, 4173.

<sup>14</sup> D. J. Robins and D. H. G. Crout, *J. Chem. Soc. (C)*, 1969, 1386; 1970, 1334.

<sup>15</sup> T. Matsumoto, M. Takahashi, and Y. Kashiara, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3329.

(2*R*,3*R*,4*S*)- and (2*S*,3*S*,4*R*)-acids (38). Resolution of (±)-(*E*)-2,3,4-trimethyl-2-pentenedioic acid gave the two separate isomers. The configuration of each isomer was assigned by correlation with (−)-(*R*)-2-phenylpropanoic acid. Then methylation of the (4*S*)-acid (39), followed by *cis*-hydroxylation, hydrolysis, and separation of the diastereoisomeric acids, yielded the (2*R*,3*S*,4*S*)- (40) and (2*S*,3*R*,4*S*)-isomers (41) of monocrotalic acid (Scheme 10). The stereochemistry

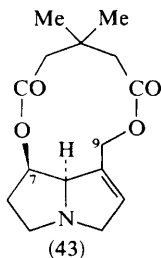


Scheme 10

of these two acids was confirmed by dehydration of their methyl esters into methyl anhydromonocrotalate (42) of known absolute configuration. The remaining two isomers of monocrotalic acid were synthesized from the (4*R*)-acid in an analogous manner. The c.d. spectra of all eight stereoisomers of monocrotalic acid were recorded. Acids with the opposite absolute configuration at C-2 and C-4 [(2*R*,4*S*) or (2*S*,4*R*)] show two distinct Cotton effects at 204 (due to C-2) and 224 nm (C-4), while acids with the same absolute configuration at C-2 and C-4 [(2*R*,4*R*) or (2*S*,4*S*)] exhibit only one effect at 204 nm.

### 3 Synthesis of a Macrocyclic Pyrrolizidine Diester

Robins and Sakdarat have achieved the first reconstruction of an eleven-membered macrocyclic pyrrolizidine diester (43).<sup>16</sup> Treatment of (+)-retronecine (13) with 3,3-dimethylglutaric anhydride gave a mixture of the 7- and 9-monoesters of (+)-retronecine. Intramolecular lactonization of this mixture *via*

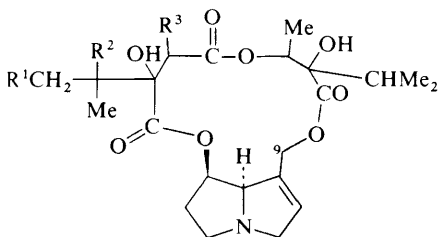


<sup>16</sup> D. J. Robins and S. Sakdarat, *J. Chem. Soc., Chem. Commun.*, 1980, 282.

the corresponding 2-pyridinethiol esters gave a 50% overall yield of the macrocyclic diester (43). The key feature in the n.m.r. spectrum of (43) in deuteriochloroform is an AB quartet at  $\delta$  4.08 and 5.32 p.p.m. ( $J = 12$  Hz) due to the non-equivalent protons at C-9. The large difference in chemical shift of 1.24 p.p.m. suggests that the conformation of (43) may be different from those of the natural eleven-membered macrocyclic diester alkaloids, where values of 0 to 0.92 p.p.m. have been observed.<sup>17</sup>

#### 4 Alkaloids of the Apocynaceae

Five new pyrrolizidine alkaloids, each containing a novel fourteen-membered macrocyclic ring, have been isolated by Edgar *et al.*<sup>18</sup> Parsonsine (44) and heterophylline (45) were present in *Parsonsia heterophylla* A. Cunn. and *P. spiralis* Wall., while spiraline (46), spiranine (47), and spiracine (48) were obtained only from *P. spiralis*. These five alkaloids are derived from retronecine that is esterified at C-9 with (–)-trachelanthic acid (*i.e.* indicine), and further diesterified by a series of substituted malic acid derivatives to complete the fourteen-membered ring. Indeed, partial hydrolysis of parsonsine (44) yielded indicine (49). The non-equivalence of the C-9 protons (ABq,  $\delta$  4.45 and 5.20 p.p.m.) in parsonsine indicates the presence of a macrocyclic system, and



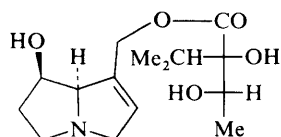
Parsonsine (44)  $R^1 = R^2 = R^3 = H$

Heterophylline (45)  $R^1 = Me, R^2 = R^3 = H$

Spiraline (46)  $R^1 = R^2 = H, R^3 = OH$

Spiranine (47)  $R^1 = Me, R^2 = H, R^3 = OH$

Spiracine (48)  $R^1 = Me, R^2 = R^3 = OH$



Indicine (49)

this was confirmed by hydrogenolysis of parsonsine to give a product which retained the necine and both acidic moieties. The unusual structure proposed for parsonsine (44) has been confirmed by X-ray diffraction of the two crystalline modifications, of m.pt. 196<sup>19</sup> and 158 °C,<sup>20</sup> which show different folding patterns for the acidic moieties. The structures of (45)–(48) follow from their electron-impact mass spectra, which are closely related to that of parsonsine (44). The fourteen-membered macrocyclic alkaloids [(44)–(48)] are related to those found previously in two other *Parsonsia* species (*cf.* Vol. 6, p. 80), modified by

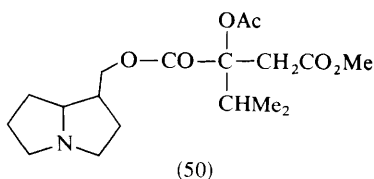
<sup>17</sup> L. B. Bull, C. C. J. Culvenor, and A. T. Dick, 'The Pyrrolizidine Alkaloids', North-Holland, Amsterdam, 1968.

<sup>18</sup> J. A. Edgar, N. J. Eggers, A. J. Jones, and G. B. Russell, *Tetrahedron Lett.*, 1980, **21**, 2657.

<sup>19</sup> N. J. Eggers and G. J. Gainsford, *Cryst. Struct. Commun.*, 1979, **8**, 597.

<sup>20</sup> G. J. Gainsford, *Cryst. Struct. Commun.*, 1980, **9**, 173.

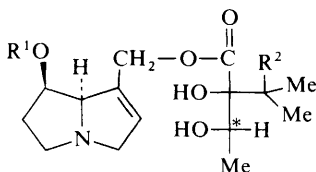
diesterification with various 2-alkylmalic acids, similar to those that occur in some pyrrolizidine alkaloids in the Orchidaceae.



Another new alkaloid (50) was also isolated from *P. heterophylla*. Mild acid hydrolysis of (50) gave a desacetyl compound which showed a prominent peak due to the loss of  $-\text{CH}_2\text{CO}_2\text{CH}_3$  in its mass spectrum, thereby indicating that the other carboxyl group is esterified to the base. Vigorous acid hydrolysis of (50) gave 1-hydroxymethylpyrrolizidine of undefined stereochemistry together with a neutral compound which yielded (–)-2-isopropylmalic acid on basic hydrolysis.

### 5 Alkaloids of the Boraginaceae

Russian comfrey (*Symphytum*  $\times$  *uplandicum* Nyman) is widely recommended as a medicinal herb and an item of human diet. A previous investigation of this species led to the isolation of three alkaloids which were not fully characterized (cf. Vol. 7, p. 57). Culvenor and co-workers have separated eight pyrrolizidine alkaloids from the leaves of this perennial plant by counter-current distribution.<sup>21</sup> The known alkaloids echimidine (51), symphytine (52), lycopsamine (53), and intermedine (54) were present. In addition, four new alkaloids, i.e. 7-acetyl-lycopsamine (55), 7-acetylintermedine (56), symlandine (57), and uplandicine (58), were characterized by spectroscopic methods, and by hydrolysis. The total alkaloidal extract caused chronic hepatotoxic effects in rats, and the authors



- Echimidine (51)  $\text{R}^1 = \text{angelyl}$ ,  $\text{R}^2 = \text{OH}$ ; stereochemistry of acid unknown  
 Symphytine (52)  $\text{R}^1 = \text{tiglyl}$ ,  $\text{R}^2 = \text{H}$   
 Lycopsamine (53)  $\text{R}^1 = \text{R}^2 = \text{H}$   
 Intermedine (54)  $\text{R}^1 = \text{R}^2 = \text{H}$ ; opposite stereochemistry at  $\text{C}^*$   
 7-Acetyl-lycopsamine (55)  $\text{R}^1 = \text{Ac}$ ,  $\text{R}^2 = \text{H}$   
 7-Acetylintermedine (56)  $\text{R}^1 = \text{Ac}$ ,  $\text{R}^2 = \text{H}$ ; opposite stereochemistry at  $\text{C}^*$   
 Symlandine (57)  $\text{R}^1 = \text{angelyl}$ ,  $\text{R}^2 = \text{H}$   
 Uplandicine (58)  $\text{R}^1 = \text{Ac}$ ,  $\text{R}^2 = \text{OH}$ ; stereochemistry of acid unknown

<sup>21</sup> C. C. J. Culvenor, M. Clarke, J. A. Edgar, J. L. Frahn, M. V. Jago, J. E. Peterson, and L. W. Smith, *Experientia*, 1980, **36**, 377; C. C. J. Culvenor, J. A. Edgar, J. L. Frahn, and L. W. Smith, *Aust. J. Chem.*, 1980, **33**, 1105.

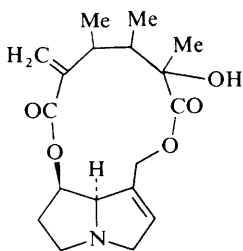
warn that although there have been no reports of toxicity of this species, the effects of ingestion of these alkaloids are cumulative, and the appearance of obvious damage may be delayed.

Another plant that is commonly used in folk medicine as a stimulant is *Anchusa officinalis* L. Broch-Due and Aasen have identified lycopsamine (53) as the main alkaloidal constituent of this species (cf. Vol. 7, p. 57).<sup>22</sup>

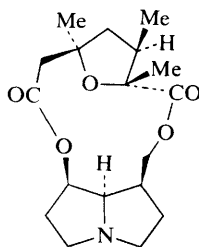
As part of an investigation of Middle Eastern plants, Zalkow *et al.* have isolated echinatine and heliosupine from *Cynoglossum creticum*; heliotrine, lasiocarpine, and europine are present in *Heliotropium arbainense*, and lasiocarpine is a minor constituent of *H. maris-mortui*.<sup>23</sup> The pyrrolizidine alkaloid content of 24 species of *Heliotropium* from Mexico and the Southern U.S.A. has been examined.<sup>24</sup> Unsaturated alkaloids were present in all 24 species, while nine species contained saturated alkaloids as well. No definite assignments were made. The variations in amounts of trichodesmine and incanine present during the life cycle of *Trichodesma incanum* (Bunge) DC have been studied.<sup>25</sup>

## 6 Alkaloids of the Compositae

The known alkaloids senecionine, senkirkine, and retrorsine have been isolated from *Senecio vernalis* Wald. et Kit. by Röder *et al.*<sup>26</sup> A new alkaloid, named senecivernine (59), was also present. The mass spectrum of (59) showed a molecular ion at  $m/z$  335, and fragment ions at  $m/z$  291, 248, and 220, characteristic for a macrocyclic diester of retronecine, arising from cleavage of the allylic ester.<sup>17</sup> Basic hydrolysis of senecivernine gave a new necic acid which had spectroscopic data in accord with the proposed structure. Retronecine was not isolated. The necic acid from senecivernine is a  $C_{10}$  acid of an unusual structural type (cf. Vol. 8, p. 55).



Senecivernine (59)



Nemorensine (60)

Previous investigations of *Senecio nemorensis* L. var. *subdecurrens* Griseb. yielded nemorensine (60) (cf. Vol. 5, p. 85). A re-investigation of this species by Klasek *et al.* has led to the isolation of two known alkaloids, *i.e.* retroisosenine

<sup>22</sup> A. I. Broch-Due and A. A. Aasen, *Acta Chem. Scand., Ser. B*, 1980, **34**, 75.

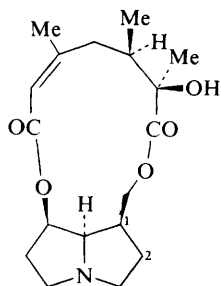
<sup>23</sup> L. H. Zalkow, S. Bonetti, L. T. Gelbaum, M. M. Gordon, B. B. Patil, A. Shami, and D. G. Van Derveer, *J. Nat. Prod.*, 1979, **42**, 603.

<sup>24</sup> H. Birecka, M. W. Frohlich, L. Hull, and M. J. Chaskes, *Phytochemistry*, 1980, **19**, 421.

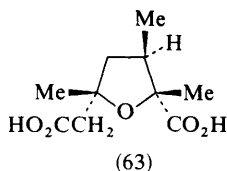
<sup>25</sup> Yu. D. Sadykov and M. Khodzimatov, *Dokl. Akad. Nauk Tadzh. SSR*, 1979, **22**, 249.

<sup>26</sup> E. Röder, H. Wiedenfeld, and U. Pastewka, *Planta Med.*, 1979, **37**, 131.

and bulgarsenine (61), together with the *N*-oxide of nemorensine.<sup>27</sup> The free acids from these alkaloids were also present in this species. The transformation of bulgarsenine into nemorensine under acidic conditions is also described.



Bulgarsenine (61)  
Doronanine (62)  $\Delta^{1,2}$



(63)

Bulgarsenine (61) has also been isolated from *Senecio doronicum* L. together with a new alkaloid, doronenine (62).<sup>28</sup> The structure and absolute configuration of doronenine were established by *X*-ray structure analysis.<sup>29</sup> The structure (63) of the saturated  $\gamma$ -lactone (*cis*-nemorensic acid) that was obtained on alkaline hydrolysis of doronenine was also determined by *X*-ray crystallography.<sup>30</sup>

A new minor constituent of *Senecio jacobaea* L. has been shown to contain chlorine from its mass spectrum, which showed a molecular ion at *m/z* 385 and an ion at *m/z* 350 due to loss of chlorine.<sup>31</sup> Senkirkine and integerrimine were previously isolated from *S. antieuphorbium* Sch. Bip. (*cf.* Vol. 3, p. 84). Senaetnine and isosenaetnine have now been found in this species.<sup>32</sup> Otosenine has again been isolated from *S. cineraria* DC.<sup>33</sup> Bulgarian *S. erucifolius* produces senecionine and seneciphylline.<sup>34</sup> The amount of senkirkine present in specimens of *Tussilago farfara* obtained from several countries has been determined.<sup>35</sup>

## 7 Alkaloids of the Leguminosae

Two new isomeric alkaloids have been isolated from the seeds of *Crotalaria candicans* W. & A. 184 by Siddiqi *et al.*<sup>36</sup> For both alkaloids, the difference in chemical shift for the C-9 protons is 0.95 p.p.m., indicating the presence of a macrocyclic diester ring. Both crocandine (64) and isocrocandine (64) yielded

<sup>27</sup> A. Klásek, P. Sedmera, J. Vokoun, A. Boeva, S. Dvořáková, and F. Šantavý, *Collect. Czech. Chem. Commun.*, 1980, **45**, 548.

<sup>28</sup> E. Röder, H. Wiedenfeld, and M. Frisse, *Phytochemistry*, 1980, **19**, 1275.

<sup>29</sup> A. Kirfel, G. Will, H. Wiedenfeld, and E. Röder, *Cryst. Struct. Commun.*, 1980, **9**, 353.

<sup>30</sup> A. Kirfel, G. Will, H. Wiedenfeld, and E. Röder, *Cryst. Struct. Commun.*, 1980, **9**, 363.

<sup>31</sup> H. T. Segall and T. P. Krick, *Toxicol. Lett.*, 1979, **4**, 193.

<sup>32</sup> F. Bohlmann and J. Ziesche, *Phytochemistry*, 1979, **18**, 1489.

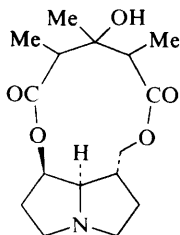
<sup>33</sup> S. Dvořáková, F. Šantavý, and A. Klásek, *Acta Univ. Palacki. Olumuc., Fac. Med.*, 1978, **86**, 33 (*Chem. Abstr.*, 1980, **92**, 37 777).

<sup>34</sup> A. Boeva, B. Stefanova-Gateva, and D. Krushovska, *Farmatsiya (Sofia)*, 1979, **29**, 32 (*Chem. Abstr.*, 1979, **91**, 181 334).

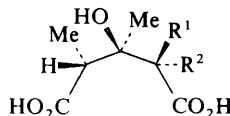
<sup>35</sup> L. Borka and I. Onshuus, *Medd. Nor. Farm. Selsk.*, 1979, **41**, 165 (*Chem. Abstr.*, 1980, **92**, 3225); J. Luethy, U. Zweifel, C. Schlatter, and M. H. Benn, *Mitt. Geb. Lebensmittelunters. Hyg.*, 1980, **71**, 73 (*Chem. Abstr.*, 1980, **93**, 22634).

<sup>36</sup> M. A. Siddiqi, K. A. Suri, O. P. Suri, and C. K. Atal, *Phytochemistry*, 1979, **18**, 1413.

turneforcidine on alkaline hydrolysis. The necic acids obtained were fulvinic (65) and cromaduric (66), respectively. The mode of esterification of the necic acids to turneforcidine remains to be established.



Crocandine and isocrocandine (64)

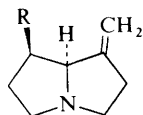


(65)  $R^1 = H, R^2 = Me$

(66)  $R^1 = Me, R^2 = H$  (or enantiomer)

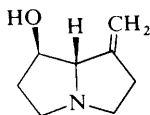
Egyptian *Crotalaria madurensis* R. Wight contains madurensine, fulvine, and crispatine.<sup>37</sup> *C. aegyptiaca* Benth., also from Egypt, yielded monocrotaline and the necine (67),<sup>37</sup> while the same species from Israel gave monocrotaline and crosemerpine,<sup>23</sup> which was originally isolated from *C. semperflorens* Vent.

A phytochemical study of *Crotalaria* species has revealed the presence of 1-methylenepyrrolizidine (68) in four new species, namely *C. grandistipulata* Harms, *C. lachnophora* A. Rich, *C. natalitia* Meissner, and *C. stolzii* (Baker fil.) Milne-Redh. ex Polhill.<sup>38</sup> The necine (69) is probably present in *C. cylindrocarpa* DC and *C. podocarpa* DC.<sup>38</sup>

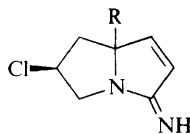


(67)  $R = OH$

(68)  $R = H$



(69)



Clazamycin A (70)  $R = \alpha-OH$

Clazamycin B (71)  $R = \beta-OH$

## 8 Alkaloids in the Lepidoptera

Male *Danaus* butterflies ingest pyrrolizidine alkaloids and convert them into dihydropyrrolizines, which are used as pheromones. The relationships between adult danaid butterflies and plants containing pyrrolizidine alkaloids have been reviewed.<sup>39</sup> Edgar *et al.* have studied eight species of African and Australian danaiids, and have shown that both sexes are able to store pyrrolizidine alkaloids.<sup>40</sup> It is suggested that this storage of unpalatable alkaloids may contribute toward the chemical defences of the danaid butterflies.

<sup>37</sup> G. Mahran, G. Wassel, B. El-Menshaw, G. El-Hossary, and A. Saeed, *Acta Pharm. Suec.*, 1979, **16**, 333.

<sup>38</sup> D. J. Pilbeam, R. M. Polhill, and E. A. Bell, *Bot. J. Linn. Soc.*, 1979, **79**, 259.

<sup>39</sup> M. Boppré, *Entomol. Exp. Appl.*, 1978, **24**, 264.

<sup>40</sup> J. A. Edgar, M. Boppré, and D. Schneider, *Experientia*, 1979, **35**, 1447.



## 9 Pyrrolizidines in Micro-organisms

Two epimeric antibiotics with a pyrrolizidine ring system, clazamycins A (70) and B (71), have been isolated from a *Streptomyces* species.<sup>41</sup> Clazamycin B (=antibiotic 354) is also present in *S. puniceus* ssp. *doliceus*.<sup>42</sup> The structure of clazamycin A was established by determining the X-ray crystal structure of its hydrochloride salt.<sup>43</sup>

## 10 General Studies

The three major alkaloids of *Senecio vulgaris*, i.e. retrorsine, seneciphylline, and senecionine, have been separated by reversed-phase high-performance liquid chromatography (h.p.l.c.) on a 500 mg scale.<sup>44</sup> A similar method has been used to separate the alkaloids from *S. jacobaea* and *Amsinckia intermedia*.<sup>45</sup> The *N*-oxides of echimidine (51) and symphytine (52), obtained from *Symphytum officinale*, have been separated by h.p.l.c.<sup>46</sup> A polystyrene-divinylbenzene resin has been used to separate the echinatine, echimidine, and symphytine that are present in *S. officinale*.<sup>47</sup> An unidentified alkaloid (with a molecular ion at *m/z* 299) was also isolated from *Cynoglossum nervosum* Benth. A new method for the analysis of the *N*-oxide of indicine (49) at nanogram levels has been described.<sup>48</sup> Indicine *N*-oxide was trimethylsilylated and subjected to gas chromatographic-mass spectrometric analysis. Some formation of pyrroles was observed. A polarographic method for the separation of platyphylline and seneciphylline has been patented.<sup>49</sup> The quantitative determination of the alkaloids in *Senecio platyphylloides* by a colorimetric method has been reported.<sup>50</sup>

Previous X-ray studies on eleven-membered macrocyclic diesters of retronecine, such as monocrotaline, fulvine, and axillarine, have demonstrated that the ester carbonyl groups are *syn*-parallel and directed below the plane of the eleven-membered ring. Further X-ray work on incanine<sup>51</sup> and trichodesmine<sup>52</sup> has shown that incanine (72) also falls into this grouping, but the conformation of trichodesmine (73) is quite different. In trichodesmine, the ester carbonyl groups are nearly *anti*-parallel (155.5°), and there is an intramolecular H-bond between adjacent oxygen-containing functions on C-12 and C-13. Macrocyclic diesters of retronecine with twelve-membered rings have ester carbonyl groups

<sup>41</sup> Y. Horiuchi, S. Kondo, T. Ikeda, D. Ikeda, K. Miura, M. Hamada, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1979, **32**, 762.

<sup>42</sup> L. A. Dolak and C. DeBoer, *J. Antibiot.*, 1980, **33**, 83.

<sup>43</sup> H. Nakamura, Y. Itaka, and H. Umezawa, *J. Antibiot.*, 1979, **32**, 765.

<sup>44</sup> H. J. Segall, *J. Liq. Chromatogr.*, 1979, **2**, 1319.

<sup>45</sup> G. P. Dimenna, T. P. Krick, and H. T. Segall, *J. Chromatogr.*, 1980, **192**, 474.

<sup>46</sup> G. Tittel, H. Hinz, and H. Wagner, *Planta Med.*, 1979, **37**, 1.

<sup>47</sup> H. J. Huizing and T. M. Malingré, *J. Chromatogr.*, 1979, **176**, 274.

<sup>48</sup> J. V. Evans, A. Peng, and C. J. Nielsen, *Biomed. Mass Spectrom.*, 1979, **6**, 38.

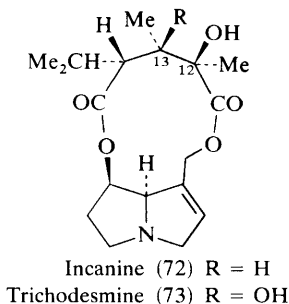
<sup>49</sup> E. A. Vdoviko, O. R. Pryakhin, and S. A. Pokhmelkina, USSR P. 693 261 (*Chem. Abstr.*, 1980, **92**, 203 668).

<sup>50</sup> N. G. Larionov, S. I. Kocherga, and B. A. Krivut, *Khim-Farm. Zh.*, 1980, **14**, 78 (*Chem. Abstr.*, 1980, **93**, 31 826).

<sup>51</sup> B. Tashkhodzhaev, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1979, 363 (*Chem. Abstr.*, 1980, **92**, 111 199).

<sup>52</sup> B. Tashkhodzhaev, M. R. Yagudaev, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1979, 368 (*Chem. Abstr.*, 1980, **92**, 111 194).

which are *anti*-parallel. The X-ray crystal structures of retrorsine hydrobromide (as its ethanol solvate) show that it too falls into this category.<sup>53</sup> X-Ray structures of retusine<sup>54</sup> and monocrotaline sulphite hydrochloride<sup>55</sup> have been reported (in Chinese).



## 11 Pharmacological and Biological Studies

Two outbreaks of human liver disease in India have been attributed to the consumption of plants containing pyrrolizidine alkaloids. In the first instance, the disease was caused by eating cereals contaminated with seeds of a *Crotalaria* species.<sup>56</sup> Haemodynamic studies were carried out on eight patients suffering from the characteristic veno-occlusive disease. In the second study, two cases of sudden liver failure that are believed to be due to the ingestion of herbal concoctions made from seeds and plants of *Heliotropium* species are reviewed.<sup>57</sup>

Some pyrrolizidine alkaloids are also carcinogens. Chromosomal aberrations were induced in cultured mammalian (hamster) cells treated with heliotrine, lasiocarpine, petasitenine, or senkirkine.<sup>58</sup> Coltsfoot (*Tussilago farfara*) and comfrey (*Symphytum officinale*) are both widely used as herbal remedies, although they have both previously been shown to have carcinogenic activity. Hepatic tumours have now been induced in rats by ingestion of senkirkine and symphytine (52), which are the main alkaloidal constituents of coltsfoot and comfrey, respectively.<sup>59</sup> The mutagenic action of integerrimine has been tested on *Drosophila melanogaster*.<sup>60</sup> A modified Ames' method was used to demonstrate the mutagenic activity of thirteen pyrrolizidine alkaloids on *Salmonella typhimurium*.<sup>61</sup> Clivorine, fukinotoxin (=petasitenine), heliotrine, lasiocarpine, ligularidine, and senkirkine were mutagenic.

<sup>53</sup> H. Stoeckli-Evans, *Acta Crystallogr., Sect. B*, 1979, **35**, 2798.

<sup>54</sup> S.-D. Wang, *K'o Hsueh T'ung Pao*, 1979, **24**, 1023 (*Chem. Abstr.*, 1980, **92**, 181 444).

<sup>55</sup> S.-D. Wang, *K'o Hsueh T'ung Pao*, 1979, **24**, 1115 (*Chem. Abstr.*, 1980, **92**, 164 133).

<sup>56</sup> T. E. Kasturi, S. C. Manchanda, R. K. Tandon, M. Rajani, and M. L. Bhatia, *Br. Heart J.*, 1979, **41**, 594.

<sup>57</sup> B. K. Aikat, V. L. Pandit, A. D. Gupta, S. R. Pal, S. Sehgal, A. G. S. Pathania, P. N. Chhuttani, and D. V. Datta, *Indian J. Med. Res.*, 1979, **70**, 105.

<sup>58</sup> H. Takanashi, M. Umeda, and I. Hirono, *Mutat. Res.*, 1980, **78**, 67.

<sup>59</sup> I. Hirono, M. Haga, M. Fujii, S. Matsuura, N. Matsubara, M. Nakayama, T. Furuya, M. Hikichi, H. Takanashi, E. Uchida, S. Hosaka, and I. Ueno, *J. Natl. Cancer Inst.*, 1979, **63**, 469.

<sup>60</sup> A. Ligia de Paula Ramos and E. K. Marques, *Rev. Bras. Genet.*, 1978, **1**, 279 (*Chem. Abstr.*, 1979, **91**, 169 368).

<sup>61</sup> H. Yamanaka, M. Nagao, T. Sugimura, T. Furuya, A. Shirai, and T. Matsushima, *Mutat. Res.*, 1979, **68**, 211.

The *N*-oxide of indicine (49) exhibits anti-tumour activity in experimental tumour systems, without some of the toxic effects associated with other pyrrolizidine alkaloids. The *N*-oxides of echinatine and europine show similar anti-tumour activity against P 388 lymphocytic leukaemia tumours.<sup>23</sup> Indicine *N*-oxide is metabolized to the free base in rabbits and humans,<sup>62</sup> although the *N*-oxide is the more active anti-tumour agent. It has been suggested that the conversion of indicine *N*-oxide into indicine is not essential for its anti-tumour activity.<sup>63</sup> Indicine *N*-oxide is the first pyrrolizidine alkaloid to be tested as an anti-tumour agent in humans. The toxicity and pharmacokinetics of this compound have been studied in 29 patients with advanced cancers.<sup>64</sup> The major toxic effect was myelosuppression, but acute liver damage was not observed.

The toxic metabolites of pyrrolizidine alkaloids are pyrrole derivatives, produced in the liver by mixed-function oxidases. These derivatives are highly reactive alkylating agents, reacting with, e.g., thiol groups to form covalent bonds. It has been found that the toxicity of monocrotaline in rats can be attenuated by the use of inhibitors of liver microsomal mixed-function oxidases, but not by the addition of thiol compounds.<sup>65</sup> In a study of the effects on mouse skin of pyrrolic metabolites with other alkylating agents, no clear relationship could be established between carcinogenic activity and alkylating reactivity.<sup>66</sup> The anti-mitotic activity of dehydroretronecine (24) has been tested on rat liver parenchymal cells.<sup>67</sup>

The large-scale poisoning of broiler chickens in Victoria, Australia, in 1974, was caused by the use of feed that was contaminated by heliotrine and lasiocarpine. The source of the alkaloids in the commercial poultry feed was probably the seeds of *Heliotropium europaeum*, harvested with the wheat.<sup>68</sup> Sheep that were fed on dried *H. europaeum* showed a marked decline in clearance rates for bromosulphophthalein dye. Observation of these rates might be developed as a measure of the liver damage that is caused by ingestion of pyrrolizidine alkaloids.<sup>69</sup>

Collagen synthesis increased in the pulmonary arteries of rats which had been treated with monocrotaline.<sup>70</sup> Doronine has an hypotensive effect when administered to cats.<sup>71</sup> Senecionine and otosenine showed spasmolytic activity on the intestinal smooth muscles of mice.<sup>72</sup>

Some semi-synthetic quaternary pyrrolizidine derivatives have marked biological activities. Ganglion- and neuromuscular-blocking activities were

<sup>62</sup> G. Powis, M. M. Ames, and J. S. Kovach, *Cancer Res.*, 1979, **39**, 3564.

<sup>63</sup> G. Powis, M. M. Ames, and J. S. Kovach, *Res. Commun. Chem. Pathol. Pharmacol.*, 1979, **24**, 559.

<sup>64</sup> J. S. Kovach, M. M. Ames, G. Powis, C. G. Moertel, R. G. Hahn, and E. T. Creagan, *Cancer Res.*, 1979, **39**, 4540.

<sup>65</sup> D. Eisenstein, J. Azari, and R. Huxtable, *Proc. West. Pharmacol. Soc.*, 1979, **22**, 193.

<sup>66</sup> A. R. Mattocks and J. R. P. Cabral, *Tumori*, 1979, **65**, 289.

<sup>67</sup> A. R. Mattocks and R. F. Legg, *Chem.-Biol. Interactions*, 1980, **30**, 325.

<sup>68</sup> D. A. Pass, G. G. Hogg, R. G. Russell, J. A. Edgar, I. M. Tence, and L. Rikard-Bell, *Austr. Vet. J.*, 1979, **55**, 284.

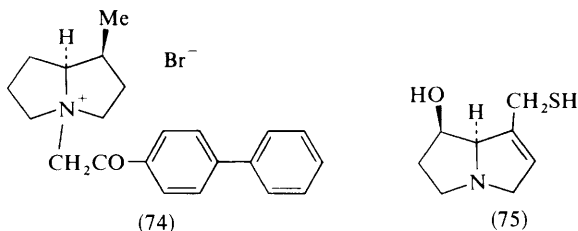
<sup>69</sup> G. W. Lanigan and J. F. Peterson, *Austr. Vet. J.*, 1979, **55**, 220.

<sup>70</sup> R. Kameji, H. Otsuka, and Y. Hayashi, *Experientia*, 1980, **36**, 441.

<sup>71</sup> D. Ya. Guseinov, P. A. Yuzbashinskaya, D. S. Khalikov, and K. T. Mamedova, *Azerb. Med. Zh.*, 1979, **56**, 21 (*Chem. Abstr.*, 1979, **91**, 151 460).

<sup>72</sup> M. T. Litvinchuk, R. I. Gaiduk, and V. I. Kit, *Farmakol. Toksikol. (Moscow)*, 1979, **42**, 509 (*Chem. Abstr.*, 1979, **91**, 168 596).

observed for nineteen of these derivatives.<sup>73</sup> The most potent member was bis-(1,10-heliotridanium)decane dibromide. The quaternary heliotridanium derivative (74) showed marked non-specific spasmolytic activity on intestinal smooth muscles.<sup>74</sup> A number of bisquaternary salts of pyrrolizidine alkaloids had growth-regulatory activity.<sup>75</sup> A series of quaternary compounds and diester derivatives of 9-thioretronecine (75) has been prepared. Some of these compounds display hypotensive activity.<sup>76</sup> The pharmacology of derivatives of 1-methylpyrrolizidine has been reviewed.<sup>77</sup>



<sup>73</sup> M. A. Siddiqi, K. A. Suri, O. P. Suri, and C. K. Atal, *Indian J. Pharm. Sci.*, 1979, **4**, 129.

<sup>74</sup> O. P. Gupta, G. B. Singh, and C. K. Atal, *Arzneim.-Forsch.*, 1979, **29**, 1715.

<sup>75</sup> C. S. Kadyrov, S. T. Akramov, K. M. Shakidoyatov, N. P. Abdullaev, and O. G. Patseva, *Khim. Priro. Soedin.*, 1979, 802 (*Chem. Abstr.*, 1980, **93**, 180 842).

<sup>76</sup> R. Manavalan, K. A. Suri, O. P. Suri, and C. K. Atal, *Indian J. Pharm. Sci.*, 1979, **4**, 131.

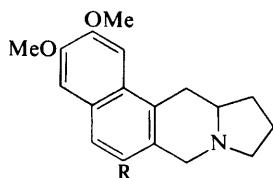
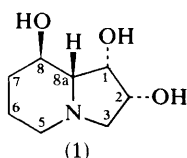
<sup>77</sup> F. S. Sadritdinov, *Farmakol. Priro. Soedin. Tashkent*, 1979, 29 (*Chem. Abstr.*, 1980, **93**, 18 681).

## Indolizidine Alkaloids

BY J. A. LAMBERTON

### 1 *Swainsona* Alkaloids

A detailed spectroscopic study has shown that swainsonine, from *Swainsona canescens* (Benth.) A. Lee, is 8 $\alpha$  $\beta$ -indolizidine-1 $\alpha$ ,2 $\alpha$ ,8 $\beta$ -triol (1), and the structure and relative configuration have been confirmed by X-ray crystallography.<sup>1</sup> Swainsonine is a potent inhibitor of  $\alpha$ -mannosidase, and in animals it produces an accumulation of mannose-rich oligosaccharides in the lysosomal system of cells, leading to organ dysfunction and clinical disease.<sup>1</sup>



(2) R = CH $\overset{Z}{=}$ CHCH(OH)Me

(3) R = Bu<sup>n</sup>

### 2 *Cynanchum* Alkaloids

*Cynanchum vincetoxicum* (L.) Pers. contains traces of an alkaloid vincetene, which shows an interesting relationship to the phenanthroindolizidines found in *Tylophora* and other genera of the Asclepiadaceae. Spectroscopic study has shown vincetene to be the benzopyrroloisoquinoline derivative (2), and this structure has been confirmed by synthesis of the racemic dihydro-desoxy-derivative (3).<sup>2</sup>

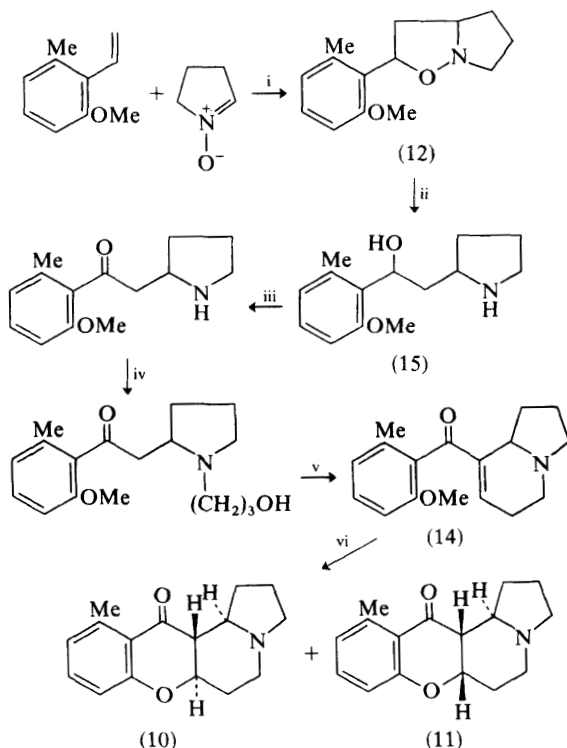
### 3 *Dendrobates* Alkaloids

Extracts from skins of the neotropical frog *Dendrobates tricolor* from Ecuador have given the alkaloid 8-hydroxy-6-(2-methylhexylidene)azabicyclo[4.3.0]nonane (4), the structure and absolute configuration of which have been determined by X-ray crystallography of the hydrochloride salt. This alkaloid is the first structurally defined member of the pumiliotoxin A class of dendrobatid alkaloids. Spectroscopic studies (m.s. and n.m.r.) have allowed the formulation of the

<sup>1</sup> S. M. Colegate, P. R. Dorling, and C. R. Huxtable, *Aust. J. Chem.* 1979, **32**, 2257.

<sup>2</sup> H. Budzikiewicz, L. Faber, E.-G. Herrmann, F. F. Perrollaz, U. P. Schlunegger, and W. Wiegreb, *Liebigs Ann. Chem.*, 1979, 1212.

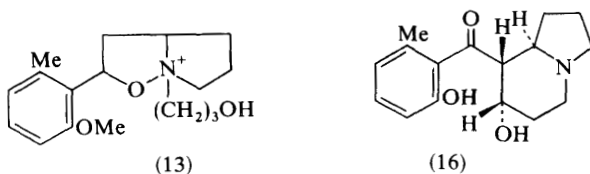


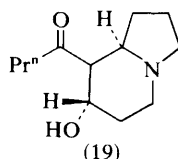
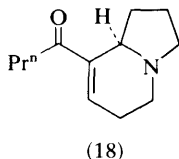
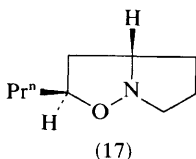


Reagents: i, PhMe, at 95 °C; ii,  $\text{H}_2$ -PtO<sub>2</sub>, EtOH; iii, Jones oxidation; iv,  $\text{Br}(\text{CH}_2)_3\text{OH}$ ,  $\text{CH}_2\text{Cl}_2$ ; v, KOBu<sup>t</sup>, Ph<sub>2</sub>CO, PhH, reflux; vi,  $\text{BBr}_3$

**Scheme 1**

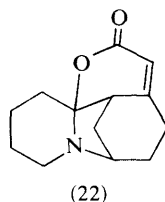
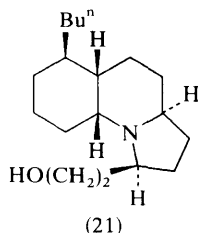
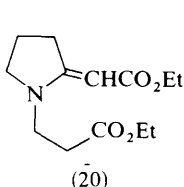
it can be extensively modified and varied. Optimum efficiency was achieved by alkylation of the isoxazolidine (12) with 3-bromo-1-propanol to give the quaternary salt (13), which on exposure to benzene containing potassium t-butyrate and benzophenone at reflux temperature produces (14) directly.<sup>6</sup> A sequence of reactions that starts with treatment of the intermediate (15) with acrolein leads to (±)-isoeleocarpine (16).<sup>6</sup> In a similar series of reactions, 1-pyrroline 1-oxide and 1-pentene are used to prepare the isoxazolidine (17), which is then converted (by several steps) into (±)-eleocanine A (18) and (±)-eleocanine C (19). The stereospecificity of the ring-closure that leads to (±)-eleocanine C has been discussed.<sup>7</sup>





An alternative and successful approach to the *Elaeocarpus* alkaloids has been based on use of the vinylogous urethane (20). This method has led to the synthesis of (±)-elaecarpine, (±)-isoelaecarpine, and the (±)-elaekanines A, B, and C.<sup>8</sup> The vinylogous urethane method has been extended to the synthesis of ipalbidine, which is the aglycon of the alkaloid ipalbine.<sup>9</sup>

The seco-phenanthroindolizidine alkaloid septicine has been synthesized by a nitron route. A cycloaddition of 1-pyrroline 1-oxide with 2,3-bis-(3,4-dimethoxyphenyl)butadiene gives two stereoisomeric isoxazolidines, one of which is converted into (±) septicine.<sup>10</sup> (±)-Tylophorine and  $\delta$ -coniceine have been prepared by a new route that makes use of an intramolecular imino-Diels-Alder reaction.<sup>11</sup> A stereoselective synthesis of 3,5-dialkyl-indolizidines has been applied to the synthesis of a stereoisomer of the trail pheromone of the Pharaoh ant and to a stereoisomer of gephyrotoxin 223.<sup>12</sup> A stereoselective total synthesis of (±)-perhydrogephyrotoxin (21)<sup>13</sup> and a simple synthesis of (±)-gephyran<sup>14</sup> have been reported.



## 5 General Studies

Carbon-13 n.m.r. assignments have been reported for a number of isomeric 3-butyl-5-methyloctahydroindolizines that were synthesized in studies of the trail pheromone of the Pharaoh ant, and for some closely related indolizidines. This work includes a detailed discussion of the preferred conformations of these compounds.<sup>15</sup> Securinegine, a minor alkaloid from *Securinega suffruticosa* Rehd., is isomeric with securinine, and the structure (22) has been proposed.<sup>16</sup>

<sup>8</sup> A. S. Howard, G. C. Gerrans, and C. A. Meerholz, *Tetrahedron Lett.*, 1980, **21**, 1373.

<sup>9</sup> A. S. Howard, G. C. Gerrans, and J. P. Michael, *J. Org. Chem.*, 1980, **45**, 1713.

<sup>10</sup> T. Iwashita, M. Suzuki, T. Kusumi, and H. Kakisawa, *Chem. Lett.*, 1980, 383.

<sup>11</sup> S. M. Weinreb, N. A. Khatri, and J. Shringarpure, *J. Am. Chem. Soc.*, 1979, **101**, 5073.

<sup>12</sup> T. L. Macdonald, *J. Org. Chem.*, 1980, **45**, 193.

<sup>13</sup> L. E. Overman and C. Fukaya, *J. Am. Chem. Soc.*, 1980, **102**, 1454.

<sup>14</sup> G. G. Habermehl and O. Thureau, *Naturwissenschaften*, 1980, **67**, 193.

<sup>15</sup> P. E. Sonnet, D. A. Netzel, and R. Mendoza, *J. Heterocycl. Chem.*, 1979, **16**, 1041.

<sup>16</sup> M. M. Shabana and A. A. Genenah, *Arch. Pharm. Chemi. Sci. Ed.*, 1979, **7**, 158.



Interest in the detection and isolation of quinolizidine alkaloids has been maintained, and Polish chemists have continued their conformational studies, but the highlights of the year are the syntheses of quinolizidine alkaloids of *Poranthera*<sup>1,2</sup> and a novel synthesis of azaphenalene alkaloids.<sup>3</sup>

### 1 The Lupinine–Cytisine–Sparteine–Matrine Group

**Occurrence.**—Table 1 records alkaloid isolations<sup>4–14</sup> and indicates that five new alkaloids have been obtained this year. A g.l.c.–m.s. examination of the alkaloids of *Lupinus polyphyllus*<sup>10</sup> resulted in the detection of two alkaloids not previously isolated from this species, but the presence of lupinine<sup>11</sup> was not confirmed; cell cultures gave much lower yields, and lupanine, the main alkaloid of the intact plant, was the only constituent identified.<sup>10</sup> Anagyrene, matrine, matrine *N*-oxide, sophocarpine *N*-oxide, and sophoranol were isolated by h.p.l.c. from the Chinese drug 'Sophorae radix',<sup>15</sup> which apparently differs in the content of these alkaloids from the root of the Japanese plant *Sophora flavescens*.

**Lupinine–Cytisine Group.**—An *X*-ray analysis of (–)-lupinine hydrochloride and of (+)-epilupinine shows that bond lengths and angles are similar to those of lupinine (*cf.* Vol. 10, p. 68).<sup>16</sup> Aminobenzoate esters of lupinine were prepared by transesterification reactions.<sup>17</sup>

<sup>1</sup> E. Gössinger, *Tetrahedron Lett.*, 1980, **21**, 2229.

<sup>2</sup> E. Gössinger, *Monatsh. Chem.*, 1980, **111**, 143.

<sup>3</sup> R. V. Stephens and A. W. M. Lee, *J. Am. Chem. Soc.*, 1979, **101**, 7032.

<sup>4</sup> Yu. K. Kushmuradov, S. Kuchkarov, and A. B. Mirzaabdullaev, *Khim. Pri. Soedin.*, 1979, 871 (*Chem. Abstr.*, 1980, **93**, 22 595).

<sup>5</sup> M. H. Radema, J. L. Van Eijk, W. Vermin, A. J. de Kok, and C. Romers, *Phytochemistry*, 1979, **18**, 2063.

<sup>6</sup> A. Daily and Kh. Dutschevska, *Planta Med.*, 1979, **36**, 188.

<sup>7</sup> G. M. Hatfield, W. J. Keller, and J. M. Rankin, *J. Nat. Prod.*, 1980, **43**, 164.

<sup>8</sup> A. D. Kinghorn and S. J. Smolenski, *Planta Med.*, 1980, **38**, 280.

<sup>9</sup> A. B. Beck, B. H. Goldspink, and J. R. Knox, *J. Nat. Prod.*, 1979, **42**, 385.

<sup>10</sup> M. Wink, L. Witte, H.-M. Schiebel, and T. Hartmann, *Planta Med.*, 1980, **38**, 238.

<sup>11</sup> E. M. Karlsson and H. W. Peter, *J. Chromatogr.*, 1978, **155**, 218.

<sup>12</sup> S. Kuchkarov and Yu. K. Kushmuradov, *Khim. Pri. Soedin.*, 1979, 413 (*Chem. Abstr.*, 1979, **91**, 189 799).

<sup>13</sup> K. J. Keller and G. M. Hatfield, *Phytochemistry*, 1979, **18**, 2068.

<sup>14</sup> J. Bourgeois, G. Faugeras, R. R. Paris, and J. F. Dobremez, *Plant. Med. Phytother.*, 1979, **13**, 87.

<sup>15</sup> N. Ota and Y. Mino, *Shoyakugaku Zasshi*, 1979, **33**, 140 (*Chem. Abstr.*, 1980, **92**, 169 114).

<sup>16</sup> A. E. Koziol, M. Gdaniec, and Z. Kosturkiewicz, *Acta Crystallogr., Sect. B*, 1980, **36**, 980.

<sup>17</sup> Kh. Khaitbaev, Sh. M. Gafurova, and A. I. Ishbaev, *Dokl. Akad. Nauk Uzb. SSR*, 1978, 41 (*Chem. Abstr.*, 1980, **92**, 59 055).

**Table 1** Isolation of alkaloids of the lupinine-cytisine-sparteine-matine group

Species	Alkaloid (Structure)	Ref.
<i>Ammodendron longiracemosum</i>	Ammodendrine	4
	Anagryne	
	Cytisine	
	Lupanine	
	N-methylcytisine	
	Pachycarpine	
<i>Calpurnia aurea</i> ssp. <i>sylvatica</i>	*Calpurmenine (7)	5
	*Calpurmenine ester	
	10,13-Dihydroxylupanine	
<i>Chamaecytisus austriacus</i>	Lupanine	6
	Lusitanine	
	17-Oxosparteine	
	Sparteine	
<i>Clathrotropis brachypetala</i>	*11-Allylcytisine (5)	7
	Anagryne	
	Cytisine	
	5,6-Dehydrolupanine	
	Lupanine	
	N-methylcytisine	
	Rhombifoline	
<i>Lupinus bicolor</i> ssp. <i>microphyllus</i>	*5,6-Dehydro- $\alpha$ -isolupanine (9)	8
	$\alpha$ -Isolupanine	
	Thermopsine	
<i>Lupinus cosentinii</i>	*Alkaloid (6a)	9
	Epilupanine esters	
	Epilupanine N-oxide esters	
	13-Hydroxymultiflorine esters	
<i>Lupinus polyphyllus</i>	13-Angeloyl-lupanine	10
	13-Cinnamoyl-lupanine	11
	Lupanine	10, 11
	Sparteine	
<i>Sophora alopecuroides</i> (cf. Vol. 9, p. 70)	N-Methylcytisine (5)	12
	Sophocarpine N-oxide	
<i>Sophora secundiflora</i> (cf. Vol. 7, p. 70)	*11-Allylcytisine	13
	$\beta$ -Isosparteine	
	Lupanine	
	Rhombifoline	
<i>Thermopsis barbata</i>	Cytisine	14
	Epilupanine	
	N-Formylcytisine	
	Lupanine	
	N-Methylcytisine	

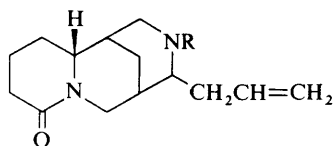
\* New alkaloids

There has been considerable interest recently in tricyclic quinolizidine alkaloids containing side-chains, for example angustifoline (1). The conformations of angustifoline and of its dihydro- and desoxy-derivatives have been studied by i.r. and n.m.r. spectroscopy and by X-ray analysis,<sup>18</sup> and rearrange-

<sup>18</sup> M. D. Bratek-Wiewiórska, *J. Mol. Struct.*, 1979, **55**, 69.

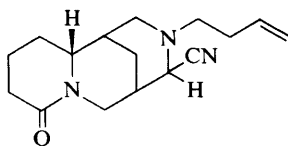
ments of angustifoline derivatives (*cf.* Vol. 10, p. 68) have been explored further. Thus, the cyanomethyl derivative (2) is converted into compound (3) in water.<sup>19</sup> The structure of albino (4) (originally called 'dehydroalbin') was established previously by X-ray crystallography of the perchlorate, and has been further defined by the same technique; rings A, B, and C are in half-chair, chair, and chair conformations, respectively, and the allyl group is axial.<sup>20</sup> Two new alkaloids of this type were isolated this year, namely 11-allylcytisine (5) from *Clathrotropis brachypetala*<sup>7</sup> and from the unripe fruit of *Sophora secundiflora*<sup>13</sup> and alkaloid (6a) from the leaves and seeds of *Lupinus cosentinii*.<sup>9</sup> The structure of 11-allylcytisine was established by i.r., <sup>1</sup>H n.m.r., and mass spectroscopy and by catalytic reduction to tetrahydrodeoxyangustifoline, *cf.* (1). Alkaloid (6a)

was shown by spectroscopic studies to contain  $\text{>NCH=CH}-\overset{\textstyle |}{\text{C}}=\text{O}$  and  $-\text{CH=CH}_2$  groups; the structure was assigned on the basis of catalytic reduction to compound (6b), which was identical with the reduction product of tetrahydro-rhombifoline.

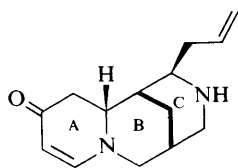


(1) R = H

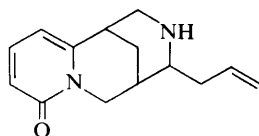
(2) R = CH<sub>2</sub>CN



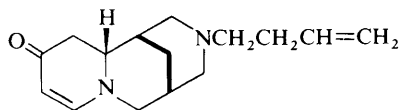
(3)



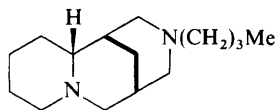
(4)



11-Allylcytisine (5)



(6a)

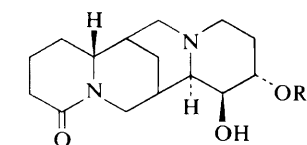


**Sparteine Group.**—The new alkaloids calpurmenine (7) and its 2-pyrroloyl derivative (8) and the known compound 10,13-dihydroxylupanine were isolated from the South African plant *Calpurnia aurea* ssp. *sylvatica* but were absent from the Ethiopian *C. aurea* ssp. *aurea*.<sup>5</sup> The structure of calpurmenine 12,13-dihydroxylupanine) was established by X-ray analysis of the ester (8).<sup>21</sup> Another new alkaloid, 5,6-dehydro- $\alpha$ -isolupanine (9) was shown by g.l.c.—

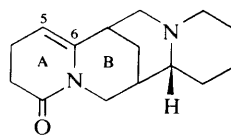
<sup>19</sup> M. D. Bratek-Wiewiórowska, U. Rychlewska, and M. Wiewiórski, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1469.

<sup>20</sup> A. Hoser, A. Katrusiak, Z. Kaluski, and J. Wolińska-Mocydlarz, *Acta Crystallogr., Sect. B*, 1980, **36**, 984.

<sup>21</sup> W. J. Vermin, A. J. de Kok, C. Romers, M. H. Radema, and J. L. van Eijk, *Acta Crystallogr., Sect. B*, 1979, **35**, 1839.



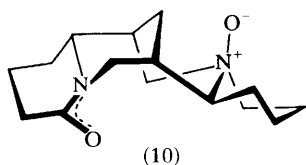
Calpurmenine (7) R = H  
(8) R = 2-pyrroloyl



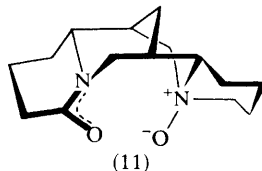
(9)

m.s. to be present in *Lupinus bicolor* but was not isolated; the absence of fragmentation peaks at  $m/z$  136 and 149 (found in  $\alpha$ -isolupanine) in the mass spectrum was attributed to inhibition of cleavage at the A-B ring junction by the presence of the 5,6-double-bond.<sup>8</sup>

The studies of Wiewiórowski and co-workers on the *N*-oxides of the sparteine group of alkaloids (cf. Vol. 9, p. 72) have been extended to *N*-oxides of lupanine,  $\alpha$ -isolupanine, 15-oxosparteine, and 17-oxosparteine.<sup>22</sup> The rigid cisoidal arrangement of lactam and *N*-oxide groups, for example in  $\alpha$ -isolupanine *N*-oxide (10), results in increased basicity compared to molecules such as lupanine *N*-oxide (11), with rigid transoidal geometry; significant differences in spectroscopic properties were also noted. When an equilibrium between two conformations is possible, as in the *N*-oxides of 15-oxo- and 17-oxo-sparteine, the data indicate that the cisoidal arrangement is favoured.



(10)



(11)

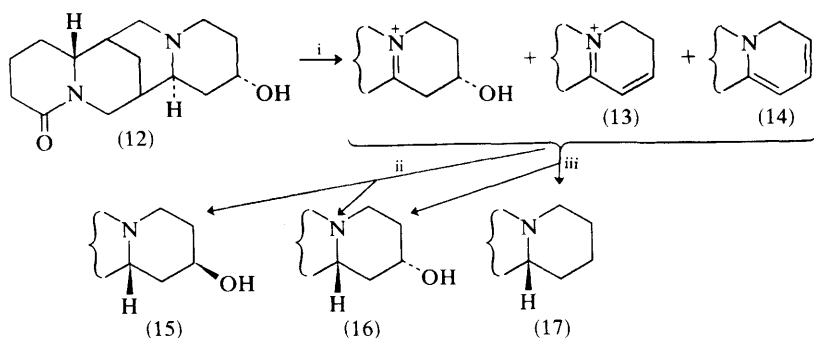
Wysocka<sup>23,24</sup> has examined reactions of 13-hydroxylupanine and related compounds. Thus, treatment of 13-hydroxylupanine (12) (axial OH) with mercuric acetate and then borohydride was reported previously to give 13-hydroxy- $\alpha$ -isolupanine (16) (axial OH), but a re-investigation (Scheme 1) shows that the product is an equimolecular mixture of compound (16) and its epimer (15) (equatorial OH); catalytic reduction in the presence of acid instead of the use of borohydride affords a mixture of compound (16) and  $\alpha$ -isolupanine (17). The results were rationalized by assuming the formation of dienes (13) and (14) from 13-hydroxylupanine; the presence of such species in the dehydrogenation mixture was supported by u.v. and c.d. measurements.<sup>24</sup>

The reaction of 13-hydroxysparteine with acetic anhydride in DMSO was shown earlier to give the inverted acetate (axial  $\rightarrow$  equatorial) instead of the expected ketone, and this has been confirmed. Application of the reaction to 3-hydroxylupanine (18) (axial OH) and to 13-*epi*-hydroxylupanine (19) (equatorial OH) gave the corresponding ketone (10% yield) and an approximately equimolecular mixture of epimeric acetate (20) in each case. The mechanism proposed (Scheme 2) indicates facile formation of a carbonium ion through transannular interactions.<sup>23</sup>

<sup>22</sup> M. Markiewicz and M. Wiewiórowski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 1979, **27**, 435.

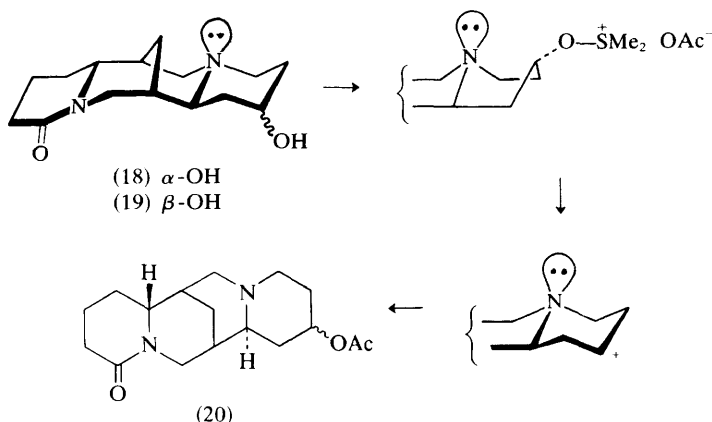
<sup>23</sup> W. Wysocka, *Pol. J. Chem.*, 1979, **53**, 1789.

<sup>24</sup> W. Wysocka, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 1979, **27**, 343.



Reagents: i,  $\text{Hg}(\text{OAc})_2$ , 5%  $\text{AcOH}$ , at  $60^\circ\text{C}$ ; ii,  $\text{NaBH}_4$ , aq.  $\text{MeOH}$ ; iii,  $\text{Pt}$ ,  $\text{H}_2$ , 2M- $\text{HCl}$

Scheme 1



Scheme 2

An earlier study of the catalytic reduction of 13-oxolupanine (*cf.* Vol. 8, p. 69) was interpreted in terms of intramolecular interaction between a protonated nitrogen atom and the carbonyl group at C-13. Direct evidence for this proposal has now been provided by c.d. data for a number of 13-oxosparteine derivatives, showing, for example, that ketone Cotton effects disappear in acid solution.<sup>25</sup>

**Matrine Group.**—X-Ray studies of matrine alkaloids have continued in Russia with the examination of sophoridine,<sup>26</sup> isosophoridine,<sup>27</sup> tetrahydro-neosophoramine,<sup>28</sup> and allomatrine and its *N*-oxide.<sup>29</sup> The mass spectra of

<sup>25</sup> W. Wysocka and J. Gawróński, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1948.

<sup>26</sup> B. T. Ibragimov, G. N. Tishchenko, Yu. K. Kushmuradov, T. F. Aripov, and A. S. Sadykov, *Khim. Pri. Soedin.*, 1979, 355 (*Chem. Abstr.*, 1980, **92**, 111 193).

<sup>27</sup> B. T. Ibragimov, S. A. Talipov, G. N. Tishchenko, Yu. K. Kushmuradov, and T. F. Aripov, *Khim. Pri. Soedin.*, 1979, 586 (*Chem. Abstr.*, 1980, **92**, 129 154).

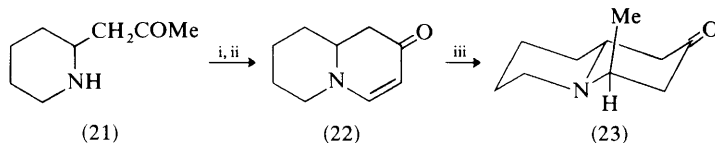
<sup>28</sup> B. T. Ibragimov, S. A. Talipov, G. N. Tishchenko, Yu. K. Kushmuradov, T. F. Aripov, and S. Kuchkarov, *Khim. Pri. Soedin.*, 1979, 588 (*Chem. Abstr.*, 1980, **92**, 147 012).

<sup>29</sup> B. T. Ibragimov, G. N. Tishchenko, Yu. K. Kushmuradov, T. F. Aripov, and A. S. Sadykov, *Khim. Pri. Soedin.*, 1979, 416 (*Chem. Abstr.*, 1980, **92**, 22 663).

sophoramine and its stereoisomers isosophoramine and neosophoramine indicate that metastable ions at  $m/z$  149 and 136 are characteristic of *trans*- and *cis*-A/B rings, respectively.<sup>30</sup>

## 2 Myrtine, Porantherilidine, and Porantheridine

An improved synthesis of myrtine (23) from ( $\pm$ )-pelletierine (21) has been reported (Scheme 3) (*cf.* Vol. 9, p. 71). Stereospecific addition of methylmagnesium iodide to the cyclic enaminone (22) gave ( $\pm$ )-myrtine, which was converted into natural (+)-myrtine by resolution with (–)-tartaric acid.<sup>31</sup>



Reagents: i,  $\text{AcOCH}_3$ , pyridine; ii,  $\text{Al}(\text{O}i\text{Bu})_3$ , PhMe, reflux; iii, MeMgI, PhH

**Scheme 3**

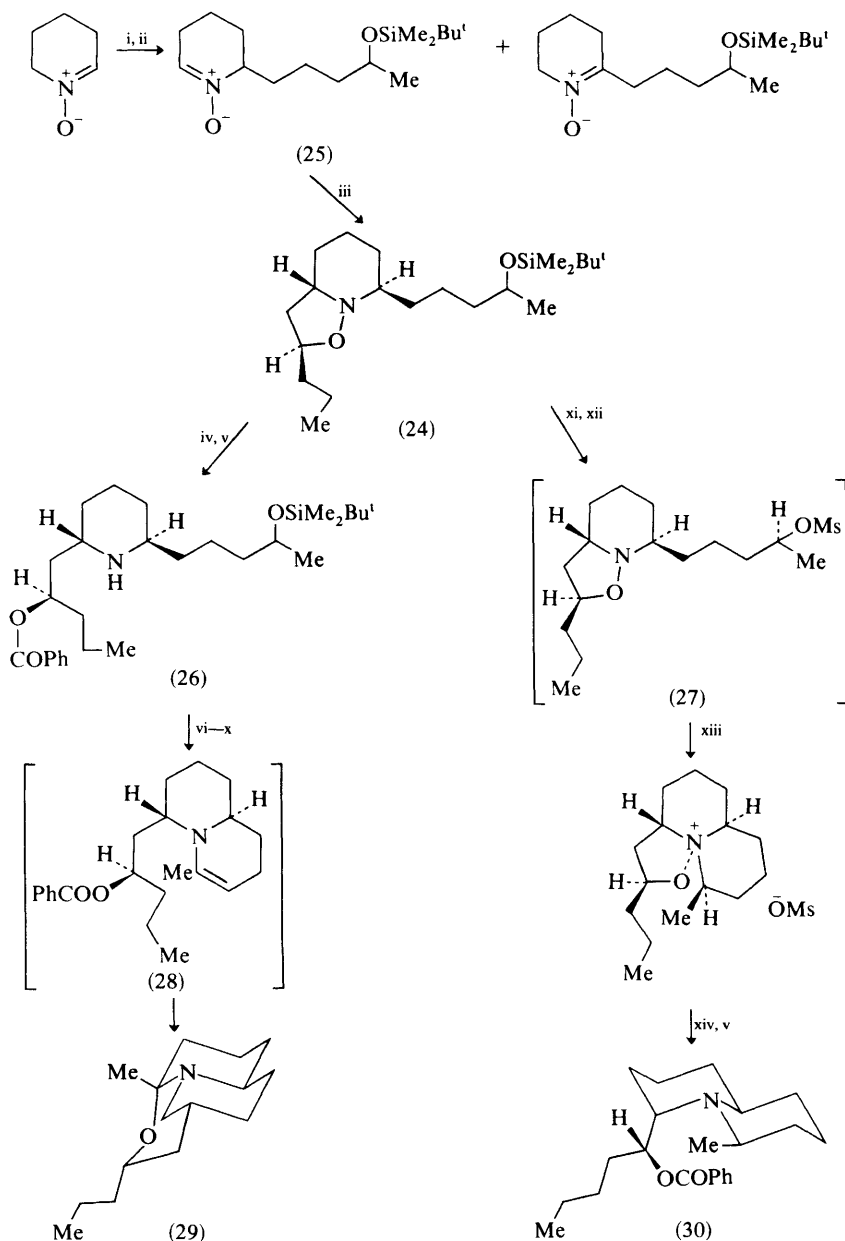
The structures of the alkaloids of *Poranthera corymbosa* were determined some years ago (*cf.* Vol. 5, p. 284 and Vol. 6, p. 100) and a tetracyclic azaphenalene member of the group, porantherine, was synthesized (*cf.* Vol. 6, p. 100). The synthesis of two more *Poranthera* alkaloids, the tricyclic porantheridine (29) and the quinolizidine derivative porantherilidine (30), has now been described by Gössinger<sup>1,2</sup> (Scheme 4). Each alkaloid contains three chiral centres in the quinolizidine ring and one in the  $\text{C}_5$  side-chain, and stereochemical control in the synthesis of both alkaloids was attained by preparation of the common intermediate (24) as a mixture of diastereoisomers. This *trans*-2,6-disubstituted piperidine derivative was prepared by the reaction of an alkene with a 6-substituted 1-piperidine *N*-oxide (25), resulting in *exo*-1,3-dipolar addition. Reductive cleavage of the isoxazolidine ring followed by inversion at a chiral centre gave the benzoate (26). The synthesis of porantheridine (29) was completed by hydrolysis of the silyl group, oxidation to a ketone, stereoselective formation of a quinolizidine derivative (28), and then intramolecular addition of a hydroxyl group to the enamine function.<sup>1</sup> The mesylate (27), prepared from compound (24) by removal of the silyl group, mesylation, and separation of stereoisomers, was converted into porantherilidine (30) by a method similar to that used for the synthesis of porantheridine.<sup>2</sup>

## 3 9b-Azaphenalene Alkaloids

9b-Azaphenalene alkaloids isolated from ladybird beetles were synthesized by Ayer and co-workers (*cf.* Vol. 7, p. 79) and by Mueller and Thompson (*cf.* Vol.

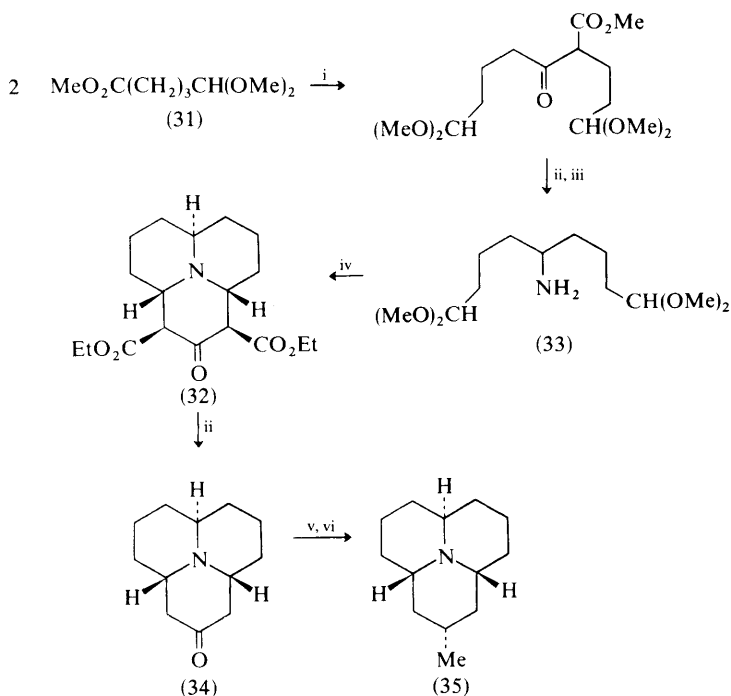
<sup>30</sup> Yu. K. Kushmuradov, F. Sh. Eshbaev, A. K. Kasymov, and S. Kuchkarov, *Khim. Prirod. Soedin.*, 1979, 353 (*Chem. Abstr.*, 1980, **92**, 147 008).

<sup>31</sup> P. Slosse and G. Hootelé, *Tetrahedron Lett.*, 1979, 4587.



Reagents: i,  $\text{ClMg}(\text{CH}_2)_3\text{CH}(\text{Me})\text{SiMe}_2\text{Bu}^t$ , ether; ii,  $\text{HgO}$ ,  $\text{CHCl}_3$ , at  $45^\circ\text{C}$ ; iii,  $\text{Me}(\text{CH}_2)_2\text{CH}=\text{CH}_2$ , at  $48^\circ\text{C}$ ; iv,  $\text{H}_2$ , Raney nickel; v,  $\text{PhCO}_2\text{H}$ ,  $\text{Ph}_3\text{P}$ ,  $\text{EtO}_2\text{CN}=\text{NCO}_2\text{Et}$ , THF; vi, 10% aq.  $\text{HCl}$ ; vii, Jones oxidation; viii, aq.  $\text{Na}_2\text{CO}_3$ , at  $0^\circ\text{C}$ ; ix,  $\text{KOH}$ ,  $\text{MeOH}$ ; x,  $\text{H}_2\text{O}$ ; xi,  $\text{Bu}_4\text{NF}$ , THF, at  $45^\circ\text{C}$ ; xii,  $\text{MsCl}$ , pyridine; xiii, heat at  $70^\circ\text{C}$ ; xiv,  $\text{LiAlH}_4$ , THF

Scheme 4



Reagents: i, NaH, DME; ii, NaCl, wet DMF, reflux; iii,  $\text{NH}_4\text{OAc}$ ,  $\text{NaCNBH}_3$ , 3A molecular sieves; iv, HCl to pH 1, then to pH 5.5, then  $(\text{MeO}_2\text{CCH})_2\text{CO}$ ; v,  $\text{Ph}_3\text{P}=\text{CH}_2$ , ether; vi, Pd/C,  $\text{H}_2$ , MeOH

**Scheme 5**

10, p. 72), and a third route has been reported by Stephens and Lee<sup>3</sup> (Scheme 5). The amine (33), prepared in three stages from acetal (31), was cyclized by means of a Robinson–Schöpf reaction with acetonedicarboxylic ester. A single stereoisomer (32) precipitated, and this was converted into precoccinelline (35) *via* the ketone (34) that featured in both earlier syntheses of the alkaloid. The publication includes an illuminating discussion of the defensive substances of ladybird beetles and an analysis of the stereochemical problems associated with the synthesis of the alkaloids.



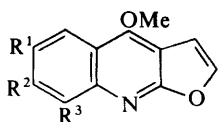
# Quinoline, Quinazoline, and Acridone Alkaloids

BY M. F. GRUNDON

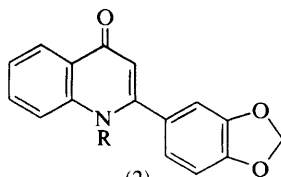
## 1 Quinoline Alkaloids

New alkaloids and alkaloids of known structure that have been obtained from new sources are listed in Table 1.<sup>1-14</sup>

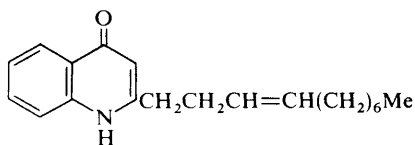
**Non-hemiterpenoid Quinolines.**—A re-examination of the alkaloids of *Haplophyllum dubium* resulted in the isolation of two members of the 2-aryl-4-quinolone group, *i.e.* graveoline (2; R = Me) and the new alkaloid norgraveoline (2; R = H).<sup>5</sup> A new bacterial pseudan (3) has been obtained from *Pseudomonas aeruginosa*.<sup>8</sup>



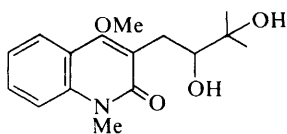
(1)



(2)



(3)



(4)

<sup>1</sup> D. L. Dreyer, *Phytochemistry*, 1980, **19**, 941.

<sup>2</sup> F. Tilleguin, M. Koch, and T. Sevenet, *Plant. Med. Phytother*, 1980, **14**, 4.

<sup>3</sup> I. H. Bowen, K. P. W. C. Perera, and J. R. Lewis, *Phytochemistry*, 1980, **19**, 1566.

<sup>4</sup> K. Rastogi, R. S. Kapil, and S. P. Popli, *Phytochemistry*, 1980, **19**, 945.

<sup>5</sup> D. M. Razakova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1979, 810 (*Chem. Abstr.*, 1980, **93**, 22 586).

<sup>6</sup> Kh. A. Abdullaeva, I. A. Bessonova, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1979, 873 (*Chem. Abstr.*, 1980, **93**, 41 504).

<sup>7</sup> T. Yajima, N. Kato, and K. Munakata, *Agric. Biol. Chem.*, 1977, **41**, 1263.

<sup>8</sup> H. Budzikiewicz, U. Schaller, H. Korth, and G. Pulverer, *Monatsh. Chem.*, 1979, **110**, 947.

<sup>9</sup> I. Mester, J. Reisch, K. Szendrei, and J. Körösi, *Liebigs Ann. Chem.* 1979, 1785.

<sup>10</sup> P. N. Sharma, A. Shueb, R. S. Kapil, and S. P. Popli, *Indian J. Chem., Sect. B*, 1979, **17**, 299.

<sup>11</sup> J. F. Ayafor, B. L. Sondengam, and B. Ngadjui, *Tetrahedron Lett.*, 1980, **21**, 3293.

<sup>12</sup> D. L. Dreyer and R. C. Brenner, *Phytochemistry*, 1980, **19**, 935.

<sup>13</sup> J. A. Swinehart and F. R. Stermitz, *Phytochemistry*, 1980, **19**, 1219.

<sup>14</sup> F. R. Stermitz, M. A. Caolo, and J. A. Swinehart, *Phytochemistry*, 1980, **19**, 1469.

**Table 1** Isolation of quinoline alkaloids

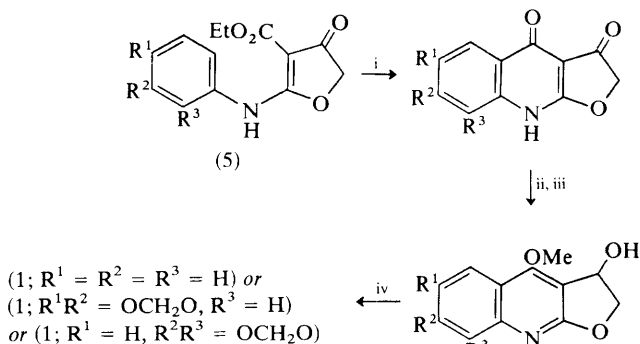
Species	Alkaloid (Structure)	Ref.
<i>Esenbeckia flava</i>	Dictamnine (1; $R^1 = R^2 = R^3 = H$ )	1
	Evolitrine (1; $R^1 = R^3 = H, R^2 = OMe$ )	
	Flindersiamine (1; $R^1R^2 = OCH_2O, R^3 = OMe$ )	
	Maculosidine (1; $R^1 = R^3 = OMe, R^2 = H$ )	
	Skimmianine (1; $R^1 = H, R^2 = R^3 = OMe$ )	
	*Alkaloid (11)	
<i>E. litoralis</i>	Dictamnine	1
	Evolitrine	
	Kokusaginine (1; $R^1 = R^2 = OMe, R^3 = H$ )	
	Maculine (1; $R^1R^2 = OCH_2O, R^3 = H$ )	
	Skimmianine	
<i>Flindersia fournieri</i>	Dictamnine	2
	$\gamma$ -Fagarine (1; $R^1 = R^2 = H, R^3 = OMe$ )	
	Skimmianine	
<i>Glycosmis bilocularis</i>	Dictamnine	3
<i>G. mauritiana</i>	Dictamnine	4
	Skimmianine	
	*Alkaloid (6; $R^1 = H, R^2 = OMe$ )	
<i>Haplophyllum dubium</i>	$\gamma$ -Fagarine	5
	Graveoline (2; $R = Me$ )	
	*Norgraveoline (2; $R = H$ )	
<i>H. perforatum</i>	*Glycohaplopine (1; $R^1 = H, R^2 = O$ -glucosyl, $R^3 = OMe$ )	6
<i>Orixa japonica</i>	Evoxine [1; $R^1 = H, R^2 = OCH_2CH(OH)-C(OH)Me_2, R^3 = OMe$ ]	7
<i>Pseudomonas aeruginosa</i>	2-(Undec-3-enyl)-4-quinolone (3)	8
<i>Ptelea trifoliata</i>	*Pteledimeridine (16)	9
<i>Toddalia asiatica</i>	$\gamma$ -Fagarine	10
	Skimmianine	
<i>Vepris louisii</i>	*N-methylpreskimmianine (6; $R^1 = R^2 = OMe$ )	11
	*Veprisine (10)	
<i>Zanthoxylum caribaeum</i>	Skimmianine	12
<i>Z. culantrillo</i>	Skimmianine (trace)	13
<i>Z. fagara</i>	Skimmianine	12
<i>Z. limoncillo</i>		
<i>Z. williamsii</i>	Edulinine (4)	14
	Skimmianine	

\* New alkaloids

**Furoquinoline Alkaloids.**—Glycohaplopine (1;  $R^1 = H, R^2 = O$ -glucosyl,  $R^3 = OMe$ ), a new alkaloid isolated from *Haplophyllum perforatum*, is believed to contain a  $\beta$ -glycosidic link.<sup>6</sup>

The identification of kokusagine (1;  $R^1 = H, R^2R^3 = OCH_2O$ ) and evoxine [1;  $R^1 = H, R^2 = OCH_2CH(OH)C(OH)Me_2, R^3 = OMe$ ] as minor insect anti-feedants that are present in the leaves of *Orixa japonica*<sup>7</sup> stimulated additional synthetic work. The Tuppy–Böhm procedure for the synthesis of furoquinolines

from anilino-4-oxodihydrofuran-3-carboxylates (5), as modified by Pai, was applied to dictamnine, maculine, and kokusagine (Scheme 1).<sup>15</sup> An efficient synthesis of kogusagine (1;  $R^1 = R^2 = \text{OMe}$ ,  $R^3 = \text{H}$ ) (13% overall yield from 2,4,6,7-tetramethoxyquinoline) was carried out by the lithiation-formylation-Wittig-reaction method (cf. Vol. 5, p. 107).<sup>16</sup>



Reagents: i, paraffin oil, at 250 °C; ii,  $\text{CH}_2\text{N}_2$ ; iii,  $\text{NaBH}_4$ ; iv,  $\text{KHSO}_4$ , THF

Scheme 1

**3-Prenyl-quinolones and Related Tricyclic Alkaloids.**—The 1-methyl-3-prenyl-2-quinolone (6;  $R^1 = \text{H}$ ,  $R^2 = \text{OMe}$ ), already known as a synthetic compound, has been isolated from the roots of *Glycosmis mauritiana*; it is converted into a mixture of the dihydropyrano-quinolones (8;  $R^1 = \text{H}$ ,  $R^2 = \text{OMe}$ ) and (9;  $R^1 = \text{H}$ ,  $R^2 = \text{OMe}$ ) by formic acid (Scheme 2).<sup>4</sup> A new 1-methyl-3-prenyl-2-quinolone, *N*-methylpreskimmianine (6;  $R^1 = R^2 = \text{OMe}$ ), was obtained from the stem bark of *Vepris louisii*; its structure was established by spectroscopy and by its preparation from preskimmianine (7) (Scheme 2).<sup>11</sup> A second new alkaloid of *Vepris louisii*, named veprisine, was shown by spectroscopic studies and by its synthesis from *N*-methylpreskimmianine to be the pyrano-quinolone (10) (Scheme 2).<sup>11</sup> Five furoquinoline alkaloids were found in the wood of *Esenbeckia flava* (see Table 1) and a non-crystalline bisprenyl compound (11) was also isolated from this source; the new alkaloid, which was first obtained as a synthetic compound,<sup>17</sup> is readily converted into the dihydropyrano-4-quinolone (9;  $R^1 = R^2 = \text{H}$ ) (Scheme 2).<sup>1</sup>

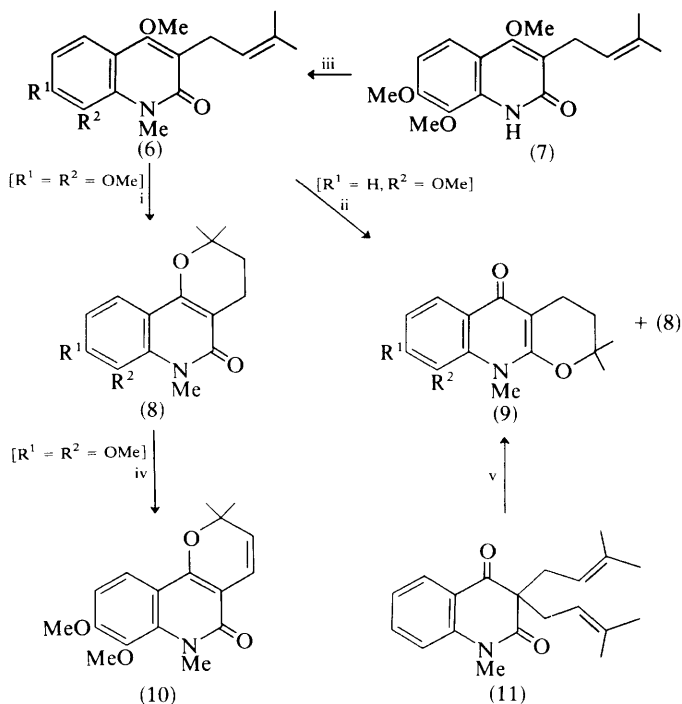
A new approach to the synthesis of 4-alkoxy-1-methyl-2-quinolones has been described (Scheme 3).<sup>18</sup> Irradiation of 4-alkoxy-2-methylquinoline 1-oxides (12) (prepared from 2-methyl-4-nitroquinoline 1-oxide) results in photo-rearrangement to give the 2-quinolones (13) as major products; a mechanism (Scheme 3) has been proposed. The alkaloids (13;  $R = \text{Me}$ ) and ravenine (13;  $R = \text{CH}_2\text{CH}=\text{CMe}_2$ ), which have been synthesized by other means, were prepared in this way.

<sup>15</sup> T. Yazima and K. Munakata, *Agric. Biol. Chem.*, 1980, **44**, 235.

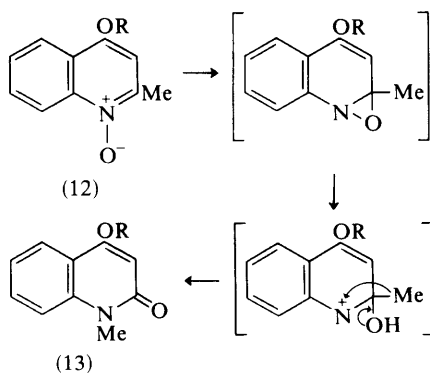
<sup>16</sup> N. S. Narasimhan, R. S. Mali, and A. M. Gokhale, *Indian J. Chem., Sect. B*, 1979, **18**, 115.

<sup>17</sup> T. R. Chamberlain and M. F. Grundon, *J. Chem. Soc. (C)*, 1971, 910.

<sup>18</sup> C. Kaneko, T. Naito, M. Hashiba, H. Fujii, and M. Somei, *Chem. Pharm. Bull.*, 1979, **27**, 1813.



Scheme 2

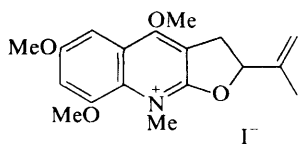


Reagents: *hν*, in MeOH

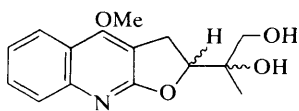
Scheme 3

A full account has been published of the synthesis of *O*-methylptelefolonium iodide (14) (*cf.* Vol. 9, p. 84) and of (±)-dubinidine (15) (*cf.* Vol. 3, p. 107); only a single diastereoisomer of dubinidine was obtained in the synthesis.<sup>19</sup>

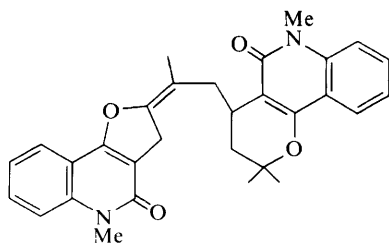
<sup>19</sup> J. L. Gaston, M. F. Grundon, and K. J. James, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1136.



(14)



(15)

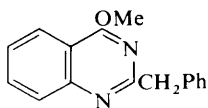


Pteledimeridine (16)

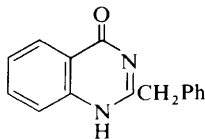
The first 'dimeric' quinoline alkaloid, pteledimerine, was isolated recently from the root bark of *Ptelea trifoliata* (cf. Vol. 10, p. 80). Several related compounds have now been found in the same species, and the structure of one of them, pteledimeridine (16), was elucidated mainly by means of  $^1\text{H}$  n.m.r. and mass spectroscopy.<sup>9</sup> The two dimeric alkaloids are isomeric and differ only in the nature of the furoquinolone portion, which has angular annelation (2-quinolone) in pteledimeridine and linear annelation (4-quinolone) in pteledimerine.

## 2 Quinazoline Alkaloids

The investigation of the constituents of *Glycosmis arborea* continues (cf. Vol. 9, p. 85; Vol. 10, p. 80) with the isolation of the new alkaloid glycophymline (17); the structure was established by spectroscopy and by its formation by methylation of glycophyimine (18).<sup>20</sup>



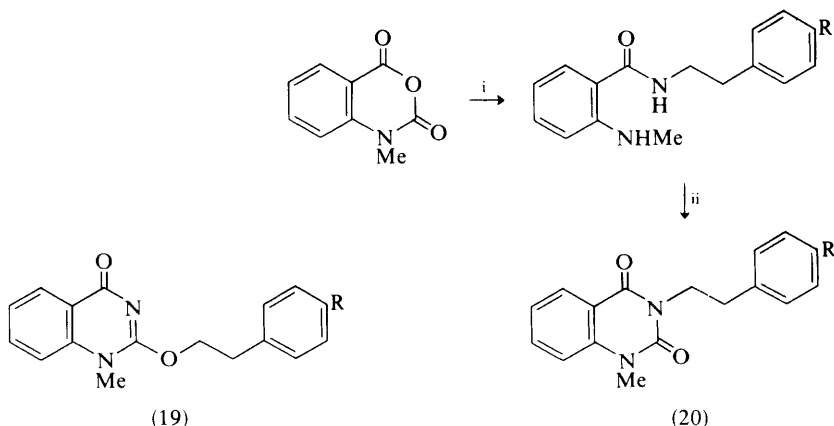
Glycophymline (17)



(18)

Two new quinazoline alkaloids of unusual structure were obtained from the seed husks of *Zanthoxylum arborescens*.<sup>12</sup> Infrared,  $^1\text{H}$  n.m.r., and mass spectroscopy showed that the major alkaloid was a quinazolone containing a phenethyl substituent. The  $^{13}\text{C}$  n.m.r. spectrum indicated that an *N*-methyl rather than an *O*-methyl group was present, but the spectroscopic studies did not distinguish between structures (19;  $\text{R} = \text{H}$ ) and (20;  $\text{R} = \text{H}$ ). The alkaloid was shown to be the *N*-phenethyl derivative (20;  $\text{R} = \text{H}$ ) by synthesis (Scheme 4), and a minor

<sup>20</sup> M. Sarker and D. P. Chakraborty, *Phytochemistry*, 1979, **18**, 694.

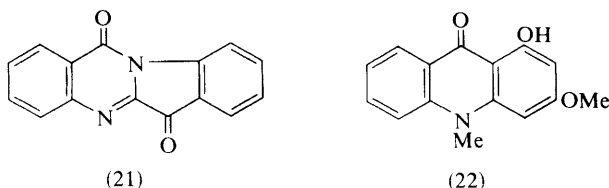


Reagents: i,  $p\text{-RC}_6\text{H}_4(\text{CH}_2)_2\text{NH}_2$  (R = H or OMe), dioxan, at  $100^\circ\text{C}$ ; ii,  $\text{ClCO}_2\text{Me}$ , aq.  $\text{Na}_2\text{CO}_3$

**Scheme 4**

constituent of *Z. arborescens* was identified by synthesis (Scheme 4) as the methoxy-analogue (20; R = OMe).

The antibiotic tryptanthrin (21), originally isolated from a micro-organism (*Candida lipolytica*),<sup>21</sup> has now been obtained from a higher plant, *Strobilanthes cusia*.<sup>22</sup>



Vaccine and some of its analogues have been synthesized from *o*-aminobenzaldehydes and 4-amino-2-hydroxybutanal,<sup>23</sup> and a series of arborine derivatives has also been prepared.<sup>24</sup>

### 3 Acridone Alkaloids

1-Hydroxy-3-methoxy-*N*-methylacridone (22), previously detected as a constituent of *Ruta graveolens* (cf. Vol. 8, p. 84), has been found in the bark of *Esenbeckia littoralis* and prepared by methylation of 1,3-dihydroxy-*N*-methylacridone.<sup>1</sup>

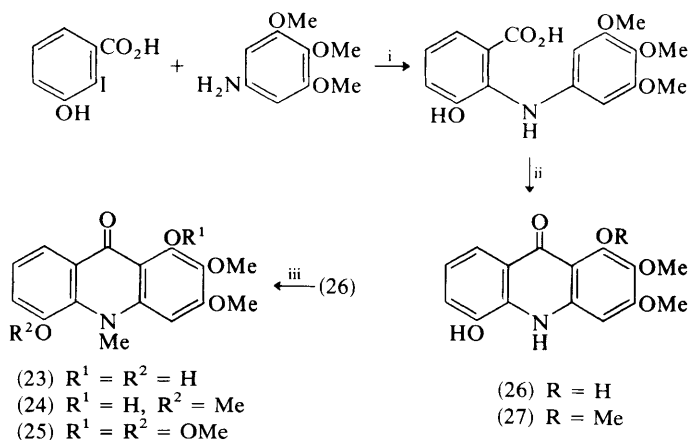
The structures of 5-hydroxyarborinine (23), a constituent of *Glycosmis bilocularis* (cf. Vol. 10, p. 82), and its mono- and di-methylation products [(24) and (25), respectively] were confirmed by synthesis (Scheme 5); a mixture of

<sup>21</sup> M. Brufani, W. Fedeli, F. Mazza, A. Gerhard, and W. Keller-Schierlein, *Experientia*, 1971, **27**, 1249.

<sup>22</sup> G. Honda and M. Tabata, *Planta Med.*, 1979, **36**, 85.

<sup>23</sup> R. L. Sharma, R. K. Gupta, B. K. Chowdhury, K. L. Dhar, and C. K. Atal, *Indian J. Chem., Sect. B*, 1979, **18**, 449.

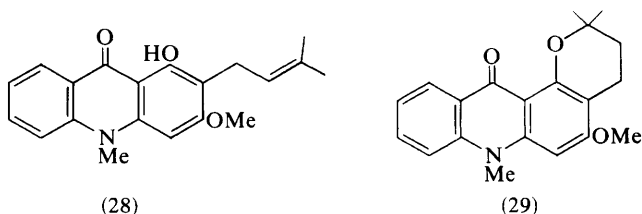
<sup>24</sup> N. R. Naik, A. F. Amin, and S. R. Patel, *J. Indian Chem. Soc.*, 1979, **56**, 708.



Reagents: i, Cu,  $Me_2CH(CH_2)_2OH$ , reflux; ii, conc.  $H_2SO_4$ , at  $100^\circ C$ ; iii, MeI,  $Me_2CO$ ,  $K_2CO_3$

**Scheme 5**

acridones (26) and (27) was obtained and the methylation of each component was studied.<sup>3</sup>



In addition to quinoline alkaloids (see Table 1), *Glycosmis mauritiana* contains 5-hydroxy-2,3-dimethoxy-*N*-methylacridone (arborinine) and a new prenyl-acridone (28).<sup>4</sup> The structure of the latter alkaloid was indicated by spectroscopy, by the presence of a *peri*-hydroxyl group, and by heating it with formic acid to give the cyclization product (29), thus showing that the prenyl group was at C-2, *i.e.* adjacent to the hydroxyl group, rather than at C-4. An unexpected by-product of the reaction with formic acid was the acridone (22).

## $\beta$ -Phenylethylamines and the Isoquinoline Alkaloids

BY K. W. BENTLEY

### 1 $\beta$ -Phenylethylamines

Mescaline has been synthesized in 42% overall yield in five steps from 2,6-dimethoxyphenol.<sup>1</sup> Analogues of mescaline with the NH<sub>2</sub> group replaced by a pyrrolidine, a piperidine, a morpholine, and a *N*-methylpiperazine group have been prepared from 3,4,5-trimethoxybenzyl chloride.<sup>2</sup> A process for the determination of mescaline in plasma by g.l.c.-mass spectrometry has been described,<sup>3</sup> and behavioural effects of the alkaloid have been studied.<sup>4-11</sup>

### 2 Isoquinolines

Corypalline, noroxyhydrastinine, and 1,2-dihydro-6,7-methylenedioxy-1-oxoisoquinoline have been isolated from *Thalictrum rugosum*.<sup>12</sup> The glucosidic alkaloid pterocereine (1; R = C<sub>6</sub>H<sub>11</sub>O<sub>5</sub>) has been isolated from the Mexican cactus *Pterocereus gaumeri*; it is hydrolysed by  $\beta$ -glucosidase and by acid to the phenol (1; R = H), the structure of which was determined by spectroscopic analysis.<sup>13</sup> *O*-Methylcorypalline (3; R = Me) has been synthesized from the isochromanone (2; R = Me) by ring-opening with hydrobromic acid followed by treatment with methylamine and reduction of the resulting amide;<sup>14</sup> the same route, starting from the benzyloxy-compound (2; R = PhCH<sub>2</sub>), afforded corypalline (3; R = H).<sup>15</sup> 3-Methyldoryamine (4; R<sup>1</sup>R<sup>2</sup> = CH<sub>2</sub>, R<sup>3</sup> = H) and 3-methylthalactamine (4; R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = OMe) have been synthesized from methylenedioxy- and trimethoxy-homophthalic acid respectively, by successive

<sup>1</sup> M. N. Aboul-Enein and A. I. Eid, *Acta Pharm. Suec.*, 1979, **16**, 267.

<sup>2</sup> A. M. Kardy, Y. A. Ibrahim, K. M. Ghoneim, and M. Khalifa, *Pharmazie*, 1979, **34**, 229.

<sup>3</sup> C. van Peteghem, A. Heyndrickx, and W. van Zele, *J. Pharm. Sci.*, 1980, **69**, 118.

<sup>4</sup> M. A. Geyer, G. J. Rose, and L. R. Petersen, *Pharmacol. Biochem. Behav.*, 1979, **10**, 293.

<sup>5</sup> C. Castellano, *Psychopharmacology (Berlin)*, 1979, **62**, 35.

<sup>6</sup> R. A. Glennon, L. B. Kier, and A. T. Shulgin, *Biochem. Biophys. Res. Commun.*, 1979, **89**, 233.

<sup>7</sup> W. H. Bridger, G. A. Barr, J. L. Gibbons, and G. T. Schimmel, *Dev. Psychiatry, Sect. A*, 1978, **2**, 170.

<sup>8</sup> L. Altomani, *Boll. Soc. Ital. Biol. Sper.*, 1979, **55**, 956.

<sup>9</sup> G. K. Aghajanian, *Brain Res.*, 1980, **186**, 492.

<sup>10</sup> R. J. Sbordone, J. A. Wingard, D. A. Gorelick, and M. L. Elliott, *Psychopharmacology (Berlin)*, 1979, **66**, 275.

<sup>11</sup> N. S. Shah, S. D. Hurdnall, D. May, D. Eargle, and J. Yates, *Biol. Psychiatry*, 1979, **14**, 587.

<sup>12</sup> W.-N. Wu, J. L. Beal, and R. W. Doskotch, *J. Nat. Prod.*, 1980, **43**, 143.

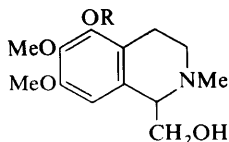
<sup>13</sup> Y. A. H. Mohamed, C. J. Chang, and J. L. McLaughlin, *J. Nat. Prod.*, 1979, **42**, 197.

<sup>14</sup> G. D. Pandey and K. P. Tiwari, *Pol. J. Chem.*, 1979, **53**, 2159.

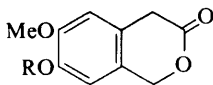
<sup>15</sup> G. D. Pandey and K. P. Tiwari, *Indian J. Chem., Sect. B*, 1979, **18**, 544.



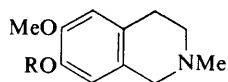
treatment with acetic anhydride and methylamine.<sup>16</sup> The 3-methyl group can be smoothly oxidized to formyl and then to carboxyl, and then decarboxylation of the acids gives doryamine (5) and thalactamine (6).



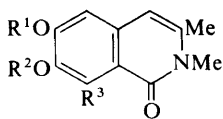
(1)



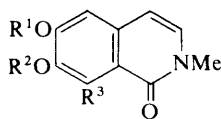
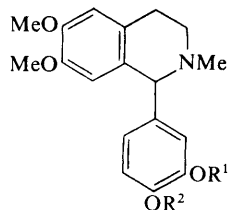
(2)



(3)



(4)

(5)  $R^1R^2 = CH_2, R^3 = H$ (6)  $R^1 = R^2 = Me, R^3 = OMe$ (7)  $R^1R^2 = CH_2$ (8)  $R^1 = R^2 = Me$ 

Hydrocotarnine has been demethylated to 8-hydroxy-6,7-methylenedioxy-2-methyltetrahydroisoquinoline by trimethylsilyl iodide in refluxing *o*-dichlorobenzene.<sup>17</sup> The effects of salsolinol on endogenous catecholamines<sup>18</sup> and on opiate receptors in guinea-pig ileum<sup>19</sup> and its opiate-receptor-binding and analgesic effects<sup>20</sup> have been studied.

The 1-phenyltetrahydroisoquinolines cryptostyline I (7) and cryptostyline II (8) have been synthesized by the condensation of 3,4-dimethoxyphenylethylamine with piperonal and veratric aldehyde respectively, followed by treatment with ethyl chloroformate and reduction with lithium aluminium hydride.<sup>21</sup>

From *Cynanchum vincetoxicum* (L.) Pers., a new base, vincetene, which is a benzopyrroloisoquinoline, has been isolated.<sup>22</sup>

### 3 Benzylisoquinolines

(+)-*O*-Methylarmepavine has been found in *Annona squamosa*.<sup>23</sup> Reticuline and its *N*-oxide (a new natural product) have been isolated from *Pachygone ovata*<sup>24</sup> and another new base, the quaternary hydroxide zanoxyline, has been isolated from the stem bark of *Zanthoxylum oxyphyllum*, its structure being

<sup>16</sup> U. C. Mashelkar and R. N. Usgaonkar, *Indian J. Chem., Sect. B*, 1979, **18**, 301.

<sup>17</sup> J. Minamikawa and A. Brossi, *Can. J. Chem.*, 1979, **57**, 1720.

<sup>18</sup> M. A. Collins, J. J. Hannigan, and C. Weiner, *Curr. Alcohol.*, 1979, **5**, 53.

<sup>19</sup> M. G. Hamilton, M. Hurst, and K. Blum, *Life Sci.*, 1979, **25**, 2205.

<sup>20</sup> R. H. Fertel, J. E. Greenwald, R. Schwarz, L. Wong, and J. Bianchine, *Res. Commun. Chem. Pathol. Pharmacol.*, 1980, **27**, 3.

<sup>21</sup> A. P. Venkov and N. Mollov, *Dokl. Bolg. Akad. Nauk*, 1979, **32**, 895.

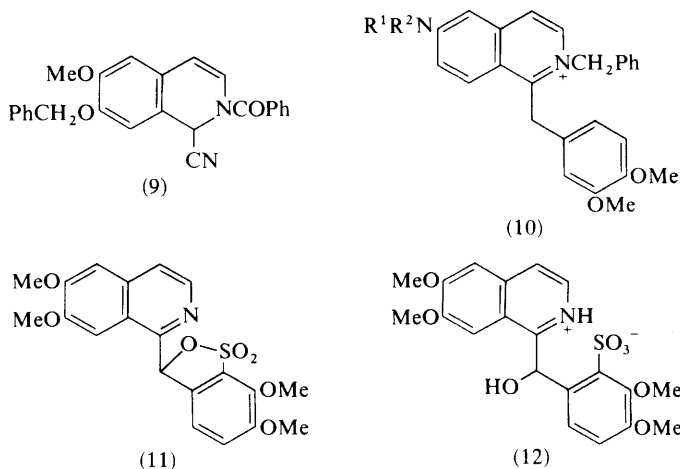
<sup>22</sup> cf. Chapter 5 in this volume.

<sup>23</sup> P. K. Bhaumik, B. Mukherjee, J. P. Juneau, N. S. Bhacca, and R. Mukherjee, *Phytochemistry*, 1979, **18**, 1584.

<sup>24</sup> S. Dasgupta, A. B. Ray, S. K. Bhattacharya, and R. Bose, *J. Nat. Prod.*, 1979, **42**, 399.

confirmed by its preparation from coclaurine.<sup>25</sup> Reticuline has been synthesized by the reaction of 4-benzyloxy-3-methoxybenzyl chloride with the Reissert compound (9), followed by aromatization, *N*-methylation, reduction, and debenzoylation.<sup>26</sup> Nor-reticuline has been synthesized by the normal Bischler-Napieralsky route, converted into the *N*-formyl and *N*-ethoxycarbonyl compounds, and demethylated to norlaudanosoline.<sup>27</sup> Laudanosine and coclaurine have been synthesized by the same route, the Willgerodt-Kindler reaction being used to generate the amides used for the ring-closure.<sup>28</sup> The synthesis of [1-<sup>14</sup>C]drotaverine (papaveroline tetraethyl ether) has been reported.<sup>29</sup>

Carbon-13 n.m.r. spectroscopy has been used to study benzyloisoquinoline and tetrahydroisoquinoline alkaloids and their *N*-methyl quaternary salts.<sup>30</sup> *N*-Benzylpapaverinium bromide has been shown to undergo aerial oxidation in alkaline solution to 2-benzyl-6,7-dimethoxyisoquinolone and to give bases of general structure (10) with methylamine, benzylamine, and pyrrolidine.<sup>31</sup> Chlorosulphonation of papaverinol affords the sulphonic acid ester (11), mild hydrolysis of which yields the acid (12), which with diazomethane is esterified and dehydrated to (13).<sup>32</sup> *N*-Methyl-1,2-dihydropapaverine has been shown by kinetic studies and orbital-symmetry requirements to rearrange to the salt (14) by the route previously postulated.<sup>33</sup>



The secondary base (15) has been shown to react with formaldehyde and hydrochloric acid, with loss of bromine and rearrangement to the carbinolamine

<sup>25</sup> K. P. Tiwari and M. Masood, *Phytochemistry*, 1979, **18**, 517.

<sup>26</sup> P. Kerekes, S. Makleit, and R. Bognar, *Acta Chim. Acad. Sci. Hung.*, 1978, **98**, 491.

<sup>27</sup> K. C. Rice and A. Brossi, *J. Org. Chem.*, 1980, **45**, 592.

<sup>28</sup> O. N. Tolkachev, E. P. Nakova, and R. P. Evstigneeva, *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod.* 11th, 1978, **3**, 47.

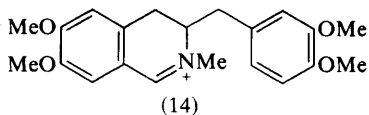
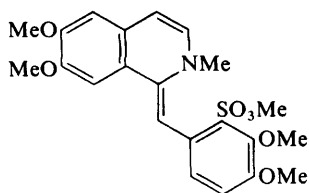
<sup>29</sup> E. Koltai, D. Banfi, J. Engler, J. Volford, and Z. Meszaros, *J. Labelled Compd. Radiopharm.*, 1979, **16**, 351.

<sup>30</sup> J. Anita, E. Ruveda, and F. de A. M. Reis, *Phytochemistry*, 1978, **17**, 1655.

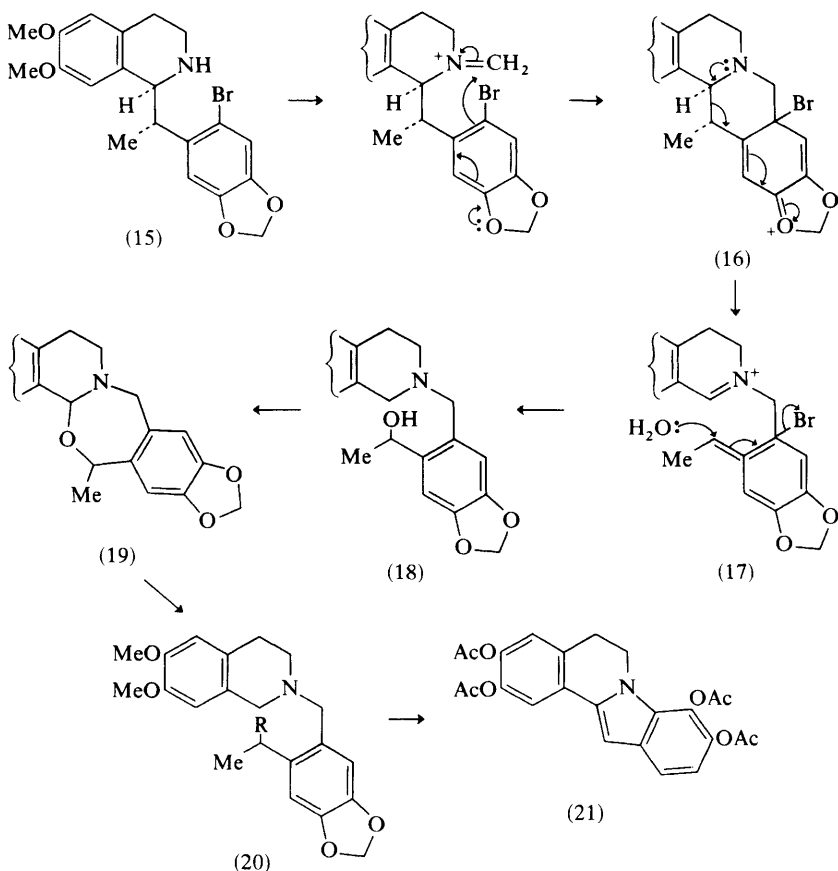
<sup>31</sup> D. Beaumont and R. D. Waigh, *Chem. Ind. (London)*, 1978, 808.

<sup>32</sup> P. Klivenyi, E. Vinkler, E. Minker, and P. Sohar, *Pharmazie*, 1979, **34**, 849.

<sup>33</sup> R. G. Kinsman and S. F. Dyke, *Tetrahedron*, 1979, **35**, 857.



ether (19), which is in equilibrium with the iminium salt (18) and which can be reduced with borohydride to the alcohol (20; R = OH) and further, catalytically, to the base (20; R = H). The reaction is believed to proceed through the intermediates (16) and (17).<sup>34</sup>

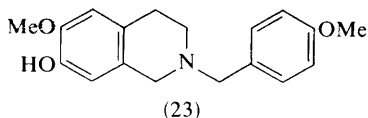
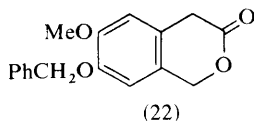


Aerial oxidation of norlaudanosoline in aqueous alkali and acetylation of the product affords the benzopyrrocoline (21), together with a dimer that is linked

<sup>34</sup> S. Natarajan, B. R. Pai, R. Rajaraman, H. Suguna, C. S. Swaminathan, K. Nagarajan, and V. Sundarsanam, *J. Chem. Soc., Perkin Trans. 1*, 1979, 283.

at the  $\beta$ - and  $\beta'$ -positions. Stereoselective *O*-methylation of the antipode of norlaudanosoline by catechol *O*-methyltransferase has been observed.<sup>35</sup>

The toxicity of papaverine has been studied,<sup>36</sup> as have its effects on energy processes in myocardial mitochondria,<sup>37</sup> on the release and metabolism of dopamine,<sup>38</sup> on contractile force and *C*-nucleotide levels in dog myocardium,<sup>39</sup> on serum-induced spasms in cerebral arterioles,<sup>40</sup> and on production of PGE<sub>2</sub> by rabbit gastric mucosa,<sup>41</sup> and the biological effects of drotaverine,<sup>42</sup> *N*-benzoylpapaverinium chloride,<sup>43</sup> and norlaudanosoline<sup>44</sup> have been studied. A rapid method for the determination of papaverine in plasma by h.p.l.c. has been described.<sup>45</sup>



The 2-benzylisoquinoline alkaloid sendaverine (23) has been synthesized from the lactone (22) by treatment with *p*-methoxybenzylamine, followed by reduction of the resulting amide to the amine, treatment of this with thionyl chloride, and ring-closure of the chloro-compound so formed.<sup>46</sup>

#### 4 Bisbenzylisoquinolines

The following species have been shown to contain the alkaloids stated:

<i>Berberis baluchistanica</i> <sup>47</sup>	baluchistine
<i>Berberis buxifolia</i> <sup>48</sup>	calfatine
<i>Daphnandra johnsonii</i> <sup>49</sup>	<i>O</i> -methylrepandine and nortenuipine
<i>Doryphora aromatica</i> <sup>50</sup>	aromoline, homoaromoline, daphnoline, daphnandrine, isotetrandrine, and 1,2- dihydroapateline
<i>Pachygone ovata</i> <sup>24</sup>	trilobine

<sup>35</sup> L. R. Meyerson, J. L. Cashaw, K. D. McMurtrey, and V. E. Davis, *Biochem. Pharmacol.*, 1979, **28**, 1745.

<sup>36</sup> N. S. Grodetskaya, N. M. Karamzina, N. V. Khoroshilova, N. S. Abalina, and T. V. Gnevkovskaya, *Toksikol. Nov. Prom. Khim. Veshchestv.*, 1979, **15**, 139.

<sup>37</sup> A. L. Urakov and A. G. Baranov, *Farmakol. Toksikol. (Moscow)*, 1979, **42**, 132.

<sup>38</sup> L. Cubbedu-Ximenez, I. S. Hoffmann, and V. B. Paris, *J. Pharmacol. Exp. Ther.*, 1979, **209**, 73.

<sup>39</sup> M. Endoh and M. Honma, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 1979, **306**, 241.

<sup>40</sup> S. Reuse-Blom, *Bibl. Anat.*, 1979, **18**, 221.

<sup>41</sup> M. Ligumsky, D. Rachmilewitz, and U. Zor, *Gut*, 1979, **20**, 882.

<sup>42</sup> P. Szentmiklosi and S. Marton, *Acta Pharm. Hung.*, 1979, **49**, 50.

<sup>43</sup> F. Kh. Sharipov, V. I. Polskii, and K. Kh. Khaidarov, *Dokl. Akad. Nauk Tadzh. SSR*, 1979, **22**, 567.

<sup>44</sup> N. Awazi and H. Guldberg, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 1979, **306**, 135.

<sup>45</sup> S. L. Pierson, J. J. Hannigan, R. E. Taylor, and J. E. McClurg, *J. Pharm. Sci.*, 1979, **68**, 1550.

<sup>46</sup> T. Kametani, Y. Enomoto, K. Takahashi, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2836.

<sup>47</sup> G. A. Miana, J. E. Foy, R. D. Minard, and M. Shamma, *Experientia*, 1979, **35**, 1137.

<sup>48</sup> V. Fajardo, A. Urzua, and B. K. Cassels, *Heterocycles*, 1979, **12**, 1559.

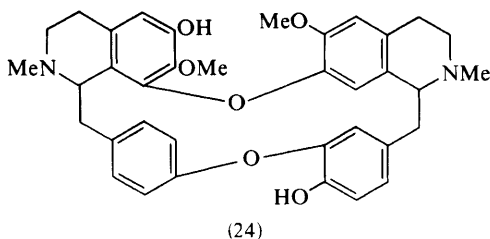
<sup>49</sup> I. R. C. Bick and H. M. Leow, *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod. 11th*, 1978, **2**, 9.

<sup>50</sup> I. R. C. Bick, H. M. Leow, and M. J. Richards, *Aust. J. Chem.*, 1980, **33**, 225.

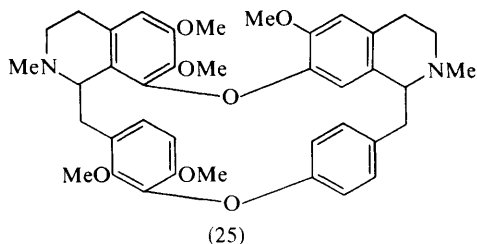
*Thalictrum rochebrunianum*<sup>51</sup> norhernandezine, *N'*-northalibrunine, thalibrunine, thalibrunimine, oxothalibrunimine, thalictrine, and dihydrothalictrine

*Thalictrum rugosum*<sup>12</sup> aromoline, obaberine, neothalifine, thalrugosinone, and thalictuberine

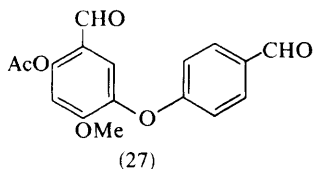
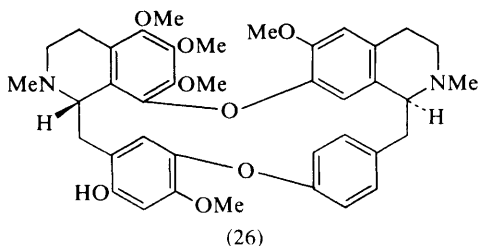
Baluchistine has been assigned the structure (24) on the basis of spectroscopic studies and its conversion into obaberine by methylation with diazomethane.<sup>47</sup>



It is the first alkaloid of the oxyacanthine/berbamine group to be found with a free hydroxyl group at position 6. Another new base of unusual structure is calfatine, to which the structure (25) has been assigned on the basis of spectroscopic analysis and as a result of its fission with sodium and liquid ammonia to 1-(2,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyltetrahydroisoquinoline.<sup>48</sup>

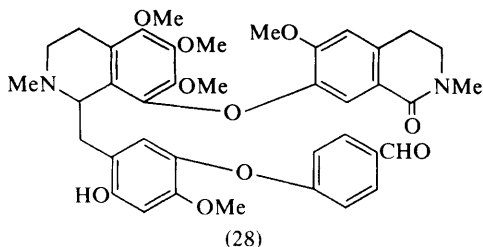


Thalibrunine and thalibrunimine have been isolated from *Thalictrum rochebrunianum* together with the new bases norhernandezine, *N'*-northalibrunine, oxothalibrunimine, thalictrine, and dihydrothalictrine.<sup>51</sup> These bases have been related as follows. Thalibrunine has been assigned the revised structure of 2'-hydroxy-hernandezine (26) on the basis of the oxidation of its *O*-acetyl derivative with ceric ammonium nitrate to the dialdehyde (27) and with

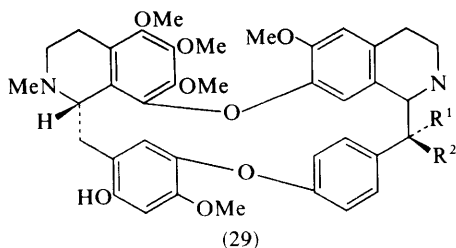


<sup>51</sup> J. Wu, J. L. Beal, and R. W. Doskotch, *J. Org. Chem.*, 1980, **45**, 213.

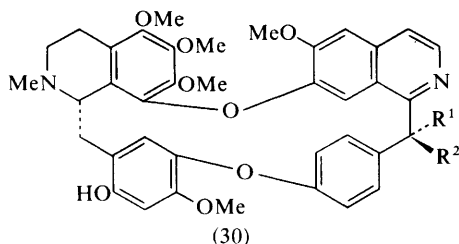
potassium permanganate to secothalibrunine aldehydo-lactam (28), its reduction with sodium and liquid ammonia to (*S*)-*N*-methylcoclaurine, and the similarity of its c.d. curve to that of hernandezine.<sup>52</sup> Since thalibrunimine can be reduced



to *N'*-northalibrunine, and *N*-methylthalibrunimine salts can be reduced to thalibrunine, the structure (29;  $R^1 = R^2 = H$ ) follows for thalibrunimine.<sup>51</sup>



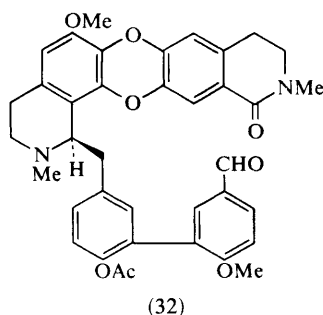
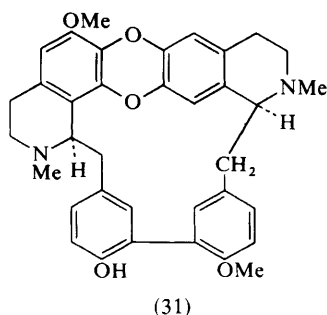
Aerial oxidation of thalibrunimine affords oxothalibrunimine (29;  $R^1R^2 = O$ ), whereas catalytic oxidation with oxygen and palladized charcoal gives thalictrimine (30;  $R^1R^2 = O$ ), the structures of both of these bases being in accord with their high-resolution mass spectra.<sup>51</sup> Reduction of thalictrimine with sodium borohydride affords the secondary alcohol (30;  $R^1 = H, R^2 = OH$ ), identical with natural dihydrothalictrimine.<sup>51</sup> Norhernandezine was isolated from *T. roche-brunianum* for the first time, although it had previously been prepared, together with its isomer epinorhernandezine, by the reduction of the thalsimine.



The structure of dinklacorine (31) has been re-examined and the position of the hydroxyl group confirmed by oxidation of the *O*-acetyl derivative with

<sup>52</sup> J. Wu, J. L. Beal, and R. W. Doskotch, *J. Org. Chem.*, 1980, **45**, 208.

potassium permanganate in methanol to the aldehydo-lactam (32), the structure of which is in accord with its spectra.<sup>53</sup>



The <sup>13</sup>C n.m.r. spectrum of isochondodendrine has been studied.<sup>30</sup> The effects of tubocurarine on membrane surface potential<sup>54</sup> and on the release of acetylcholine from perfused cerebral ventricles<sup>55</sup> have been studied, as has its binding by brain gangliosides,<sup>56</sup> its use against *Hydrophis cyanocinctus* venom,<sup>57</sup> its pharmacokinetics and pharmacodynamics in anaesthesia,<sup>58,59</sup> its autonomic effects compared with other neuromuscular blocking agents,<sup>60</sup> its behavioural effects in cats,<sup>61</sup> and its pharmacokinetics and pharmacodynamics in comparison with those of metocurine (its dimethyl ether).<sup>62,63</sup> The preparation of tubocurarine from tubocurine by *N*-methylation of the monohydrochloride has been described.<sup>64</sup> Metocurine has been shown to prevent the hypothermia that is associated with halothane anaesthesia in pigs.<sup>65</sup>

## 5 Pavines and Isopavines

Partial reduction of the benzylisoquinolines (33; R<sup>1</sup> = Me, R<sup>2</sup> = CH<sub>2</sub>Ph) and (33; R<sup>1</sup> = CH<sub>2</sub>Ph, R<sup>2</sup> = Me) with sodium borohydride gives the corresponding 1,2-dihydro-compounds, which are cyclized by phosphoric and formic acids (with removal of the benzyl group) to the pavines caryachine (34; R<sup>1</sup> = Me, R<sup>2</sup> = H) and isocaryachine (34; R<sup>1</sup> = H, R<sup>2</sup> = Me),<sup>66</sup> but attempts to repeat

<sup>53</sup> D. Dwuma-Badu, S. F. Withers, S. A. Ampofo, M. M. El Azizi, D. J. Slatkin, P. L. Schiff, and J. E. Knapp, *J. Nat. Prod.*, 1979, **42**, 116.

<sup>54</sup> W. G. Van der Kloot and I. Cohen, *Science*, 1979, **203**, 1351.

<sup>55</sup> H. V. Bhatt, R. S. Rao, and P. S. R. K. Haranath, *Indian J. Med. Res.*, 1979, **70**, 487.

<sup>56</sup> H. Roesner, G. Merz, and H. Rahman, *Z. Physiol. Chem.*, 1979, **360**, 413.

<sup>57</sup> S. B. Bhise and M. B. Bhide, *Bull. Haffkine Inst.*, 1978, **6**, 92.

<sup>58</sup> J. Ham, R. D. Miller, L. B. Sheiner, and R. S. Matteo, *Anesthesiology*, 1979, **50**, 528.

<sup>59</sup> D. R. Stanski, J. Ham, R. D. Miller, and L. B. Sheiner, *Anesthesiology*, 1979, **51**, 235.

<sup>60</sup> R. J. Marshall and J. A. O. Ojewole, *Br. J. Pharmacol.*, 1979, **66**, 77P.

<sup>61</sup> R. B. Asharobi, D. Guha, and S. N. Pradhan, *Psychopharmacology (Berlin)*, 1979, **64**, 349.

<sup>62</sup> D. K. F. Meijer, J. G. Weitering, G. A. Vermeer, and A. H. J. Scaf, *Anesthesiology*, 1979, **51**, 402.

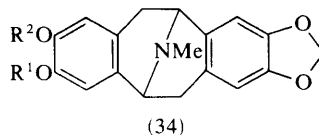
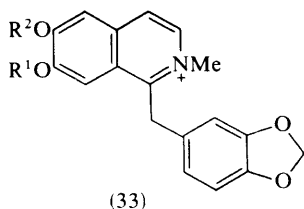
<sup>63</sup> R. P. Antonio, D. M. Philbin, and J. J. Savarese, *Br. J. Anaesth.*, 1979, **51**, 1007.

<sup>64</sup> J. Naghaway and T. O. Soine, *J. Pharm. Sci.*, 1979, **68**, 655.

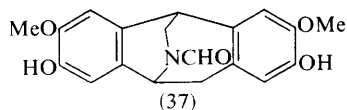
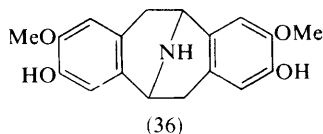
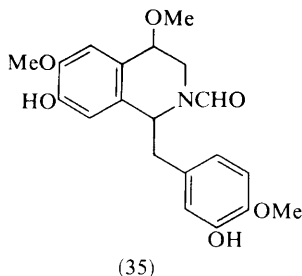
<sup>65</sup> G. P. Hoech, jr., J. T. Roberts, C. H. Williams, S. D. Waldman, S. T. Simpson, C. Trim, and J. Brazile, *Thermoregul. Mech. Their Ther. Implic., Int. Symp. Pharmacol. Thermoregul.*, 4th, 1979 (publ. 1980), p. 137.

<sup>66</sup> C.-H. Chen, J. Wu, N. A. Shaath, and T. O. Soine, *T'ai-wan Yao Hsueh Tsa Chih*, 1977, **29**, 19.

this sequence of reactions with a bromine substituent in the benzyl group failed, only tetrahydroisoquinolines being formed in the reduction step.<sup>67,68</sup>



(+)-*N*-Formylnor-reticuline, on treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in methanol, is oxidized to the 4-methoxy-compound (35), which can be cyclized to *N*-norbisanorargemonine (36) (converted by *N*- and *O*-methylation into argemonine) by mineral acid or to the isopavine *N*-formyl-northalidine (37) by treatment with methanesulphonic acid in acetonitrile. The *N*-formyl compounds can be reduced to *N*-methyl by borane or converted into the secondary bases by hydrazinolysis.<sup>69</sup>



## 6 Berberines and Tetrahydroberberines

Alkaloids of this group have been isolated as follows:

*Corydalis cava*<sup>70</sup>

berberine, (+)-canadine, coptisine, coralydine, corybulbine, corycavine, corycavidine, corypalmine, isocorypalmine, corysamine, dehydrocorybulbine, dehydrocorydaline, dehydrothalictricavine, palmatine, (–)-scoulerine, (+)-stylopine, tetrahydrocorysamine, (±)-tetrahydropalmatine, and (+)- and (–)-thalictricavine

*Corydalis ophiocarpa*<sup>71</sup>

berberine, (–)-canadine, coptisine, (–)-corypalmine, corysamine, (–)-ophiocarpine, (–)-ophiocarpine *N*-oxide, and (–)-stylopine

*Duguetia calycina*<sup>72</sup>

discretamine and (+)-10-desmethylxylopine

<sup>67</sup> S.-W. Sun and C.-H. Chen, *T'ai-wan Yao Hsueh Tsa Chih*, 1977, **29**, 35.

<sup>68</sup> C.-H. Chen and H.-I. Chen, *T'ai-wan Yao Hsueh Tsa Chih*, 1978, **30**, 88.

<sup>69</sup> K. C. Rice, W. C. Ripka, J. Reden, and A. Brossi, *J. Org. Chem.*, 1980, **45**, 801.

<sup>70</sup> J. Slavik and L. Slavikova, *Collect. Czech. Chem. Commun.*, 1979, **44**, 2261.

<sup>71</sup> V. Preininger, L. Dolejs, B. Smysl, and V. Simanek, *Planta Med.*, 1979, **36**, 213.

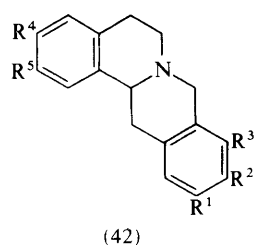
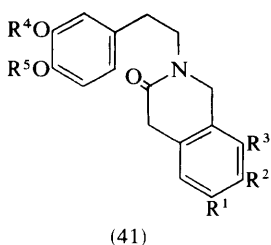
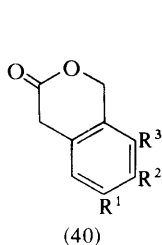
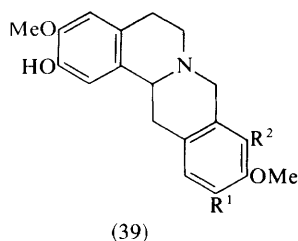
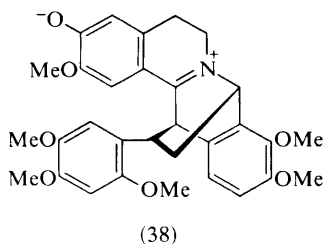
<sup>72</sup> F. Roblot, R. Hocquemiller, H. Jacquemin, and A. Cavé, *Plant. Med. Phytother.*, 1978, **12**, 259.



<i>Monanthotaxis cauliflora</i> <sup>73</sup>	stepholidine
<i>Pachypodanthium staudii</i> <sup>74</sup>	staudine
<i>Papaver rupifragum</i> <sup>75</sup>	coptisine and (-)-stylopine
<i>Thalictrum minus</i> <sup>76</sup>	berberine
<i>Thalictrum rugosum</i> <sup>12</sup>	oxyberberine

Of these bases, (-)-ophiocarpine *N*-oxide is a new natural product,<sup>71</sup> (+)-10-desmethylxylopine is a new alkaloid that is isomeric with govanine,<sup>72</sup> and staudine is a new base that has been shown to have the bridged tetrahydroberberine structure (38) by spectroscopic studies and an *X*-ray crystallographic examination.<sup>74</sup>

The isomeric bases corexamine (39;  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ) and scoulerine (39;  $R^1 = \text{H}$ ,  $R^2 = \text{OH}$ ) have been synthesized from reticuline *N*-oxide by treatment with ferrous sulphate and methanol, scoulerine being produced only in the presence of acid.<sup>77</sup> Tetrahydroberberines have also been synthesized from isochromanones of general structure (40) by ring-opening to the bromo-esters, treatment with  $\beta$ -phenylethylamines to give lactams (41), followed by Bischler-Napieralsky cyclization and reduction. Scoulerine (39;  $R^1 = \text{H}$ ,  $R^2 = \text{OH}$ ),<sup>78</sup> isocoptisine (42;  $R^1R^2 = R^4R^5 = \text{OCH}_2\text{O}$ ,  $R^3 = \text{H}$ ),<sup>79</sup> tetrahydropalmatine (42;  $R^1 = \text{H}$ ,  $R^2 = R^3 = R^4 = R^5 = \text{OMe}$ ),<sup>80</sup> and 3-hydroxy-9,10-dimethoxyberberine (42;  $R^1 = \text{H}$ ,  $R^2 = R^3 = \text{OMe}$ ,  $R^4 = \text{OH}$ )<sup>81</sup> have been synthesized in this way.



<sup>73</sup> P. G. Waterman and K. Pootakahn, *Planta Med.*, 1979, **37**, 247.

<sup>74</sup> A. Cavé, N. Kunesch, M. Leboeuf, F. Bevalot, A. Chiaroni, and C. Riche, *J. Nat. Prod.*, 1980, **43**, 103.

<sup>75</sup> L. Slavikova and J. Slavik, *Collect. Czech. Chem. Commun.*, 1980, **45**, 761.

<sup>76</sup> Y. Ayneci, *Pazhoohandeh (Tehran)*, 1979, **23**, 165.

<sup>77</sup> T. Kametani and M. Ihara, *Heterocycles*, 1979, **12**, 893.

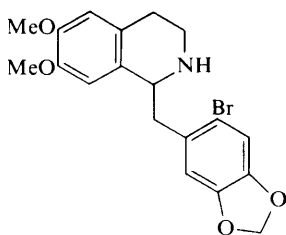
<sup>78</sup> G. D. Pandey and K. P. Tiwari, *Heterocycles*, 1979, **12**, 1327.

<sup>79</sup> G. D. Pandey and K. P. Tiwari, *Synth. Commun.*, 1980, **10**, 43.

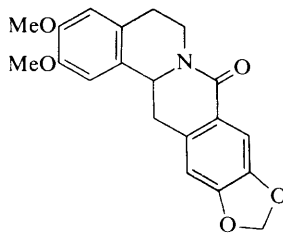
<sup>80</sup> G. D. Pandey and K. P. Tiwari, *Indian J. Chem., Sect. B*, 1979, **18**, 545.

<sup>81</sup> G. D. Pandey and K. P. Tiwari, *Synth. Commun.*, 1979, **10**, 895.

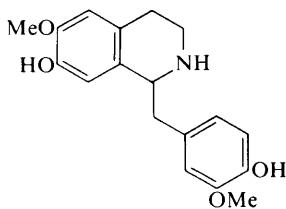
An alternative approach to synthesis of this ring system involves insertion of CO into the brominated secondary base (43), by treatment with carbon monoxide, lead tetra-acetate, and triphenylphosphine in tributylamine, the product being the amide (44), reduction of which affords the amine.<sup>81</sup> Govadine (42;  $R^1 = R^4 = \text{OMe}$ ,  $R^2 = R^5 = \text{OH}$ ,  $R^3 = \text{H}$ ) has been synthesized by the conventional ring-closure, with formaldehyde, of the diphenolic base (45), or of its dibenzyl ether, in acid solution.<sup>82</sup> Tetrahydroberberines, together with *N*-benzyltetrahydroisoquinolines, have also been obtained by the electrolytic reduction of 3,4-dihydroisoquinolines of structure (46).<sup>83</sup>



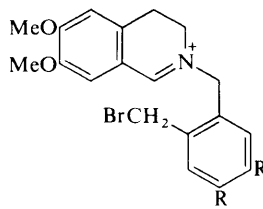
(43)



(44)



(45)



(46)

Oxidation of the phenol (47) with lead tetra-acetate in acetic acid has been shown to afford the acetoxy-compound (50), presumably through the intermediates (48) and (49).<sup>84</sup> Oxidation of palmatine chloride (51;  $R = \text{H}$ ) with *m*-chloroperbenzoic acid gives a 40% yield of polycarpine (52).<sup>85</sup>

Reduction of palmatine salts by sodium borohydride in tetrahydrofuran gives the enamine (53;  $R^1 = R^2 = \text{Me}$ ), treatment of which with methyl iodide gives iodides of palmatine (51;  $R = \text{H}$ ), 13-methylpalmatine (51;  $R = \text{Me}$ ), and 13-methyltetrahydropalmatine, presumably as a result of disproportionation; similar results were observed when the enamine was treated with ethyl iodide.<sup>86</sup> The corresponding enamine from berberine (53;  $R^1R^2 = \text{CH}_2$ ) reacts with benzyl bromide to give the iminium salt (54) (which may be reduced by sodium borohydride to 13-benzyltetrahydroberberine), with toluene-*p*-sulphonyl azide to give the betaine (55), and with dimethyl acetylenedicarboxylate to afford the isoquinolono[2,1-*c*]benzazocine (56).<sup>87</sup> Berberine reacts with acetone in the

<sup>82</sup> H.-C. Chiang, Y.-C. Cheng, and J.-C. Liu, *T'ai-wan Yao Hsueh Tsa Chi*, 1978, **30**, 54.

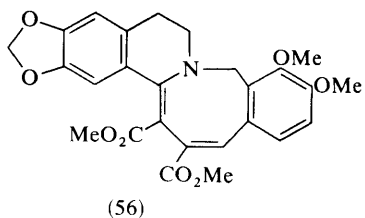
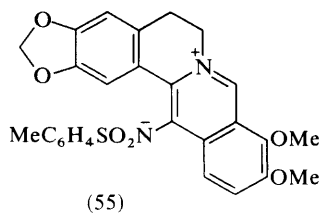
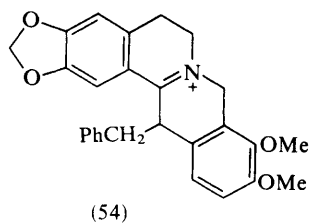
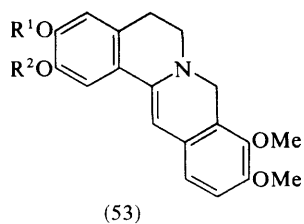
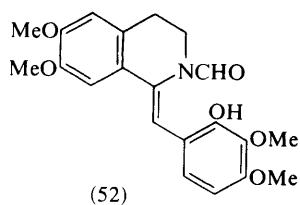
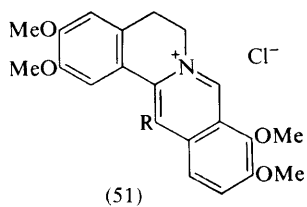
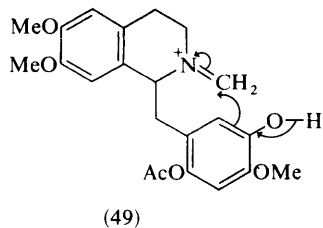
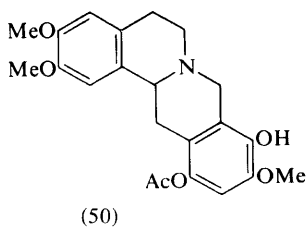
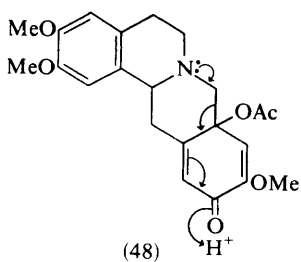
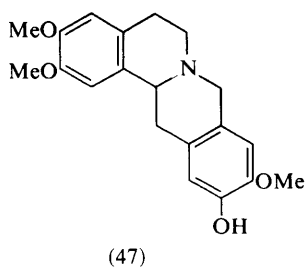
<sup>83</sup> T. Shono, K. Yoshida, K. Ando, Y. Usui, and H. Hamaguchi, *Tetrahedron Lett.*, 1978, 4819.

<sup>84</sup> H. Hara, M. Hosaka, O. Hoshino, and B. Umezawa, *Tetrahedron Lett.*, 1978, 3809.

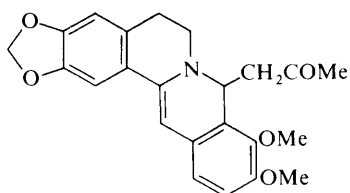
<sup>85</sup> N. Murugesan and M. Shamma, *Tetrahedron Lett.*, 1979, 4521.

<sup>86</sup> C.-N. Lin, *T'ai-wan Yao Hsueh Tsa Chi*, 1977, **29**, 65.

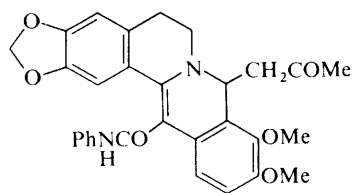
<sup>87</sup> N. Viswanathan and V. Balakrishnan, *Indian J. Chem., Sect. B*, 1978, **16**, 1100.



presence of sodium hydroxide at pH 10—11 to give 8-acetonyldihydroberberine (57),<sup>88</sup> which is an enamine and which reacts with phenyl isocyanate to give the amide (58);<sup>87</sup> similar reactions are observed with isothiocyanates and between 8-benzoyldihydroberberine and isocyanates.<sup>87</sup>

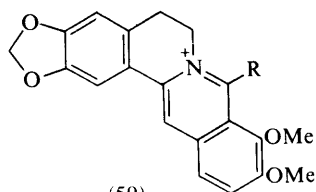


(57)

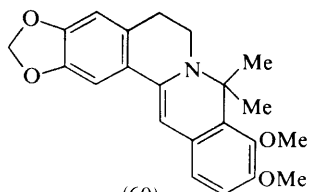


(58)

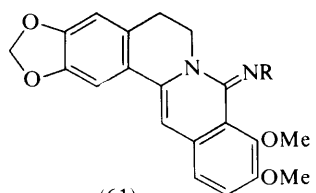
8-Hydroxyberberine (59; R=OH), on treatment with phosphorus oxychloride, yields 8-chloroberberine (59; R = Cl); this reacts with Grignard reagents to give 8,8-dialkyl-dihydroberberines such as (60), with primary amines to give 8-iminodihydroberberines (61), and with the sodium salts of ethyl acetoacetate, diethyl malonate, and malonodinitrile to give compounds of structures (62; R<sup>1</sup> = COMe, R<sup>2</sup> = CO<sub>2</sub>Et), (62; R<sup>1</sup> = R<sup>2</sup> = CO<sub>2</sub>Et), and (62; R<sup>1</sup> = R<sup>2</sup> = CN). The diester (62; R<sup>1</sup> = R<sup>2</sup> = CO<sub>2</sub>Et) is readily converted into the berberinylacetic acid (63), which can be reduced to the tetrahydro-compound.<sup>89</sup>



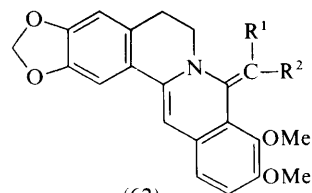
(59)



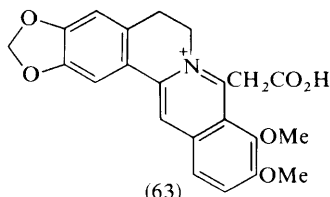
(60)



(61)



(62)

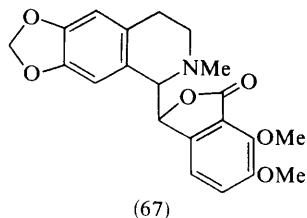
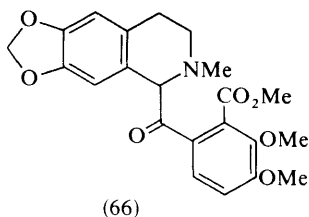
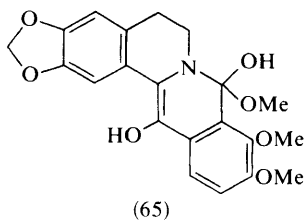
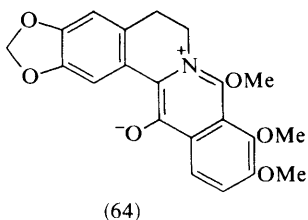


(63)

<sup>88</sup> N. M. Turkevich, L. I. Petlichnaya, and T. S. Kuzheliyuk, *Khim. Prom-st., Ser.: Reakt., Osobo Chist. Veshchestva*, 1979, 1.

<sup>89</sup> J. L. Moniot, T. M. Kravetz, A. E. R. Abd El Rahman, and M. Shamma, *J. Pharm. Sci.*, 1979, **68**, 705.

8-Methoxyberberine phenol betaine (64), on treatment with water in ether, gives the enaminal (65), *N*-methylation of which results in ring-opening of the carbinolamine to give dehydrohydrastine methyl ester (66), which can be reduced to  $\alpha$ - and  $\beta$ -hydrastine (67). Reduction of the enaminal (65) affords  $\alpha$ - and  $\beta$ -norhydrastines, and reduction of the  $\beta$ -isomer with di-isobutylaluminium hydride gives ( $\pm$ )-epiophiocarpine, whereas reduction of the betaine (64) with borohydride gives ( $\pm$ )-ophiocarpine.<sup>90</sup>

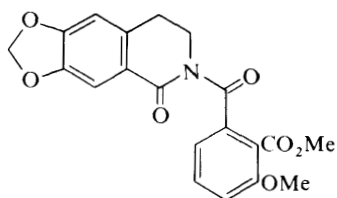


The betaine (64) can be hydrolysed by water in tetrahydrofuran to methyl isoanhydroberberilate (68) and converted by acetic anhydride into 13-acetoxy-oxyberberine, which may be hydrolysed to methyl anhydroberberilate (69).<sup>90</sup> If (64) is treated with aqueous acid then allowed to oxidize in pyridine solution in air, it is converted into 14-hydroxy-8,13-dioxotetrahydroberberine (75),<sup>91,92</sup> which can also be prepared by the action of pyridine hydrochloride in pyridine on oxybisberberine, which is the product of oxidation of berberine with potassium ferricyanide. The dioxo-compound (75) is rearranged by ammonium hydroxide in chloroform to the highly oxidized aporhoadane (70), which suffers a solvolytic ring-contraction in strong acid to give (71), reduction and methylation of which affords  $\beta$ -hydrastine. In strong base, fission of the carbinolamine occurs, with the production of the acid (72), and this can be cyclized, with decarboxylation, by strong acids to *C*-noroxyberberine (73). Reduction of the keto-carbinolamine (70) with borohydride yields the *trans*-diol (74), whereas reduction of the carbinolamine methyl ether in the same way gives the *cis*-glycol monomethyl ether.<sup>91,92</sup> Concentrated hydrochloric acid converts the dioxo-compound (75) into a dimeric 14,14'-ether, presumably *via* the imonium ion, whereas 25% sulphuric acid converts it into the ring-opened base (76), related to hydrastine.<sup>92</sup>

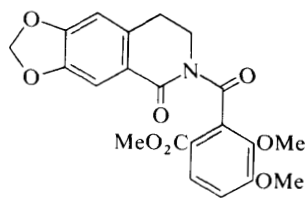
<sup>90</sup> J. L. Moniot and M. Shamma, *J. Org. Chem.*, 1979, **44**, 4337.

<sup>91</sup> J. L. Moniot, D. M. Hindenlang, and M. Shamma, *J. Org. Chem.*, 1979, **44**, 4347.

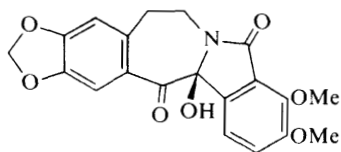
<sup>92</sup> J. L. Moniot, D. M. Hindenlang, and M. Shamma, *J. Org. Chem.*, 1979, **44**, 4343.



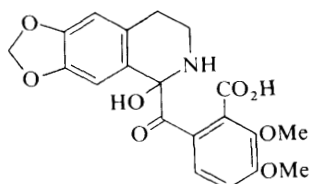
(68)



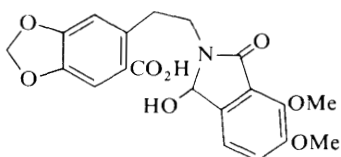
(69)



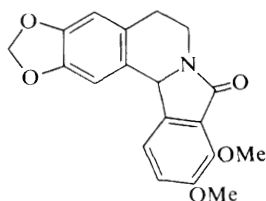
(70)



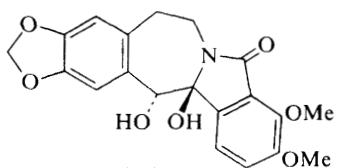
(71)



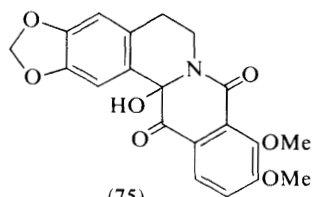
(72)



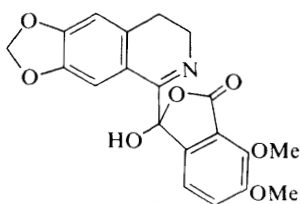
(73)



(74)



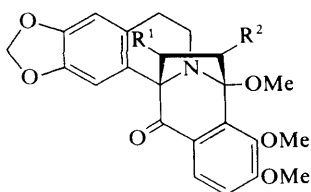
(75)



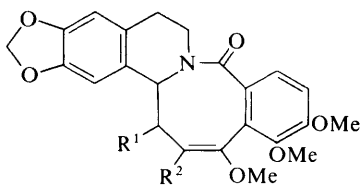
(76)

The betaine (64) will react with acetylenes to yield the bridged compounds (77;  $R^1 = R^2 = \text{CO}_2\text{Me}$ ), (77;  $R^1 = R^2 = \text{COPh}$ ), (77;  $R^1 = \text{CO}_2\text{Me}$ ,  $R^2 = \text{H}$ ), (77;  $R^1 = \text{COMe}$ ,  $R^2 = \text{H}$ ), (77;  $R^1 = \text{H}$ ,  $R^2 = \text{CO}_2\text{Me}$ ), (77;  $R^1 = \text{H}$ ,  $R^2 = \text{COMe}$ ). These compounds are rearranged, on heating, to the lactams (78).<sup>93</sup> Similar reactions have been observed with the 8-desmethoxy-betaine.<sup>93</sup>

<sup>93</sup> M. Hanaoka, A. Wada, S. Yasuda, C. Mukai, and T. Imanishi, *Heterocycles*, 1979, **12**, 511.

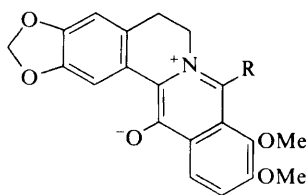


(77)

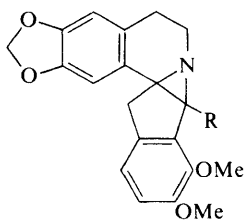


(78)

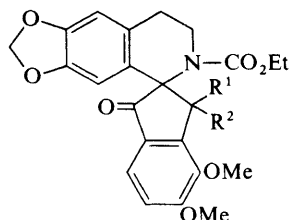
Photolytic rearrangement of the betaines (79; R = H, Me, or Et) gives the 8,14-cyclo-compounds (80). When these are treated with ethyl chloroformate, (80; R = H) gives the chloro-compound (81; R¹ = H, R² = Cl), whereas the compounds (80; R = Me) and (80; R = Et) lose hydrogen chloride in the process, giving (81; R¹R² = CH₂) and (81; R¹R² = CHMe) respectively.<sup>94</sup>



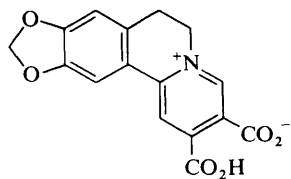
(79)



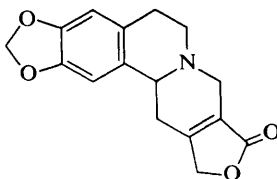
(80)



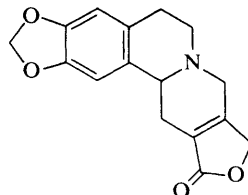
(81)



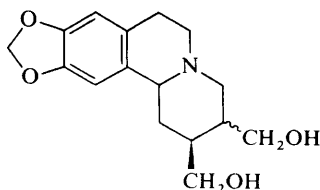
(82)



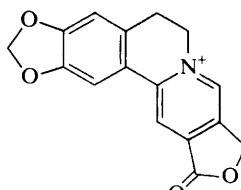
(83)



(84)



(85)



(86)

Berberine can be oxidized by nitric acid to berberidic acid (82), which forms two isomeric monomethyl esters; these can be reduced first to the isomeric unsaturated lactones (83) and (84) and further to saturated lactones and to *cis*- and *trans*-diols (85). Hydrogenation of berberidic acid diester affords an allo-hexahydro-compound, which is isomerized by base to a normal hexahydro-compound. Oxidation of the lactone (84) with mercuric acetate affords the aromatized lactone (86).<sup>95</sup>

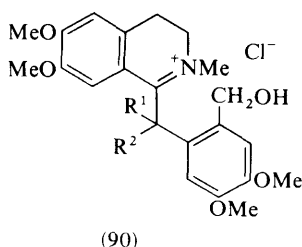
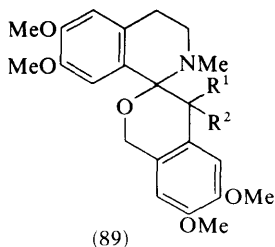
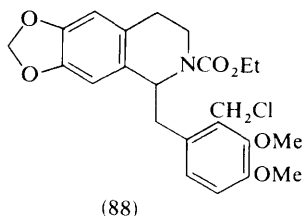
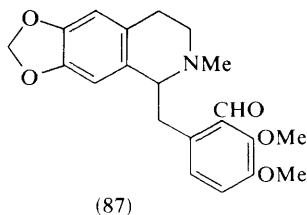
<sup>94</sup> M. Hanaoka, S. Yasuda, K. Najami, K. Okajima, and T. Imanishi, *Tetrahedron Lett.*, 1979, 3749.

<sup>95</sup> P. Chinnsamy and M. Shamma, *Can. J. Chem.*, 1979, **57**, 1647.

A paper-chromatographic method for the estimation of berberine in blood, urine, and faeces has been described.<sup>96</sup> The hypotensive,<sup>97</sup> cytotoxic,<sup>98</sup> anti diarrhoeal,<sup>99</sup> and biochemical<sup>100,101</sup> effects of berberine have been studied. The dimerization and interactions with DNA of coralynine and of its *C*-propyl analogue have been compared.<sup>102</sup>

## 7 Secoberberines

Macrantaline has been isolated from *Papaver pseudo-orientale*<sup>103</sup> and from *P. lisae*.<sup>102</sup> (±)-Canadaline (87) has been synthesized from tetrahydroberberine by regioselective cleavage with ethyl chloroformate to produce (88), followed by hydrolysis, reduction of the CO<sub>2</sub>Et group, and oxidation.<sup>105</sup> Analogues of hypecorine have been prepared by treatment of 3,4-dihydropapaverine with formaldehyde, followed by *N*-methylation and cyclization of the resulting 2'-hydroxymethyl-iminium salt to the base (89; R<sup>1</sup> = R<sup>2</sup> = H),<sup>106,107</sup> a similar route from dihydropapaveraldine yielding (89; R<sup>1</sup>R<sup>2</sup> = O).<sup>107</sup> Biological transformation of the intermediates in these syntheses, *i.e.* (90; R<sup>1</sup> = R<sup>2</sup> = H) and



<sup>96</sup> Z. Kowalewski, K. Drost-Karbowska, A. Mrozikiewicz, and T. Bobkiewicz, *Herba. Pol.*, 1978, **24**, 193.

<sup>97</sup> Y. T. Chun, T. T. Yip, K. L. Lau, Y. C. Kong, and U. Sankawa, *Gen. Pharmacol.*, 1979, **10**, 177.

<sup>98</sup> B. Hladon, Z. Kowalewski, T. Bobkiewicz, and K. Gronostaj, *Ann. Pharm. (Poznan)*, 1978, **13**, 61.

<sup>99</sup> M. A. Akhter, M. Sabir, and N. K. Bhide, *Indian J. Med. Res.*, 1979, **70**, 233.

<sup>100</sup> Y. C. Clement-Cormier, L. R. Meyerson, H. Phillips, and V. E. Davis, *Biochem. Pharmacol.*, 1979, **28**, 3123.

<sup>101</sup> W. A. Creasey, *Biochem. Pharmacol.*, 1979, **28**, 1081.

<sup>102</sup> A. N. Gough, R. L. Jones, and W. D. Wilson, *J. Med. Chem.*, 1979, **22**, 1551.

<sup>103</sup> G. Sariyar and T. Baytop, *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod. 11th*, 1978, **2**, 387.

<sup>104</sup> V. V. Melik-Guseinov, D. A. Murav'eva, and V. A. Mnatsakanyan, *Khim. Priir. Soedin.*, 1979, 239.

<sup>105</sup> M. Hanaoka, K. Nagami, and T. Imanishi, *Heterocycles*, 1979, **12**, 497.

<sup>106</sup> V. Simanek and V. Preininger, *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod. 11th*, 1978, **2**, 58.

<sup>107</sup> V. Simanek, V. Preininger, F. Grambal, and L. Dolejs, *Heterocycles*, 1978, **9**, 1233.



(90;  $R^1R^2 = O$ ), with rat liver enzymes gives 6,7-dimethoxy-2-methyltetrahydroisoquinolone as the main metabolite, whereas papaverine is oxidized to the *N*-oxide under the same conditions.<sup>108</sup>

### 8 Protopines

Protopine, cryptopine, and allocryptopine have been isolated from *Papaver rupifragum*,<sup>75</sup> protopine and allocryptopine from *Glaucium vitellinum*,<sup>109</sup> *Corydalis ophiocarpa*,<sup>71</sup> and *C. cava*,<sup>70</sup> and protopine from *Nandina domestica*<sup>110</sup> and *Thalictrum rugosum*.<sup>12</sup>

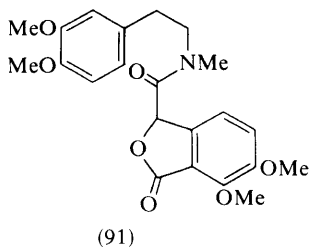
Allocryptopine has been prepared<sup>111</sup> by the photolytic oxidation of tetrahydroberberine methiodide; its antiarrhythmic effects have been studied.<sup>112</sup>

### 9 Phthalide-isoquinolines

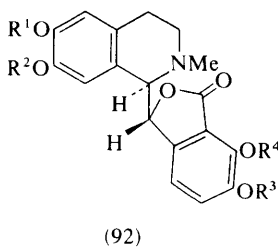
$\beta$ -Hydrastine has been isolated from *Corydalis pseudoadunca*,<sup>113</sup> capnoidine from *C. cava*,<sup>70</sup> and narlumidine from *Fumaria indica*.<sup>114</sup>

Cordrastine I (92;  $R^1 = R^2 = R^3 = R^4 = Me$ ) and its diastereoisomer cordrastine II have been synthesized from dimethoxybromohomophthalic anhydride, which on treatment with *N*-methyl-3,4-dimethoxyphenylethylamine gives the amide (91), cyclization of which gives dehydrocordrastine; reduction of this gives cordrastine and its isomer.<sup>115,116</sup> Similar syntheses have been achieved of adlumine (92;  $R^1 = R^2 = Me$ ,  $R^3R^4 = CH_2$ ) and its diastereoisomer corlumine and of bicuculline (92;  $R^1R^2 = R^3R^4 = CH_2$ ) and its diastereoisomer adlumidine.<sup>117</sup>

A second synthesis of cordrastine starts from a Reissert compound, the 6,7-dimethoxy-analogue of (9), which was condensed with 2-methoxycarbonyl-3,4-dimethoxybenzaldehyde; the product was hydrolysed, lactonized, hydrogenated, and *N*-methylated.<sup>118</sup>



(91)



(92)

<sup>108</sup> D. Walterova, A. Nemeckova, V. Preininger, V. Simanek, and L. Dolejs, *Heterocycles*, 1979, **12**, 247.

<sup>109</sup> A. Shafiee, A. Ghanbarpour, I. Lalezari, and S. Lajevardi, *J. Nat. Prod.*, 1979, **42**, 174.

<sup>110</sup> J. Kunitomo and Y. Murakami, *Shoyakugaku Zasshi*, 1979, **33**, 84.

<sup>111</sup> M. Hanaoka, C. Mukai, H. Nagayama, and Y. Arata, *Pol. J. Chem.*, 1979, **53**, 79.

<sup>112</sup> Z. S. Akbarov and Kh. U. Aliev, *Farmakol. Pri. Veschestv.*, 1978, 11.

<sup>113</sup> A. S. Sadikov, D. A. Rakhimova, T. Sadikov, E. K. Dobronravova, and T. T. Shakirov, *Khim. Pri. Soedin.*, 1978, 815.

<sup>114</sup> K. K. Seth, V. B. Pandey, A. B. Ray, B. Dasgupta, and S. A. H. Shah, *Chem. Ind. (London)* 1979, 744.

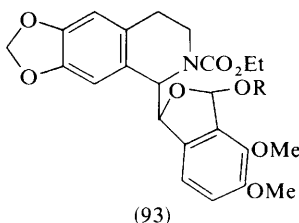
<sup>115</sup> S. O. De Silva, I. Ahmad, and V. Snieckus, *Tetrahedron Lett.*, 1978, 5107.

<sup>116</sup> S. O. De Silva, I. Ahmad, and V. Snieckus, *Can. J. Chem.*, 1979, **57**, 1598.

<sup>117</sup> B. C. Nalliah, D. M. MacLean, H. L. Holland, and R. Rodrigo, *Can. J. Chem.*, 1979, **57**, 1545.

<sup>118</sup> B. Kerekes, G. Gaal, and R. Bognar, *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod. 11th*, 1978, **4**, 274.

In addition to the preparation of  $\alpha$ - and  $\beta$ -hydrastine described above from the betaine (64), another conversion of a tetrahydroberberine into hydrastine has been reported. Acetylphiocarpine, on treatment with ethyl chloroformate, gives the acetoxy-derivative of (88), which can be hydrolysed to the hydroxy-methyl compound and then oxidized to the aldehyde by pyridinium perchlorate. Hydrolysis of the acetoxy group afforded the hemi-acetal (93; R = H), conversion of which into the mixed acetal (93; R = Et) protected the aldehyde system during reduction of N—CO<sub>2</sub>Et to NMe by lithium aluminium hydride. Hydrolysis of the acetal, followed by oxidation, then gave  $\alpha$ -hydrastine, and a similar sequence of reactions starting from *O*-acetyl-13-*epi*-ophiocarpine afforded  $\beta$ -hydrastine.<sup>119</sup> Methods of synthesis of alkaloids of this group have been reviewed.<sup>120</sup>

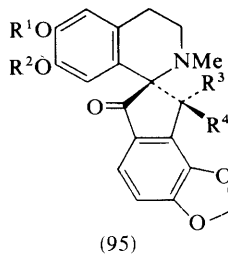
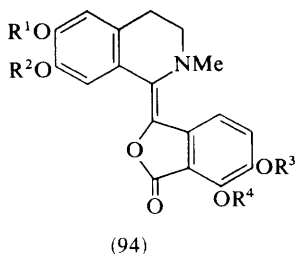


Pharmacological properties of bicuculline have been studied.<sup>121–124</sup>

## 10 Spiro-benzylisoquinolines

Fumariline has been isolated from *Fumaria indica*.<sup>125</sup>

Cyclization of amides of the type (91) yields dehydro-phthalide isoquinolines (94), which are enamines and which can be reduced by di-isobutylaluminium hydride in tetrahydrofuran, at  $-10^{\circ}\text{C}$ , with the formation of spirobenzyl-isoquinolines. Starting from the amides used for the synthesis of adlumine and adlumidine (described above), the diastereoisomeric alkaloids corydaine (95;  $\text{R}^1\text{R}^2 = \text{CH}_2$ ,  $\text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{OH}$ ) and sibiricine (95;  $\text{R}^1\text{R}^2 = \text{CH}_2$ ,  $\text{R}^3 = \text{OH}$ ,  $\text{R}^4 = \text{H}$ ) and the related pair yenusomidine (95;  $\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{OH}$ ) and raddeanone (95;  $\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{OH}$ ,  $\text{R}^4 = \text{H}$ ) have



<sup>119</sup> M. Hanaoka, K. Nagami, and T. Imanishi, *Chem. Pharm. Bull.*, 1979, **27**, 1947.

<sup>120</sup> D. B. MacLean, *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod.* 11th, 1978, **4**, 204.

<sup>121</sup> S. M. Susan and G. L. Geber, *J. Pharmacol. Exp. Ther.*, 1979, **209**, 67.

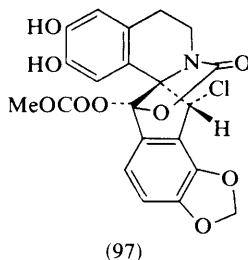
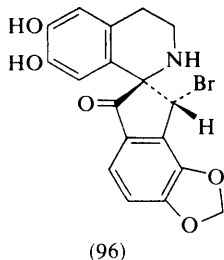
<sup>122</sup> J. A. Di Miceo and R. A. Gillis, *J. Pharmacol. Exp. Ther.*, 1979, **210**, 1.

<sup>123</sup> A. Sulcova, R. J. Adams, and R. K. Riemer, *Eur. J. Pharmacol.*, 1979, **60**, 323.

<sup>124</sup> M. A. Simmonds, *Neuropharmacology*, 1980, **19**, 39.

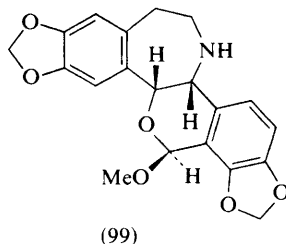
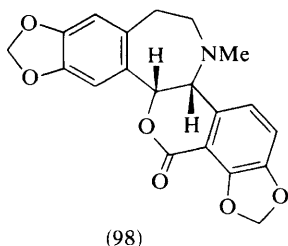
<sup>125</sup> V. B. Pandey, A. B. Ray, and B. Dasgupta, *Phytochemistry*, 1979, **18**, 695.

been synthesized.<sup>117</sup> An alternative approach to the synthesis of these bases involves Pictet-Spengler synthesis of (96), from  $\beta$ -(3,4-dihydroxyphenyl)ethylamine and 3-bromo-4,5-methylenedioxyindane-1,2-dione, the *N*-formyl-derivative of which undergoes a stereospecific assisted replacement of bromine by hydroxyl in the presence of silver ions, to give secondary alcohols from which corydaine and yenhusomidine can be prepared.<sup>126</sup> Treatment of the bromide (96) with ethyl chloroformate was found to give the chloride (97), the structure of which was determined crystallographically.<sup>126</sup> The structure of sibiricine has also been confirmed by a crystallographic study.<sup>127</sup> Methods of synthesis of alkaloids of this group have been reviewed.<sup>120</sup>



## 11 Rhoeadines

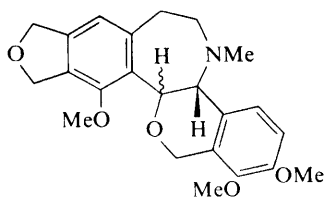
Rhoeadine, isorhoeadine, rhoeagenine, and papaverrubines A, B, C, D, and E have been isolated from *Papaver rupifragum*.<sup>75</sup> Papaverrubine E (99) has been synthesized from (-)-biccuculline by rearrangement to the lactone (98), followed by conversion through the *N*-oxide to the secondary base, protection of the nitrogen by reaction with toluene-*p*-sulphonyl isocyanate, reduction of the lactone to the hemi-acetal by sodium di-(2-methoxyethoxy)aluminium hydride, and methylation of this to the mixed acetal with methyl orthoformate and sulphuric acid.<sup>128</sup> Oxyrhoeagenine (100; *cis*-isomer) has been converted into iso-oxyrhoeagenine (100; *trans*-isomer) by hydrolysis to the hydroxy-acid followed by re-lactonization by triphenylphosphine and diethyl azodicarboxylate, some



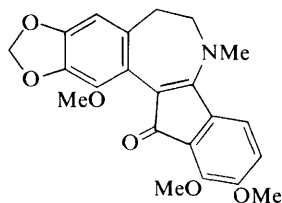
<sup>126</sup> D. Dime and S. McLean, *Can. J. Chem.*, 1979, **57**, 1569.

<sup>127</sup> S. M. Nasirov, I. A. Israilov, L. G. Kuz'mina, M. S. Yunusov, Yu. T. Struchkov, and S. Yu. Yunusov, *Khim. Priir. Soedin.*, 1978, 752.

<sup>128</sup> R. Hohlbrugger and W. Kloetzer, *Chem. Ber.*, 1979, **112**, 849.

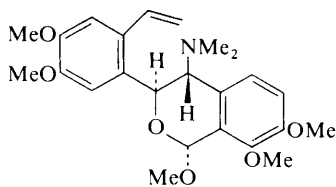


(100)



(101)

of the  $\alpha\beta$ -unsaturated ketone (101) being formed in the process.<sup>129</sup> Hofmann degradation of methylalpinigenine proceeds with formation of the styrene (102), and the reaction of the base (which is a benzylamine) with cyanogen bromide proceeds mainly with production of the *N*-cyano-nor-compound rather than by ring-fission.<sup>130</sup>

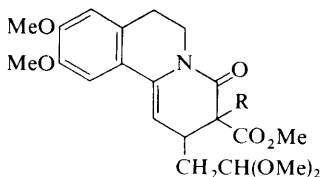


(102)

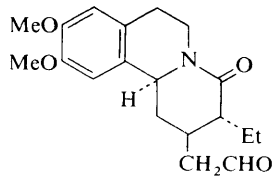
Methods of synthesis of rheadines have been reviewed.<sup>120</sup>

## 12 Emetine and Related Bases

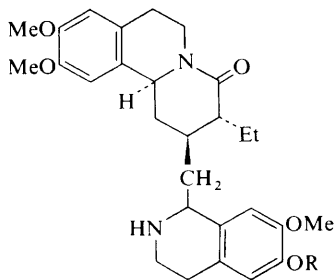
Emetine has been synthesized from 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline by condensation with dimethyl 3-methoxyallylidene malonate in meth-



(103)



(104)



(105) R = H

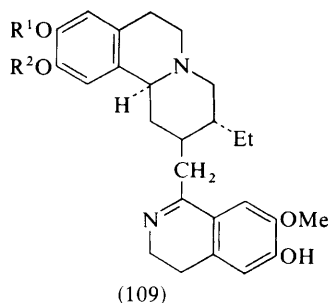
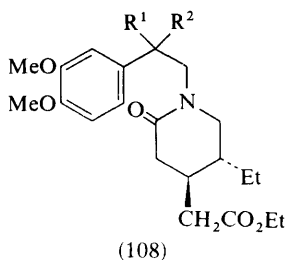
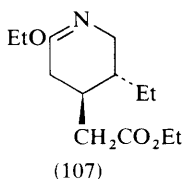
(106) R = Me

<sup>129</sup> R. Hohlbrugger and W. Kloetzer, *Chem. Ber.*, 1979, **112**, 3486.

<sup>130</sup> H. Roensch, *Symp. Pap. IUPAC. Int. Symp. Chem. Nat. Prod.* 11th, 1978, **2**, 38.

anol to give (103; R = H), *C*-ethylation of this to form (103; R = Et), catalytic reduction, and hydrolysis to the lactam (104) (related to protoemetine), which was condensed with (3-hydroxy-4-methoxyphenyl)ethylamine to give the phenol (105); this was methylated by diazomethane to (106), the lactam carbonyl of which was reduced by lithium aluminium hydride to give emetine.<sup>131,132</sup> Oxoprotoemetine (104) has also been converted by a similar route, using serotonin and tryptamine, into tubulosine and deoxytubulosine<sup>133,134</sup> (*cf.* Chapter 12, p. 168).

An alternative stereospecific synthesis of emetine has been accomplished from ethyl *trans*-5-ethyl-2-oxopiperidine-4-acetate by conversion into the lactim ether (107), which was allowed to react with 3,4-dimethoxyphenacyl bromide to give the ketone (108; R<sup>1</sup>R<sup>2</sup> = O). Reduction of this with sodium borohydride, followed by hydrogenolysis of the resulting alcohol, gave (108; R<sup>1</sup> = R<sup>2</sup> = H), which has previously been converted into emetine.<sup>135</sup> The reaction of (107) with 3-benzyloxy-4-methoxyphenacyl bromide and with 4-benzyloxy-3-methoxyphenacyl bromide afforded analogues of (108; R<sup>1</sup>R<sup>2</sup> = O), which were converted into 9-*O*-desmethylpsychotrine (109; R<sup>1</sup> = H, R<sup>2</sup> = Me) and 10-*O*-desmethylpsychotrine (109; R<sup>1</sup> = Me, R<sup>2</sup> = H) respectively.<sup>136,137</sup>



Secologanin has been converted (by stages) into the hydrazone (110), which, on Bischler-Napieralsky ring-closure, reduction, and hydrolysis, yields protoemetine; this was converted into cephaeline and deoxytubulosine by its reaction with (3-hydroxy-4-methoxyphenyl)ethylamine and with tryptamine respectively.<sup>138</sup> The dithioacetal (111), prepared from norcamphor (see Volume

<sup>131</sup> T. Kametani, Y. Suzuki, H. Terasawa, and M. Ihara, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1211.

<sup>132</sup> T. Kametani, Jpn. Kokai Tokkyo Koho 79 103 897 (*Chem. Abstr.*, 1980, **92**, 129 165).

<sup>133</sup> T. Kametani, Y. Suzuki, and M. Ihara, *Heterocycles*, 1978, **11**, 415.

<sup>134</sup> T. Kametani, Y. Suzuki, and M. Ihara, *Can. J. Chem.*, 1979, **57**, 1679.

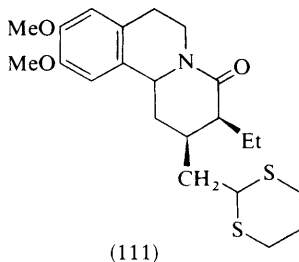
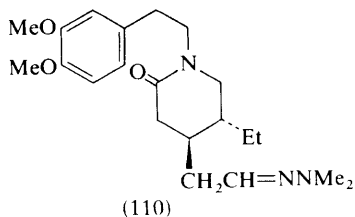
<sup>135</sup> T. Fujii and S. Yoshifujii, *Chem. Pharm. Bull.*, 1979, **27**, 1486.

<sup>136</sup> T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, *Heterocycles*, 1979, **12**, 1463.

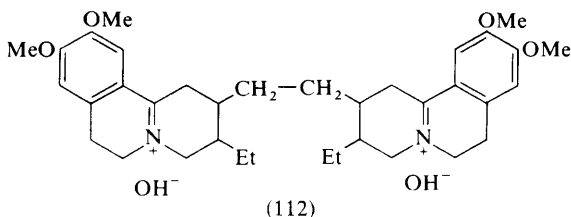
<sup>137</sup> T. Fujii and M. Ohba, *Fukusoku Kagaku Toronkai Koen Yoshishu* 12th, 1979, 31.

<sup>138</sup> R. T. Brown, A. G. Lashford, and S. B. Pratt, *J. Chem. Soc., Chem. Commun.*, 1979, 367.

10), has been epimerized by boron trifluoride in ether and converted into protoemetine and protoemetinol,<sup>139</sup> and the last-named has been prepared from the alcohol related to (104) by reduction with lithium aluminium hydride.<sup>140</sup>



The photolytic and thermolytic decomposition of emetine have been studied. Photolysis has been shown to involve oxidation and fragmentation, whilst thermolysis involves only oxidation. Compounds identified were emetamine, *O*-methylpsychotrine, 1',2'-didehydroemetine, tetrahydroemetinium bromide, rubremetinium bromide, 6,7-dimethoxy-3,4-dihydroisoquinoline, 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 3-ethyl-9,10-dimethoxy-1,4-dihydrobenzo[*a*]quinolizinium chloride, its 2-methyl-derivative, and the dimerized compound (112).<sup>141</sup>



A method of estimation of emetine by h.p.l.c. after its oxidative activation to a fluorescent product has been described.<sup>142</sup> The biological effects of emetine<sup>143,144</sup> and of dehydroemetine<sup>145</sup> have been studied.

### 13 Morphine Alkaloids

Salutaridine has been isolated from *Glaucium vitellinum*,<sup>109</sup> *Papaver bracteatum*,<sup>103</sup> *P. lasiothrix*,<sup>103</sup> and *P. pseudo-orientale*,<sup>103</sup> thebaine<sup>103</sup> and its methochloride<sup>146</sup> from *P. bracteatum*, oripavine from *P. orientale*,<sup>103</sup> and

<sup>139</sup> S. Takano, Y. Takahashi, S. Hatakeyama, and K. Ogasawara, *Heterocycles*, 1979, **12**, 765.

<sup>140</sup> T. Kametani, Jpn. Kokai Tokkyo Koho 79 125 699 (*Chem. Abstr.*, 1980, **92**, 147 020).

<sup>141</sup> C. Schuijt, G. M. J. Beijersbergen van Henegouwen, and K. W. Gerritsma, *Pharm. Weekblad, Sci. Ed.*, 1979, **1**, 186.

<sup>142</sup> S. J. Bannister, J. Stevens, D. Musson, and L. A. Sternson, *J. Chromatogr.*, 1979, **126**, 381.

<sup>143</sup> L. N. Drozdovskaya, *Khim. Mutagen. Gibr.*, 1978, 194.

<sup>144</sup> M. A. Dubick and W. C. T. Yang, *Proc. West. Pharmacol. Soc.*, 1979, **22**, 411.

<sup>145</sup> D. S. Shah, S. P. Rathod, and M. P. Patel, *Indian J. Pharmacol.*, 1979, **11**, 189.

<sup>146</sup> H. Roensch and W. Schade, *Phytochemistry*, 1979, **18**, 1089.

*O*-methylflavanantine from *Rhiziocarpa racemifera*.<sup>147</sup> The influence of day-length and of light intensity on the production of alkaloids in *P. somniferum* has been studied.<sup>148</sup>

Methods for the conversion of derivatives of morphine into their *N*-nor-compounds, using vinyl chloroformate,<sup>149</sup> trichloroethyl chloroformate,<sup>150</sup> and phenyl chloroformate,<sup>151</sup> have been patented. Norneopine has been prepared from neopine and diethyl azodicarboxylate and by the hydrolysis of *N*-nitrosoneopine.<sup>152</sup> The conversion of *N*-nor-bases into *N*-alkyl-compounds by the reduction of amides has been covered by a further patent.<sup>153</sup>

6-(*O*-Nitrobenzene-*p*-sulphonyl)neopine has been converted into the 6 $\beta$ -chloro- and 6 $\beta$ -bromo-6-deoxy-compounds by heating with lithium chloride and bromide,<sup>154</sup> and the 6-*O*-methanesulphonyl analogue gives the same products together with the  $\Delta^{6,8}$ -deoxy-compound, which is the sole product when the ester is heated with sodium iodide.<sup>155</sup> 2-Nitromorphine and 2-nitrocodeine have been reduced to the 2-amino-compounds in 60% and 81% yield respectively.<sup>156</sup>

Codeinone has been shown to react with lithium dialkylcuprates to give 8 $\beta$ -alkyl-dihydrocodeinones with low yields of 8 $\alpha$ -isomers in some cases.<sup>157</sup> 8 $\beta$ -Acyl compounds can also be obtained by using the equivalent of an acyl carbanion; e.g., lithium bis( $\alpha$ -ethoxyvinyl)cuprate gives the enol ether (113), which can be hydrolysed to 8 $\beta$ -acetylcodeinone. This diketone does not react with methylmagnesium iodide, but reduction of the enol ether (113) with sodium borohydride gives 8 $\beta$ -ethoxyvinyl-dihydrocodeine, which may be hydrolysed to 8 $\beta$ -acetyl-dihydrocodeine, and this reacts with alkyl-lithiums to give tertiary alcohols of general structure (114), which can be oxidized to the corresponding dihydrocodeinones by dimethyl sulphoxide and acetic anhydride.<sup>157</sup> The 8 $\beta$ -methyl- and 8 $\beta$ -ethyl-dihydrocodeinones are active analgesics and have been converted into *N*-cyclopropylmethyl- and *N*-cyclobutylmethyl-analogues and demethylated to the corresponding dihydromorphinones.<sup>157</sup> Similar reactions have been carried out on compounds lacking the 4,5 oxygen bridge.<sup>158</sup> Oxidation of codeinone with hydrogen peroxide has been accomplished to give the 7,8 $\beta$ -epoxide.<sup>159</sup>

Structures assigned to bases of the cyclohexenodihydrocodeinone series<sup>160</sup> have been confirmed by an X-ray crystallographic examination of the ketone

<sup>147</sup> D. Dwuma-Badu, J. S. K. Ayim, S. F. Withers, N. O. Agyemang, A. M. Ateya, M. M. El-Azizi, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, jr., *J. Nat. Prod.*, 1980, **43**, 123.

<sup>148</sup> J. Bernath and P. Tetenyi, *Biochem. Physiol. Pflanz.*, 1979, **174**, 468.

<sup>149</sup> R. A. Olofson and J. P. Pepe, U.S. P. 4 141 897 (*Chem. Abstr.*, 1979, **91**, 57 263).

<sup>150</sup> J. Hartenstein and G. Satzinger, Ger. Offen. 2 727 805 (*Chem. Abstr.*, 1979, **91**, 20 861).

<sup>151</sup> J. Sistare Noguera, Spanish P. 465 073 (*Chem. Abstr.*, 1979, **91**, 57 264).

<sup>152</sup> S. Hosztafi, S. Makleit, and R. Bognar, *Magy. Kem. Foly.*, 1980, **86**, 15.

<sup>153</sup> R. A. Olofson and J. P. Pepe, U.S. P. 4 161 597 (*Chem. Abstr.*, 1980, **92**, 22 671).

<sup>154</sup> L. Maat, J. A. De Groot, and H. C. Beyerman, *Synth. Commun.*, 1979, **9**, 713.

<sup>155</sup> S. Berenyi, S. Makleit, R. Bognar, and A. Tegdes, *Magy. Kem. Foly.*, 1979, **85**, 499.

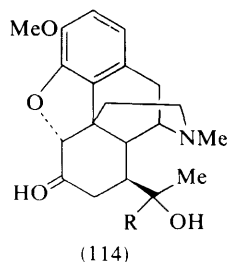
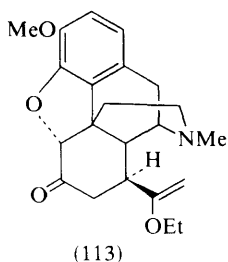
<sup>156</sup> N. Chatterjee, A. Minar, and D. D. Clarke, *Synth. Commun.*, 1979, **9**, 647.

<sup>157</sup> M. P. Kotick, D. L. Leland, J. O. Polazzi, and R. N. Schut, *J. Med. Chem.*, 1980, **23**, 166.

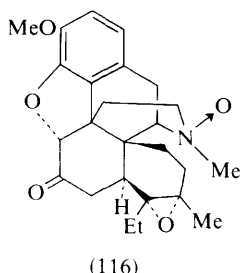
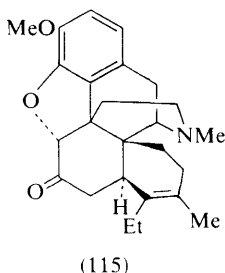
<sup>158</sup> J. O. Polazzi, R. N. Schut, M. P. Kotick, J. F. Howes, P. F. Osgood, R. K. Razdan, and J. E. Villareal, *J. Med. Chem.*, 1980, **23**, 174.

<sup>159</sup> K. Uba, N. Miyata, K. Watanabe, and M. Hirobe, *Chem. Pharm. Bull.*, 1979, **27**, 2257.

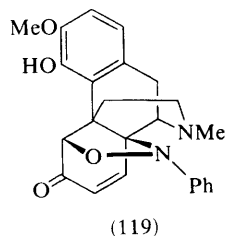
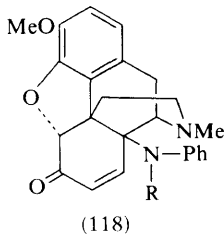
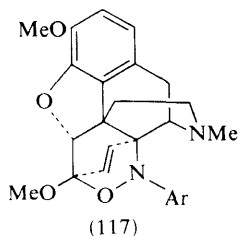
<sup>160</sup> K. W. Bentley, D. G. Hardy, C. F. Howell, W. Fulmor, L. E. Lancaster, J. J. Brown, G. O. Morton, and R. A. Hardy, *J. Am. Chem. Soc.*, 1967, **89**, 3303.



(115).<sup>161</sup> This base has been oxidized to the *N*-oxide epoxide (116), which can be reduced to the tertiary base, but attempts to open the epoxide ring gave complex mixtures.<sup>161</sup>



Details of the Diels-Alder addition of aromatic nitroso-compounds to thebaine to give adducts (117), the ring-opening of these to 14-hydroxylamino-compounds (118; R = OH), the reduction of these to 14-aryl-amino-compounds (118; R = H), and cyclization to (119) have been published.<sup>162</sup> Dihydrothebaine-*o*-4-phenyl ether (120; R = OPh) has been transformed into the benzyloisoquinoline (121) by potassamide in liquid ammonia, but the same transformation could not be effected with the free phenol (120; R = H) or with the deoxy-compound (120; R = H).<sup>163</sup>

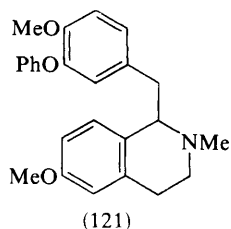
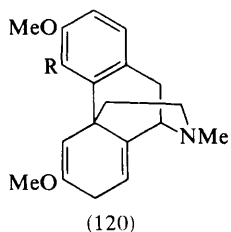


<sup>161</sup> A. Freer, G. A. Sim, I. G. Guest, A. C. B. Smith, and S. Turner, *J. Chem. Soc., Perkin Trans. 2*, 1979, 401.

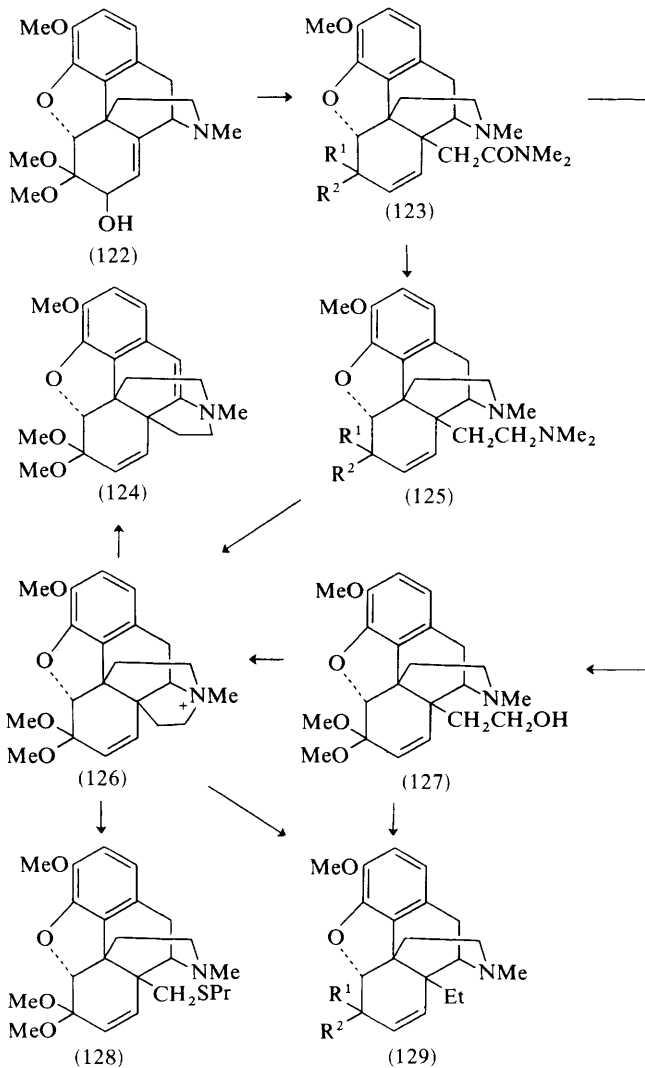
<sup>162</sup> G. W. Kirby, K. W. Bentley, P. Horsewood, and S. Singh, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3064.

<sup>163</sup> R. K. Razdan, P. Herlihy, H. C. Dalzell, and D. E. Portlock, *J. Org. Chem.*, 1979, **44**, 3730.





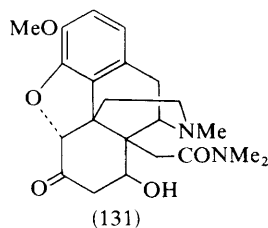
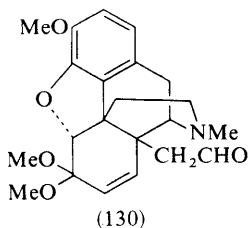
Claisen–Eschenmoser rearrangement of 7-hydroxyneopine dimethyl ketal (122), on treatment with *NN*-dimethylacetamide dimethyl ketal in xylene at



160 °C, affords the 14 $\beta$ -substituted compound (123; R<sup>1</sup> = R<sup>2</sup> = OMe), which can be reduced to the amine (125; R<sup>1</sup> = R<sup>2</sup> = OMe) by lithium aluminium hydride<sup>164</sup> and to the alcohol (127) by lithium triethylaluminium hydride.<sup>165</sup> Treatment of the amine (125; R<sup>1</sup> = R<sup>2</sup> = OMe) with methyl iodide gives the quaternary ion (126),<sup>164</sup> also obtained from the alcohol (127) by heating with sodium acetate and acetic anhydride or by the action of methanesulphonyl chloride in pyridine.<sup>165</sup> Hofmann degradation of the quaternary salt (126) gives the tertiary base (124) [also produced by Cope degradation of the *N*-oxide of (125; R<sup>1</sup> = R<sup>2</sup> = OMe)], treatment of (126) with lithium hydride and propanethiol gives (128), and Emde reduction of (126) yields the 14 $\beta$ -ethyl compound (129; R<sup>1</sup> = R<sup>2</sup> = OMe), also obtained by reduction of the methanesulphonyl ester of the *N*-oxide of (127).<sup>164</sup> The compounds (123; R<sup>1</sup> = R<sup>2</sup> = OMe), (125; R<sup>1</sup> = R<sup>2</sup> = OMe), and (129; R<sup>1</sup> = R<sup>2</sup> = OMe) have all been converted into the corresponding codeinones (123; R<sup>1</sup>R<sup>2</sup> = O), (125; R<sup>1</sup>R<sup>2</sup> = O), and (129; R<sup>1</sup>R<sup>2</sup> = O); (125; R<sup>1</sup>R<sup>2</sup> = O) has been reduced to the saturated ketone and this demethylated to 14 $\beta$ -(dimethylaminoethyl)dihydromorphinone.<sup>164</sup> The 14 $\beta$ -ethylcodeinone ketal has been demethylated and hydrolysed to 14 $\beta$ -ethylmorphinone, and has been converted into the secondary base and the *N*-cyclobutylmethyl derivative.<sup>164</sup>

Reduction of the amide (123; R<sup>1</sup> = R<sup>2</sup> = OMe) with sodium aluminium hydride gave a mixture of the bases (125; R<sup>1</sup> = R<sup>2</sup> = OMe), (127), and (130),<sup>165</sup> and the last of these lost carbon monoxide when heated with tris(triphenylphosphine)rhodium chloride in benzene to give the dimethyl ketal of 14 $\beta$ -methylcodeinone, which could be hydrolysed to 14 $\beta$ -methylcodeinone, the 7,8-dihydro-derivative of which proved to be identical with material previously prepared by a different route (see Volume 9, p. 116). The corresponding morphinone and dihydromorphinone have been prepared.<sup>164</sup>

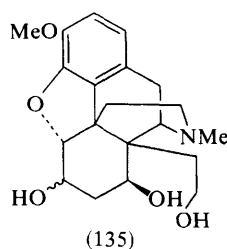
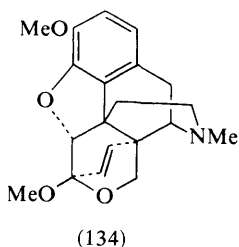
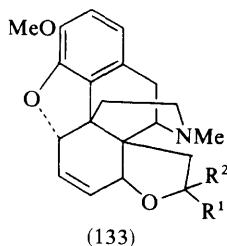
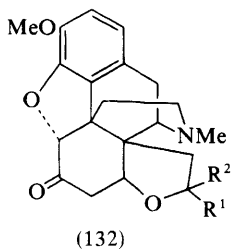
Hydrolysis of the amide acetal (123; R<sup>1</sup> = R<sup>2</sup> = OMe) to the related codeinone (123; R<sup>1</sup>R<sup>2</sup> = O) is effected by 0.1 M hydrochloric acid at room temperature. Use of more concentrated acid or elevated temperatures leads to



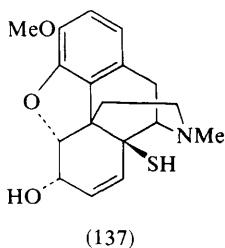
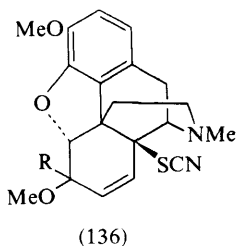
the bases (131), (132; R<sup>1</sup>R<sup>2</sup> = O), or (133; R<sup>1</sup>R<sup>2</sup> = O), according to the conditions. Reduction of the keto-lactone (132; R<sup>1</sup>R<sup>2</sup> = O) with lithium aluminium hydride leads to a mixture of the triols (135) with both  $\alpha$  and  $\beta$  orientation of the 6-hydroxyl group, and these can be cyclized by concentrated acid to the alcohols derived from (132; R<sup>1</sup> = R<sup>2</sup> = H). Similar results were observed with

<sup>164</sup> W. Fleischhacker and B. Richter, *Chem. Ber.*, 1979, **112**, 2539.

the hydrolysis of the acetal (127), which gave the bases (134), (133;  $R^1 = R^2 = H$ ), and (132;  $R^1 = R^2 = H$ ) under successively more vigorous conditions.<sup>165</sup> Esters of 14β-(carboxymethyl)codeinone can be prepared from the amide (123;  $R^1R^2 = O$ ) by heating with alcohols and toluene-*p*-sulphonic acid.<sup>165</sup>



Thebaine has been converted into the 14-substituted compound (136;  $R = SCN$ ) by treatment with  $(SCN)_2$ , and this gives the ketal (136;  $R = OMe$ ) when treated with methanol. The initial product (136;  $R = SCN$ ) is hydrolysed to the codeinone by sodium bicarbonate, and reduction of this with lithium aluminium hydride gives 14-mercaptocodeine (137), which can be demethylated to 14-mercaptomorphine by boron trifluoride.<sup>166</sup>

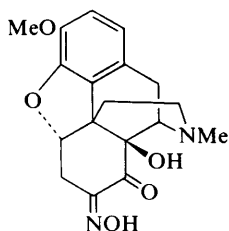


Attempts to prepare 7-keto-compounds from the bases (138) and (139) by the action of manganese dioxide and titanium chloride gave the ring-opened compounds (140) and (141).<sup>167</sup>

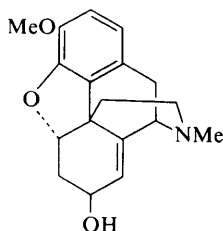
<sup>165</sup> W. Fleischhacker and B. Richter, *Chem. Ber.*, 1979, **112**, 3054.

<sup>166</sup> P. Osei-Gyimah and S. Archer, *J. Med. Chem.*, 1980, **23**, 162.

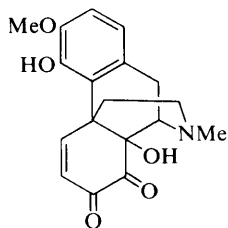
<sup>167</sup> W. Fleischhacker and E. Leitner, *Monatsh. Chem.*, 1979, **110**, 97.



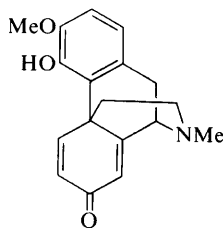
(138)



(139)



(140)

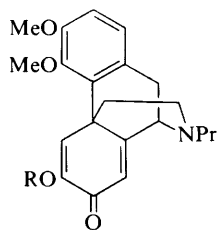


(141)

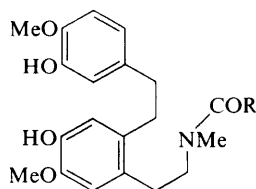
2,2'-Bis-ethers of morphine with poly(ethylene glycol) and with 2,6-bis(bromoethyl)pyridine have been prepared,<sup>168</sup> as have quaternary salts with alkyl, cyclopropylmethyl, and propargyl halides.<sup>169</sup>

Conformational studies of diastereoisomeric alcohols of the 6,14-*endo*-ethenotetrahydrothebaine series, using a PCILO semi-empirical quantum-mechanical method, have been made in relation to the different agonist/antagonist properties of the isomers.<sup>170</sup> [*N*-Methyl-<sup>11</sup>C]- and [*N*-methyl-<sup>14</sup>C]-morphine have been prepared.<sup>171,172</sup>

The bases (142; R = H) and (142; R = Me) have been synthesized by Pschorr cyclizations of the appropriate benzyloisoquinolines.<sup>173</sup> Oxidative cyclization of *N*-(carbethoxy)nor-reticuline with titanium trifluoroacetate gives *N*-(carbethoxy)norsalutaridine, and the same process with the seco-reticuline



(142)



(143)

<sup>168</sup> K. Frensch and F. Voegtler, *Liebigs Ann. Chem.*, 1979, 2118.

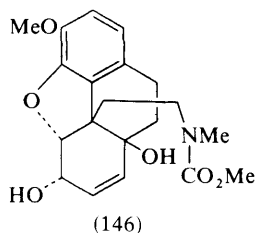
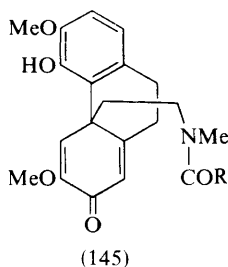
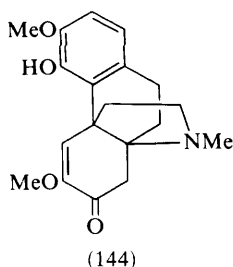
<sup>169</sup> L. I. Goldberg, H. Merz, and K. Stockhaus, U.S. P. 4 176 186 (*Chem. Abstr.*, 1980, **92**, 147 018).

<sup>170</sup> G. H. Loew and D. S. Berkowitz, *J. Med. Chem.*, 1979, **22**, 603.

<sup>171</sup> G. Kloster, E. Roeder, and H. J. Machulla, *J. Labelled Compd. Radiopharm.*, 1979, **16**, 441.

<sup>172</sup> D. R. Allen and P. L. Beaumier, *J. Labelled Compd. Radiopharm.*, 1979, **16**, 61.

<sup>173</sup> D. R. Elmaleh, F. E. Granchelli, and J. I. Neumeyer, *J. Heterocycl. Chem.*, 1979, **16**, 87.



derivatives (143; R = OMe and CF<sub>3</sub>) gives the seco-salutaridines (145). Hydrolysis of (145; R = CF<sub>3</sub>) involves spontaneous cyclization of the secondary amine through the  $\alpha\beta$ -unsaturated ketone to give the hasubanan derivative (144), and (145; R = OMe) has been converted into the 14-hydroxycodeine derivative (146) by reduction to the secondary alcohol, acid-catalysed closure of the 4,5 oxygen bridge, photo-oxidation, and reduction.<sup>174,175</sup>

10-Oxomorphine has been isolated from morphine solutions.<sup>176</sup> Morphine *N*-oxide, dihydromorphine, dihydroisomorphine,  $\beta$ - or  $\gamma$ -isomorphine, hydroxymorphine, and dihydroxymorphine have been isolated as metabolites of morphine from the urine of rats, rabbits, and guinea pigs.<sup>177</sup> The following other biological transformations have been observed: of codeine into norcodeine, dihydrocodeinone, nordihydrocodeinone, and dihydroisocodeine in rabbits,<sup>178</sup> into codeine 7,8 $\beta$ -epoxide by a suspension of rat liver microsomes<sup>179</sup> and into norcodeine by *Streptomyces* and *Cunninghamella* species,<sup>180</sup> of 14-hydroxydihydrocodeinone into its *N*-oxide and nor-base, 14-hydroxydihydromorphinone, and 14-hydroxydihydroisocodeine and its *N*-oxide in the rabbit,<sup>181</sup> and the *N*-demethylation and *O*-desethylation of *O*-ethylmorphine by rat enzymes.<sup>182</sup> The formation of conjugated metabolites of morphine, codeine, and nalorphine has been reviewed.<sup>183</sup>

Methods for the detection of morphine in liver,<sup>184</sup> bile,<sup>185</sup> urine,<sup>186</sup> body fluids,<sup>187</sup> and opium,<sup>188</sup> and of heroin in street drugs<sup>189</sup> have been described.

<sup>174</sup> M. A. Schwartz, *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod.* 11th, 1978, 4, 274.

<sup>175</sup> M. A. Schwartz and R. A. Wallace, *Tetrahedron Lett.*, 1979, 3257.

<sup>176</sup> B. Proska, Z. Voticky, L. Molnar, J. Putek, and M. Stefek, *Chem. Zvesti*, 1978, 32, 710.

<sup>177</sup> S. Y. Yeh, H. A. Krebs, and C. W. Gorodetsky, *J. Pharm. Sci.*, 1979, 68, 133.

<sup>178</sup> E. J. Cone, W. D. Darwin, and C. W. Gorodetsky, *J. Pharm. Pharmacol.*, 1979, 31, 314.

<sup>179</sup> K. Uba, N. Miyata, K. Watanabe, and M. Hirobe, *Chem. Pharm. Bull.*, 1980, 28, 356.

<sup>180</sup> G. J. Sewell, C. J. Soper, and R. T. Parfitt, *J. Pharm. Pharmacol.*, 1979, 31 (Suppl.), 90P.

<sup>181</sup> T. Ishida, K. Oguri, and H. Yoshimura, *Drug Metab. Dispos.*, 1979, 7, 162.

<sup>182</sup> P. H. Duquette and J. L. Holtzman, *J. Pharmacol. Exp. Ther.*, 1979, 211, 213.

<sup>183</sup> K. Oguri, *Yakugaku Zasshi*, 1980, 100, 117.

<sup>184</sup> M. Stajic, Y. H. Caplan, and R. C. Backer, *J. Forensic Sci.*, 1979, 24, 732.

<sup>185</sup> Y. H. Caplan, R. C. Backer, M. Stajic, and B. C. Thompson, *J. Forensic Sci.*, 1979, 24, 745.

<sup>186</sup> R. D. Budd, D. F. Mathis, and W. J. Leung, *Clin. Toxicol.*, 1980, 16, 61.

<sup>187</sup> A. Ciardetti, F. Lambardi, and M. Acocella, *Quadr. Sclavo Diagn. Clin. Lab.*, 1979, 15, 319.

<sup>188</sup> G. L. Dadisch and G. Machata, *Beitr. Gerichtl. Med.*, 1979, 37, 35.

<sup>189</sup> D. J. Reuland and W. A. Trinler, *Forensic Sci.*, 1978, 11, 195.

Methods for the estimation of morphine and its derivatives by h.p.l.c.,<sup>190</sup> g.l.c.<sup>191,192</sup> g.c.,<sup>193</sup> mass spectrometry<sup>194—196</sup> radioimmunoassay,<sup>197,198</sup> and immunofluorescence<sup>199</sup> have been described, as has an improved method for the isolation of morphine and naloxone from biological samples.<sup>200</sup>

The pharmacokinetics of morphine have been studied,<sup>201—203</sup> as has its receptor binding,<sup>204—206</sup> and its effects on hypothermia,<sup>207</sup> on calcium uptake by synaptosomes,<sup>208</sup> and lysed synaptosomes,<sup>209</sup> on metabolism of catecholamine in brain,<sup>210</sup> on levels of corticosteroids and growth hormone in plasma,<sup>211</sup> on leuteinising hormone,<sup>212</sup> follicle-stimulating hormone,<sup>212</sup> and prolactin,<sup>212—215</sup> on neuroendocrine function,<sup>216</sup> on brain function and biochemistry,<sup>217—226</sup> on behaviour,<sup>227—240</sup> on the gastrointestinal tract<sup>241</sup> and on the cardiovascular

<sup>190</sup> M. White, *J. Chromatogr.*, 1979, **178**, 229.

<sup>191</sup> S. H. Weinstein and J. C. Gaylord, *J. Pharm. Sci.*, 1979, **68**, 527.

<sup>192</sup> M. J. Prager, S. M. Harrington, and T. F. Governo, *J. Assoc. Off. Anal. Chem.*, 1979, **62**, 304.

<sup>193</sup> S. Felby, *Forensic Sci. Int.*, 1979, **13**, 145.

<sup>194</sup> D. Reed, *Clin. Toxicol.*, 1979, **14**, 169.

<sup>195</sup> G. Paulig, *Instrum. Appl. Forensic Drug Chem. Proc. Int. Symp.*, 1978, 210.

<sup>196</sup> R. Saferstein, J. Manura, and T. A. Brettell, *J. Forensic Sci.*, 1979, **24**, 312.

<sup>197</sup> A. M. Baumgartner, P. F. Jones, W. A. Baumgartner, and C. T. Black, *J. Nucl. Med.*, 1979, **20**, 748.

<sup>198</sup> J. W. A. Findlay, E. C. Jones, and R. M. Welch, *Drug Metab. Dispos.*, 1979, **7**, 310.

<sup>199</sup> S. Balkon, J. H. Bidanset, and V. D. Lynch, *J. Forensic Sci.*, 1980, **25**, 88.

<sup>200</sup> G. L. Sprague and A. E. Takemori, *J. Pharm. Sci.*, 1979, **68**, 660.

<sup>201</sup> E. R. Garrett and A. J. Jackson, *J. Pharm. Sci.*, 1979, **68**, 753.

<sup>202</sup> K. Nishitaten, S. H. Nagai, A. D. Fink, and B. A. Berkowitz, *Anesthesiology*, 1979, **50**, 520.

<sup>203</sup> J. C. Young, W. C. Clark, S. H. Nagai, B. A. Berkowitz, and S. Spector, *Anesthesiology*, 1979, **51**, 495.

<sup>204</sup> W. Hoss, K. Okamura, M. Formaniak, and R. Tanaka, *Life Sci.*, 1979, **24**, 1003.

<sup>205</sup> J. Dum, G. Meyer, V. Hoell, and A. Herz, *Eur. J. Pharmacol.*, 1979, **58**, 453.

<sup>206</sup> J. Judis, *J. Pharm. Sci.*, 1980, **69**, 71.

<sup>207</sup> T. F. Burke and G. C. Rosenfeld, *Life Sci.*, 1979, **24**, 1067.

<sup>208</sup> F. Guerrero-Munoz, K. V. Cerreta, M. Guerrero, and E. L. Way, *J. Pharmacol. Exp. Ther.*, 1979, **209**, 132.

<sup>209</sup> F. Guerrero-Munoz, M. Guerrero, and E. L. Way, *J. Pharmacol. Exp. Ther.*, 1979, **211**, 370.

<sup>210</sup> I. P. Anokhina, B. M. Kogan, and N. A. Khristolyubova, *Ann. Ist. Super Sanita*, 1978, **14**, 71.

<sup>211</sup> E. D. French, J. F. Garcia, and R. George, *Psychoneuroendocrinology*, 1978, **3**, 237.

<sup>212</sup> T. Muraki, H. Nakadate, Y. Tokunaga, R. Kato, and T. Makino, *Neuroendocrinology*, 1979, **28**, 241.

<sup>213</sup> I. S. Login and R. M. MacLeod, *Eur. J. Pharmacol.*, 1979, **60**, 253.

<sup>214</sup> T. Ieiri, H. T. Chen and J. Meites, *Neuroendocrinology*, 1979, **29**, 288.

<sup>215</sup> J. I. Koenig, M. A. Mayfield, S. M. McCann, and L. Kruhlich, *Life Sci.*, 1979, **25**, 853.

<sup>216</sup> J. Meites, J. F. Bruni, D. A. Van Vugt, and A. F. Smith, *Life Sci.*, 1979, **24**, 1325.

<sup>217</sup> W. R. Klemm and C. G. Mallari, *Arch. Int. Pharmacodyn. Ther.*, 1979, **237**, 237.

<sup>218</sup> W. R. Klemm and C. G. Mallari, *Prog. Neuro-Psychopharmacol.*, 1978, **2**, 535.

<sup>219</sup> R. V. Esposito, S. McLean, and C. Kornetsky, *Brain Res.*, 1979, **168**, 425.

<sup>220</sup> N. Dafny, M. Brous, B. M. Rigor, and T. F. Burks, *Neurol. Res.*, 1979, **1**, 77.

<sup>221</sup> G. J. Bennett and D. J. Mayer, *Brain Res.*, 1979, **172**, 243.

<sup>222</sup> J. M. Besson and D. Le Bars, *Encephale*, 1979, **5**, 205.

<sup>223</sup> A. W. A. Crossley and P. Slater, *J. Neurosci. Res.*, 1979, **4**, 423.

<sup>224</sup> F. Jackler, S. S. Steiner, R. J. Bodnar, R. F. Ackermann, W. T. Nelson, and S. J. Ellman, *Int. J. Neurosci.*, 1979, **9**, 21.

<sup>225</sup> C. Van der Wende and M. T. Sparlein, *Res. Commun. Chem. Pathol. Pharmacol.*, 1979, **24**, 103.

<sup>226</sup> L. Eroglu, *Psychopharmacology (Berlin)*, 1979, **63**, 13.

<sup>227</sup> M. J. Kallman, R. M. Spencer, A. T. White, W. T. Chance, and J. A. Rosencrans, *Res. Commun. Chem. Pathol. Pharmacol.*, 1979, **24**, 116.

<sup>228</sup> M. Davis, *Eur. J. Pharmacol.*, 1979, **54**, 341.

<sup>229</sup> H. Watanabe, M. Ikeda, and K. Watanabe, *J. Pharmacobio-Dyn.*, 1979, **2**, 169.

system,<sup>242,243</sup> on intrabiliary pressure,<sup>244</sup> on clearance of endogeneous creatinine and sodium-, potassium-, and chloride-ion balance,<sup>245</sup> on discrimination of electroshock,<sup>246</sup> on incorporation of leucine<sup>247</sup> and lysine<sup>248</sup> into protein, on mydriasis,<sup>249</sup> on visual responses,<sup>250</sup> on renal transport,<sup>251</sup> on arterial smooth muscle,<sup>252</sup> spinal cord,<sup>253,254</sup> and spinal units,<sup>255</sup> on the accumulation of DOPA after decarboxylase inhibition,<sup>256</sup> on levels of dopamine receptors,<sup>257</sup> enkephalin,<sup>258</sup> and endorphin<sup>259</sup> in brain, on human neuromuscular transmission,<sup>260</sup> on ventilatory response to exercise,<sup>261</sup> on release of dopamine from the hypothalamus,<sup>262</sup> on phosphodiesterase inhibitors,<sup>263</sup> on water intake,<sup>264</sup> on myocardial ischaemia,<sup>265</sup> on the uptake<sup>266</sup> and metabolism<sup>267</sup> of serotonin, on

- <sup>230</sup> E. Schioerring and A. Hecht, *Psychopharmacology (Berlin)*, 1979, **64**, 67, 73.  
<sup>231</sup> E. R. Seidel, J. M. Beaton, and R. S. Teague, *Eur. J. Pharmacol.*, 1979, **56**, 75.  
<sup>232</sup> E. D. French, S. Vasquez, and R. George, *Eur. J. Pharmacol.*, 1979, **57**, 387.  
<sup>233</sup> J. Panksepp, N. Najam, and F. Soares, *Pharmacol. Biochem. Behav.*, 1979, **11**, 131.  
<sup>234</sup> C. L. Boekkamp, A. G. Phillips, and A. R. Cools, *Pharmacol. Biochem. Behav.*, 1979, **11**, 289.  
<sup>235</sup> E. M. Joyce, and S. D. Iversen, *Neurosci. Lett.*, 1979, **14**, 207.  
<sup>236</sup> A. Bacotti, *J. Pharmacol. Exp. Ther.*, 1980, **212**, 280.  
<sup>237</sup> L. G. Frey and J. C. Winter, *Psychopharmacology (Berlin)*, 1979, **66**, 263.  
<sup>238</sup> G. Friedler and H. S. Wheeler, *Pharmacol. Biochem. Behav.*, 1979, **11** (Suppl.), 23.  
<sup>239</sup> G. Urca, R. L. Nahin, and J. C. Liebeskind, *Exp. Neurol.*, 1979, **66**, 248.  
<sup>240</sup> C. G. Lineberry and A. T. Kulics, *Neuropharmacology*, 1980, **19**, 107.  
<sup>241</sup> R. Schultz, M. Wuester, and A. Herz, *Arch. Pharm. (Weinheim, Ger.)*, 1979, **308**, 255.  
<sup>242</sup> M. C. Wallenstein, *Eur. J. Pharmacol.*, 1979, **59**, 253.  
<sup>243</sup> F. F. Beloyartsev, B. I. Islamov, V. M. Bobkova, T. E. Kolesnik, I. M. Shvetsov, and G. N. Madaminov, *Anesteziol. Reanimatol.*, 1979, 32.  
<sup>244</sup> J. E. Arguelles, Y. Franatovic, F. Romo-Salas, and J. A. Aldrete, *Anesth. Analg. (Cleveland)* 1979, **58**, 120.  
<sup>245</sup> F. Huidobro, R. Croxatto, and J. P. Huidobro-Toro, *Arch. Int. Pharmacodyn. Ther.*, 1979, **237**, 31.  
<sup>246</sup> L. Dykstra, *J. Pharmacol. Exp. Ther.*, 1979, **209**, 297.  
<sup>247</sup> D. H. Clouet and M. Ratner, *J. Neurosci. Res.*, 1979, **4**, 93.  
<sup>248</sup> R. S. Sinatra, D. H. Ford, and R. K. Rhines, *Brain Res.*, 1979, **171**, 307.  
<sup>249</sup> A. D. Korczyn, R. Boyman, and L. Shifter, *Life Sci.*, 1979, **24**, 1667.  
<sup>250</sup> J. G. Salamy, S. F. Sands, and N. Dafny, *Life Sci.*, 1979, **24**, 1241.  
<sup>251</sup> W. O. Berndt and I. K. Ho, *Toxicol. Appl. Pharmacol.*, 1979, **48**, 263.  
<sup>252</sup> T. Pasch and L. A. Bugsch, *Anaesthesist*, 1979, **28**, 283.  
<sup>253</sup> I. Jurna and G. Heinz, *Brain Res.*, 1979, **171**, 573.  
<sup>254</sup> Th. Yaksh and G. M. Tyce, *Brain Res.*, 1979, **172**, 176.  
<sup>255</sup> O. Cavillo, J.L. Henry, and R. S. Neuman, *Can. J. Physiol. Pharmacol.*, 1979, **57**, 652.  
<sup>256</sup> S. Perrson, *Eur. J. Pharmacol.*, 1979, **55**, 121.  
<sup>257</sup> S. De La Baume, G. Patey, H. Marcais, J. Protais, J. Costentin, and J. C. Schwarz, *Life Sci.*, 1979, **24**, 2333.  
<sup>258</sup> J. Shani, R. Azov, and B. A. Weissman, *Neurosci. Lett.*, 1979, **12**, 319.  
<sup>259</sup> R. Przewlocki, V. Hoellt, T. Duka, G. Keber, C. Gramsch, and L. Haarmann, *Brain Res.*, 1979, **174**, 357.  
<sup>260</sup> P. C. Duke, C. H. Johns, C. Pinsky, and P. Goertzen, *Can. Anaesth. Soc. J.*, 1979, **26**, 201.  
<sup>261</sup> T. V. Santiago, J. C. Johnson, D. J. Riley, and N. H. Edelman, *J. Appl. Physiol.: Respir., Environ. Exercise Physiol.*, 1979, **47**, 112.  
<sup>262</sup> D. A. Van Vugt, J. F. Bruni, P. W. Sylvester, H. T. Chen, T. Ieiri, and J. Meites, *Life Sci.*, 1979, **24**, 2361.  
<sup>263</sup> J. Swaynok and K. Jhamandes, *Can. J. Physiol. Pharmacol.*, 1979, **57**, 853.  
<sup>264</sup> D. Atanakovic and A. Suinonic, *Acta Pharm. Jugosl.*, 1979, **29**, 77.  
<sup>265</sup> I. Kisin, W. Markiewicz, and J. Birkhahan, *Isr. J. Med. Sci.*, 1979, **15**, 588.  
<sup>266</sup> B. A. Donzanti and R. O. Warwick, *Eur. J. Pharmacol.*, 1979, **59**, 107.  
<sup>267</sup> F. Miranda, R. Invernizzi, and R. Samanin, *Pharmacol. Res. Commun.*, 1979, **11**, 455.

concanavalin-A-mediated blastogenesis,<sup>268</sup> on the pituitary-adrenal system,<sup>269</sup> on the immune properties of serum and the morphology of bone marrow,<sup>270</sup> on hippocampal cells,<sup>271</sup> on foetuses,<sup>272</sup> on plasma proteins,<sup>273</sup> on synaptic transmission,<sup>274</sup> on release of acetylcholine,<sup>275,276</sup> on memory,<sup>277</sup> on body weight in addicts,<sup>278</sup> on spontaneously discharging neurones,<sup>279</sup> on dopaminergic neurones<sup>280</sup> and on hypothalamic thermosensitive<sup>281</sup> and glucoreponsive<sup>282</sup> neurones, on thermoregulation,<sup>283,284</sup> on L-asparaginase,<sup>285</sup> on immunosuppression,<sup>286</sup> on sexual behaviour,<sup>287</sup> on enzyme activity in neuroblastoma-glioma cells,<sup>288</sup> on neonate to adult development,<sup>289,290</sup> on calcium-induced release of noradrenalin,<sup>291</sup> and on results of electrical stimulation of acupuncture points.<sup>292</sup> The analgesic effects of morphine have been compared with those of pethidine,<sup>293</sup> assessed in combination with methotrimeprazine,<sup>294</sup> and studied in spinal anaesthesia.<sup>295</sup> The effects of sub-analgesic doses of morphine<sup>296</sup> and the attenuation of the effects of the alkaloid by conjugated morphine-protein antigen<sup>297</sup> have been examined, as have the interactions of morphine with bradykinin<sup>298</sup> and

<sup>268</sup> W. K. K. Ho and A. Leung, *Pharmacol. Res. Commun.*, 1979, **11**, 413.

<sup>269</sup> C. Guaza, A. Torrellas, J. Borrell, and S. Borrell, *Pharmacol. Biochem. Behav.*, 1979, **11**, 57.

<sup>270</sup> T. I. Ul'yankina, V. V. Lakin, and M. I. Ul'yanov, *Farmakol. Toksikol. (Moscow)*, 1979, **42**, 474.

<sup>271</sup> S. A. Deadwyler and J. H. Robinson, *Brain Res. Bull.*, 1979, **4**, 609.

<sup>272</sup> M. L. Kirby, *Proc. Soc. Exp. Biol. Med.*, 1979, **162**, 287.

<sup>273</sup> M. V. Komendantova, K. I. Bender, V. V. Kupchikov, and L. K. Pashuk, *Farmakol. Toksikol. (Moscow)*, 1979, **42**, 611.

<sup>274</sup> J. Bornstein and H. L. Fields, *Neurosci. Lett.*, 1979, **15**, 77.

<sup>275</sup> Y. Kondo and K. Iwatsubo, *J. Osaka. Univ. Dent. Sch.*, 1978, **18**, 23.

<sup>276</sup> L. Beani, A. Siniscalchi, and G. Sarto, *Pharmacol. Res. Commun.*, 1979, **11**, 663.

<sup>277</sup> I. Isquierdo, *Psychopharmacology (Berlin)*, 1979, **66**, 199.

<sup>278</sup> M. I. Martin, A. Aleixandre, L. Lastra, and P. D. Garia de Jalon, *Arch. Pharmacol. Toxicol.*, 1979, **5**, 103.

<sup>279</sup> E. P. Finnerty and S. H. H. Chan, *Eur. J. Pharmacol.*, 1979, **59**, 307.

<sup>280</sup> P. Moleman and J. Bruinvels, *J. Neural Transm.*, 1979, **46**, 225.

<sup>281</sup> F. Baldino, A. L. Beckman, and M. W. Alder, *Thermoregul. Mech. Their Ther. Implic., Int. Symp. Pharmacol. Thermoregul., 4th*, 1979 (publ. 1980), p. 157.

<sup>282</sup> T. Ono, Y. Oomura, H. Nishino, K. Sasaki, K. Muramoto, and I. Yano, *Brain Res.*, 1980, **185**, 208.

<sup>283</sup> B. Cox, T.-F. Lee, and J. Vale, *Thermoregul. Mech. Their Ther. Implic., Int. Symp. Pharmacol. Thermoregul., 4th*, 1979 (publ. 1980), p. 157.

<sup>284</sup> P. W. Dettmar and A. Cowan, *Thermoregul. Mech. Their Ther. Implic., Int. Symp. Pharmacol. Thermoregul., 4th*, 1979 (publ. 1980), p. 173.

<sup>285</sup> H. Koyuncuoglu, M. Keyer-Uysal, K. Berkman, M. Gungor, and E. C. Genc, *Eur. J. Pharmacol.*, 1979, **60**, 639.

<sup>286</sup> S. Yanagiura, T. Nishimura, H. Takeda, and T. Misawa, *Koen Yoshishu-Yakubutsu Kassei Shinpo-jumu, 8th*, 1979, 115.

<sup>287</sup> N. L. Ostrowski, J. M. Stapleton, R. G. Noble, and L. D. Reid, *Pharmacol. Biochem. Behav.*, 1979, **11**, 763.

<sup>288</sup> U. Bacharach, D. Benalal, and A. Reches, *Life Sci.*, 1979, **25**, 1879.

<sup>289</sup> T. Sonderegger, S. O'Shea, and E. Zimmerman, *Neurobehav. Toxicol.*, 1979, **1**, 161.

<sup>290</sup> T. Sonderegger, S. O'Shea, and E. Zimmerman, *Pharmacol. Biochem. Behav.*, 1979, **11** (Suppl.), 29.

<sup>291</sup> M. Goethert and E. Wehking, *Experientia*, 1980, **36**, 239.

<sup>292</sup> M. V. Komendantova, E. V. Zoryan, and V. V. Yasnetsov, *Farmakol. Toksikol. (Moscow)*, 1980, **43**, 29.

<sup>293</sup> A. Quevauviller and F. Boizard, *Bull. Acad. Natl. Med. (Paris)*, 1979, **163**, 203.

<sup>294</sup> A. B. St. John and C. K. Born, *Res. Commun. Chem. Pathol. Pharmacol.*, 1979, **26**, 25.

<sup>295</sup> T. L. Yaksh, P. R. Wilson, R. F. Kaiko, and C. E. Inturrisi, *Anesthesiology*, 1979, **51**, 386.

<sup>296</sup> Yu. D. Ignatov and A. S. Morozova, *Farmakol. Toksikol. (Moscow)*, 1979, **42**, 225.

<sup>297</sup> I. E. Kovalev, O. Yu. Polevaya, S. Metkalova, L. A. Basharova, M. M. Borisov, and A. K. Yakubovskii, *Farmakol. Toksikol. (Moscow)*, 1979, **42**, 615.

<sup>298</sup> Yu. Z. Anisimov, V. M. Bulaev, and V. V. Sherstnev, *Byull. Eksp. Biol. Med.*, 1979, **88**, 683.



with nalorphine.<sup>299</sup> A toxic interaction of morphine with choline<sup>300</sup> and a lethal synergism between morphine and propranolol, antagonized by naloxone and by naltrexone,<sup>301</sup> have been described. Neurobiological data concerning morphine have been reviewed.<sup>302</sup>

The pharmacology of naloxone has been reviewed<sup>303</sup> and further studied,<sup>304,305</sup> and its clinical effects have been reviewed.<sup>306</sup> Studies have also been made of its effects on the blockade of the action of endorphin,<sup>307</sup> on behaviour,<sup>308–315</sup> on the inhibition of the growth of mammary tumours,<sup>316</sup> on brain activity and biochemistry,<sup>218,317,318</sup> on intake of food<sup>319,320</sup> and of water,<sup>321</sup> on skeletal muscle,<sup>322</sup> on prolactin secretion,<sup>214,323,324</sup> on smooth muscle,<sup>252</sup> on spinal units,<sup>256</sup> on calcium uptake in synaptosomes,<sup>325</sup> on stress-induced analgesia,<sup>326</sup> on halothane anaesthesia,<sup>327</sup> on diazepam-induced feeding,<sup>328</sup> on newborn infants,<sup>329</sup> on the lethality of barium chloride,<sup>330</sup> on peripheral analgesia,<sup>331</sup> on body temperature,<sup>332</sup> on hypovolaemic shock,<sup>333</sup> on response to amphetamine,<sup>334</sup> on audiogenic seizures,<sup>335</sup> on blood pressure and heart rate after electro-shock,<sup>336</sup>

- <sup>299</sup> M. S. Shin and Y. S. Cheon, *Koryo Taehakkyo Uikwa Taehak Chapchi*, 1979, **16**, 443.  
<sup>300</sup> I. K. Ho, H. M. Loh, and E. L. Way, *Toxicol. Appl. Pharmacol.*, 1979, **51**, 203.  
<sup>301</sup> W. M. Davis and N. S. Hatoum, *Toxicology*, 1979, **14**, 141.  
<sup>302</sup> J. M. Besson, D. Le Bars, and J. L. Oliveras, *Ann. Anesthesiol. Fr.*, 1979, **19**, 343.  
<sup>303</sup> Anonymous, *Pharm. Weekblad*, 1979, **114**, 365.  
<sup>304</sup> L. B. Wallnau and G. G. Gallup, *Pharmacol. Biochem. Behav.*, 1979, **10**, 499.  
<sup>305</sup> W. Wouters, M. E. C. Ermes-Busio, and J. Van der Bercken, *Eur. J. Pharmacol.*, 1979, **55**, 431.  
<sup>306</sup> C. P. O'Brien, R. Greenstein, J. Ternes, and G. E. Woody, *Ann. N.Y. Acad. Sci.*, 1978, **311**, 232.  
<sup>307</sup> R. Schultz, M. Wuester, and A. Herz, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 1979, **306**, 93.  
<sup>308</sup> G. L. Gessa, E. Paglietti, and B. Pellegrini-Quarantotti, *Science*, 1979, **204**, 203.  
<sup>309</sup> B. Pellegrini-Quarantotti, E. Paglietti, M. Peta, and G. L. Gessa, *Experientia*, 1979, **35**, 524.  
<sup>310</sup> D. Ruffing, B. Kovacic, S. Demetriou, and E. F. Domino, *Psychopharmacology (Berlin)*, 1979, **62**, 207.  
<sup>311</sup> A. M. Young and T. Thompson, *Psychopharmacology (Berlin)*, 1979, **62**, 307.  
<sup>312</sup> B. M. Myers and M. J. Baum, *Pharmacol. Biochem. Behav.*, 1979, **10**, 615.  
<sup>313</sup> R. J. Rodgers and R. M. J. Deacon, *Psychopharmacology (Berlin)*, 1979, **65**, 103.  
<sup>314</sup> D. L. Margolin and B. H. Moon, *J. Neurol. Sci.*, 1979, **43**, 13.  
<sup>315</sup> A. T. Arnsten and D. S. Segal, *Life Sci.*, 1979, **25**, 1035.  
<sup>316</sup> C. F. Aylsworth, C. A. Hodson, and J. Meites, *Proc. Soc. Exp. Biol. Med.*, 1979, **161**, 18.  
<sup>317</sup> S. W. Gumulka, V. Dinnendahl, and P. S. Schoenhoefer, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 1979, **306**, 169.  
<sup>318</sup> J. P. Rosenfeld and P. E. Rice, *Brain Res.*, 1979, **178**, 609.  
<sup>319</sup> D. R. Brown and S. G. Holtzman, *Pharmacol. Biochem. Behav.*, 1979, **11**, 567.  
<sup>320</sup> B. Brands, J. A. Thornhill, M. Hirst, and C. W. Gowdey, *Life Sci.*, 1979, **24**, 1773.  
<sup>321</sup> J. M. Stapleton, N. L. Ostrowski, V. J. Merriman, M. Lind, and L. D. Reid, *Bull. Psychon. Soc.*, 1979, **13**, 237.  
<sup>322</sup> G. B. Frank and J. Marwaha, *J. Pharmacol. Exp. Ther.*, 1979, **209**, 382.  
<sup>323</sup> J. B. Martin, G. Tolis, I. Woods, and H. Guyda, *Brain Res.*, 1979, **168**, 210.  
<sup>324</sup> M. S. Gold, A. L. C. Pottash, I. Extein, D. E. Redmond, and H. D. Kleber, *Am. J. Psychiatry*, 1979, **136**, 1339.  
<sup>325</sup> F. Guerrero-Munoz, M. Guerrero, and E. L. Way, *Dev. Neurosci.*, 1978, **4**, 311.  
<sup>326</sup> R. J. Bodnar, D. D. Kelly, A. Spaggianga, C. Pavlides, and M. Glusman, *Bull. Psychon. Soc.*, 1978, **12**, 125.  
<sup>327</sup> J. O. Arndt and E. Freze, *Anesthesiology*, 1979, **51**, 58.  
<sup>328</sup> J. M. Stapleton, M. D. Lind, V. Merriman, and L. D. Reid, *Life Sci.*, 1979, **24**, 2421.  
<sup>329</sup> J. E. H. Brice, T. A. Moreland, and C. M. M. Walker, *Arch. Dis. Child.*, 1979, **54**, 356.  
<sup>330</sup> A. Segretti, F. J. Vocci, and W. L. Dewey, *Toxicol. Appl. Pharmacol.*, 1979, **50**, 25.  
<sup>331</sup> S. H. Ferreira and M. Nakamura, *Prostaglandins*, 1979, **18**, 191, 201.  
<sup>332</sup> J. Stewart and R. Eikelboom, *Life Sci.*, 1979, **25**, 1165.  
<sup>333</sup> A. I. Faden and J. W. Holaday, *Science*, 1979, **205**, 317.  
<sup>334</sup> S. Amir, R. Blair, and Z. Amit, *Life Sci.*, 1979, **25**, 1407.  
<sup>335</sup> R. A. Schreiber, *Psychopharmacology (Berlin)*, 1979, **66**, 205.  
<sup>336</sup> G. L. Belenky and J. W. Holaday, *Brain Res.*, 1979, **177**, 414.

on male impotence and frigidity,<sup>337</sup> on levels of cyclic AMP,<sup>338</sup> on electroacupuncture analgesia,<sup>339</sup> on memory,<sup>277</sup> and on sexual behaviour.<sup>287</sup> The narcotic antagonist action of naloxone has been further studied,<sup>340-354</sup> as has its ability to increase pain perception.<sup>355,356</sup>

The narcotic-antagonist properties,<sup>357,358</sup> plasma kinetics,<sup>359</sup> and clinical pharmacology<sup>360</sup> of naltrexone have been studied, as well as its effects on skeletal muscle,<sup>322</sup> on water intake,<sup>361</sup> on metabolism of other drugs,<sup>362</sup> on male impotence,<sup>337</sup> on hormonal balance,<sup>363</sup> on prolactin secretion,<sup>364</sup> on behaviour,<sup>312,365</sup> and on mammary tumours.<sup>316</sup> The narcotic-antagonist properties of nalorphine<sup>342,343</sup> and its effects on newborn infants,<sup>329</sup> on male impotence and frigidity,<sup>337</sup> on biochemical processes,<sup>366</sup> and on the *N*-demethylation of morphine,<sup>367</sup> and the effects of heroin on secretion of thyrotropin, thyroid hormones, and prolactin in man<sup>368</sup> and of prolactin in addicts,<sup>369</sup> on intestinal propulsion,<sup>370</sup> and on memory<sup>371</sup> have been studied.

The pharmacological effects of *N*-allyl- and *N*-cyclopropylmethyl-6 $\beta$ -azidodeoxydihydronormorphine have been compared with those of naloxone

<sup>337</sup> G. L. Gessa, Belg. P. 876 968 (*Chem. Abstr.*, 1980, **92**, 104 582).

<sup>338</sup> R. D. Dias, M. A. Carrasco, D. O. Souza, and I. Izquierdo, *Eur. J. Pharmacol.*, 1979, **60**, 345.

<sup>339</sup> S.-G. Fan, J. Tang, X.-L. Chen, Q.-Z. Zhai, and J.-S. Han, *K'o Hsueh T'ung Pao*, 1979, **24**, 1149.

<sup>340</sup> G. Paalzow, *Psychopharmacology (Berlin)*, 1979, **62**, 235.

<sup>341</sup> Y. Shiwaku, H. Nagashima, R. M. Duncalf, D. Duncalf, and F. Foldes, *Anesth. Analg. (Cleveland)*, 1979, **58**, 93.

<sup>342</sup> P. Janicki and J. Libich, *Pharmacol. Biochem. Behav.*, 1979, **10**, 623.

<sup>343</sup> V. R. O. Spiehler and L. Paalzow, *Life Sci.*, 1979, **24**, 2125.

<sup>344</sup> I. Yano, H. Nishino, and T. Muramo, *Jpn. J. Pharmacol.*, 1979, **29**, 357.

<sup>345</sup> M. Frid and G. Singer, *Psychopharmacology (Berlin)*, 1979, **63**, 211.

<sup>346</sup> R. McGivern, C. Berka, G. G. Bernston, J. M. Walker, and C. A. Sandman, *Life Sci.*, 1979, **25**, 885.

<sup>347</sup> J. N. Wiley and D. A. Downs, *Life Sci.*, 1979, **25**, 797.

<sup>348</sup> I. J. Bodycote and G. B. Cheshier, *Eur. J. Pharmacol.*, 1979, **57**, 259.

<sup>349</sup> H. K. Lee, C. Y. Chai, M. J. Wayner, and L. C. Kao, *Pharmacol. Biochem. Behav.*, 1979, **11**, 227.

<sup>350</sup> W. R. Buckett, *Eur. J. Pharmacol.*, 1979, **58**, 169.

<sup>351</sup> N. N. Ardentova, *Farmakol. Toksikol. (Moscow)*, 1980, **43**, 23.

<sup>352</sup> L. P. Dwoskin, G. L. Sprague, A. E. Takemori, and S. B. Sparber, *Life Sci.*, 1980, **26**, 377.

<sup>353</sup> J. Swaynok, C. Pinsky, and F. S. LaBella, *Life Sci.*, 1979, **25**, 1621.

<sup>354</sup> H. H. Holst-Larsen, A. O. Aasen, and H. E. Rugstad, *Acta Pharmacol. Toxicol.*, 1979, **45**, 91.

<sup>355</sup> J. J. Carmody, P. R. Carrol, and D. Morgans, *Life Sci.*, 1979, **24**, 1149.

<sup>356</sup> H. Monder, Y. Yasukawa, and J. J. Christian, *Pharmacol. Biochem. Behav.*, 1979, **11**, 235.

<sup>357</sup> R. J. Katz, *Int. J. Neurosci.*, 1979, **9**, 49.

<sup>358</sup> T. U. C. Jaerbe, P. Loman, and M. D. B. Swedberg, *Pharmacol. Biochem. Behav.*, 1979, **10**, 493.

<sup>359</sup> R. H. Reuning, V. K. Batra, T. M. Ludden, M. Y. Jao, B. E. Morrison, D. A. McCarthy, S. E. Harrigan, S. B. Ashcroft, and R. A. Sams, *J. Pharm. Sci.*, 1979, **68**, 411.

<sup>360</sup> G. L. Sprague and A. E. Takemori, *J. Pharm. Sci.*, 1979, **68**, 660.

<sup>361</sup> H. Frenk and J. B. Rosen, *Pharmacol. Biochem. Behav.*, 1979, **11**, 387.

<sup>362</sup> T. M. Lehman, P. Pyati, and G. K. Peterson, *Life Sci.*, 1979, **25**, 1591.

<sup>363</sup> J. Volavka, A. Mallya, J. Bauman, J. Pevenik, D. Cho, D. Reker, B. James, and R. Dornbush, *Adv. Exp. Med. Biol.*, 1979, **116**, 291.

<sup>364</sup> J. Ellingboe, J. H. Mendelson, and J. C. Kuehnle, *Pharmacol. Biochem. Behav.*, 1980, **12**, 163.

<sup>365</sup> G. J. Harry and J. A. Rosencrans, *Pharmacol. Biochem. Behav.*, 1979, **11** (Suppl.), 19.

<sup>366</sup> K. I. Bender and N. N. Ardentova, *Farmakol. Toksikol. (Moscow)*, 1979, **42**, 358.

<sup>367</sup> L. Tampier, *Ach. Biol. Med. Exp.*, 1978, **11**, 77.

<sup>368</sup> V. Chan, C. Wang, and R. T. T. Yeung, *Clin. Endocrinol.*, 1979, **10**, 557.

<sup>369</sup> F. Brambilla, C. L. Cazzullo, L. Bellodi, D. De Maio, A. Zamboni, and W. Zamboni-Muciaccia, *Neuropsychobiology*, 1979, **5**, 294.

<sup>370</sup> M. G. Northway and T. F. Burks, *Eur. J. Pharmacol.*, 1979, **59**, 237.

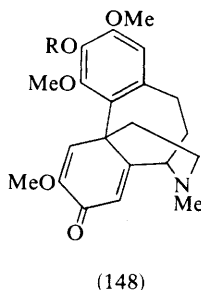
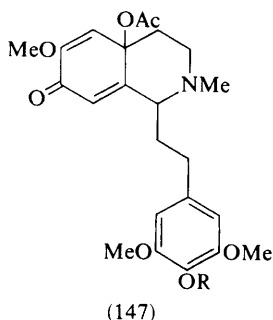
<sup>371</sup> C. Castellano, *Psychopharmacology*, 1980, **67**, 235.

and naltrexone,<sup>372</sup> and the effects of buprenorphine on the human respiratory centre<sup>373</sup> and on body temperature<sup>284</sup> have been studied. The properties of 6β-[di-(2-chloroethyl)amino]deoxydihydromorphine and of its 14-hydroxy- and 14-hydroxy-*N*-cyclobutylmethyl-nor-derivatives, and their reactions with opioid-receptor sites, have been reviewed.<sup>374,375</sup> 6β-Aminodeoxydihydromorphine has been converted into the half-methyl-ester half-amide of fumaric acid, which behaves as a potent reversible agonist that is inhibited by prior administration of naltrexone. The *N*-cyclopropylmethyl-nor-derivative has also been prepared.<sup>376</sup>

A review of the use of opium and of morphine and its synthetic analogues has been published.<sup>377</sup>

#### 14 β-Phenylethylisoquinolines

Cyclization of (147; R = CH<sub>2</sub>Ph) by the action of trifluoroacetic acid yields androcymbine benzyl ether (148; R = CH<sub>2</sub>Ph), which has been converted into androcymbine (148; R = H); androcymbine methyl ether (148; R = Me) has been prepared from (147; R = Me) in a similar manner. Homoaporphines and homoproaporphines are produced, as well as homomorphinandienones, during this cyclization.<sup>378</sup>



#### 15 Benzophenanthridines

Chelidonine, dihydrochelerythrine, and dihydrosanguinarine have been isolated from *Glaucium vitellinum*,<sup>109</sup> chelerythrine and sanguinarine from *Corydalis ophiocarpa*,<sup>71</sup> oxysanguinarine and 8-methoxysanguinarine from *Fumaria indica*,<sup>125</sup> a new base corynolamine (149; R = CH<sub>2</sub>OH) from *Corydalis incisa*,<sup>379</sup>

<sup>372</sup> J. Knoll, *Orvostudomány*, 1978, **29**, 131.

<sup>373</sup> S. N. Steen, R. L. Smith, S. Jeretin, M. Petrun, M. S. Mok, and M. Lippmann, *IRCS Med. Sci.: Libr. Compend.*, 1979, **7**, 597.

<sup>374</sup> P. S. Portoghese, D. L. Carson, T. P. Caruso, and A. E. Takemori, *Recent Adv. Recept. Chem. Proc. Int. Symp.*, 1978, 235.

<sup>375</sup> T. P. Caruso, A. E. Takemori, D. L. Carson, and P. S. Portoghese, *Science*, 1979, **204**, 316.

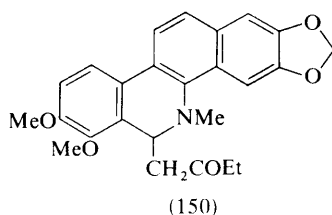
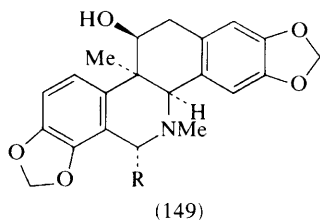
<sup>376</sup> P. S. Portoghese, D. L. Carson, L. M. Sayre, D. S. Fries, and A. E. Takemori, *J. Med. Chem.*, 1980, **23**, 233.

<sup>377</sup> B. R. Belleau, *Can. J. Chem.*, 1980, **32**, 24.

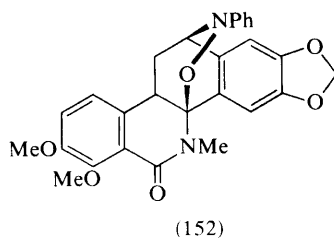
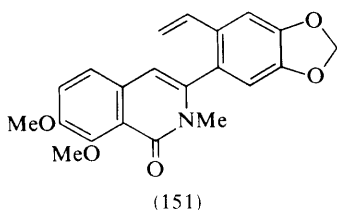
<sup>378</sup> H. Hara, O. Hoshino, B. Umezawa, and Y. Iitaka, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2657.

<sup>379</sup> N. Takao and K. Iwasa, *Chem. Pharm. Bull.*, 1979, **27**, 2194.

and another new base of structure (150) from *Fagara mayu*.<sup>380</sup> The structure of corynolamine was determined by spectroscopic studies and by conversion into the base (149; R = Me), identical with material prepared by C-methylation of corynoline,<sup>379</sup> and the base (150) was prepared from chelerythrine chloride and methyl ethyl ketone.<sup>380</sup> 9,10-Desmethylenesanguinarine and its 9,10-dehydro-derivative (*i.e.* the related *ortho*-quinone) have been isolated from the purification of samples of sanguinarine and chelerythrine, and they are assumed to be artefacts of isolation or of long storage.<sup>381</sup>



The absolute stereochemistry of chelidonine has been determined by an *X*-ray crystallographic study of its *p*-bromobenzoyl ester.<sup>382</sup> Further details of the photolysis of the unsaturated amide (151) to the two dimers reported previously (Vol. 10) have been published. Attempts have been made to trap the initial product with dieneophiles; with nitrosobenzene, the adduct (152) was obtained, and this was decomposed by heat to form oxochelerythrine.<sup>383</sup> A review of methods of synthesis of (±)-corynoline and of 12-hydroxy-, 11-*epi*-, and homo-chelidonine has been published.<sup>384</sup>



The cytotoxic effects of sanguinarine,<sup>385</sup> chelidonine,<sup>385</sup> and chelidonine methiodide<sup>386</sup> and the effect of sanguinarine on cardiac ATPase<sup>387</sup> have been studied.

<sup>380</sup> E. M. Assem, I. A. Benages, and S. Albonico, *Phytochemistry*, 1979, **18**, 511.

<sup>381</sup> O. E. Lasskaya and O. N. Tolkachev, *Khim. Prir. Soedin.*, 1978, 764.

<sup>382</sup> N. Takao, N. Bessho, M. Kamigauchi, K. Iwasa, K. Tomita, T. Fujiwara, and S. Fujii, *Tetrahedron Lett.*, 1979, 495.

<sup>383</sup> M. Onda and H. Yamagushi, *Chem. Pharm. Bull.*, 1979, **27**, 2076.

<sup>384</sup> I. Ninomiya, O. Yamamoto, T. Kiguchi, and T. Naito, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 21st*, 1978, 42.

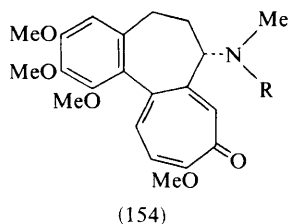
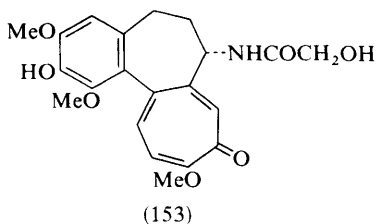
<sup>385</sup> B. Hladon, Z. Kowalewski, T. Bobkiewicz, and K. Gronostaj, *Ann. Pharm. (Poznan)*, 1978, **13**, 61.

<sup>386</sup> J. Zbierska and Z. Kowalewski, *Herba Pol.*, 1979, **25**, 209.

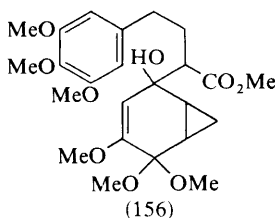
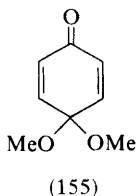
<sup>387</sup> E. Siefen, R. J. Adams, and R. K. Reiner, *Eur. J. Pharmacol.*, 1979, **60**, 323.

## 16 Colchicine

2-Desmethylcolchifoline, a new base of structure (153), assigned on the basis of spectroscopic studies, has been isolated from *Colchicum autumnale*.<sup>388</sup> *N*-Trifluoroacetyl-*N*-desacetylcolchicine can be methylated with methyl iodide and potassium carbonate to *N*-trifluoroacetyldemecolcine (154; R = CF<sub>3</sub>CO) (together with the isomeric tropolone ether), and this may be hydrolysed to demecolcine (154; R = H). A more practical route to demecolcine effects the *O*- and *N*-methylations separately with diazomethane and methyl iodide, respectively.<sup>389</sup>



In a variant of the synthesis of colchicine from the methoxyquinone ketal (155) reported in the previous volume, the alkaloid has been synthesized *via* the ester (156).<sup>390</sup> A new assignment of the <sup>13</sup>C n.m.r. signals of the 22 carbon atoms of colchicine, differing considerably from those given by Singh and co-workers,<sup>391</sup> has been made.<sup>392</sup>



The effects of colchicine on inflammation,<sup>393—395</sup> on arthritis induced by uric acid,<sup>396</sup> on the action of suppressor cells generated against human  $\gamma$ -globulin,<sup>397</sup> on atherosclerosis,<sup>398</sup> on nephritis,<sup>399</sup> on the formation of dentine in teeth,<sup>400,401</sup>

<sup>388</sup> P. Sedmera, H. Potesilova, V. Malichova, V. Preininger, and F. Santavy, *Heterocycles*, 1979, **12**, 337.

<sup>389</sup> H. G. Capraro and A. Brossi, *Helv. Chim. Acta*, 1979, **62**, 965.

<sup>390</sup> D. A. Evans, D. J. Hart, P. M. Koelsch, and P. A. Cain, *Pure Appl. Chem.*, 1979, **51**, 1285.

<sup>391</sup> S. P. Singh, S. S. Parmar, V. I. Stenberg, and S. A. Farnum, *Spectrosc. Lett.*, 1977, **10**, 1001.

<sup>392</sup> A. Blade-Font, R. Muller, J. Elguero, R. Fauré, and E. J. Vincent, *Chem. Lett.*, 1979, 233.

<sup>393</sup> K. R. Min, C. Mizuno, and S. Tsurufuji, *J. Pharmacobio-Dyn.*, 1979, **2**, 1.

<sup>394</sup> S. Tsurufuji, K. R. Min, and C. Mizuno, *J. Pharmacobio-Dyn.*, 1979, **2**, 113.

<sup>395</sup> D. Bradshaw, M. Roch-Arveiller, and J. P. Giroud, *Eur. J. Rheumatol. Inflamm.*, 1978, **1**, 249.

<sup>396</sup> I. Spilberg, B. Mandell, J. Mehta, L. Simchowicz, and D. Rosenberg, *J. Clin. Invest.*, 1979, **64**, 775.

<sup>397</sup> D. E. Parks, D. A. Shaller, and W. O. Weigle, *J. Exp. Med.*, 1979, **149**, 1168.

<sup>398</sup> W. Hollander, J. Paddock, S. Nagraj, M. Colombo, and B. Kirkpatrick, *Atherosclerosis*, 1979, **33**, 111.

<sup>399</sup> S. Penchas, I. Charuzi, and J. H. Boss, *Eur. J. Clin. Invest.*, 1979, **9**, 161.

<sup>400</sup> T. Okayasu, *Shika Kiso Igakki Zasshi*, 1978, **20**, 381.

<sup>401</sup> A. Karim and H. Warshawsky, *Anat. Rec.*, 1979, **195**, 587.

on the behaviour of goldfish,<sup>402</sup> on the secretion of insulin,<sup>403</sup> on the synthesis of hyaluronate in bone cultures,<sup>404</sup> on eye-lens cells,<sup>405</sup> on the morphology of chondrocytes,<sup>406</sup> on the release of prostaglandins from macrophages,<sup>407</sup> on the degradation of epidermal growth factor,<sup>408</sup> on the formation of cyclic AMP,<sup>409</sup> on interphase cells,<sup>410</sup> and on the permeability of epithelium,<sup>411</sup> and the healing of wounds<sup>412</sup> and the mutagenic activity of colchicine<sup>413</sup> have been studied.

<sup>402</sup> G. Clingbine and C. E. Heading, *Physiol. Behav.*, 1979, **23**, 229.

<sup>403</sup> N. H. Ertel and S. Akgun, *Metab. Clin. Exp.*, 1979, **28**, 1255.

<sup>404</sup> A. Severson, *J. Cell. Physiol.*, 1979, **101**, 341.

<sup>405</sup> D. C. Beebe, D. E. Feagans, E. J. Blanchette-Mackie, and M. E. Nau, *Science*, 1979, **206**, 836.

<sup>406</sup> K. Madsen, S. Moskalewski, J. Thyberg, and U. Friberg, *Experientia*, 1979, **35**, 1572.

<sup>407</sup> D. Gesma, W. Kramer, M. Brenner, G. Till, and K. Resch, *J. Immunol.*, 1980, **124**, 376.

<sup>408</sup> K. D. Brown, M. Friedkin, and E. Rozengurt, *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 480.

<sup>409</sup> V. Stolc, *Exp. Cell Biol.*, 1979, **47**, 401.

<sup>410</sup> D. Davidson, *Cytologia*, 1979, **44**, 633.

<sup>411</sup> M. Svelto, D. Cremaschi, and C. Lipp, *J. Bioenerg. Biomembr.*, 1979, **11**, 103.

<sup>412</sup> M. Chvapil, E. E. Peacock, E. C. Carlson, S. Balu, K. Steinbronn, and D. Morton, *J. Surg. Res.*, 1980, **28**, 49.

<sup>413</sup> T. Tsuchimoto and B. E. Matter, *Arch. Toxicol.*, 1979, **42**, 239.

## Aporphinoid Alkaloids

BY M. SHAMMA

### 1 Introduction

A useful and timely supplementary listing of new aporphines, oxoaporphines, phenanthrenes, and 4,5-dioxoaporphines has appeared.<sup>1</sup> The alkaloids of *Glaucium* species, which include several aporphines and oxoaporphines, have been tabulated<sup>2</sup> and a general discussion of the chemistry and biogenesis of isoquinoline alkaloids, including the aporphines, has been presented.<sup>3</sup>

*Ocotea minarum* has proven to be a rich repository of new aporphinoids.<sup>4</sup> Two completely new routes for the biogenesis of the aporphines in Nature have been suggested. The first involves the photolysis of proaporphines<sup>5</sup> and the second the oxidative cleavage of protoberberinium salts to *N*-formylbenzylisoquinolines, which can then undergo cyclization to the aporphine skeleton.<sup>6</sup> The synthetic compound (–)-*N*-(2-chloroethyl)norapomorphine,<sup>7</sup> structurally related to the powerful dopaminergic agonist (–)-*N*-(*n*-propyl)norapomorphine,<sup>8</sup> could prove to be of value as a probe of dopamine receptors in the brain, and as a neuroleptic drug.<sup>7</sup>

### 2 Proaporphines

Pronuciferine (1) has been synthesized by photocyclization of the brominated phenol (2).<sup>9a</sup> The light-induced rearrangement of proaporphines yields aporphines that are substituted at C-9 or at both C-8 and C-9.<sup>5</sup> This topic is further discussed below, under the sections on aporphines and aporphine dimers. The known alkaloid *N*-methylecrotsparine has been found in *Pachygone ovata*.<sup>9b</sup>

<sup>1</sup> H. Guinaudeau, M. Leboeuf, and A. Cavé, *J. Nat. Prod.*, 1979, **42**, 325.

<sup>2</sup> I. A. Israilov, S. U. Karimova, and M. S. Yunusov, *Khim. Priir. Soedin.*, 1979, 125 [*Chem. Nat. Compd. (Engl. Transl.)*, 1979, 103].

<sup>3</sup> T. Kametani and M. Ihara, *Heterocycles*, 1979, **13**, 497.

<sup>4</sup> V. Vecchietti, C. Casagrande, G. Ferrari, and G. Severinicca, *Farmaco., Ed. Sci.*, 1979, **34**, 829.

<sup>5</sup> S. F. Hussain, M. T. Siddiqui, G. Manikumar, and M. Shamma, *Tetrahedron Lett.*, 1980, **21**, 723.

<sup>6</sup> N. Murugesan and M. Shamma, *Tetrahedron Lett.*, 1979, 4521.

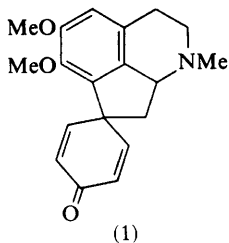
<sup>7</sup> J. L. Neumeyer, S.-J. Law, R. J. Baldessarini, and N. S. Kula, *J. Med. Chem.*, 1980, **23**, 594. See also *Chem. Eng. News*, May 26, 1980, p. 24 and B. Costall, D. H. Fortune, S.-J. Law, R. J. Naylor, J. L. Neumeyer, and V. Nohria, *Nature (London)*, 1980, **285**, 571.

<sup>8</sup> M. K. Menon, W. G. Clark, and J. L. Neumeyer, *Eur. J. Pharmacol.*, 1979, **52**, 1; J. L. Neumeyer, W. P. Dafeldecker, B. Costall, and R. J. Naylor, *J. Med. Chem.*, 1977, **20**, 190; M. Titeler and P. Seeman, *Eur. J. Pharmacol.*, 1979, **56**, 291.

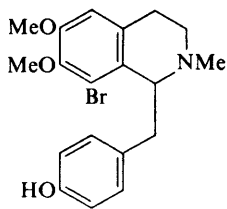
<sup>9</sup> (a) Z. Horii, C. Iwata, and Y. Nakashita, *Chem. Pharm. Bull.*, 1978, **26**, 481; (b) S. Dasgupta, A. B. Ray, S. K. Bhattacharya, and R. Bose, *J. Nat. Prod.*, 1979, **42**, 399.

### 3 Aporphines

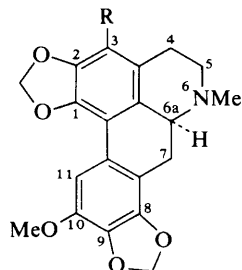
A careful investigation of the alkaloidal content of the Brazilian plant *Ocotea minarum* (Lauraceae) has led to five new aporphines, namely ocotominarine (3), ocominarine (4), norleucoxytonine (5), iso-oconovine (6), and 4-hydroxydicentrine (7).<sup>4</sup>



(1)

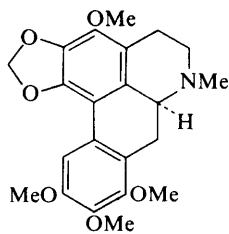


(2)

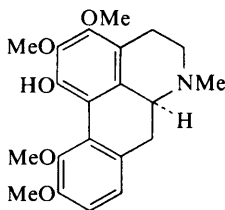


(3) R = OMe

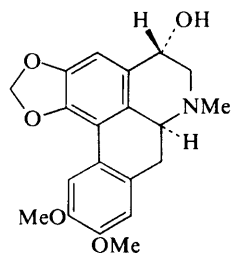
(4) R = H



(5)

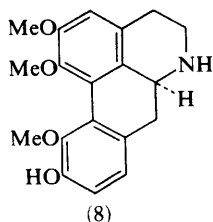


(6)

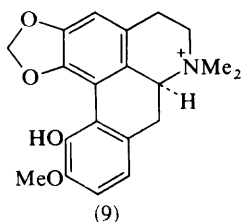


(7)

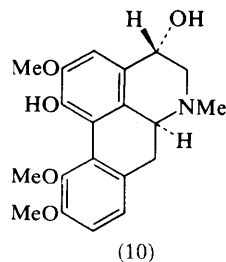
Other new aporphines are (+)-hernagine (8), found in *Hernandia nymphaefolia* (Hernandiaceae),<sup>10</sup> (+)-bulbocapnine *N*-metho-salt (9), obtained from *Corydalis cava* (Fumariaceae),<sup>11</sup> and glaufidine (10), which is present in *Glaucium fimbriigerum* (Papaveraceae).<sup>12</sup>



(8)



(9)



(10)

<sup>10</sup> K. Yakushijin, S. Sugiyama, Y. Mori, H. Murata, and H. Furukawa, *Phytochemistry*, 1980, **19**, 161.

<sup>11</sup> J. Slavík and L. Slavíková, *Collect. Czech. Chem. Commun.*, 1979, **44**, 2261.

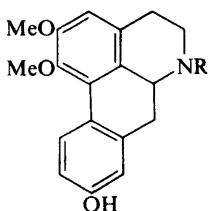
<sup>12</sup> I. A. Israilov, S. U. Karimova, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin*, 1979, 104.



Known aporphines that have recently been re-isolated, and their sources, are:

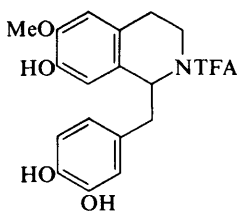
Corydine	<i>Mahonia aquifolium</i> <sup>13</sup>
<i>N</i> -Methylcorydine	<i>Kolobopetalum auriculatum</i> <sup>14</sup>
	<i>Stephania dinklagei</i> <sup>15</sup>
Isocorydine	<i>Mahonia aquifolium</i> <sup>13</sup>
<i>N</i> -Methylisocorydine	<i>Zanthoxylum culantrillo</i> <sup>16</sup>
	<i>Zanthoxylum coriaceum</i> <sup>16</sup>
	<i>Rhigiocarya racemifera</i> <sup>15</sup>
	<i>Fumaria parviflora</i> <sup>15</sup>
Isoboldine	<i>Mahonia aquifolium</i> <sup>13</sup>
	<i>Thalictrum alpinum</i> <sup>17</sup>
<i>N</i> -Methylglauicine	<i>Stephania dinklagei</i> <sup>15</sup>
<i>N,N</i> -Dimethyl-lindcarpine	<i>Coscinium fenestratum</i> <sup>18</sup>
Thaliporphine	<i>Thalictrum alpinum</i> <sup>17</sup>
Magnoflorine	<i>Thalictrum alpinum</i> <sup>17</sup>
	<i>Zanthoxylum culantrillo</i> <sup>16</sup>
	<i>Kolobopetalum auriculatum</i> <sup>14</sup>
	<i>Rhigiocarya racemifera</i> <sup>15</sup>
Xylopine	<i>Annona squamosa</i> <sup>19</sup>
Leucoxylophine	<i>Ocotea minarum</i> <sup>4</sup>
Dicentrine	<i>Ocotea minarum</i> <sup>4</sup>
Ocoteine	<i>Ocotea minarum</i> <sup>4</sup>
Leucoxine	<i>Ocotea minarum</i> <sup>4</sup>
Ocopodine	<i>Ocotea minarum</i> <sup>4</sup>
Predicentrine	<i>Ocotea minarum</i> <sup>4</sup>

A new route to the aporphines, with definite biogenetic implications, has been furnished by the finding that the light-catalysed rearrangement of the proaporphines pronuciferine (1) and *N*-acetylnorpronuciferine yields the corresponding 9-hydroxylated aporphines (11) and (12). As a result of these transformations, possible biogenetic schemes for the formation of naturally occurring 8- and 9-substituted and 8,9-disubstituted aporphines have been presented.<sup>5</sup> Acid-catalysed rearrangement of pronuciferine is known to give 10-hydroxyaporphine.

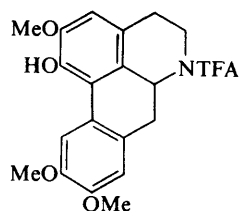


(11) R = Me

(12) R = Ac



(13)



(14)

TFA = trifluoroacetyl

<sup>13</sup> H. Ripperger, *Pharmazie*, 1979, **34**, 435.

<sup>14</sup> D. Dwuma-Badu, J. S. K. Ayim, O. Rexford, A. M. Ateya, D. J. Slatkin, J. E. Knapp, and P. L. Schiff, Jr., *Phytochemistry*, 1980, **19**, 1564.

<sup>15</sup> D. Dwuma-Badu, J. S. K. Ayim, S. F. Withers, N. O. Agyemang, A. M. Ateya, M. M. El-Azizi, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, Jr., *J. Nat. Prod.*, 1980, **43**, 123.

<sup>16</sup> J. A. Swinehart and F. R. Stermitz, *Phytochemistry*, 1980, **19**, 1219.

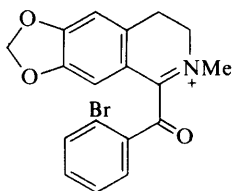
<sup>17</sup> W.-N. Wu, J. L. Beal, and R. W. Duskotch, *J. Nat. Prod.*, 1980, **43**, 372.

<sup>18</sup> J. Siwon, R. Verpoorte, G. F. A. van Essen, and A. B. Svendsen, *Planta Med.*, 1980, **38**, 24.

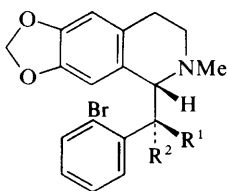
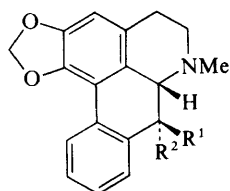
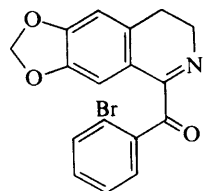
<sup>19</sup> P. K. Bhaumik, B. Mukherjee, J. P. Juneau, N. S. Bhacca, and R. Mukherjee, *Phytochemistry*, 1979, **18**, 1584.

The readily available reagent diphenyl selenoxide has been used as a mild and selective oxidant in the synthesis of aporphines (and homoaporphines). When the benzyloisoquinoline (13) was treated with one equivalent of the reagent at room temperature in methanol, and the product was *O*-methylated with diazomethane, the aporphine (14) was obtained in 80% yield. The alternative use of chloranil, which is a commonly used oxidant for catechols, yielded less than 10% of (14).<sup>20</sup>

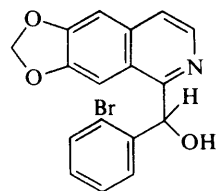
Reduction of the keto-iminium salt (15) with sodium borohydride furnished a mixture of alcohols (16) and (17); upon photolysis in acid solution, this mixture afforded oliveroline (18) and ushinsunine (19). The preparation of oliveroline represents the first synthesis of an aporphine that bears an alcohol function attached to C-7 that is *cis* to the proton attached to C-6 $\alpha$ .<sup>21</sup>



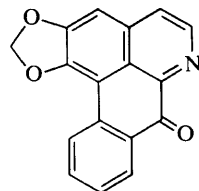
(15)

(16)  $R^1 = \text{OH}, R^2 = \text{H}$ (17)  $R^1 = \text{H}, R^2 = \text{OH}$ (18)  $R^1 = \text{OH}, R^2 = \text{H}$ (19)  $R^1 = \text{H}, R^2 = \text{OH}$ 

(20)



(21)



(22)

Alternatively, reduction of the keto-imine (20) with sodium borohydride gave a mixture of two carbinols corresponding to *N*-demethylated (16) and (17). Irradiation of this mixture produced norushinsunine together with a little noroliveroline. Photolysis of the alcohol (21) gave rise to the oxoaporphine liriodenine (22).<sup>21</sup> Synthetic routes to those aporphines that incorporate a hydroxyl group at C-7 that is *trans* to the proton at C-6 $\alpha$  are already known.<sup>22,23</sup>

A novel synthesis of aporphines *via* 3-phenylphenethylamines has been developed, and is described in Scheme 1. The aporphine (23) and related species were then synthesized by a modified route.<sup>24</sup>

The mechanistic aspects of the rearrangement of thebaine and codeine analogues in methanesulphonic acid have been clarified, and have led to an

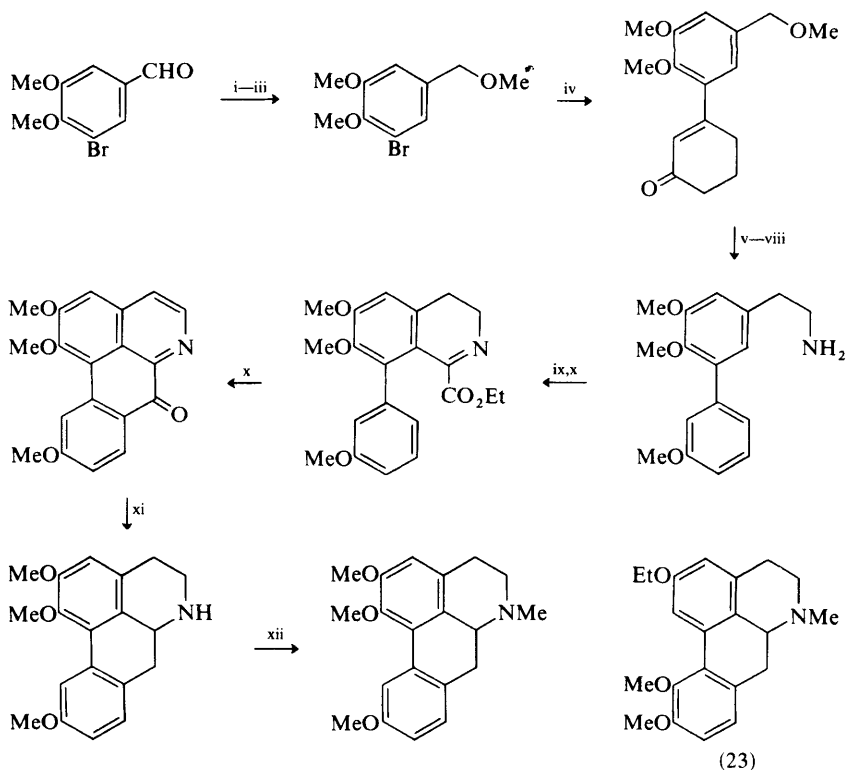
<sup>20</sup> J. P. Marino and A. Schwartz, *Tetrahedron Lett.*, 1979, 3253.

<sup>21</sup> S. V. Kessar, Y. P. Gupta, V. S. Yadav, M. Narula, and T. Mohammad, *Tetrahedron Lett.*, 1980, **21**, 3307.

<sup>22</sup> J. Kunitomo, M. Miyoshi, E. Yoge, T. H. Yang, and C. M. Chen, *Chem. Pharm. Bull.*, 1971, **19**, 1502.

<sup>23</sup> F. E. Granchelli and J. L. Neumeyer, *Tetrahedron*, 1974, **30**, 3701.

<sup>24</sup> M. Gerecke and A. Brossi, *Helv. Chim. Acta*, 1979, **62**, 1549.



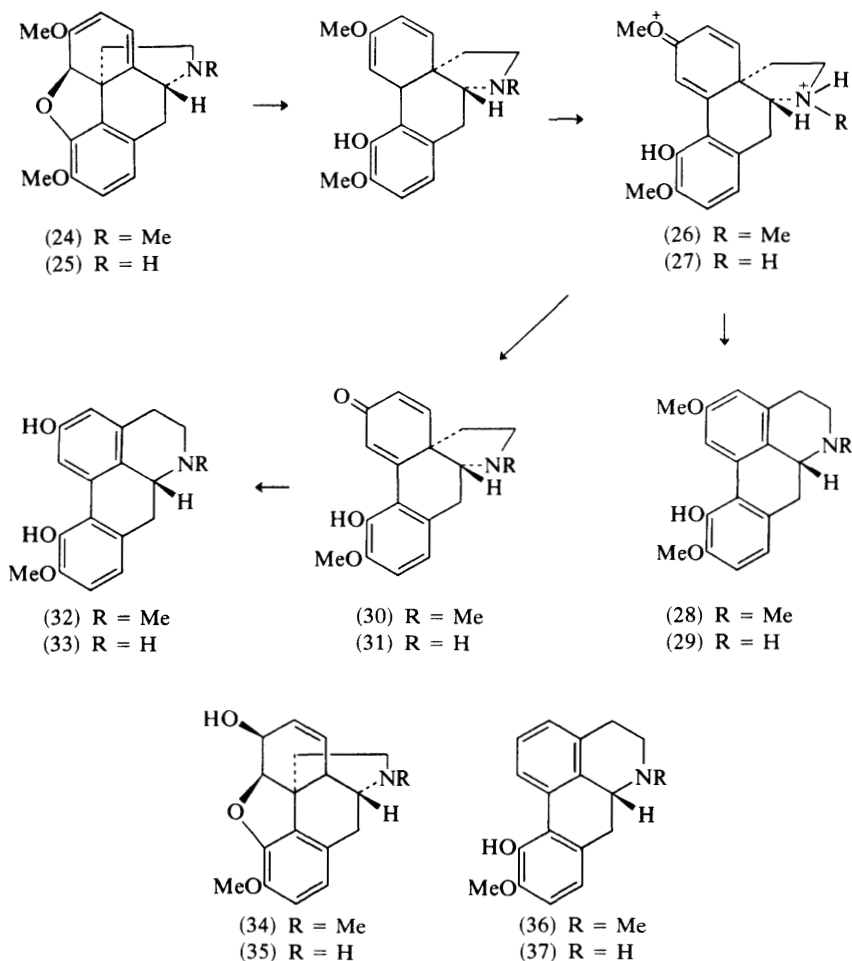
Reagents: i,  $\text{LiBH}_4$ , THF; ii,  $\text{SOCl}_2$ ; iii, NaOMe; iv, Mg, THF, then 3-ethoxy-cyclohex-2-en-1-one; v,  $\text{CuBr}_2$ ; vi, HCl; vii, NaCN; viii,  $\text{H}_2$ , Raney nickel,  $\text{NH}_3$ , MeOH; ix,  $(\text{EtO}_2\text{C})_2$ ; x, PPA; xi, Zn, HCl, HOAc; vii, HCHO,  $\text{HCO}_2\text{H}$

**Scheme 1**

improved method for the synthesis of *N*-alkylated noraporphines.<sup>25</sup> It had previously been shown that quaternary salts of thebaine (24) in TFA containing concentrated sulphuric acid formed the relatively stable red methoxonium cation (26).<sup>26</sup> It has now been observed that solutions of thebaine (24) and northebaine (25) in methanesulphonic acid also form the red ions (26) and (27), which remain stable for periods of more than 16 hours at room temperature. Heating the solutions at 90–100 °C for 30 minutes then furnished the aporphines (28) and (29), respectively. Under somewhat different conditions, methoxonium cations (26) and (27) underwent *O*-demethylation to (30) and (31), which then led to morphothebaine (32) and normorphothebaine (33). Similarly, the rearrangement of codeine (34) and norcodeine (35) to apocodeine (36) and norapocodeine (37), again using methanesulphonic acid, has been studied.<sup>25</sup>

<sup>25</sup> F. E. Granchelli, C. N. Filer, A. H. Soloway, and J. L. Neumeyer, *J. Org. Chem.*, 1980, **45**, 2275.

<sup>26</sup> R. T. Channon, G. W. Kirby, and S. R. Massey, *J. Chem. Soc. C*, 1969, 1215.

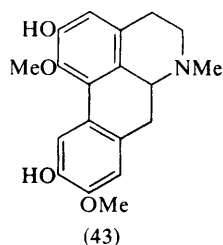
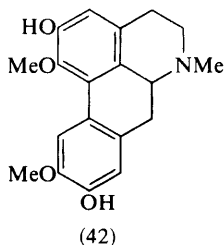
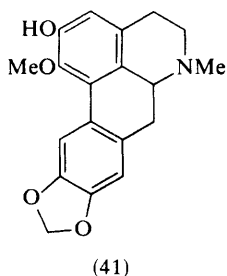
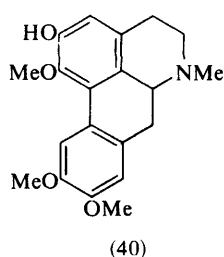
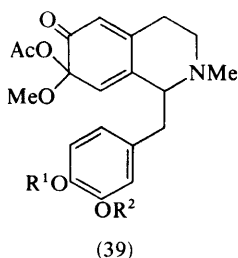
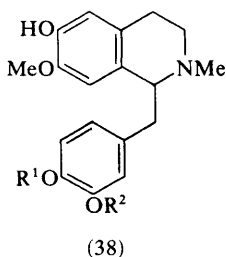


A full paper has appeared describing the oxidation of 6-hydroxylated tetrahydrobenzylisoquinolines of type (38) with lead tetra-acetate, to furnish the corresponding *ortho*-quinol acetates (39), which can readily undergo cyclization to the corresponding aporphines in acid solution. Predicentrine (40), isodomeesticine (41), boldine (42), and 2,10-dihydroxy-1,9-dimethoxyaporphine (43) were prepared by such a route, which is, therefore, a practical pathway for the synthesis of 2-hydroxylated aporphines.<sup>27</sup>

The conversion of reticuline *N*-oxide into the aporphine corydine under the influence of cuprous chloride has been described in full.<sup>28</sup>

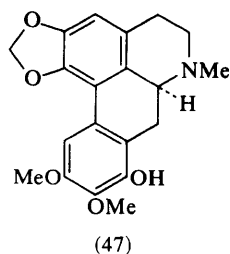
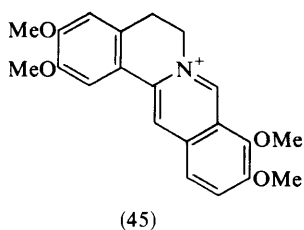
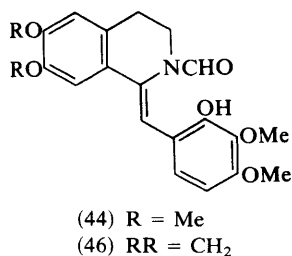
<sup>27</sup> O. Hoshino, M. Ohtani, and B. Umezawa, *Chem. Pharm. Bull.*, 1979, **27**, 3101.

<sup>28</sup> T. Kametani and M. Ihara, *J. Chem. Soc., Perkin Trans. 1*, 1980, 629.



The synthesis of three 1,2,10,11-tetrasubstituted *N*-(*n*-propyl)noraporphines, using either the Bischler–Napieralski–Pschorr sequence or a Reissert alkylation–Pschorr cyclization, has been achieved.<sup>29</sup> Patents have been taken out on the morphine–apomorphine rearrangement that is induced by phosphoric acid and which leads to *N*-alkylated norapomorphines.<sup>30</sup> Other patents concern the vanadium–trichloride-induced cyclization of tetrahydrobenzylisoquinolines that are hydroxylated at C-7, to furnish a series of 1-hydroxylated aporphines such as thaliporphine.<sup>31,32</sup>

A new biogenetic route to the aporphines has been proposed which does not involve phenolic oxidative coupling, and which proceeds through the intermediacy of protoberberinium salts.<sup>6</sup> The alkaloid polycarpine (44) must be derived biogenetically from palmatine (45), and indeed oxidation of (45) *in vitro* with *m*-chloroperoxybenzoic acid, followed by hydrolysis, leads to polycarpine (44). Since it is known that photocyclization of simple benzylisoquinoline



<sup>29</sup> D. R. Elmaleh, F. E. Granchelli, and J. L. Neumeyer, *J. Heterocycl. Chem.*, 1979, **16**, 87.

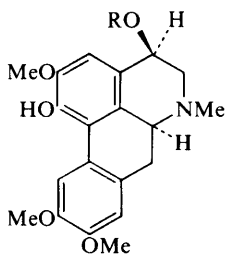
<sup>30</sup> R. R. Lorenz, E. D. Parady, and W. H. Thielking, *Chem. Abstr.*, 1978, **89**, 16 384; 1979, **91**, 175 595.

<sup>31</sup> Warner-Lambert Co., Belg. P. 872 842 (*Chem. Abstr.*, 1979, **91**, 91 814).

<sup>32</sup> J. Hartenstein and G. Satzinger, *Chem. Abstr.*, 1980, **92**, 129 164.

enamides and enurethanes supplies aporphines, it follows that the polycarpine analogue (46) derived from berberine should lead to the aporphine leucoxine (47) in the plant. Other 8,9,10-trisubstituted aporphines should then be formed *in vivo* by a parallel route, involving the sequence protoberberine salt  $\rightarrow$  benzylisoquinoline enamide  $\rightarrow$  aporphine.<sup>6</sup>

The reactions of 4 $\beta$ -acetoxythaliporphine (48) with nucleophiles have been studied. On dissolution in methanol, the 4-methoxy-analogue (49) is obtained, but the bulkier alcohols ethanol and benzyl alcohol require the presence of boron trifluoride etherate to generate the ethers (50) and (51). Loss of stereo-specificity at C-4 was observed when isopropyl alcohol and cyclohexanol were the nucleophiles.<sup>33</sup>

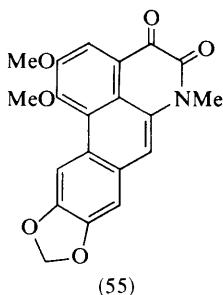
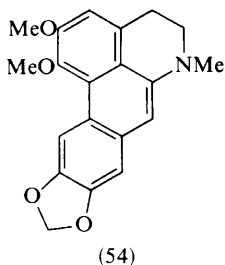
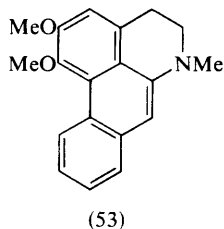
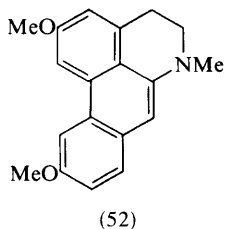


(48) R = Ac

(49) R = Me

(50) R = Et

(51) R = CH<sub>2</sub>Ph



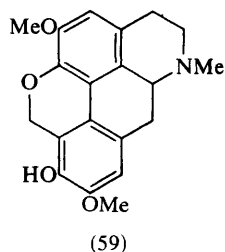
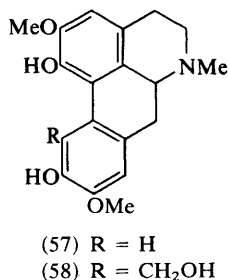
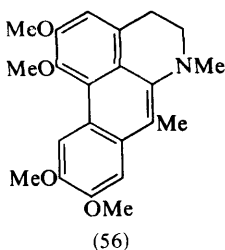
Aerial oxidation of the dehydroaporphines (52)—(54) with alkali catalysts gives the corresponding oxoaporphines, 4,5-dioxoaporphines, and *N*-methylaristolactams in low yields. The 4,5-dioxoaporphine (55) from the oxidation of (54) corresponds to 4,5-dioxodehydronantenine, which is found as a natural product in the dried fruits of *Nandina domestica*.<sup>34</sup>

Glaucine reacts with formaldehyde and air in neutral solution to afford 7-methyldehydroglaucine (56), presumably through the intermediacy of dehydroglaucine. Alternatively, treatment of bracteoline (57) with formaldehyde in base supplies the carbinol (58), which cyclizes (upon heating) to the methyleneoxy-bridged compound (59), thus affording a new route to aporphines of the thalphenine series.<sup>35</sup>

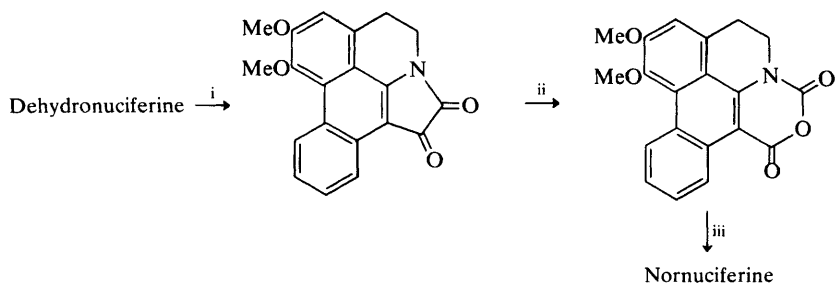
<sup>33</sup> O. Hoshino, H. Hiroshi, O. Masashi, and B. Umezawa, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1165.

<sup>34</sup> J. Kunitomo, Y. Murakami, and M. Akasu, *Yakagaku Zasshi*, 1980, **100**, 337; J. Kunitomo and Y. Murakami, *Shoyakugaku Zasshi*, 1979, **33**, 84.

<sup>35</sup> N. Mollov and S. Philipov, *Chem. Ber.*, 1979, **112**, 3737.



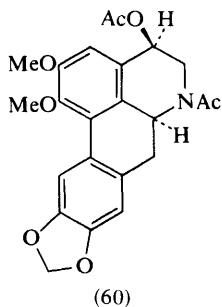
*O*-Demethylation of glaucine, using hydrobromic acid in acetic acid, produces bracteoline (57),<sup>35</sup> while *N*-demethylation of dehydronuciferine (1, 2-dimethoxydehydroaporphine) to nornuciferine has been achieved through the sequence shown in Scheme 2.<sup>36</sup>



Reagents: i, (COCl)<sub>2</sub>, Et<sub>2</sub>O, THF, K<sub>2</sub>CO<sub>3</sub>; ii, *m*-chloroperoxybenzoic acid; iii, hydrolysis, and then Zn, HCl

Scheme 2

A detailed study of the carbon-13 n.m.r. spectra of aporphines has appeared,<sup>37</sup> and an *X*-ray analysis of *N,O*-diacetyl-4-hydroxynornantenine (60) has been carried out.<sup>38</sup> The gas-chromatographic and/or mass spectral behaviour of a series of aporphines as their trimethylsilyl or trifluoroacetyl derivatives has been



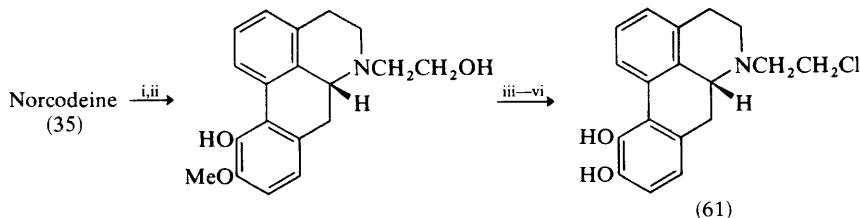
<sup>36</sup> R. Ahmad, *Islamabad J. Sci.*, 1977, 4, 36.

<sup>37</sup> L. M. Jackman, J. C. Trewella, J. L. Moniot, M. Shamma, R. L. Stephens, E. Wenkert, M. Leboeuf, and A. Cavé, *J. Nat. Prod.*, 1979, 42, 437.

<sup>38</sup> V. Zabel, W. H. Watson, A. Urzua, and B. K. Cassels, *Acta Crystallogr., Sect. B*, 1979, 3126.

described in detail.<sup>39,40</sup> By using mixtures of trifluoroacetic acid and tritiated water, apomorphine and *N*-(*n*-propyl)norapomorphine have been labelled at C-8 and C-9, *i.e.* *ortho* and *para* to the phenolic groups.<sup>41</sup>

Dopaminergic drugs are those that can affect the neurotransmitter system in the brain. It had previously been established that (–)-apomorphine and (–)-*N*-(*n*-propyl)norapomorphine are powerful dopaminergic agonists, being highly selective in binding to dopaminergic receptors. The greater potency of the latter compound points to the importance of an alkyl side-chain of optimal size and hydrophobic properties. The synthesis of (–)-*N*-(2-chloroethyl)norapomorphine (61) has now been reported, and is described in Scheme 3. This aporphine

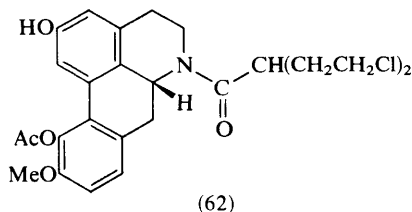


Reagents: i,  $\text{BrCH}_2\text{CH}_2\text{OH}$ ; ii,  $\text{MeSO}_3\text{H}$ ; iii,  $\text{HBr}$ ; iv,  $\text{HCl}$ ; v,  $\text{SOCl}_2$ ,  $\text{MeCN}$ ; vi,  $\text{NH}_4\text{OH}$

**Scheme 3**

derivative could prove to be of value as a pharmacological and biochemical probe of the dopaminergic receptors, and also as a long-acting antidopamine or neuroleptic drug. The aporphine (61) inhibits dopamine-sensitive adenylate cyclase, probably by alkylation of receptors. When administered peripherally or intrastriatally, it can produce selective, potent, and long-lasting (5 days) behavioural effects that are indicative of dopamine-receptor blockade. Alternatively, compound (61) may be considered to be an affinity label for dopamine receptors in the central nervous system.<sup>7</sup>

The aporphine mustard (62) and closely related analogues have shown significant anti-tumour activity.<sup>42</sup>



The antiparkinsonism activity of a series of *N*-(*n*-propyl)norapomorphine diesters has been tabulated.<sup>43</sup> The stability of apomorphine in solutions contain-

<sup>39</sup> J. F. Green, J. V. Evans, J. L. Neumeyer, and P. Vouros, *Biomed. Mass Spectrom.*, 1979, **6**, 282.

<sup>40</sup> J. F. Green, G. N. Jham, J. L. Neumeyer, and P. Vouros, *J. Pharm. Sci.*, 1980, **69**, 936.

<sup>41</sup> W. H. Soine, P. Salgo, and R. V. Smith, *J. Labelled Compd. Radiopharm.*, 1979, **16**, 597.

<sup>42</sup> S.-J. Law, J. L. Neumeyer, F. E. Granchelli, C. N. Filer, and A. H. Soloway, *Abstr. 179th ACS Meeting, Houston, March 1980*, MEDI-63.

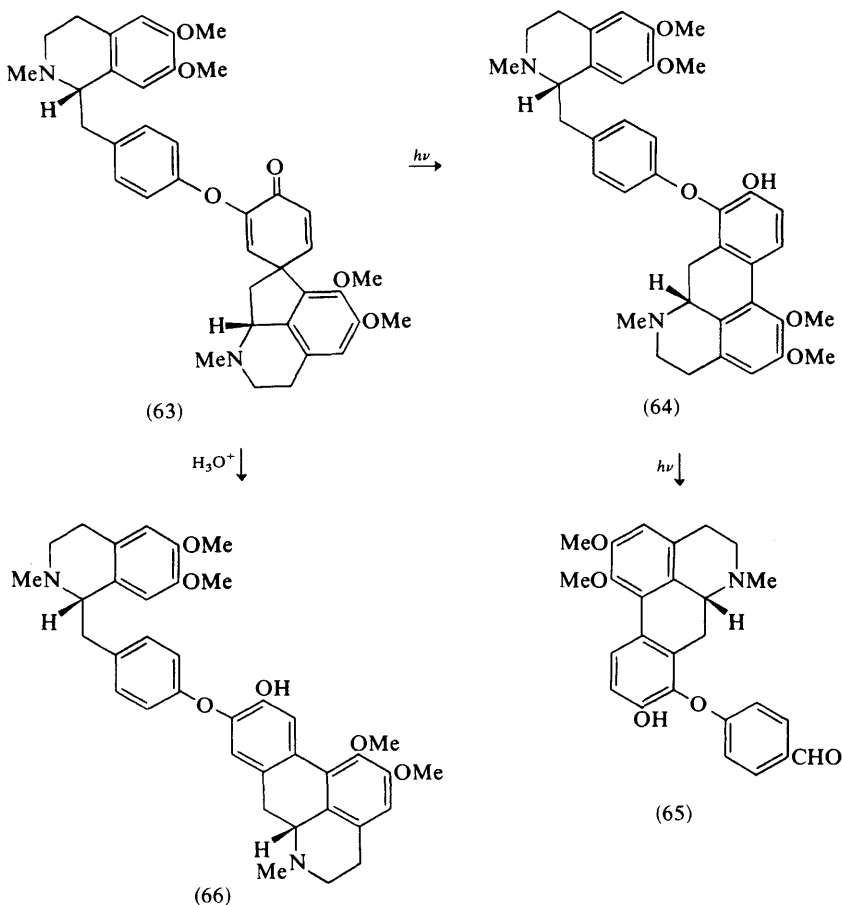
<sup>43</sup> W. B. Hinshaw, Jr., and J. Pearl, *Chem. Abstr.*, 1979, **89**, 129 773.



ing ascorbic acid and bisulphite anion and the effects of anti-oxidants on apomorphine-induced cage climbing and hypothermia in mice have been investigated.<sup>44</sup>

#### 4 Aporphine Dimers

Irradiation with sunlight of pakistanamine (63), which is the only known pro-aporphine-benzylisoquinoline alkaloid, yields lumipakistanine (64), together with a trace amount of neolumipakistanine (65),<sup>5</sup> while it is known that the acid-catalysed rearrangement of (63) takes a different course and generates the dimer (66) (Scheme 4).<sup>45</sup>

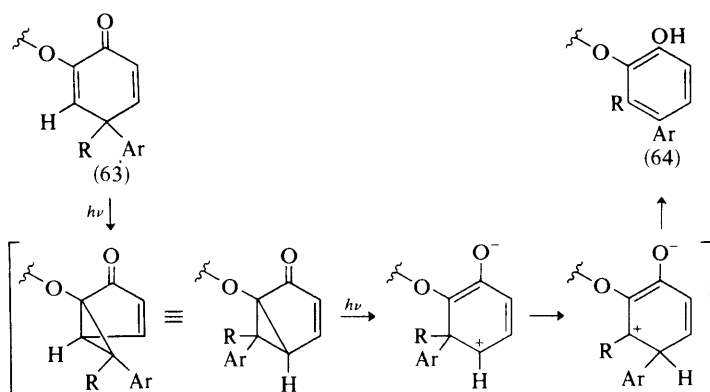


Scheme 4

<sup>44</sup> R. E. Wilcox, D. W. Humphrey, W. H. Riffe, and R. V. Smith, *J. Pharm. Sci.* 1980, **69**, 974.

<sup>45</sup> M. Shamma, J. L. Moniot, S. Y. Yao, G. A. Miana, and M. Ikram, *J. Am. Chem. Soc.*, 1978, **95**, 5742.

The genesis of lumipakistanine (64) can be understood in terms of a sequence of two distinct photochemical processes (Scheme 5).<sup>5</sup>

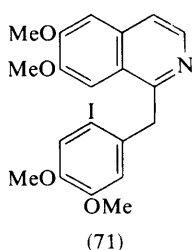
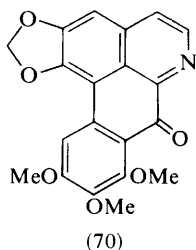
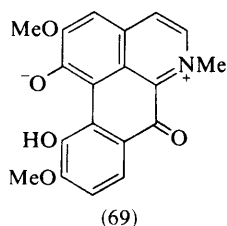
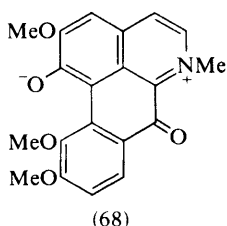
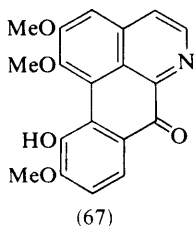


Scheme 5

Pakistanamine (63), which had originally been found in *Berberis baluchistanica*,<sup>45</sup> has now been obtained from the seeds of *B. julianae*<sup>46</sup> and from the roots of *B. calliobotrys*.<sup>5</sup>

## 5 Oxoaporphines

Glaunine (67) and glaunidine (68) are two new oxoaporphines from *Glaucium fimbrilligerum* (Papaveraceae).<sup>47</sup> Arosine, found in *G. flavum* Cr. var. *vestitum*, must be identical with glaunidine, while arosinine, from the same source, possesses structure (69).<sup>48</sup> Oxidation of the aporphine corydine with iodine and



<sup>46</sup> D. Kostalova, B. Brazdovicova, and J. Tomko, *Chem. Zvesti*, 1978, **32**, 706.

<sup>47</sup> I. A. Israilov, S. U. Karimova, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin*, 1979, 415.

<sup>48</sup> L. Castedo, D. Domínguez, J. M. Saá, and R. Suau, *Tetrahedron Lett.*, 1979, 4589.

sodium acetate in dioxan furnished glaunidine (68) in 30% yield.<sup>48</sup> Another new oxoaporphine is ocominarone (70), which is present, together with several aporphines, in *Ocotea minarum*.<sup>4</sup>

Photolysis of the hydrochloride of (71) gave the corresponding oxoaporphine *O*-methylatheroline, in 38% yield, which was converted into the aporphine glaucine by successive methylation and reduction with zinc in hydrochloric acid.<sup>49</sup>

Following the isolation of liriodenine and oxolaureline from the bark of *Laurelia novae-zelandiae*, a careful n.m.r. analysis has revealed that H-11 of oxoaporphines does not necessarily absorb downfield from H-8.<sup>50</sup>

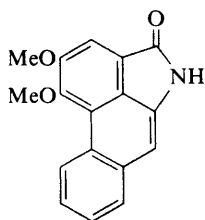
*Ocotea minarum* contains the known oxoaporphines dicentrinone and thalicminine.<sup>4</sup> Liriodenine is present in *Rhigiocarya racemifera*<sup>15</sup> and in *Pachygone ovata*,<sup>9b</sup> and lanuginosine is found in *Anona squamosa*.<sup>19</sup>

## 6 4,5-Dioxoaporphines

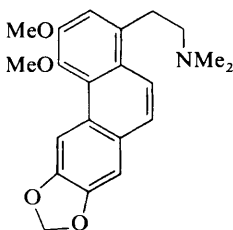
As mentioned previously, the dried fruits of *Nandina domestica* contain the new alkaloid 4,5-dioxodehydronantenine (55).<sup>34</sup>

## 7 Aristolactams

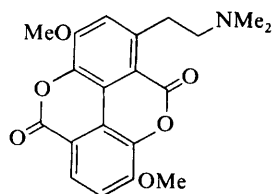
Alkaloid Y, isolated from the bark of *Schefferomitra subaequalis* (Annonaceae), has now been shown to correspond to the known aristolactam BII (cepharanone-B) (72).<sup>51</sup>



(72)



(73)



(74)

## 8 Phenanthrenes

The known base thalictuberine (73) has been re-isolated from *Thalictrum rugosum* (Ranunculaceae).<sup>52</sup>

## 9 Taspine

The known alkaloid taspine (74), which possesses anti-inflammatory activity, has been found in *Croton lechleri*.<sup>53</sup>

<sup>49</sup> L. S. Trifonov and A. Orakhovats, *Izv. Khim.*, 1978, **11**, 297.

<sup>50</sup> A. Urzua and B. K. Cassels, *Contrib. Cient. Tecnol. (Univ. Tec. Estado, Santiago, Chile)*, 1978, **28**, 25 (*Chem. Abstr.*, 1978, **89**, 215 620).

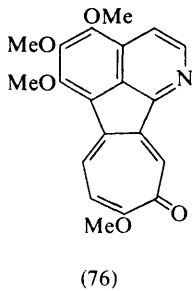
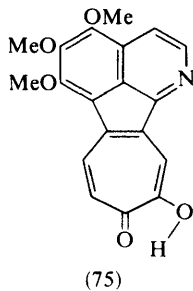
<sup>51</sup> S. F. Dyke and E. Gellert, *Phytochemistry*, 1978, **17**, 599.

<sup>52</sup> W.-N. Wu, J. L. Beal and R. W. Doskotch, *J. Nat. Prod.*, 1980, **43**, 143.

<sup>53</sup> G. P. Perdue, R. N. Blomster, P. A. Blake, and N. R. Farnsworth, *J. Pharm. Sci.*, 1979, **68**, 124.

### 10 Tropoloisoquinolines

The new reddish-brown alkaloid grandirubrine (75), as well as the known imerubrine (76), are present in *Abuta grandifolia* (Menispermaceae).<sup>54</sup>



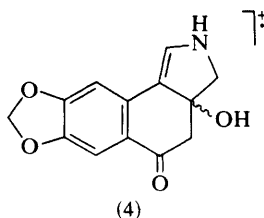
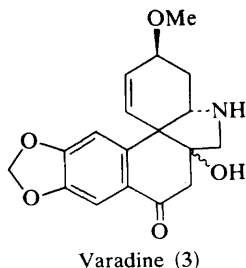
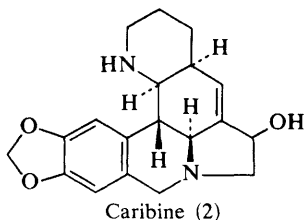
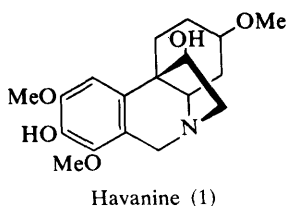
<sup>54</sup> M. D. Menachery and M. P. Cava, *Heterocycles*, 1980, **14**, 943.

Recent advances in the chemistry of alkaloids of the Amaryllidaceae have been mostly concerned with synthesis, and substantial progress has again occurred in this area during the year now under review; two new syntheses of the lycorine ring system and a synthesis of tazettine are particularly noteworthy.

### 1 Isolation and Structural Studies

The bulbs of *Ungernia vvedenski* are a good source of lycorine, and the above-ground parts have been shown to contain lycorine, tazettine, ungminorine, ungminoridine, hippeastrine, galanthamine, and narwedine.<sup>1</sup>

Doepke and co-workers have isolated more new alkaloids from *Hymenocallis arenicola*. Havanine (1) is a new member of the crinine group; the presence of two methoxyl groups and one attached to an  $sp^3$  carbon was indicated by the  $^1\text{H}$  n.m.r. spectrum, and the structure of the alkaloid was proposed mainly on the basis of the mass spectrum.<sup>2</sup> Structure (2) for caribine was assigned as a

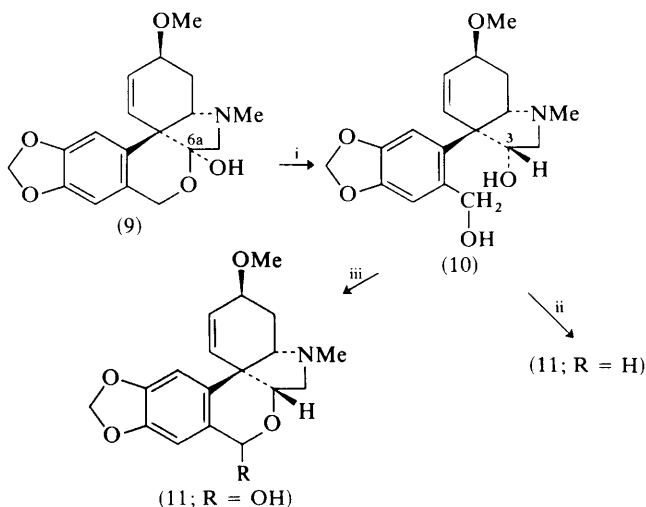
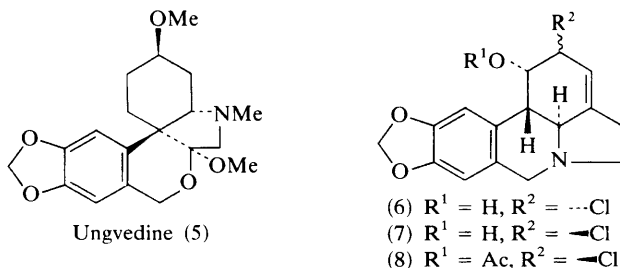


<sup>1</sup> Kh. A. Kadyrov and S. A. Khamidkhodzhaev, *Khim. Prir. Soedin.*, 1979, 418 (*Chem. Abstr.*, 1979, **91**, 189 801).

<sup>2</sup> W. Doepke and Z. Trimino, *Z. Chem.*, 1979, **19**, 377.

result of i.r. absorption at 3580 (OH) and  $928\text{ cm}^{-1}$  ( $-\text{OCH}_2\text{O}-$ ).<sup>3</sup> Varadine (3), the third new alkaloid of *H. arenicola*, was shown by i.r. and  $^1\text{H}$  n.m.r. spectroscopy to contain a methylenedioxy, a methoxyl, and a hydroxyl group. In the mass spectrometer the ion (4) was formed by retro-Diels-Alder fragmentation of ring C, indicating that varadine is a new structural type within the tazettine group of alkaloids.<sup>4</sup> Ungvedine (5), a new alkaloid isolated from *Ungernia vvedenski*, is the *O*-methyl ether of dihydrotazettine; its structure was established by spectroscopy and by its formation by hydrogenation of *O*-methyltazettine.<sup>5</sup>

Lycorine chlorohydrin, formed by the action of  $\text{POCl}_3$  and  $\text{HCl}$  on lycorine, has been used as a synthetic intermediate; it was regarded as the *cis*-derivative (6). An alternative preparation now indicates that the chlorohydrin has the *trans* configuration (7), and this has been confirmed by *X*-ray analysis of the acetate (8).<sup>6</sup>



Reagents: i,  $\text{LiAlH}_4$ ; ii, 3% aq.  $\text{H}_2\text{SO}_4$ , at  $100^\circ\text{C}$ ; iii,  $\text{MnO}_2$ ,  $\text{CHCl}_3$

**Scheme 1**

<sup>3</sup> W. Doecke, E. Sewerin, and Z. Trimino, *Z. Chem.*, 1980, **20**, 26.

<sup>4</sup> W. Doecke, E. Sewerin, and Z. Trimino, *Z. Chem.*, 1979, **19**, 215.

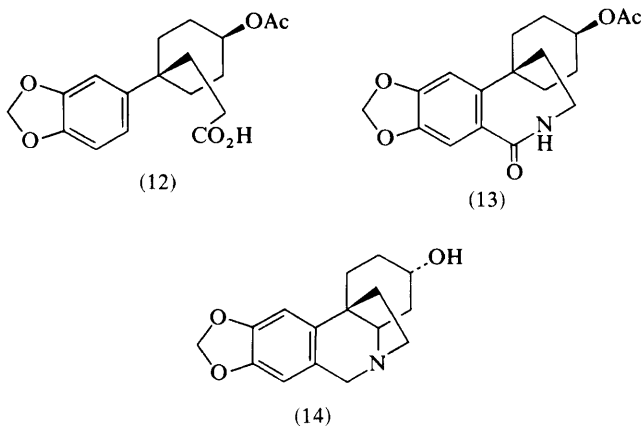
<sup>5</sup> Kh. A. Kadyrov, A. Abdusamatov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1979, 585 (*Chem. Abstr.*, 1980, **92**, 147 003).

<sup>6</sup> J. Toda, T. Sano, Y. Tsuda, M. Kaneda, and Y. Iitaka, *Tetrahedron Lett.*, 1980, **21**, 369.

The transformation of tazettine (9) into pretazettine (11; R = OH) (Scheme 1) confirms the stereochemistry of the latter alkaloid. Reduction of tazettine with lithium aluminium hydride gives a mixture of diols that are epimeric at C-3, *cf.* (10), presumably *via* a keto-alcohol. Compound (10) was made to cyclize to desoxypretazettine (11; R = H), which was shown by o.r.d., c.d., and  $^1\text{H}$  n.m.r. data to have the same configuration at C-6a as pretazettine (11; R = OH). Oxidation of compound (10) gave pretazettine, without affecting the configuration at C-3.<sup>7</sup>

## 2 Synthesis

Irie and co-workers have described an improved synthesis of the alkaloid elwesine (dihydrocrinine) (14).<sup>8</sup> Application of Tsuda's two-stage method for the preparation of lactams (POCl<sub>3</sub>, then SnCl<sub>4</sub>) to the isocyanate that was derived from the 4-arylbutyric acid derivative (12) gave the benzazepinone (13) in 70% yield; this compound has already been converted into elwesine.



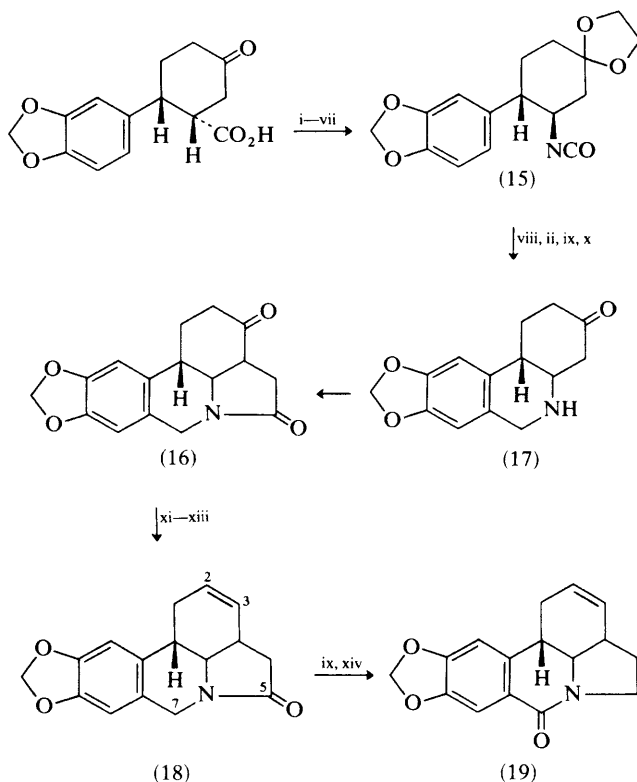
Umezawa and co-workers<sup>9</sup> have reported a new synthesis of the tetracyclic lactam (19), which is a key intermediate in Torssell's synthesis of lycorine (*cf.* Vol. 9, p. 139); the Japanese work (Scheme 2), therefore, represents a formal synthesis of the alkaloid. The cyclohexyl isocyanate (15) (*trans*-diequatorial aryl and isocyanate groups) cyclized to a tricyclic lactam, which by reduction with a hydride and hydrolysis gave the ketone (18). The tetracyclic ketone (16) was converted into the 2,3-ene (17) by a Cope elimination reaction, and the synthesis of compound (19) was completed by transposition of the lactam carbonyl group from C-5 to C-7.

A disappointing feature of Stork's synthesis of the lycorine ring system by intramolecular Diels–Alder reaction of a tricyclic intermediate was that the 'natural' stereoisomer was not the major product of ring-closure (*cf.* Vol. 10,

<sup>7</sup> S. Kobayashi, M. Kihara, and T. Shingu, *Heterocycles*, 1979, **12**, 1547.

<sup>8</sup> T. Fushimi, H. Ikuta, H. Irie, K. Nakadachi, and S. Uyeo, *Heterocycles*, 1979, **12**, 1311.

<sup>9</sup> B. Umezawa, O. Hoshino, S. Sawaki, H. Sashida, and K. Mori, *Heterocycles*, 1979, **12**, 1475.



Reagents: i, MeOH, conc.  $\text{H}_2\text{SO}_4$ ; ii, acetalization; iii,  $\text{KOBu}^t$ ,  $\text{HOBu}^t$ , reflux; iv, 20% KOH, EtOH, reflux; v,  $\text{ClCO}_2\text{Et}$ ,  $\text{Et}_3\text{N}$ ,  $\text{Me}_2\text{CO}$ ; vi,  $\text{NaN}_3$ ,  $\text{H}_2\text{O}$ ; vii, PhH, reflux; viii,  $\text{H}_3\text{PO}_4$ ; ix,  $\text{LiAlH}_4$ ,  $\text{MeOCH}_2\text{CH}_2\text{OMe}$ , reflux; x, 6M-HCl; xi,  $\text{Me}_2\text{NH}_2^+ \text{Cl}^-$ ,  $\text{NaBH}_3\text{CN}$ , MeOH; xii,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$ ; xiii, heat, at  $200^\circ\text{C}$ ; xiv,  $\text{MnO}_2$ ,  $\text{CHCl}_3$ , reflux

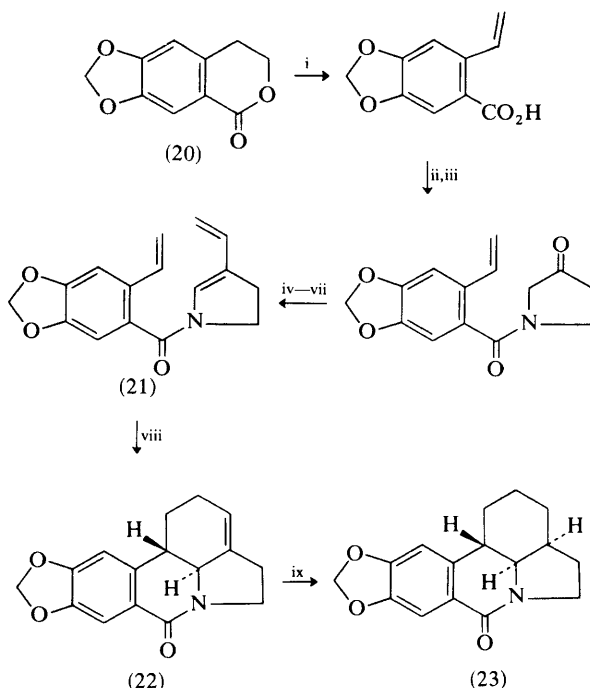
**Scheme 2**

p. 137). This problem has now been overcome in a synthesis of 7-oxo- $\alpha$ -lycorane (23) (Scheme 3). The elegant synthesis of the critical intermediate (21) was accomplished in seven stages from lactone (20). The planarity of the amide function in the bicyclic compound (21) apparently imposes constraint on the molecule, so that intramolecular cyclization occurs *via* an *exo* transition state to give the required stereoisomer of compound (22).<sup>10</sup>

Previous syntheses of tazettine by Hendrickson and by Tsuda were based on the synthesis of haemanthidine and its conversion into pretazettine and tazettine. Danishefsky has now announced a direct total synthesis of (*dl*)-tazettine (30)

<sup>10</sup> G. Stork and D. J. Morgans, *J. Am. Chem. Soc.*, 1979, **101**, 7110.



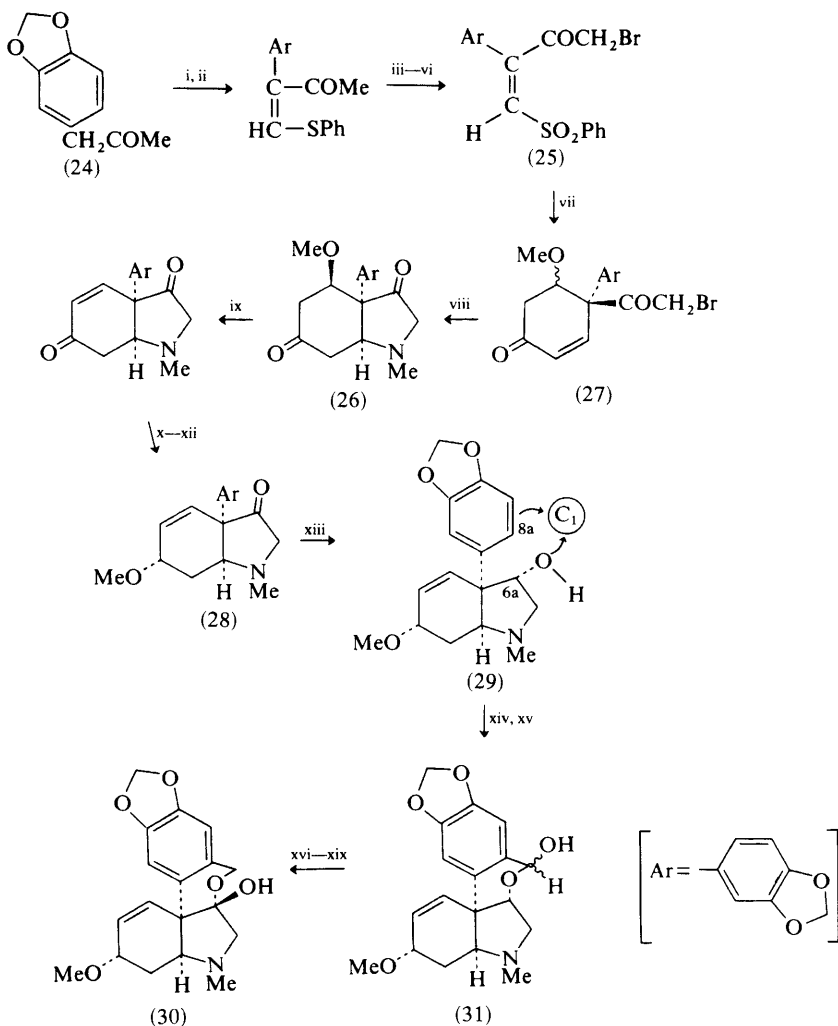


Reagents: i, HMPA,  $\text{LiN}(\text{SiMe}_3)_2$ , THF, at  $-78^\circ\text{C}$ ; ii,  $\text{Ph}_3\text{P}$ ,  $\text{CCl}_4$ , MeCN, then 3-pyrrolidinol; iii, pyridine- $\text{SO}_3$ , DMSO,  $\text{Et}_3\text{N}$ ; iv,  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$ , NaH, glyme, at  $0^\circ\text{C}$ ; v,  $\text{LiBH}_4$ , THF; vi, *o*-nitrophenyl selenocyanate,  $\text{Bu}_3\text{P}$ ,  $\text{CH}_2\text{Cl}_2$ ; vii,  $\text{NaIO}_4$ ,  $\text{NaHCO}_3$ , THF, aq. MeOH; viii,  $\text{PhCl}$ , 3-Bu<sup>1</sup>-4-OH-5-Me- $\text{C}_6\text{H}_2\text{SH}$  (trace),  $\text{MeC}(\text{OSiMe}_3)=\text{NHSiMe}_3$ , at  $140^\circ\text{C}$ ; ix, Pd/C,  $\text{H}_2$ , EtOAc

**Scheme 3**

(Scheme 4).<sup>11</sup> The strategy involved the preparation of a tricyclic intermediate (29) and then insertion of a  $\text{C}_1$  fragment between an oxygen atom at C-6a and the carbon of the aromatic ring at C-8a, as shown in the diagram. The stereoselective eleven-step preparation of compound (29) from the arylacetone derivative (24) involves the Diels-Alder reaction of the dienophile (25) to give a mixture of stereoisomers (27), which were reduced to give (26) as the major product; reduction of the ketone (28) with potassium Selectride furnished mainly the  $\alpha$ -alcohol (29). The  $\text{C}_1$ -insertion reaction was carried out with trimethyl orthoformate; after hydrolysis, 6a-*epi*-pretazettine (31) was obtained, and this was converted into tazettine. The stereoisomer of compound (29) containing a  $\beta$ -OH group was also obtained, but attempts to interpolate a carbon atom to yield pretazettine (11; R = OH) were unsuccessful.

<sup>11</sup> S. Danishefsky, J. Morris, G. Mullen, and R. Gammill, *J. Am. Chem. Soc.*, 1980, **102**, 2838.

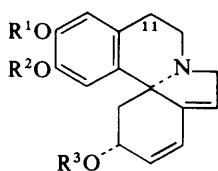


Reagents: i,  $(\text{MeO})_2\text{CHNMe}_2$ , at  $80^\circ\text{C}$ ; ii, PhSH; ii, LDA, THF, at  $-78^\circ\text{C}$ ; iv,  $\text{Me}_3\text{SiCl}$ , at  $-78^\circ\text{C}$ ; v, NBS; vi,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ , at  $0^\circ\text{C}$ ; vii,  $\text{MeOCH}=\text{CHC}(\text{OSiMe}_3)=\text{CH}_2$ , PhH, at  $70^\circ\text{C}$ ; viii, aq.  $\text{MeNH}_2$ , THF; ix,  $\text{Al}_2\text{O}_3$ ; x,  $(\text{Me}_2\text{CHCH}_2)_2\text{AlH}$ , THF; xi,  $\text{Ms}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , THF; xii, MeOH; xiii, potassium Selectride, THF, at  $0^\circ\text{C}$ ; xiv,  $\text{HC}(\text{OMe})_3$ , PPA, at  $100^\circ\text{C}$ ; xv,  $\text{H}_3\text{O}^+$ ; xvi,  $\text{LiAlH}_4$ ; xvii,  $\text{Bu}^t_3\text{SiCl}$ ,  $\text{Et}_3\text{N}$ , 4-pyrrolidinopyridine; xviii, Moffat-Pfitzner oxidation; xix, desilylation

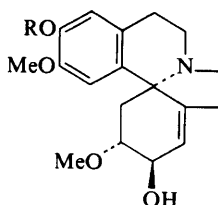
Scheme 4

## 1 Isolation and Structure Determination

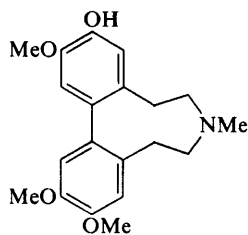
The present review covers work published during 1978–80 on the isolation, structure determination, and synthesis of *Erythrina* and *Cephalotaxus* alkaloids. Preliminary studies<sup>1</sup> of the alkaloid content of the seeds of fourteen *Erythrina* species (*E. addisoniae*, *E. amazonica*, *E. americana*, *E. breviflora*, *E. crista-galli*, *E. dominguezii*, *E. falcata*, *E. flabelliformis*, *E. herbacea*, *E. pallida*, *E. sacleuxii*, *E. suberosa*, *E. velutina*, and *E. verna*), using gas chromatography–mass spectrometry, revealed the presence of erysodine (1a), erysovine (1b), and erysopine (1c) in all the species; these were also present in greatest abundance. Erysonine (1d), erythratidine (2a), erysoline (1e), and erysotine (2b) were also widespread, but erysotrine (1f) and erybidine (3) were only found in *E. crista-galli*, and erythravine (1g) only in *E. breviflora*. The seeds of *E. americana* contained both  $\alpha$ - and  $\beta$ -erythroidines (4) and (5), whereas in *E. addisoniae* seeds, surprisingly, only one of the isomers, *i.e.* (5), was present. Small variations between the



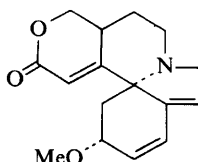
- (1) a;  $R^1 = H, R^2 = R^3 = Me$   
 b;  $R^1 = R^3 = Me, R^2 = H$   
 c;  $R^1 = R^2 = H, R^3 = Me$   
 d;  $R^1 = R^3 = H, R^2 = Me$   
 e;  $R^1 = Me, R^2 = R^3 = H$   
 f;  $R^1 = R^2 = R^3 = Me$   
 g;  $R^1 = R^2 = Me, R^3 = H$   
 h; 11-OH derivative of (1f)



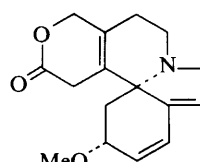
- (2) a;  $R = Me$   
 b;  $R = H$



(3)

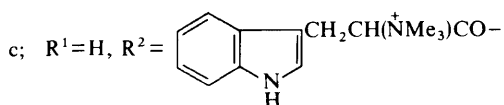
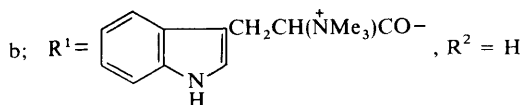
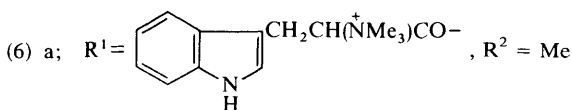
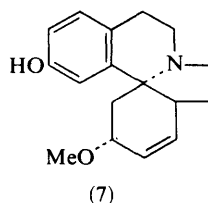
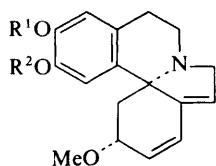


(4)



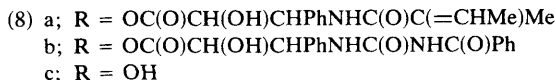
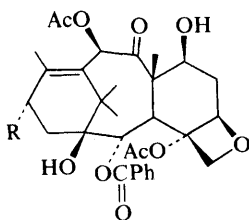
(5)

<sup>1</sup> M. I. Abdullah, I. E. Barakat, D. E. Games, P. Ludgate, V. G. Mavraganis, V. U. Ratnayake, and A. H. Jackson, *Ann. Missouri Bot. Gard.*, 1979, **66**, 533.



alkaloid content of different samples of the same seeds were also observed. The pod walls of *E. arborescens* contained the new quaternary alkaloids erysodinophorine (6a)<sup>2</sup> and erysopinophorine (6b)<sup>3</sup> in addition to erysodine (1a), orientaline, and hypaphorine; subsequently, the same workers<sup>4</sup> also reported the isolation of iso-erysopinophorine (6c) from the seeds, besides the other alkaloids reported previously. The isolation of erysotrine (1f),<sup>5</sup> 11-hydroxyerysotrine (1h),<sup>5</sup> and erybidine (3)<sup>6</sup> from the leaves of *E. herbacea* has also been described.

A new abnormal *Erythrina* alkaloid, obtained from the leaves of *Cocculus laurifolius*, was assigned the structure isococculine (7) on the basis of spectral and chemical studies.<sup>7</sup>



<sup>2</sup> K. P. Tiwari and M. Masood, *Phytochemistry*, 1979, **18**, 704.

<sup>3</sup> K. P. Tiwari and M. Masood, *Phytochemistry*, 1979, **18**, 2069.

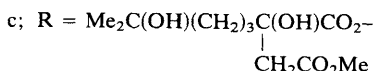
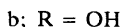
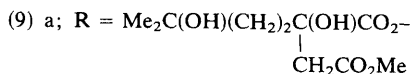
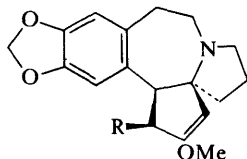
<sup>4</sup> M. Masood and K. P. Tiwari, *Phytochemistry*, 1980, **19**, 490.

<sup>5</sup> V. U. Ahmad, Q. Najmus-Saqib, K. Usmanhane, and G. A. Miana, *J. Chem. Soc. (Pakistan)*, 1979, **1**, 1.

<sup>6</sup> V. U. Ahmad, Q. Najmus-Saqib, K. Usmanhane, and G. A. Miana, *Sci. Pharm.*, 1980, **48**, 169.

<sup>7</sup> R. S. Singh, S. Jain, and D. S. Bhakuni, *Natl. Acad. Sci. Lett. (India)*, 1978, **1**, 93.

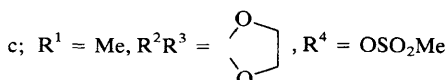
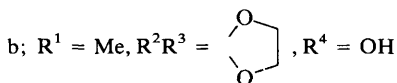
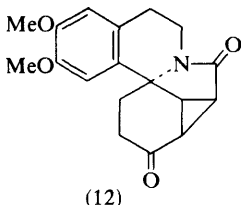
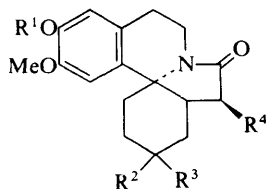
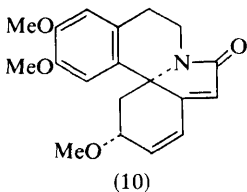
Chemical examination of the stems and roots of *Cephalotaxus mannii* has led to the isolation of cephalomannine (8a), a new anti-tumour alkaloid, as the major active principle, in addition to taxol (8b) and baccatin II (8c).<sup>8,9</sup>



Cephalomannine is cytotoxic in KB cell culture ( $\text{LD}_{50} = 3.8 \times 10^{-3} \mu\text{g ml}^{-1}$ ) and it shows potent inhibition of PS leukaemia in mice.<sup>10</sup> The compounds (8b) and (8c) have previously been reported only in the genus *Taxus*,<sup>11,12</sup> but neither they, nor cephalomannine, are structurally related to the harringtonine series of alkaloids (9).

## 2 Synthesis

In the *Erythrina* series, the total synthesis of ( $\pm$ )-erysotramidine (10), an oxo-erythrinan alkaloid, isolated from *Erythrina arborescens* Roxb.,<sup>13</sup> has been



<sup>8</sup> R. G. Powell, R. W. Miller, and C. R. Smith, Jr., *Lloydia*, 1978, **41**, 655.

<sup>9</sup> R. G. Powell, R. W. Miller, and C. R. Smith, Jr., *J. Chem. Soc., Chem. Commun.*, 1979, 102.

<sup>10</sup> R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, 1972, Vol. 3, Issue No. 2.

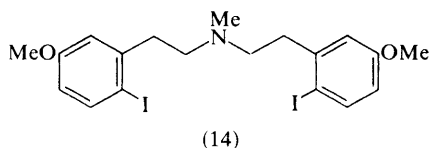
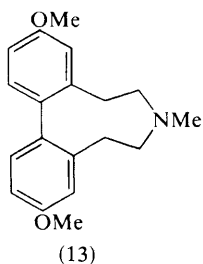
<sup>11</sup> M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325.

<sup>12</sup> D. P. Della Casa de Marcano and T. G. Halsall, *J. Chem. Soc., Chem. Commun.*, 1975, 365.

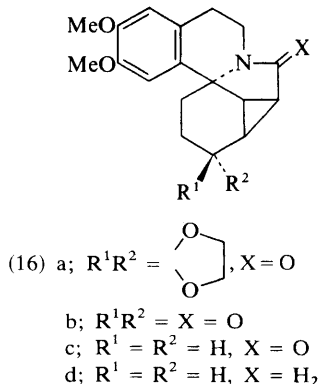
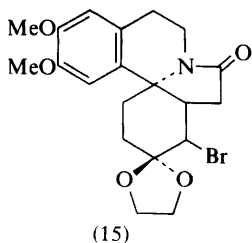
<sup>13</sup> K. Ito, H. Furukawa, and M. Haruna, *Yakugaku Zasshi*, 1973, **93**, 1611, 1617.

achieved.<sup>14</sup> It involved the novel ring-cleavage of the aza-tricyclo[3.2.0.0]-compound (12) with phenylselenenyl chloride. The compound (12) was prepared from the 7 $\beta$ -hydroxylated acetal lactam (11b) by reaction with methanesulphonyl chloride in pyridine, followed by hydrolysis with dilute acid and treatment of the resulting compound (11c) with methanolic sodium hydroxide. The preparation of key intermediate (11a) in the syntheses of erythrinan alkaloids has already been reported.<sup>15</sup> The synthetic ( $\pm$ )-erysotramidine was identical (i.r., <sup>1</sup>H n.m.r.) with natural erysotramidine.

The dibenzazonine (13), related to a biosynthetic precursor of the *Erythrina* alkaloids, has been prepared in 35% yield by the intramolecular nickel-promoted coupling of the bis-(2-phenylethyl)amine (14), which in turn was obtained from the commercially available (3-methoxyphenyl)acetic acid by a conventional series of reactions.<sup>16</sup>



Several *cis*-erythrinan derivatives have been synthesized in Mondon's laboratories;<sup>17</sup> e.g., the cycloerythrinane (16a) was obtained by heating the bromo-compound (15) with potassium hydroxide in diethylene glycol at 180 °C. On hydrolysis, it yielded the keto-amide (16b), which afforded the amide (16c) and the amine (16d) *via* the unsaturated amide (17). Bromination of the ketone



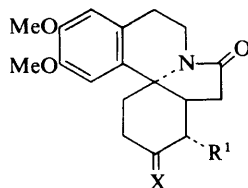
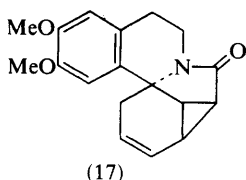
<sup>14</sup> K. Ito, F. Suzuki, and M. Haruna, *J. Chem. Soc., Chem. Commun.*, 1978, 733.

<sup>15</sup> M. Haruna and K. Ito, *J. Chem. Soc., Chem. Commun.*, 1976, 345.

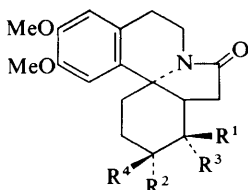
<sup>16</sup> S. Brandt, A. Marfat, and P. Helquist, *Tetrahedron Lett.*, 1979, 2193.

<sup>17</sup> A. Mondon, H. G. Vilhuber, C. Fischer, M. Epe, B. Epe, and C. Wolff, *Chem. Ber.*, 1979, **112**, 1110.

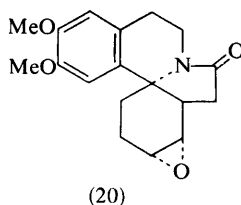
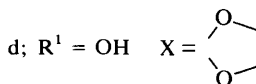
(18a) (or of the corresponding ketal, followed by hydrolysis) yielded the bromo-keto-lactam (18b); on reduction with  $\text{NaBH}_4$ , this gave the bromohydrins (19a, b, and c) and the epoxide (20).<sup>18</sup> The bromo-keto-lactam (18b), on reaction with potassium hydroxide in methanol, or ethylene glycol, gave the hydroxy-acetals (18c) and (18d), respectively.<sup>18</sup>



- (18) a;  $\text{R}^1 = \text{H}, \text{X} = \text{O}$   
 b;  $\text{R}^1 = \text{Br}, \text{X} = \text{O}$   
 c;  $\text{R}^1 = \text{OH}, \text{X} = (\text{OMe})_2$



- (19) a;  $\text{R}^1 = \text{R}^4 = \text{H}, \text{R}^2 = \text{OH}, \text{R}^3 = \text{Br}$   
 b;  $\text{R}^1 = \text{Br}, \text{R}^2 = \text{R}^3 = \text{H}, \text{R}^4 = \text{OH}$   
 c;  $\text{R}^1 = \text{Br}, \text{R}^2 = \text{OH}, \text{R}^3 = \text{R}^4 = \text{H}$



The partial synthesis of (–)-erysotrine (1f), starting from acetoxy-*cis*-erythrinan-1-en-8-one (21), has also been described (Scheme1).<sup>19</sup> The conversion of (23) into (±)-erysotrine (1f) was achieved *via* its mesylate, and the resolution of the (±)-erysotrine was carried out through the hydrogen dibenzoyltartrates. (±)-3-*epi*-Erysotrine was prepared by the same route, but *via* the epimer (22b).

Mondon and Nestler<sup>19</sup> have also described ring-closure reactions leading to the formation of the new cyclic ethers (24a), (24b), and (25), having the *cis*-erythrinane skeleton. Furthermore, Mondon has reported<sup>20</sup> that acetylation of the diol (26) yielded the rearranged product (27a), which reverted to (26) on hydrolysis. The corresponding *cis*-diol formed a monoacetate without any rearrangement. Assessment of the scope of the reversible rearrangement showed that the rearrangement step consisted of a spontaneous 1,2-shift involving four reaction centres.<sup>21</sup> Further studies<sup>22</sup> revealed that fragmentation of the acetate-mesylate (27b) with sodium methoxide led to the β-lactam aldehyde (28a), which

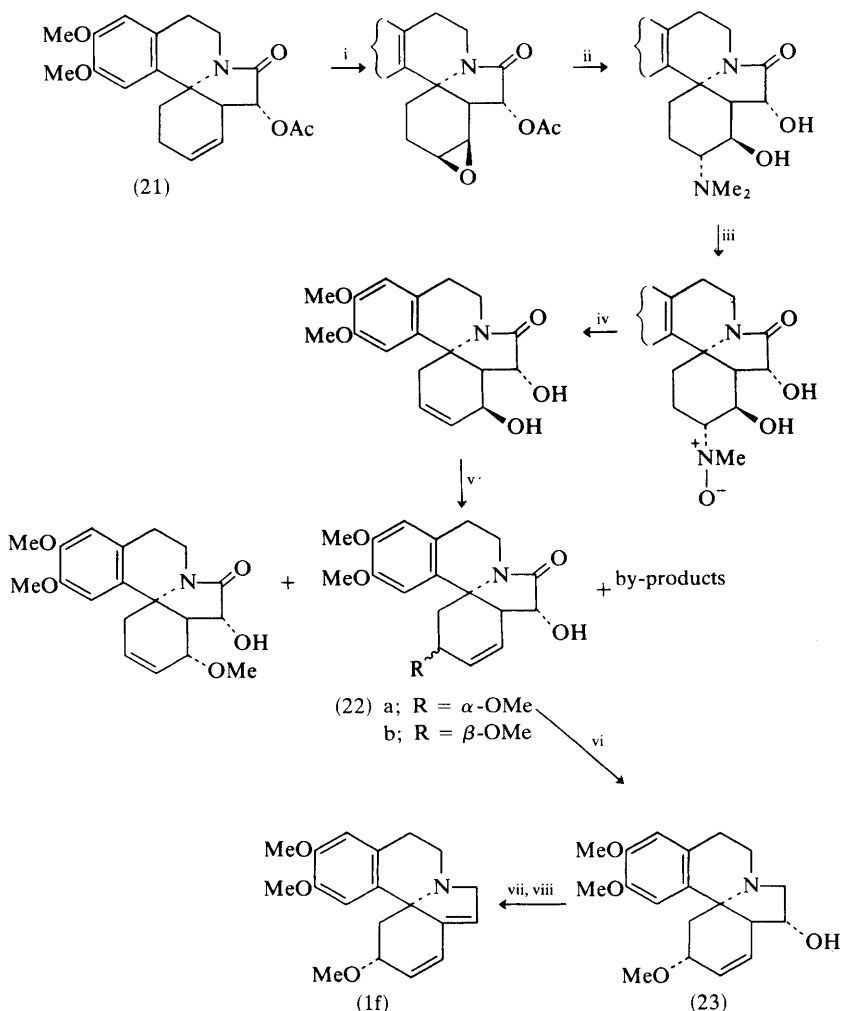
<sup>18</sup> A. Mondon, M. Epe, C. Wolff, T. Clausen, and H. G. Vilhuber, *Chem. Ber.*, 1979, **112**, 1126.

<sup>19</sup> A. Mondon and H. J. Nestler, *Chem. Ber.*, 1979, **112**, 1329.

<sup>20</sup> A. Mondon, S. Mohr, C. Fischer, and H. G. Vilhuber, *Chem. Ber.*, 1979, **112**, 2472.

<sup>21</sup> S. Mohr, C. Fischer, T. Clausen, and A. Mondon, *Chem. Ber.*, 1979, **112**, 3110.

<sup>22</sup> S. Mohr, T. Clausen, B. Epe, C. Wolff, and A. Mondon, *Chem. Ber.*, 1979, **112**, 3795.



Reagents: i, perbenzoic acid; ii, aq.  $\text{Me}_2\text{NH}$ ; iii, 30%  $\text{H}_2\text{O}_2$ ; iv, thermal fission; v,  $\text{HCl-MeOH}$ ; vi, lithium alanate; vii,  $\text{MeSO}_2\text{Cl}$ ; viii,  $\text{KOH}$  in glycol monomethyl ether

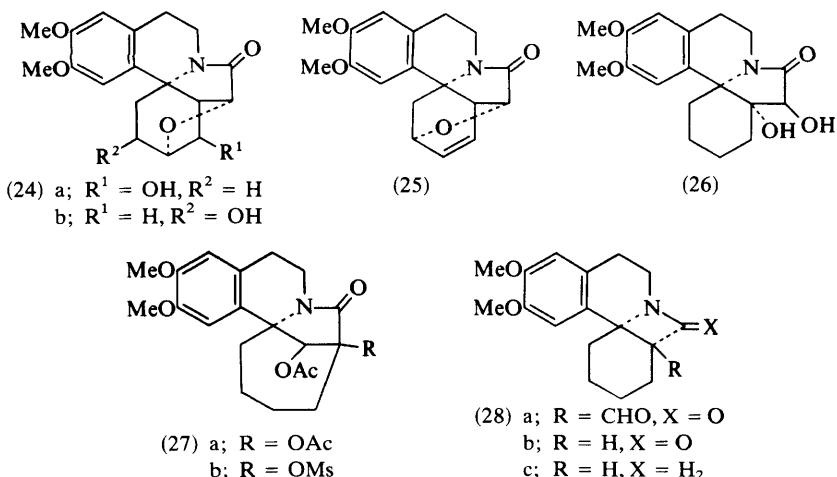
**Scheme 1**

was degraded to the  $\beta$ -lactam (28b) *via* the carboxylic acid. The constitution of (28a) was determined with the aid of deuteration experiments, and confirmed by X-ray analysis. Reduction of (28b), followed by cyclodehydration, yielded the  $\beta$ -nor-*cis*-erythrinan base (28c).

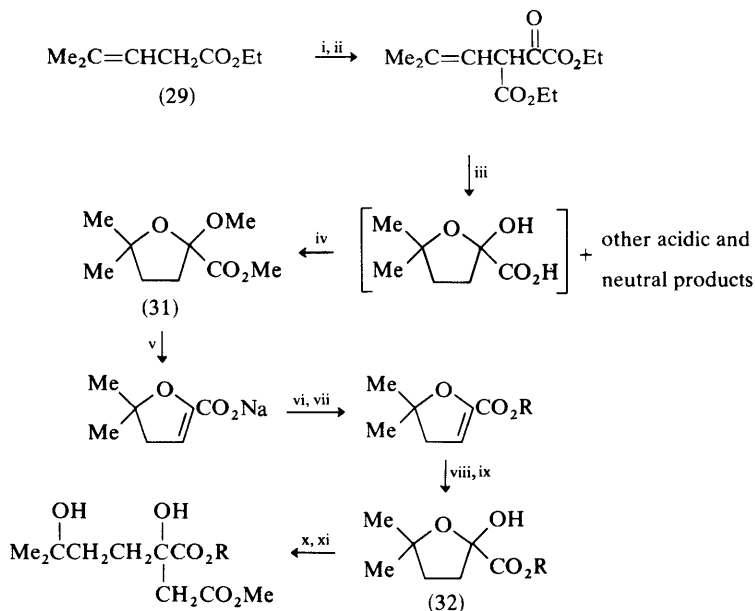
Harringtonine (9a), an anti-tumour alkaloid ester from *Cephalotaxus harringtonia*, referred to above, has now been synthesized<sup>23</sup> from cephalotaxine (9b)

<sup>23</sup> K. L. Mikolajczak and C. R. Smith, Jr., *J. Org. Chem.*, 1978, **43**, 4762.





by an indirect method involving a series of cyclic and hemiketal intermediates. Claisen condensation of the unsaturated ester (29) with diethyl oxalate in the presence of sodium hydride yielded (30) (65%), which on aqueous acid hydrolysis followed by reaction with methanolic acid afforded methyl 2-methoxy-5,5-dimethyltetrahydro-2-furoate (31) (36%). This was then converted into



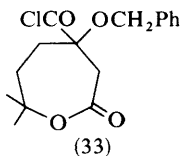
$R = (-)\text{-Cephalotaxine moiety}$

Reagents: i,  $\text{EtO}_2\text{CCO}_2\text{Et}$ ; ii,  $\text{NaH}$ ; iii,  $\text{HCl}$ , reflux; iv,  $\text{HCl-MeOH}$ ; v,  $\text{NaOH}$ ; vi, oxalyl chloride; vii, cephalotaxine; viii,  $\text{HCl}$ ; ix,  $\text{HOAc}$ ; x,  $\text{BrCH}_2\text{CO}_2\text{Me}$ ; xi,  $\text{Zn}$

Scheme 2

cephalotaxyl 2-hydroxy-5,5-dimethyltetrahydro-2-furoate (32) (88%) as a mixture of two diastereoisomers by the series of transformations shown in Scheme 2. Treatment of the diastereoisomeric mixture with methyl bromoacetate and zinc *via* the Reformatsky reaction yielded harringtonine and its acyl C-2 epimer, epiharringtonine.

The synthesis of a mixture of two diastereoisomers of harringtonine has also been reported<sup>24</sup> by esterifying cephalotaxine (9b) with the acid chloride (33) of racemic 4-benzyloxy-7,7-dimethyl-2-oxo-1-oxacycloheptane-4-carboxylic acid and converting the functionality of the acyl moiety into that of harringtonine. Isomerically pure harringtonine (9a) was made formally accessible by optical resolution of a hydroxy-acid precursor.



A brief report mentioning studies on the synthesis of homoharringtonine (9c) has been published, but no details are yet available.<sup>25</sup>

Recently, Weisleder *et al.*<sup>26</sup> have reported the carbon-13 chemical-shift assignments for cephalotaxine and related alkaloids.

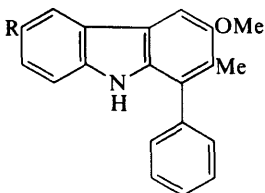
<sup>24</sup> R. W. McNutt, *Diss. Abstr. Int. B*, 1978, **38**, 5943.

<sup>25</sup> P. N. Kaul, *Diss. Abstr. Int. B*, 1980, **40**, 5273.

<sup>26</sup> D. Weisleder, R. G. Powell, and C. R. Smith, Jr., *Org. Magn. Reson.*, 1980, **13**, 114.

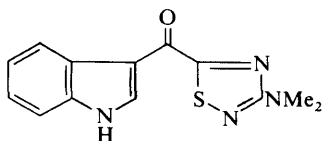
## 1 Simple Alkaloids

**Non-tryptamines.**—Mukonidine, a constituent of the stem bark of *Murraya koenigii* Spreng., is simply 2-hydroxy-3-methoxycarbonylcarbazole.<sup>1</sup> Carbazole derivatives also occur in blue-green algae; for example, hyellazole (1) and its 6-chloro-derivative, chlorohyellazole (2), have been isolated from *Hyella caespitosa* Born. et Flah.<sup>2</sup> The <sup>13</sup>C n.m.r. data for the pyranocarbazole alkaloid mupamine and for several simple substituted carbazoles have been reported.<sup>3</sup>

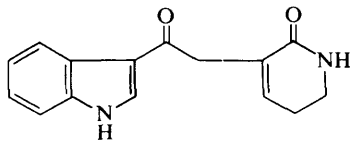


Hyellazole (1) R = H  
Chlorohyellazole (2) R = Cl

Novel indole derivatives continue to be found in marine organisms; those reported recently include dendrodoine (3), a cytotoxic thiadiazole derivative, which occurs in the tunicate *Dendrodoa grossularia*, from Brittany,<sup>4</sup> and the keto-lactam (4), one of two lactams isolated from the Caribbean sponge *Hali-chondria melanodocia*.<sup>5</sup>



Dendrodoine (3)



(4)

<sup>1</sup> D. P. Chakraborty, S. Roy, and R. Guha, *J. Indian Chem. Soc.*, 1978, **55**, 1114.

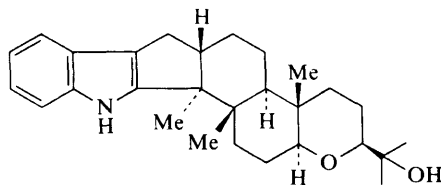
<sup>2</sup> J. H. Cardellina, M. P. Kirkup, R. E. Moore, J. S. Mynderse, K. Seff, and C. J. Simmons, *Tetrahedron Lett.*, 1979, 4915.

<sup>3</sup> I. Mester, D. Bergenthal, and J. Reisch, *Z. Naturforsch., Teil B*, 1979, **34**, 650.

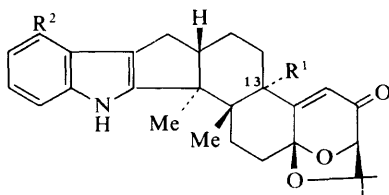
<sup>4</sup> S. Heitz, M. Durgeat, M. Guyot, C. Brassy, and B. Bachet, *Tetrahedron Lett.*, 1980, **21**, 1457.

<sup>5</sup> Y. Gopichand and F. J. Schmitz, *J. Org. Chem.*, 1979, **44**, 4995.

The fungus *Claviceps paspali* Stevens et Hall elaborates a series of metabolites derived from indole and a diterpenoid unit. The structures of paspaline (5) and paspalicine (6) were proposed earlier, together with the partial stereochemistry of paspaline. These conclusions have now been confirmed, and the complete stereochemistry of paspaline and paspalicine has been elucidated, by *X*-ray



Paspaline (5)

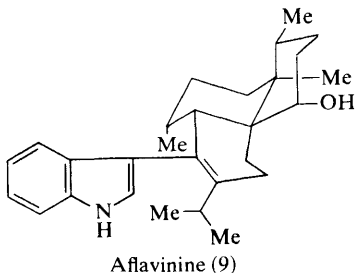


Paspalicine (6)  $R^1 = R^2 = H$

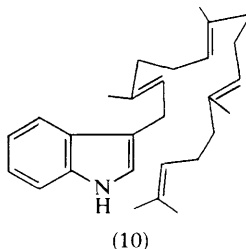
Paspalinine (7)  $R^1 = OH, R^2 = H$

Aflatrem (8)  $R^1 = OH, R^2 = CMe_2CH=CH_2$

crystal-structure determination.<sup>6</sup> Paspalinine is a hydroxy-paspalicine of structure and absolute configuration (7),<sup>7</sup> while aflatrem (8) has an additional isopentenyl group attached to the aromatic ring.<sup>8</sup> Aflavinine (9)<sup>9</sup> presumably derives from the same biosynthetic precursor (10) as do paspaline, paspalicine, and paspalinine,<sup>10</sup> but it arises by a different mode of cyclization, and migration of a methyl group. It is of some interest to note that those metabolites which have a hydroxy-group at position 13, *i.e.* paspalinine (7), aflatrem (8), and the closely



Aflavinine (9)



(10)

<sup>6</sup> J. P. Springer and J. Clardy, *Tetrahedron Lett.*, 1980, **21**, 231.

<sup>7</sup> R. T. Gallagher, J. Finan, J. Clardy, A. Leutwiler, F. Weibel, W. Acklin, and D. Arigoni, *Tetrahedron Lett.*, 1980, **21**, 235.

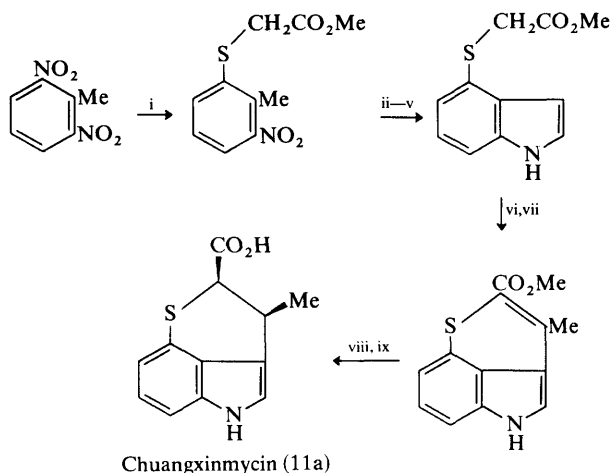
<sup>8</sup> R. T. Gallagher, J. Clardy, and B. J. Wilson, *Tetrahedron Lett.*, 1980, **21**, 239.

<sup>9</sup> R. T. Gallagher, T. McCabe, K. Hirotsu, J. Clardy, J. Nicholson, and B. J. Wilson, *Tetrahedron Lett.*, 1980, **21**, 243.

<sup>10</sup> W. Acklin, F. Weibel, and D. Arigoni, *Chimia*, 1977, **31**, 63.

related paxilline,<sup>11</sup> have pronounced tremorgenic properties; in contrast, paspaline (6) appears to be inactive.

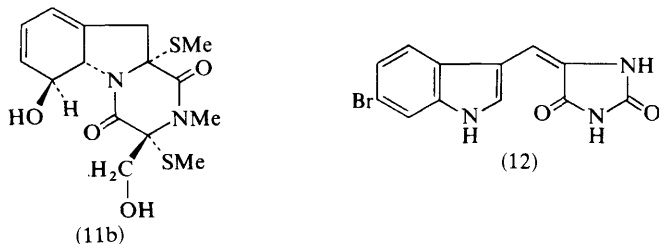
The structure and stereochemistry of chuangxinmycin (11a), a new antibiotic isolated from the micro-organism *Actinoplanes tsinanensis*, collected from a soil sample in Shantung Province, China, have been confirmed by synthesis (Scheme 1).<sup>12a</sup> Chuangxinmycin contains a novel heterocyclic ring system, and is claimed to be effective in the treatment of septicaemia and urinary and biliary infections.



Reagents: i, HSCH<sub>2</sub>CO<sub>2</sub>Me, HMPA, LiOH, at r.t.; ii, KOH, MeOH; iii, Me<sub>2</sub>NCH(OMe)<sub>2</sub>, DMF, reflux, then cold 6M-HCl; iv, FeSO<sub>4</sub>, NH<sub>4</sub>OH; v, CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O; vi, MeCOCl, SnCl<sub>4</sub>; vii, NH<sub>4</sub>OAc, AcOH, PhH, reflux; viii, H<sub>2</sub>, Pd-S; ix, Pr<sup>n</sup>SLi, HMPA

**Scheme 1**

Bisdethiobis(methylthio)gliotoxin (11b) is an amorphous minor metabolite of *Gliocladium deliquescens*; the structure (11b) was confirmed by its formation from gliotoxin, by methylation and reduction (MeI-MeOH-NaBH<sub>4</sub>).<sup>12b</sup>



**Non-isoprenoid Tryptamines.**—Tryptamine and *N*<sub>b</sub>-methyltryptamine have been shown to be present in the inflorescences of *Tachigalia paniculata* (Family

<sup>11</sup> J. P. Springer, J. Clardy, J. M. Wells, R. J. Cole, and J. W. Kirksey, *Tetrahedron Lett.*, 1975, 2531.

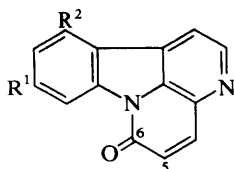
<sup>12</sup> (a) A. P. Kozikowski and M. N. Greco, *J. Am. Chem. Soc.*, 1980, **102**, 1165; (b) G. W. Kirby, D. J. Robins, M. A. Sefton, and R. R. Talekar, *J. Chem. Soc., Perkin Trans. 1*, 1980, 119.

Leguminosae).<sup>13</sup> Harman and an ethylharman have been isolated<sup>14a</sup> from the leaves of Venezuelan *Rauwolfia psychotrioides* H.B. and K., and *N*<sub>b</sub>-(*p*-coumaroyl)tryptamine and *N*<sub>b</sub>-feruloyltryptamine from the bark of *Cinnamosma madagascariensis*.<sup>14b</sup>

Erysopinophorine and iso-erysopinophorine, the two possible hypaphorine esters of erysopine, are among the constituents of the pod walls of *Erythrina arborescens*.<sup>15</sup>

The marine sponge *Smenospongia echina* Laubenfels contains 5,6-dibromo-*NN*-dimethyltryptamine, and the related species *S. aurea* Hyatt contains 5-bromo-*NN*-dimethyltryptamine and the bromo-indole derivative (12).<sup>16</sup>

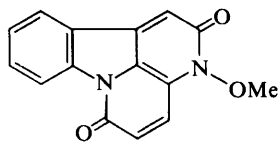
New canthinone derivatives have been found in *Simaba cuspidata* Spruce ex Engl. var. *typica* Cronquist, a shrub or small tree that is common in the Brazilian Rio Negro forest; the two identified so far are 8-methoxycanthin-6-one (13a) and 3-methoxycanthin-2,6-dione (13b).<sup>17a</sup> Amamoline (13c), amamoridine (13d), and 5-methoxycanthin-6-one are three more canthinone derivatives, which have recently been isolated from the monotypic genus *Amamoria soulameoides* A. Gray (Family Simaroubaceae) from Fiji.<sup>17b</sup> Homobrevicolline [4-(*N*-methyl-2-piperidyl)- $\beta$ -carboline] has been reported to be present in an unspecified Russian sedge.<sup>18</sup>



(13a)  $R^1 = \text{OMe}$ ,  $R^2 = \text{H}$

Amamoline (13c)  $R^1 = \text{H}$ ,  $R^2 = \text{OH}$

Amamoridine (13d)  $R^1 = \text{H}$ ,  $R^2 = \text{OMe}$



(13b)

New syntheses of *NN*-dimethyltryptamine and *O*-methylbufotenine, by way of dimethylaminoacetylation of the parent oxindole followed by reduction stages, have been reported;<sup>19</sup> this constitutes a new and convenient route to tryptamine derivatives.

A new approach to the synthesis of racemic tryptophan derivatives employs as the essential starting material the enamine (14), prepared by the reaction of *o*-nitrotoluene with dimethylformamide dimethyl acetal. One of the two new

<sup>13</sup> K. S. Svoboda, S. J. Smolenski, and A. D. Kinghorn, *J. Nat. Prod.*, 1979, **42**, 307.

<sup>14</sup> (a) H. E. Córdova B. and C. A. Peña, *Phytochemistry*, 1979, **18**, 1419; (b) V. Vecchiotti, G. Ferrari, F. Orsini, and F. Pellizzoni, *ibid.*, p. 1847.

<sup>15</sup> K. P. Tiwari and M. Masood, *Phytochemistry*, 1979, **18**, 2069; M. Masood and K. P. Tiwari, *ibid.*, 1980, **19**, 490.

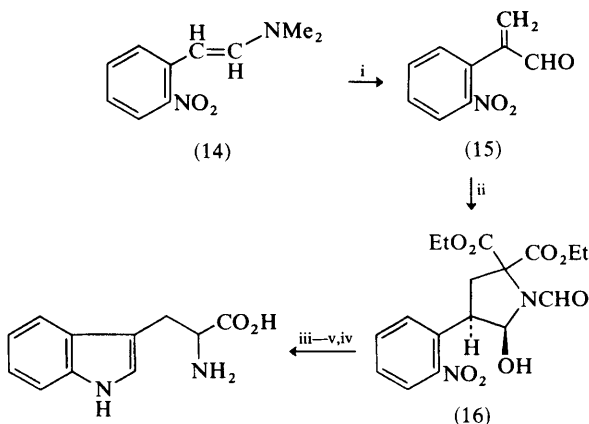
<sup>16</sup> P. Djura, D. B. Stierle, B. Sullivan, D. J. Faulkner, E. Arnold, and J. Clardy, *J. Org. Chem.*, 1980, **45**, 1435.

<sup>17</sup> (a) A. M. Giesbrecht, H. E. Gottlieb, O. R. Gottlieb, M. O. F. Goulart, R. A. De Lima, and A. E. G. Sant'ana, *Phytochemistry*, 1980, **19**, 313; (b) P. J. Clarke, K. Jewers, and H. F. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1614.

<sup>18</sup> I. N. Sharipov, I. V. Terent'eva, and G. V. Lazur'evskii, *Izv. Akad. Nauk Mold. SSR, Ser. Biol. Khim. Nauk* 1979, 86 (*Chem. Abstr.*, 1979, **91**, 87 295).

<sup>19</sup> E. Wenkert and A. C. Kryger, *J. Indian Chem. Soc.*, 1978, **55**, 1122.

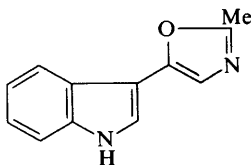
routes reported is illustrated in Scheme 2. Mannich condensation of (14) affords the substituted acrolein (15); on Michael reaction with formamidomalonic ester, this gives an adduct, which was isolated as the pyrrolidine derivative (16). Reductive cyclization to the  $\beta$ -substituted indole, followed by obvious hydrolysis and decarboxylation stages, then completes the synthesis (Scheme 2).<sup>20</sup>



Reagents: i,  $\text{CH}_2\text{O}$ ,  $\text{Me}_2\text{NH}$ ; ii,  $\text{OHCNHCH}(\text{CO}_2\text{Et})_2$ ,  $\text{NaOEt}$ ; iii,  $\text{H}_2$ ,  $\text{Ni}$ ; iv, heat; v,  $\text{NaOH}$

**Scheme 2**

Benzylic oxidation of *N*-acetyltryptamines by means of DDQ in aqueous THF affords the corresponding 3-oxo-derivatives; cyclization (using  $\text{POCl}_3$ ) then gives the related oxazolidine. Pimprinine (17), an alkaloid of *Streptomyces pimprina*, which exhibits anti-epileptic and monoamine-oxidase-inhibitory activities, was thus synthesized in 60% overall yield from *N*-acetyltryptamine.<sup>21</sup>



Pimprinine (17)

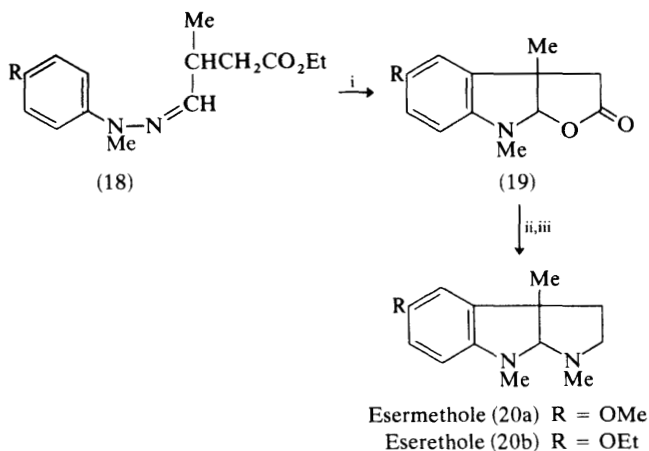
The Fischer cyclization of phenylhydrazones of structure (18) gives rise to the carbinolamine-lactones (19). Reaction with methylamine, followed by reduction, then affords a short synthesis of esermethole (20a) and eserethole (20b) (Scheme 3).<sup>22</sup>

A neat, biomimetic synthesis of brevicolline (21a) employs as essential starting material the (1*S*,3*S*)-tetrahydro- $\beta$ -carboline derivative (22), which is the major

<sup>20</sup> U. Hengartner, A. D. Batcho, J. F. Blount, W. Leimgruber, M. E. Larscheid, and J. W. Scott, *J. Org. Chem.*, 1979, **44**, 3748.

<sup>21</sup> Y. Oikawa, T. Yoshioka, K. Mohri, and O. Yonemitsu, *Heterocycles*, 1979, **12**, 1457.

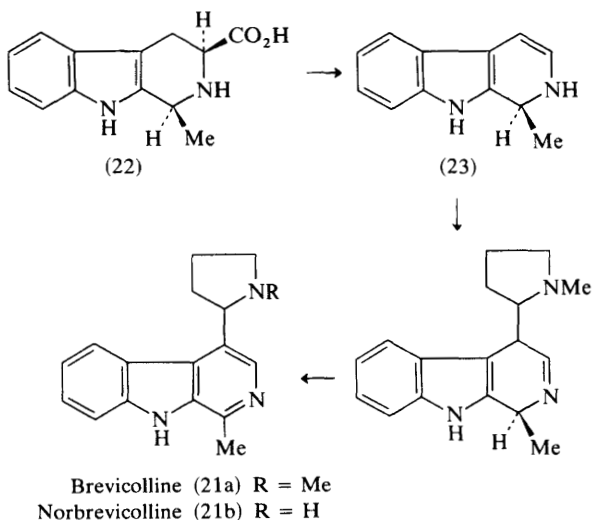
<sup>22</sup> P. Rosenmund and E. Sadri, *Liebigs Ann. Chem.*, 1979, 927.



Reagents: i, HCl, EtOH; ii, MeNH<sub>2</sub>; iii, LiAlH<sub>4</sub>

**Scheme 3**

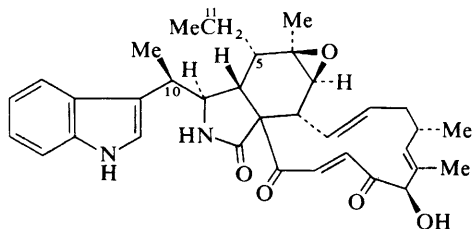
condensation product of L-tryptophan with acetaldehyde. Oxidative decarboxylation of (22) gives a 1,4-dihydro- $\beta$ -carboline, which isomerizes to the enamine (23). Condensation of (23) with *N*-methyl- $\Delta^1$ -pyrrolinium acetate then gives a dihydrobrevicolline, which is dehydrogenated in the reaction medium, so that brevicolline (21a) is produced in 1—2% yield. Alternatively, oxidative decarboxylation of (22) and proline gives norbrevicolline (21b) directly, presumably *via* the enamine (23) and  $\Delta^1$ -pyrroline; methylation then gives brevicolline (21a).<sup>23</sup>



<sup>23</sup> E. Leete, *J. Chem. Soc., Chem. Commun.*, 1979, 821.

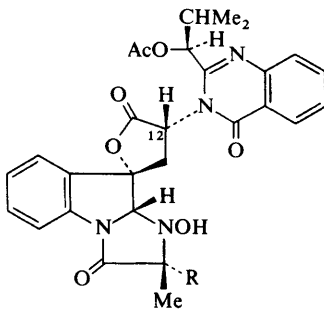


A new toxic cytochalasin, chaetoglobosin K, isolated from *Diplodia macrospora*, has the structure (24), according to the X-ray crystal-structure determination.<sup>24</sup> Compared with chaetoglobosin A, metabolite K has additional methyl groups at positions 10 and 11; this raises the interesting possibility (among others) that propionic acid may be implicated in its biosynthesis.



Chaetoglobosin K (24)

Some further work on the tryptoquivaline-related metabolites of *Aspergillus fumigatus* has been reported, but some features of their chemistry still remain to be elucidated.<sup>25</sup> On the basis of its n.m.r. spectrum, tryptoquivaline D (FTD) is now regarded as a secondary acetate, and is formulated as (25), i.e. the structure attributed to nortryptoquivaline; direct comparison of specimens subsequently confirmed this conclusion. Similar arguments led to the conclusion that tryptoquivaline C (FTC) is also a secondary acetate, rather than an *O*-acetylhydroxylamine derivative, and should be identical with Büchi's tryptoquivaline (26); however, direct comparison of specimens failed to support this conclusion, and the relationship between these two compounds is still not clear.



Tryptoquivaline D (Nortryptoquivaline) (25) R = H

Tryptoquivaline (26) R = Me

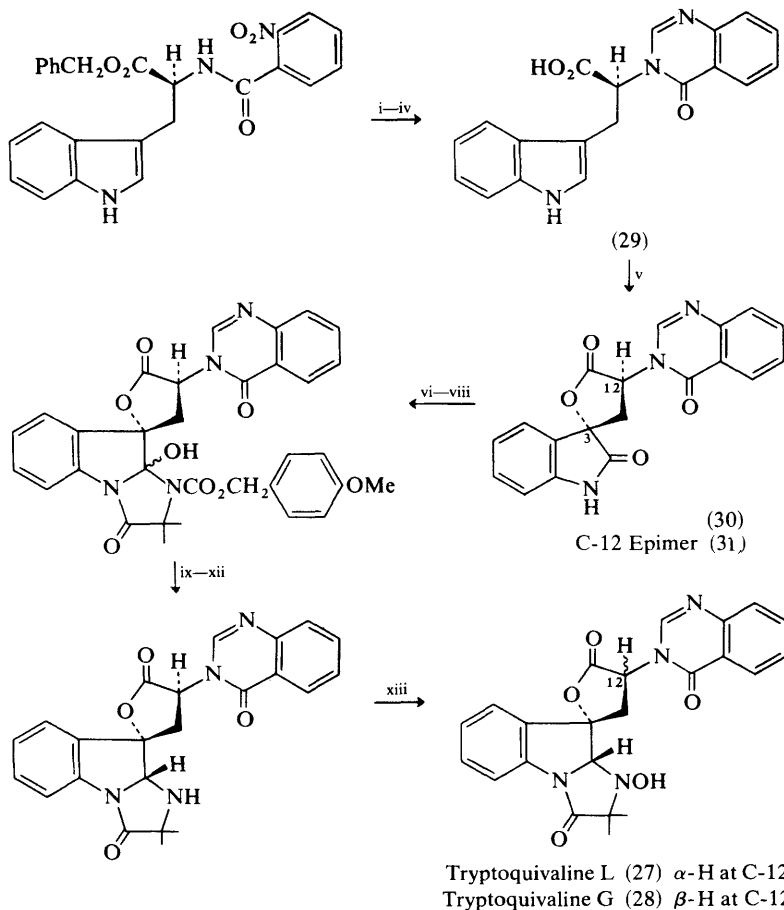
Of three new metabolites isolated from this same micro-organism, tryptoquivaline L (FTL) (27) is 12-*epi*-tryptoquivaline G, and can be obtained by the base-catalysed isomerization of tryptoquivaline G (28). Tryptoquivaline M (FTM) is a secondary acetate which was proved indirectly to be 12-*epi*-nortryp-

<sup>24</sup> J. P. Springer, R. H. Cox, H. G. Cutler, and F. G. Crumley, *Tetrahedron Lett.*, 1980, **21**, 1905.

<sup>25</sup> M. Yamazaki, E. Okuyama, and Y. Maebayashi, *Chem. Pharm. Bull.*, 1979, **27**, 1611.

toquivaline (12-*epi*-FTD), and tryptoquivaline N (FTN) was proved to be identical with Büchi's deoxynortryptoquivalone.\*

The synthesis of tryptoquivalines G (28) and L (27), by Büchi and his collaborators, constitutes the first contribution to total synthesis in this area.<sup>27</sup> The most noteworthy stage in this synthesis (Scheme 4) involves the oxidative



Reagents: i, Fe, HCl, EtOH; ii, HCO<sub>2</sub>H, PhH; iii, TsOH, xylene, heat; iv, Pd/C, H<sub>2</sub>, EtOH; v, 2 eq. (MeSO<sub>2</sub>)<sub>2</sub>O, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, at -20°C, for 5 h; vi, MeCON(SiMe<sub>3</sub>)<sub>2</sub>; vii, *p*-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>O<sub>2</sub>CCMe<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OMe-*p*, DMF, Me<sub>4</sub>N<sup>+</sup> Cl<sup>-</sup>; viii, NEt<sub>3</sub>; ix, CF<sub>3</sub>CO<sub>2</sub>H, EtOAc, PhOMe, at 0°C; x, NaBH<sub>3</sub>CN, THF, H<sub>2</sub>O, HCl for 1 h; xi, separate the diastereoisomers; xii, DDO, CHCl<sub>3</sub>; xiii, *m*-ClC<sub>6</sub>H<sub>4</sub>CO<sub>3</sub>H; xiv, KH, THF, DMF, then 1% HCl, THF, at -70°C.

**Scheme 4**

\* The absolute configurations depicted here for (25)–(28) are based on the absolute stereochemistry deduced for nortryptoquivaline (25) by Springer;<sup>26</sup> it should be noted that in ref. 25 the enantiomeric structures are illustrated.

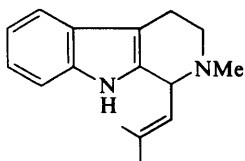
<sup>26</sup> J. P. Springer, *Tetrahedron Lett.*, 1979, 339.

<sup>27</sup> G. Büchi, P. R. DeShong, S. Katsumura, and Y. Sugimura, *J. Am. Chem. Soc.*, 1979, **101**, 5084.

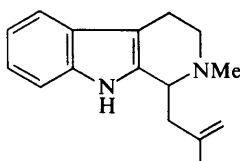
lactonization of the indole-quinazolinone derivative (29) (prepared by unexceptional stages from *L*-tryptophan) to a mixture of the tetracyclic spiro-lactone (30) and its C-3 epimer (31) (minor product). The stereochemistry of (30) was elucidated by base-catalysed epimerization at C-12, which gave the *enantiomer* (31) of the minor product; and the accompanying change in optical rotation was *opposite* in sign to that observed in the epimerization of tryptoquivaline G to give tryptoquivaline L. From this and similar experiments with model compounds it was concluded that (30) has the desired absolute configuration at C-3, and the synthesis was pursued with this product rather than with the very labile (towards base) isomer (31). The product ultimately obtained was thus tryptoquivaline L (27), which was then subjected to contrathermodynamic epimerization, with the formation of tryptoquivaline G.

## 2 Isoprenoid Tryptamine and Tryptophan Derivatives

The leaves of *Flindersia fournieri* Panch. et Seb. contain<sup>28a</sup> ten alkaloids, of which the structures of eight have so far been elucidated. Seven are dimeric alkaloids, each derived from the eighth, which is the monomeric base borrerine (32a), previously isolated from *Borreria verticillata*. Isoborrerine (32b), a double-bond isomer of borrerine, was subsequently isolated from the borrerine mother liquor; its structure was deduced from its spectroscopic data and confirmed by synthesis from *N*<sub>6</sub>-methyltryptamine and acetoacetaldehyde, followed by reaction with Grignard reagent (MeMgI) and dehydration.<sup>28b</sup>

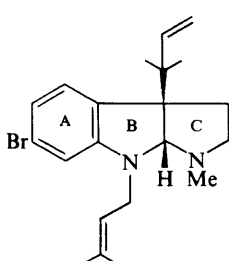


Borrerine (32a)

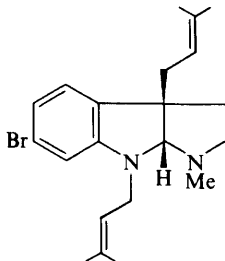


Isoborrerine (32b)

*Flustra foliacea* L., a marine bryozoan, or moss animal, contains<sup>29</sup> two isomeric metabolites, flustramine A and flustramine B, which are eserine derivatives that contain one bromine and two isoprenyl substituents, at positions 6, 3a, and 8. In



Flustramine A (33a)



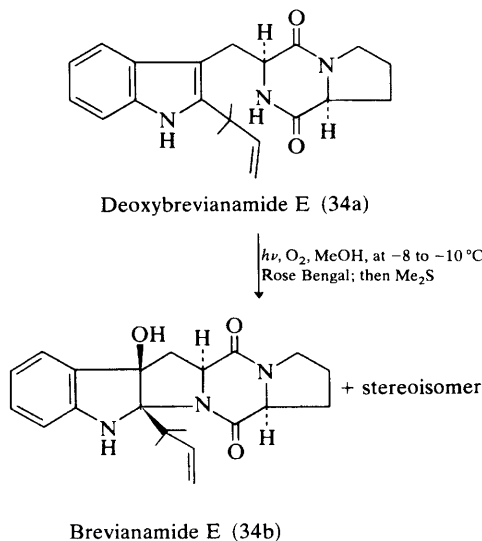
Flustramine B (33b)

<sup>28</sup> (a) F. Tillequin, R. Rousselet, M. Koch, M. Bert, and T. Sevenet, *Ann. Pharm. Fr.*, 1979, **37**, 543; (b) F. Tillequin and M. Koch, *Phytochemistry*, 1980, **19**, 1282.

<sup>29</sup> J. S. Carlé and C. Christophersen, *J. Am. Chem. Soc.*, 1979, **101**, 4012; *J. Org. Chem.*, 1980, **45**, 1586.

flustramine A (33a) the isoprenyl group at position 3a is reversed and, according to nuclear Overhauser enhancement difference spectroscopy, rings B and C are *cis*-fused. Structures (33a) and (33b) indicate the relative, but not necessarily the absolute, configurations of these metabolites.

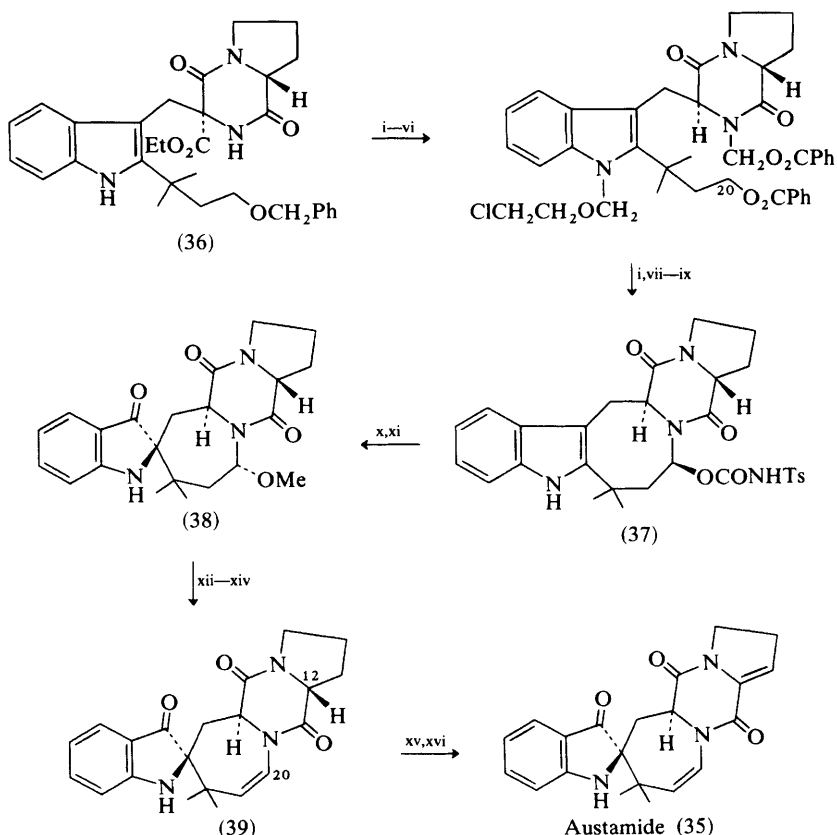
**Mould Metabolites.**—A second synthesis of deoxybrevianamide E has been reported;<sup>30a</sup> in essence, it is similar to the earlier synthesis,<sup>30b</sup> the major difference being simply the order in which the various stages are effected. Photochemical oxidation of deoxybrevianamide E (34a) provides the first satisfactory laboratory synthesis of brevianamide E (34b), which was obtained in 42% yield, together with its stereoisomer, the alternative *cis*-fused cyclization product. The stereochemistry depicted in (34b) rests on a comparison of the n.m.r. spectra of these two stereoisomers.<sup>30a</sup>



Hutchinson and Kishi<sup>30c</sup> have completed the first synthesis of the toxic metabolite of *Aspergillus ustus*, austamide (35), which contains two enamide functions and a spirocyclic indoxyl unit. The synthetic sequence is shown in Scheme 5, the starting material being the previously prepared<sup>31</sup> dioxopiperazine derivative (36). Protection of both indole and dioxopiperazine nitrogen atoms was necessary during the course of the synthesis, since cyclization of the aldehyde function generated at C-20 occurred preferentially on the indole nitrogen, if it was unprotected; and initial protection of the dioxopiperazine nitrogen was found to be necessary since intermolecular introduction of protecting groups occurred preferentially on this nitrogen atom. A notable outcome of this sequence of reactions was the development of a new protecting group for indole nitrogen,

<sup>30</sup> (a) T. Kametani, N. Kanaya, and M. Ihara, *J. Am. Chem. Soc.*, 1980, **102**, 3974; (b) R. Ritchie and J. E. Saxton, *J. Chem. Soc., Chem. Commun.*, 1975, 611; (c) A. J. Hutchinson and Y. Kishi, *J. Am. Chem. Soc.*, 1979, **101**, 6786.

<sup>31</sup> A. J. Hutchinson and Y. Kishi, *Tetrahedron Lett.*, 1978, 539.



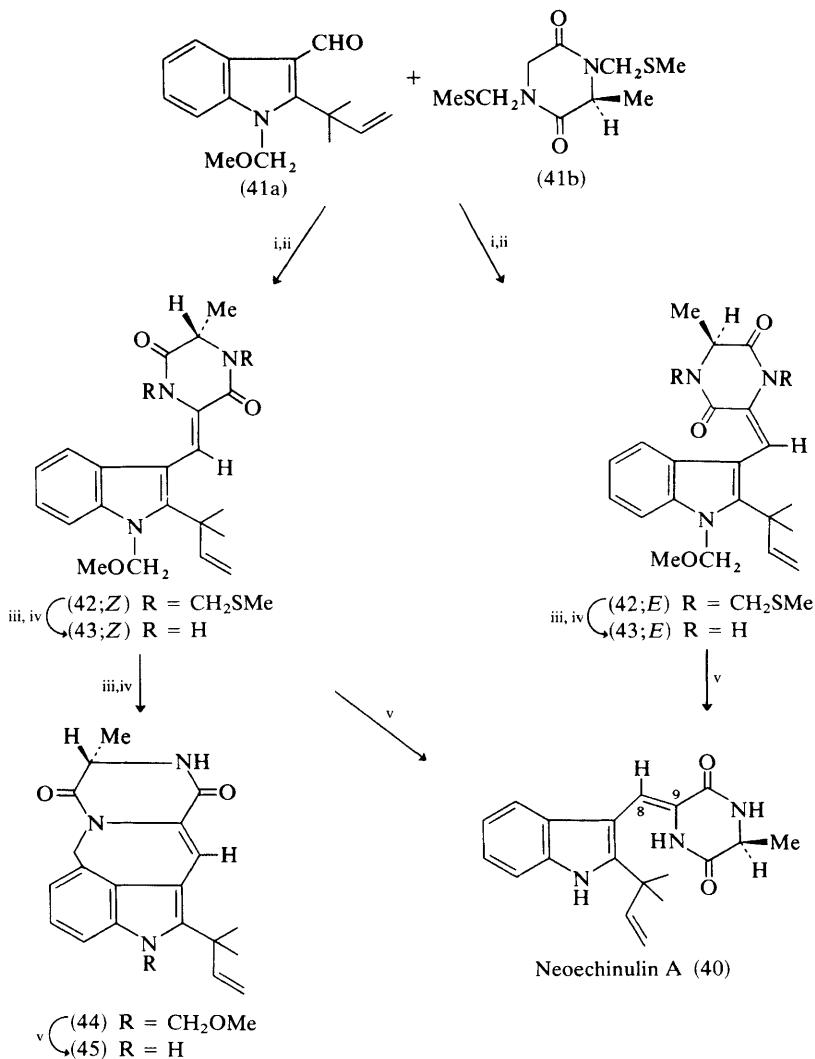
Reagents: i, 1M-NaOH, dioxan; ii, heat, dioxan; iii, hydrogenolysis; iv,  $\text{CH}_2\text{O}$ ,  $\text{H}_2\text{O}$ ,  $\text{K}_2\text{CO}_3$ , dioxan, at  $100^\circ\text{C}$ ; v, benzoylation; vi,  $\text{ClCH}_2\text{OCH}_2\text{CH}_2\text{Cl}$ ,  $\text{KH}$ ,  $\text{DMF}$ ,  $\text{THF}$ ; vii,  $\text{MnO}_2$ ,  $\text{MeCN}$ ; viii,  $\text{TsNCO}$ ,  $\text{CH}_2\text{Cl}_2$ ; ix,  $\text{KCN}$ ,  $\text{MeCN}$ , 18-crown-6, heat; x, *m*- $\text{ClC}_6\text{H}_4\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ ; xi,  $\text{NaOMe}$ ,  $\text{MeOH}$ , heat; xii,  $\text{PhSH}$ ,  $\text{BF}_3\cdot\text{Et}_2\text{O}$ ; xiii, *m*- $\text{ClC}_6\text{H}_4\text{CO}_2\text{H}$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{CaCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; xiv, *o*- $\text{C}_6\text{H}_4\text{Cl}_2$ , at  $150^\circ\text{C}$ ; xv,  $\text{O}_2$ ,  $\text{THF}$ ,  $(\text{PhCO}_2)_2$ , at  $50^\circ\text{C}$ , for 24 h, then  $\text{Me}_2\text{S}$ , at r.t.; xvi,  $\text{MeSO}_2\text{Cl}$ ,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$

Scheme 5

since none of the existing conventional methods proved satisfactory. The 2-chloroethoxymethylene group that was eventually used could be removed by a combination of cyanide ion and base, which are reagents that were compatible with the other functions in the molecule. As noted earlier,<sup>31</sup> the stereochemical course of the oxidation-rearrangement sequence (37)  $\rightarrow$  (38) was not in doubt, provided that (37) reacts in the folded conformation; this reaction sequence presumably mimics the biosynthesis of austamide. Finally, the  $12\alpha$ -hydroxy-compound which is the intermediate between (39) and austamide (35) was shown to be identical with a minor metabolite of *A. ustus*, isolated earlier by Steyn.<sup>32</sup>

<sup>32</sup> P. S. Steyn and R. Vlegaar, *Phytochemistry*, 1976, **15**, 355.

Complete  $^{13}\text{C}$  n.m.r. data have been recorded for echinulin, the neoechoinulins, the cryptoechoinulins,<sup>33</sup> and isoechoinulins A—C,<sup>34</sup> and complete assignments have been made. The (*Z*) configuration about the 8,9 double-bond in isoechoinulin B was deduced from the coupling constant of the proton at C-8 in the proton-undecoupled spectrum, and is the same as that deduced for neoechoinulin A (40).<sup>34</sup>



Reagents: i,  $\text{LiNPr}_2$ , THF, at  $-78$  to  $0^\circ\text{C}$ ; ii,  $\text{MeSO}_2\text{Cl}$ , at  $0^\circ\text{C}$  to r.t.; iii, MeI,  $\text{NaHCO}_3$ , acetone, at  $40^\circ\text{C}$ ; iv, dioxan, at  $100^\circ\text{C}$ , for 1 h; v,  $\text{HCO}_2\text{H}$ ,  $\text{H}_2\text{O}$

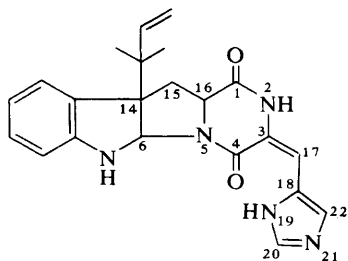
**Scheme 6**

<sup>33</sup> G. Gatti and C. Fuganti, *J. Chem. Res.* 1979, (S), 366; (M), 4457.

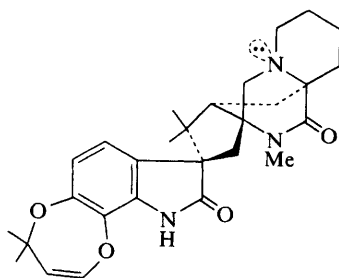
<sup>34</sup> H. Nagasawa, A. Isogai, A. Suzuki, and S. Tamura, *Agric. Biol. Chem.*, 1979, **43**, 1759.

The synthesis of neoechinulin A can be directly achieved by base-catalysed condensation of the indole aldehyde (41a) with the protected dioxopiperazine (41b), followed by removal of the protecting groups with formic acid (Scheme 6).<sup>35</sup> Unfortunately, the introduction of the protecting groups in the formation of (41b) was accompanied by racemization of the asymmetric centre; hence the final product was ( $\pm$ )-neoechinulin A. The condensation of (41a) and (41b) gave a mixture of (42;*Z*) and its geometrical isomer (42;*E*); however, both gave ( $\pm$ )-neoechinulin A on deprotection with aqueous formic acid, and no trace of the (*E*)-isomer could be detected. The configuration of (42;*Z*) became apparent from the formation of a sulphonium salt followed by intramolecular alkylation, which gave the tetracyclic product (44), deprotection of which gave (45); in contrast, (42;*E*) gave only the deprotected product (43;*E*) under the same conditions.<sup>35</sup>

Comparison of the <sup>13</sup>C n.m.r. data for oxaline, of known configuration, and roquefortine (46) reveals that the latter also has the (*E*) configuration about the 3,17 double-bond,<sup>36a</sup> a conclusion which confirms that made earlier<sup>36b</sup> on the basis of the proton n.m.r. spectra of roquefortine and its geometrical isomer, isoroquefortine. Biosynthetic studies with [3-<sup>3</sup>H]histidine have shown that the 3-*pro-S* hydrogen of (2*S*)-histidine is eliminated during the formation of roquefortine in *P. roqueforti* and of oxaline in *P. oxalicum*; this, together with the obvious structural similarity of roquefortine and oxaline, argues a close biogenetic relationship between these two metabolites, which is underlined by their co-occurrence in *P. oxalicum*.<sup>36a</sup>



Roquefortine (46)



Marcfortine A (47)

A Russian group has isolated<sup>36c</sup> roquefortine and 3,17-dihydroroquefortine from *Penicillium roqueforti* Thom F-141; the latter metabolite is presumably identical with Alkaloid Z (roquefortine D), isolated from the same micro-organism by Abe's group.<sup>36d</sup>

Evidence has also been obtained for the presence of roquefortine in *P. commune*.<sup>36e</sup> Marcfortine A, a new metabolite of *P. roqueforti* strain B26, has the

<sup>35</sup> S. Nakatsuka, H. Miyazaki, and T. Goto, *Tetrahedron Lett.*, 1980, **21**, 2817.

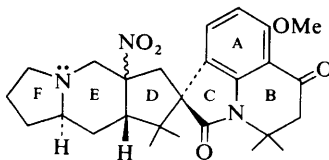
<sup>36</sup> (a) R. Vleggaar and P. L. Wessels, *J. Chem. Soc., Chem. Commun.*, 1980, 160; (b) P. M. Scott, J. Polonsky, and M. A. Merrien, *J. Agric. Food Chem.*, 1979, **27**, 201; (c) A. G. Kozlovskii, T. A. Reshetilova, T. N. Medvedeva, M. U. Arinbasarov, V. G. Sakharovskii, and V. M. Adanin, *Biokhimiya*, 1979, **44**, 1690 (English transl., p. 1335); (d) S. Ohmomo, K. Oguma, T. Ohashi, and M. Abe, *Agric. Biol. Chem.*, 1978, **42**, 2387; (e) R. E. Wagener, N. D. Davis, and U. L. Diener, *Appl. Environ. Microbiol.*, 1980, **39**, 882; (f) J. Polonsky, M. A. Merrien, T. Prangé, C. Pascard, and S. Moreau, *J. Chem. Soc., Chem. Commun.*, 1980, 601.

interesting structure (47), as determined by the *X*-ray method.<sup>36f</sup> This metabolite clearly originates from tryptamine, two isoprene units, and a molecule of pipercolic acid; this last component, and the linkage of one isoprene unit to two phenolic hydroxy-groups, are unique features of the marcfortine A molecule. Two other metabolites, marcfortines B and C, of unknown constitution, were also isolated.

Details of the structure elucidation of fomitremorgin A<sup>37a</sup> and fomitremorgin B<sup>37b</sup> have now been published.

Neoxaline, C<sub>23</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub>, a new metabolite of *Aspergillus japonicus*, exhibits similarities to oxaline in its i.r. and n.m.r. spectra, and may be an indole derivative, but nothing further is known of its constitution as yet.<sup>38a</sup> Similarly, three new tremorgenic mycotoxins from *Penicillium janthinellum*, janthitrems A, B, and C, may also be indole derivatives.<sup>38b</sup>

Cyclopiamines A and B are two new toxic metabolites of *P. cyclopium* Westling and *P. urticae* Bainier<sup>39</sup> which appear to be derived from tryptophan, proline, and two units of dimethylallyl pyrophosphate. The structure and relative stereochemistry of cyclopiamine B (48a) were deduced by *X*-ray crystal-structure analysis; those of cyclopiamine A (48b) were inferred from its isomerization to the thermodynamically more stable cyclopiamine B in polar solvents, the isomerization simply involving reversible cleavage of the  $\beta$ -nitroalkylamine system present in these two metabolites; in accordance with this, the ring-E-cleaved intermediate could be trapped by reduction with potassium borohydride. In view of the relative stabilities of cyclopiamines A and B, it seems likely that the former is the true fungal metabolite, and the latter is an artefact.<sup>39</sup>



Cyclopiamine B (48a)  $\beta$ -NO<sub>2</sub>  
Cyclopiamine A (48b)  $\alpha$ -NO<sub>2</sub>

**Ergot Alkaloids.**—New alkaloids isolated recently include 8-hydroxyergotamine (49; configuration at C-8 unspecified), which was found as a contaminant of commercial ergotamine,<sup>40</sup> and ergovaline (50), ergoptine (51), and ergonine (52), which were isolated from *Claviceps purpurea* or from mother liquors of the ergokryptine-ergocornine extraction.<sup>41a</sup> These last three alkaloids have already been synthesized<sup>41b,c</sup> but have not hitherto been found in Nature.

<sup>37</sup> (a) M. Yamazaki, H. Fujimoto, and T. Kawasaki, *Chem. Pharm. Bull.*, 1980, **28**, 245; (b) M. Yamazaki, K. Suzuki, H. Fujimoto, T. Akiyama, U. Sankawa, and Y. Iitaka, *ibid.*, p. 861.

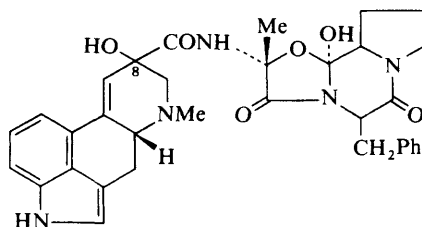
<sup>38</sup> (a) A. Hirano, Y. Iwai, R. Masuma, K. Tei, and S. Omura, *J. Antibiot.*, 1979, **32**, 781; (b) R. T. Gallagher, G. C. M. Latch, and R. G. Keogh, *Appl. Environ. Microbiol.*, 1980, **39**, 272.

<sup>39</sup> R. F. Bond, J. C. A. Boeyens, C. W. Holzapfel, and P. S. Steyn, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1751.

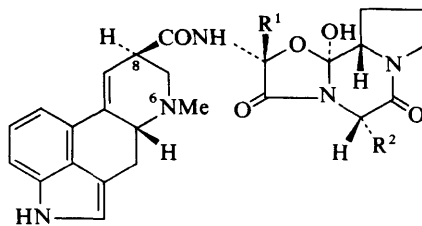
<sup>40</sup> A. Kraljiček, B. Trtík, J. Spáčil, P. Sedmera, J. Vokoun, and Z. Řeháček, *Collect. Czech. Chem. Commun.*, 1979, **44**, 2255.

<sup>41</sup> (a) R. Brunner, P. L. Stütz, H. Tschertter, and P. A. Stadler, *Can. J. Chem.*, 1979, **57**, 1638; (b) P. A. Stadler, A. J. Frey, H. Ott, and A. Hofmann, *Helv. Chim. Acta*, 1964, **47**, 1911; (c) P. Stütz, P. A. Stadler, and A. Hofmann, *ibid.*, 1970, **53**, 1278.





8-Hydroxyergotamine (49)



		R <sup>1</sup>	R <sup>2</sup>
Ergovaline	(50)	Me	CHMe <sub>2</sub>
Ergoptine	(51)	Et	CH <sub>2</sub> CHMe <sub>2</sub>
Ergonine	(52)	Et	CHMe <sub>2</sub>

*Balansia epichloë* (Weese) Diehl and *B. claviceps* are two systemic phytopathogens, taxonomically related to the genus *Claviceps*, which have been implicated as possible causes of unexplained toxicoses occurring in cattle grazing on infected pastures. Extraction of *B. epichloë* has revealed<sup>42</sup> the presence of chanoclavine I, isochanoclavine I, agroclavine, elymoclavine, penniclavine, ergonovine, ergonovinine, and two unidentified clavine alkaloids, and *B. claviceps* has been shown to contain chanoclavine I, ergonovine, and ergonovinine. The identification of clavine alkaloids, and particularly ergonovine/ergonovinine, suggests that *Balansia* species may well be responsible for the symptoms of ergotism observed.<sup>42</sup>

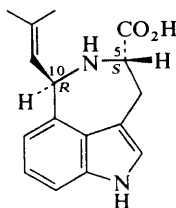
Lysergic acid diethylamide is biotransformed into norlysergic acid diethylamide by *Streptomyces lavendulae*, and into a mixture of lysergic acid monoethylamide, lysergic acid ethyl(2-hydroxyethyl)amide (LEO), and lysergic acid ethylvinylamide by *S. roseochromogenes*; all four metabolites are produced by *S. massasporeus*, *S. platensis*, *S. rimosus*, *S. fulvissimus*, and *Cunninghamella echinulata*.<sup>43a,b</sup> In amides which do not have a methylene group on the penultimate ( $\beta$ ) carbon atom attached to the amide nitrogen, oxidation in the presence of *S. roseochromogenes* occurs at the  $\alpha$ -carbon atom, with subsequent loss of the alkyl group; thus lysergic acid dimethylamide and lysergic acid diallylamide give the corresponding monoalkylamide.<sup>43c</sup> In amides which possess a methylene

<sup>42</sup> J. K. Porter, C. W. Bacon, and J. D. Robbins, *J. Nat. Prod.*, 1979, **42**, 309.

<sup>43</sup> (a) H. Ishii, M. Hayashi, T. Niwaguchi, and Y. Nakahara, *Chem. Pharm. Bull.*, 1979, **27**, 1570; (b) H. Ishii, T. Niwaguchi, Y. Nakahara, and M. Hayashi, *J. Chem. Soc., Perkin Trans. 1*, 1980, 902; (c) H. Ishii, M. Hayashi, T. Niwaguchi, and Y. Nakahara, *Chem. Pharm. Bull.*, 1979, **27**, 3029.

group on the  $\beta$ -carbon atom to the amide nitrogen, oxidation occurs at this position (*cf.* LSD  $\rightarrow$  LEO, mentioned above) to give the corresponding  $\beta$ -hydroxy-derivative.<sup>43c</sup>

The revised structure for clavicipitic acid, suggested earlier by King *et al.*,<sup>44a</sup> has been confirmed, and the stereochemistry elucidated, by *X*-ray crystal-structure analysis.<sup>44b</sup> The major component of the naturally occurring mixture that constitutes clavicipitic acid was obtained pure by t.l.c. on silica gel, and proves to have the (5*S*,10*R*) stereochemistry depicted in (53). The minor component of the mixture is presumably the (5*S*,10*S*)-diastereoisomer. It should be noted that, at present, the absolute configuration of clavicipitic acid rests only on its biogenetic derivation from L-tryptophan.<sup>44b</sup>



Clavicipitic acid (53)

Details of the synthesis of costaclavine<sup>45a</sup> and of the elucidation of its stereochemistry and that of its C-8 and C-10 epimers, epicostaclavine, festuclavine, and pyroclavine, have now been published.<sup>45b</sup>

In the search for new prolactin inhibitors, several 6-alkyl-derivatives of (D-8-ergolin-1-yl)acetamide have been made,<sup>46a</sup> together with several bis(ergolin-2-yl)alkanes,<sup>46b</sup> the latter being the products of acid-catalysed condensation of ergoline with ketones.

High-performance liquid chromatography on silica is recommended<sup>47a</sup> for the separation of some, but not all, mixtures of ergot alkaloids; an improved procedure, which is claimed to be satisfactory for the separation and determination of mixtures of cyclol ergot alkaloids obtained from fermentation media, involves the use of silica gel modified with alkylamines as the stationary phase, with gradient elution by diethyl ether-ethanol mixtures.<sup>47b</sup>

**Monoterpenoid Alkaloids.**—*Aristotelia Alkaloids.* Fruticosonine is a novel alkaloid, containing an unarranged monoterpene unit, which occurs<sup>48</sup> in *Aristotelia fruticosa* Hook. f; the structure (54) (relative stereochemistry only) was deduced by *X*-ray crystallography, and confirmed by the synthesis of ( $\pm$ )-fruticosonine

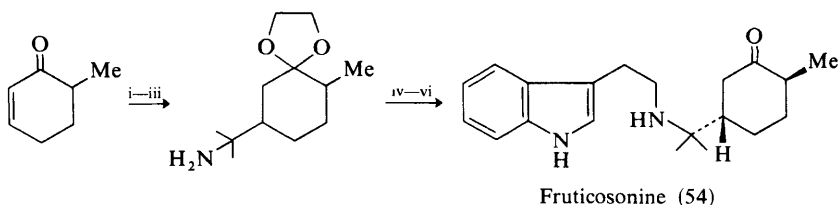
<sup>44</sup> (a) G. S. King, E. S. Waight, P. G. Mantle, and C. A. Szczyrbak, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2099; (b) J. E. Robbers, H. Otsuka, H. G. Floss, E. V. Arnold, and J. Clardy, *J. Org. Chem.*, 1980, **45**, 1117.

<sup>45</sup> (a) I. Ninomiya and T. Kiguchi, *J. Chem. Soc., Chem. Commun.*, 1976, 624; (b) I. Ninomiya, T. Kiguchi, and T. Naito, *J. Chem. Soc., Perkin Trans. 1*, 1980, 208.

<sup>46</sup> (a) M. Beran, J. Křepelka, and M. Semonský, *Collect. Czech. Chem. Commun.*, 1979, **44**, 3385; (b) J. Křepelka, J. Holubek, and M. Semonský, *ibid.*, 1980, **45**, 755.

<sup>47</sup> (a) G. Szepesi, M. Gazdag, and L. Terdy, *J. Chromatogr.*, 1980, **191**, 101; (b) M. Wurst, M. Flieger, and Z. Reháček, *ibid.*, 1979, **174**, 401.

<sup>48</sup> N. Chaichit, B. M. Gatehouse, I. R. C. Bick, M. A. Hai, and N. W. Preston, *J. Chem. Soc., Chem. Commun.*, 1979, 874.

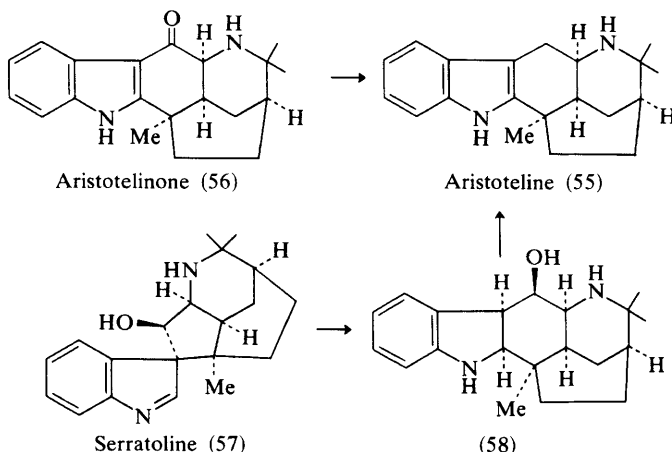


Reagents: i,  $\text{Me}_2\text{CHNO}_2$ ,  $\text{EtONa}$ ; ii,  $(\text{CH}_2\text{OH})_2$ ,  $\text{TsOH}$ ; iii,  $\text{NaBH}_4$ ,  $\text{Pd/C}$ ,  $\text{MeOH}$ ; iv, indole  $\beta$ -glyoxylyl chloride; v,  $\text{LiAlH}_4$ ; vi,  $\text{H}_3\text{O}^+$

Scheme 7

according to the route outlined in Scheme 7. It seems likely that fruticosonine represents an early stage in the biosynthesis of the more complex *Aristotelia* alkaloids.

Aristotelinone, one of the minor alkaloids<sup>49</sup> of *A. serrata*, is a 3-acylindole which can be reduced (by  $\text{LiAlH}_4$ ) to aristoteline (55), and it therefore has the structure and stereochemistry expressed in (56). The proton n.m.r. spectrum of serratoline, another minor alkaloid of *A. serrata*, shows a particular resemblance to that of one of the  $\beta$ -hydroxy-compounds obtained as by-products in the reduction of aristotelinone; however, serratoline exhibits an extra singlet at  $\delta$  7.30 p.p.m., the broad indole NH signal is absent, and its u.v. spectrum is that of an indolenine. These data suggest that serratoline has the constitution (57), a conclusion which is confirmed by reduction (by  $\text{NaBH}_4$ ) of serratoline (with concomitant rearrangement) to an indoline derivative (58), the acid-catalysed dehydration of which is accompanied by a proton shift to give aristoteline (55).<sup>49</sup>

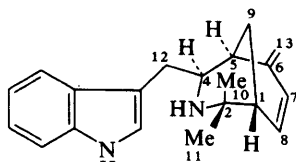


Sorelline and hobartine are two new alkaloids of *A. peduncularis* (Labill.) Hook. f. which were isolated by chromatography after removal of the major alkaloid, peduncularine.<sup>50</sup> Both alkaloids, whose structures were elucidated

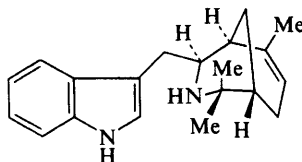
<sup>49</sup> I. R. C. Bick, M. A. Hai, N. W. Preston, and R. T. Gallagher, *Tetrahedron Lett.*, 1980, **21**, 545.

<sup>50</sup> R. Kyburz, E. Schöpp, I. R. C. Bick, and M. Hesse, *Helv. Chim. Acta*, 1979, **62**, 2539.

mainly from a detailed analysis of their n.m.r. and mass spectra, contain an unrearranged monoterpenoid unit, hobartine (60) simply being the 8,13-dihydro-derivative of sorelline (59).



Sorelline (59)



Hobartine (60)

*Corynantheine-Heteroyohimbine-Yohimbine Group, and Related Oxindoles.* Amongst the new alkaloids in this group is  $N_{b,21}$ -dehydrogeissoschizine (61), which has been isolated from the leaves of *Guettarda eximia*.<sup>51a</sup> This alkaloid is a most important link<sup>51b</sup> in the biosynthetic sequence from strictosidine to the heteroyohimbine alkaloids, and is the immediate precursor of cathenamine (62), into which it is converted by treatment with dilute aqueous alkali.<sup>51a</sup> Reduction (by  $\text{NaBH}_4$ ) of (61) affords a mixture of geissoschizine, isositsirikine, 16-*epi*-isositsirikine, and tetrahydroalstonine, which is the same mixture as that obtained by the analogous reduction of cathenamine. These results establish the equilibrium  $(61) \rightleftharpoons (62)$  in solution, but do not exclude for the new alkaloid the structure (63), which is known to be formed from cathenamine in solution;<sup>51c</sup> however, the chemical shift ( $\delta$  2.05) of the ethylidene methyl group effectively eliminates structure (63) from consideration (Scheme 8).

Biomimetic conversions reported<sup>51a</sup> on  $N_{b,21}$ -dehydrogeissoschizine include the formation of 17-hydroxydihydrocatenamine (64) on treatment with 2% aqueous hydrochloric acid and of isovallesiachotamine (65) in buffered solution at pH 4. Reduction (by  $\text{NaBH}_4$ ) of (64), followed by dehydration, affords 19-*epi*-ajmalicine (66); hence the configuration at C-19 is as depicted in (64). 19-*epi*-Ajmalicine (66) can also be obtained by the reaction of (61) with alumina, followed by reduction; this may involve the intermediate formation of the fugitive dienamine (67), which can equilibrate with the (*Z*)-isomer of (61) before cyclization to the (19*R*) product (64) (Scheme 8).<sup>52</sup>

Whether the dienamine (67) actually participates in this reaction at an alumina surface remains to be proved; however, it appears not to be an intermediate in analogous reactions in solution, according to the recent studies of Brown and Leonard,<sup>53</sup> which have added further clarification to the processes occurring in the biomimetic syntheses from strictosidine.

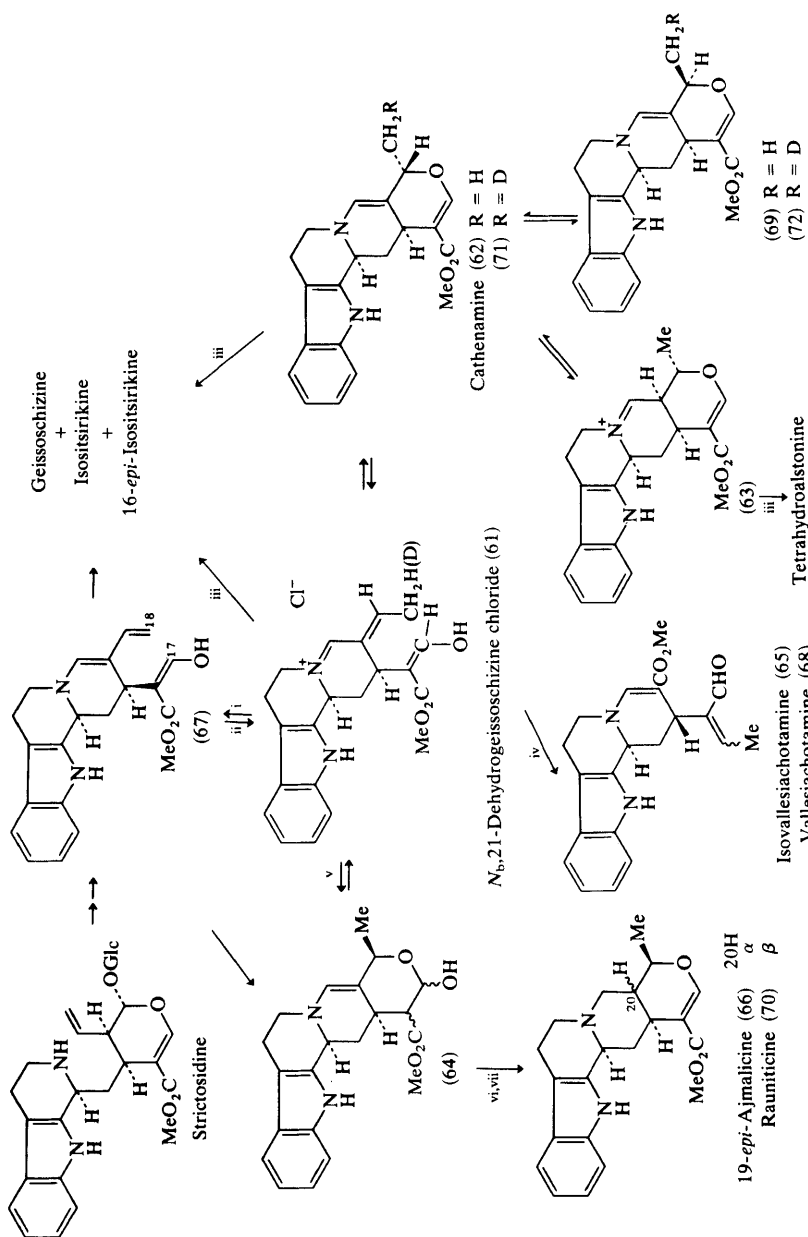
Brown's one-pot synthesis<sup>54a</sup> affords mainly (19*S*)-heteroyohimbine alkaloids (e.g. tetrahydroalstonine) by a kinetically controlled process involving preferential formation of an (*E*)-alkene (61?) from the *initially* formed dienamine

<sup>51</sup> (a) C. Kan-Fan and H. P. Husson, *J. Chem. Soc., Chem. Commun.*, 1979, 1015; (b) M. Rueffer, C. Kan-Fan, H. P. Husson, J. Stöckigt, and M. H. Zenk, *ibid.*, p. 1016; (c) P. Heinsteint, J. Stöckigt, and M. H. Zenk, *Tetrahedron Lett.*, 1980, **21**, 141.

<sup>52</sup> C. Kan-Fan and H. P. Husson, *Tetrahedron Lett.*, 1980, **21**, 1463.

<sup>53</sup> R. T. Brown and J. Leonard, *J. Chem. Soc., Chem. Commun.*, 1979, 877.

<sup>54</sup> J. E. Saxton, in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Chemical Society, London, 1979, Vol. 9; (a) p. 182; (b) p. 213; (c) p. 215; (d) p. 218.

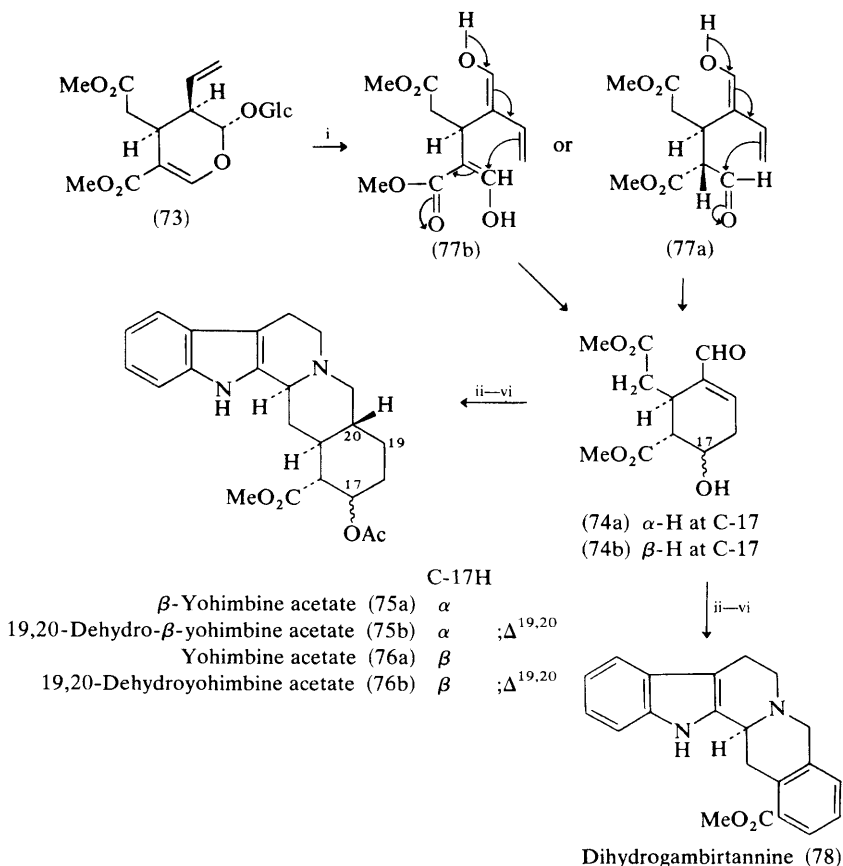


Reagents: i,  $\text{Al}_2\text{O}_3$ ; ii,  $\text{H}^+$  (or  $\text{D}^+$ ); iii,  $\text{NaBH}_4$ ,  $\text{MeOH}$ ; iv,  $\text{pH } 4$ ; v, 2%  $\text{HCl}$ ; vi,  $\text{NaBH}_4$ ; vii,  $\text{TsOH}$

### Scheme 8

(67). The formation of (19*R*) alkaloids would require equilibration to the (*Z*)-alkene (or equivalent) at the 20,21-dehydro stage. This in fact occurs when strictosidine is incubated with  $\beta$ -glucosidase in buffered solution at pH 6.0, the products being cathenamine (62), vallesiachotamine (68), and a third product, which must be 19-*epi*-catenamine (69), since reduction (by  $\text{NaBH}_4$ ) gives 19-*epi*-ajmalicine (66), or (with  $\text{NaBH}_3\text{CN}$ , at pH 6) rauniticine (70). When the glucolysis reaction was conducted overnight, the proportion of (69) increased, more vallesiachotamine was formed, and two isomeric compounds of general structure (64) were obtained.

The mechanism of formation of the (19*R*)-bases was studied by means of  $^2\text{H}$  and  $^{18}\text{O}$  experiments. In  $\text{D}_2\text{O}$ , at pH 6, strictosidine gives the monodeuterio-compounds (71) and (72), as expected, but whereas the proportion of (72) increases with time, *no further deuterium is incorporated*. Hence cathenamine does not revert in acid to the dienamine (67). Evidently cathenamine is protonated to



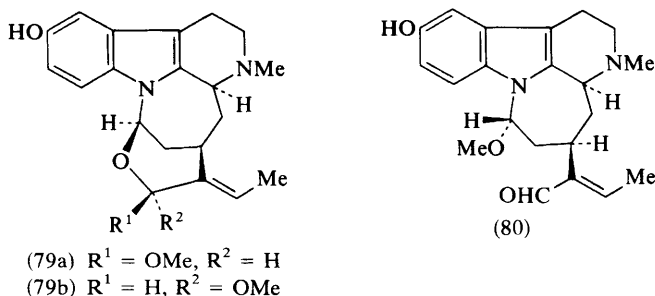
Reagents: i,  $\beta$ -Glucosidase, pH 7.0; ii, acetylation; iii, tryptamine; iv,  $\text{NaBH}_3\text{CN}$ ; v,  $\text{POCl}_3$ ; vi,  $\text{NaBH}_4$

Scheme 9

the immonium ion (61), which can add water *reversibly* at C-19, and thus allow isomerization to the (*Z*)-alkene. The absence of  $^{18}\text{O}$  in the final alkaloids when these were prepared in  $\text{H}_2^{18}\text{O}$  solution demonstrates that this newly introduced oxygen atom is not subsequently involved in the closure of ring E.<sup>53</sup>

A major development in this area is the first biomimetic synthesis<sup>55</sup> (see Scheme 9) of the ring-E-carbocyclic yohimbine alkaloids from secoxyloganin methyl ester (73), which on treatment with  $\beta$ -glucosidase at pH 7.0 gave a mixture of the two carbocyclic aldehyde diesters (74a) (major product) and (74b). Acetylation, condensation with tryptamine, and completion of the synthesis as in Woodward's reserpine synthesis finally gave  $\beta$ -yohimbine acetate (75a) and its 19,20-dehydro-analogue (75b), together with yohimbine acetate (76a) and its dehydro-analogue (76b). The carbocyclic ring in (74a) and (74b) is presumably formed by a vinylogous aldol reaction on the intermediate unsaturated aldehyde-ester (77a), or possibly *via* a Michael addition on the enolic form (77b). A further minor product was the unstable dihydrogambirtannine (78), which has also been obtained<sup>52</sup> from the reaction of  $N_6,21$ -dehydrogeissoschizine with alumina, followed by reduction (with  $\text{NaBH}_4$ ); this is evidently the result of nucleophilic attack at C-17 by C-18 in the dienamine (67).

The root and stem bark of *Strychnos decussata* (Pappe) Gilg. contain akagerine, 17-*O*-methylakagerine, and three new alkaloids, *i.e.* 10-hydroxy-21-*O*-methylkribine (79a) and its 21-epimer (79b) and 10-hydroxy-*O*-methylakagerine (80);<sup>56</sup> these alkaloids may be responsible for the muscle-relaxant properties of extracts of the bark of this plant.



The leaves of *Nauclea latifolia* contain naufoline, angustine, cadambine,  $3\alpha$ -dihydrocadambine, and a new alkaloid, naulafine, which has been formulated,<sup>57</sup> on spectroscopic evidence, as (81). Another new alkaloid is strychno-rubigine (10-methoxyxisositsirikine), which occurs in the root bark of *Strychnos rubiginosa* DC.<sup>58</sup> Antirrhine and pleiocarpamine have been found in the leaves and stem bark of *Alstonia odontophora* Boiteau [*A. roeperi* van Heurck et Müll.-Arg.],<sup>59</sup> and pleiocarpamine, pleiocarpamine *N*-oxide, geissoschizine,

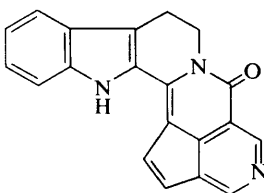
<sup>55</sup> R. T. Brown and S. B. Pratt, *J. Chem. Soc., Chem. Commun.*, 1980, 165.

<sup>56</sup> W. N. A. Rolfsen, A. A. Olaniyi, and P. J. Hylands, *J. Nat. Prod.*, 1980, **43**, 97.

<sup>57</sup> F. Hotellier, P. Delaveau, and J. L. Pousset, *Planta Med.*, 1979, **35**, 242.

<sup>58</sup> G. B. Marini-Bettolo, C. Galeffi, M. Nicoletti, and I. Messina, *Phytochemistry*, 1980, **19**, 992.

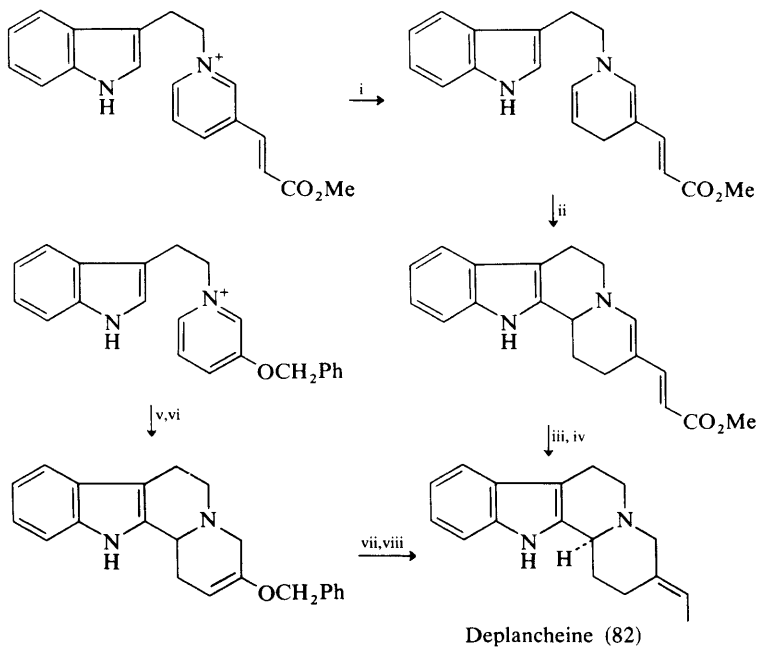
<sup>59</sup> J. Vercauteren, G. Massiot, T. Sevenet, J. Lévy, L. Le Men-Olivier, and J. Le Men, *Phytochemistry*, 1979, **18**, 1729.



Naulafine (81)

tetrahydroalstonine, 10-methoxypleiocarpamine, 10-methoxy-2,7-dihydropleiocarpamine, and *N*<sub>6</sub>-methyltetrahydroalstonine in the leaves of *Rauwolfia volkensii* Stapf, a shrub whose natural habitat is the Mount Kilimanjaro region.<sup>60</sup>

In the oxindole group, formosanine and mitraphylline have been isolated from the bark of *Uncaria elliptica* R.B. ex G. Dm.,<sup>61a</sup> and rumberine (10-hydroxyisopteropodine) and palmirine (10-methoxyisopteropodine) from the aerial parts of *Hamelia patens* Jacq.<sup>61b</sup> Rauvoxinine has been reported<sup>14a</sup> to be present in the leaves of *R. psychotrioides*, but the identification rests mainly on its mass spectrum.



Deplancheine (82)

Reagents: i,  $\text{Na}_2\text{S}_2\text{O}_4$ ,  $\text{KHCO}_3$ ,  $\text{H}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ; ii,  $\text{HCl}$ ,  $\text{MeOH}$ , at r.t.; iii,  $4\text{M-HCl}$ , heat; iv,  $\text{NaBH}_4$ ,  $\text{MeOH}$ ; v,  $\text{KCN}$ ,  $\text{NaBH}_4$ ,  $\text{MeOH}$ ,  $\text{H}_2\text{O}$ ,  $\text{Et}_2\text{O}$ , at  $0^\circ\text{C}$ ; vi,  $\text{H}_2\text{O}$ ,  $\text{AcOH}$ , at  $20^\circ\text{C}$ ; vii,  $6\text{M-HCl}$ , at  $20^\circ\text{C}$ ; viii,  $\text{Ph}_3\text{P=CHMe}$ ,  $\text{DMSO}$ , at  $40^\circ\text{C}$

Scheme 10

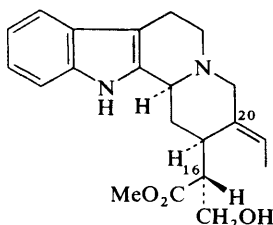
<sup>60</sup> B. A. Akinloye and W. E. Court, *Phytochemistry*, 1980, **19**, 307.

<sup>61</sup> (a) W. H. W. M. Herath, M. U. S. Sultanbawa, G. P. Wannigama, and A. Cavé, *Phytochemistry*, 1979, **18**, 1385; (b) J. Borges, M. T. Manresa, J. L. M. Ramón, C. Pascual, and A. Rumbero, *Tetrahedron Lett.*, 1979, 3197.



Deplancheine (82), from the stem bark of *Alstonia deplanchei* van Heurck et Müll.-Arg., is an indoloquinolizidine alkaloid of a novel type in which the three-carbon unit that is normally attached to C-15 is missing.<sup>62a</sup> The structure (82) was deduced from its spectroscopic properties, and has been confirmed by two independent syntheses (Scheme 10).<sup>62a,b</sup> It is of some interest that racemic (82) had been prepared,<sup>62c</sup> and its configuration established, some six years before its isolation from natural sources.

The absolute configuration of isositsirikine (83) at C-16 has been established<sup>63a</sup> by hydrogenation to two 19,20-dihydroisositsirikines epimeric at C-20, the *normal* epimer of which is identical with 18,19-dihydrositsirikine, of known (16*R*) configuration.<sup>63b</sup> Since the isositsirikine used in the investigation was obtained from *Catharanthus roseus*, this reverses the previous assignment of configuration at C-16 in isositsirikine obtained from this source.



Isositsirikine (83) 16*R*

A 400 MHz <sup>1</sup>H n.m.r. study<sup>64a</sup> of the eight parent heteroyohimbine alkaloids has permitted the chemical shifts of all the protons to be established. Carbon-13 n.m.r. data have also been recorded<sup>64b</sup> for the *allo*- and *epiallo*-oxindole alkaloids containing a heterocyclic ring E.

The chromogenic reactions of 41 indole alkaloids, 27 of which belong to this group, have been examined, using eleven different reagents, and the extent to which the various alkaloids can be differentiated has been discussed.<sup>64c</sup>

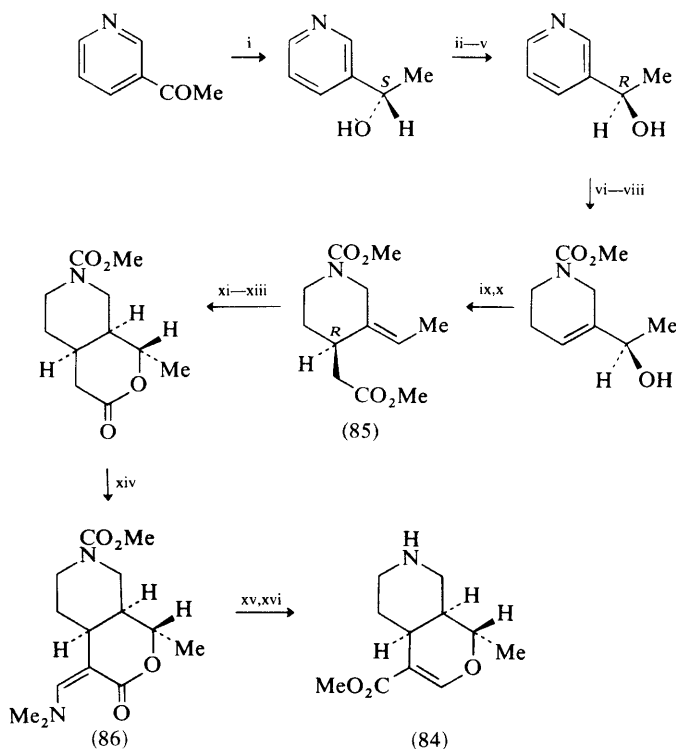
The synthesis of racemic heteroyohimbine alkaloids of *allo* stereochemistry has previously<sup>65a</sup> been achieved from the bicyclic amino-ester (84). Uskoković and his collaborators have now reported<sup>65b</sup> an extremely ingenious asymmetric synthesis of the (15*S*,19*S*,20*S*)-amino-ester (84), which therefore affords an efficient route to the natural *allo*-alkaloids. The synthetic sequence is outlined in Scheme 11, in which noteworthy stages are the microbiological reduction of the starting 3-acetylpyridine, which leads to (*S*) configuration at the future C-19, the

<sup>62</sup> (a) R. Besselièvre, J. P. Cosson, B. C. Das, and H. P. Husson, *Tetrahedron Lett.*, 1980, **21**, 63; (b) W. R. Ashcroft and J. A. Joule, *ibid.*, p. 2341; (c) D. Thielke, J. Wegener, and E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 602.

<sup>63</sup> (a) T. Hirata, S. L. Lee, and A. I. Scott, *J. Chem. Soc., Chem. Commun.*, 1979, 1081; (b) R. T. Brown and J. Leonard, *Tetrahedron Lett.*, 1979, 1805.

<sup>64</sup> (a) M. Lounasmaa and S. K. Kan, *Tetrahedron*, 1980, **36**, 1607; (b) M. R. Yagudaev and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1980, 217; (c) W. E. Court and M. M. Iwu, *J. Chromatogr.*, 1980, **187**, 199.

<sup>65</sup> (a) J. Gutzwiller, G. Pizzolato, and M. R. Uskoković, *J. Am. Chem. Soc.*, 1971, **93**, 5907; (b) M. R. Uskoković, R. L. Lewis, J. J. Partridge, C. W. Despreaux, and D. L. Pruess, *ibid.*, 1979, **101**, 6742.



Reagents: i, *Sporotrichum exile*; ii, NaH, THF; iii, TsCl; iv,  $\text{Et}_4\text{N}^+ \text{AcO}^-$ , acetone, at 60 °C; v, NaOH, MeOH; vi,  $\text{PhCH}_2\text{Cl}$ ; vii,  $\text{NaBH}_4$ ; viii,  $\text{ClCO}_2\text{Me}$ ,  $\text{CH}_2\text{Cl}_2$ ; ix,  $\text{MeC(OMe)}_3$ ; x, heat; xi, 9-borabicyclononane THF, at 0 °C; xii, 30%  $\text{H}_2\text{O}_2$ , 6M-NaOH; xiii, 1M-HCl; xiv,  $(\text{Me}_2\text{N})_2\text{CHOBu}^t$ , at r.t.; xv, 10% HCl, MeOH, at 120 °C; xvi, AcOH, HBr, at 50 °C

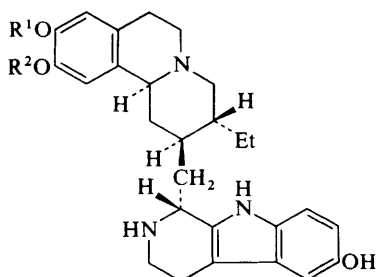
**Scheme 11**

inversion of this centre, the transference of asymmetry by means of a 3,3-sigmatropic rearrangement to the intermediate (85), and the generation of the heterocyclic ring E by rearrangement of the vinylogous carbamate (86).

Details of Kametani's synthesis<sup>66a</sup> of (±)-tubulosine and (±)-deoxytubulosine have now been published.<sup>66b</sup> An exactly analogous route has been used in the synthesis of (±)-*O*-methyltubulosine.<sup>66c</sup> A conventional synthesis<sup>67a</sup> of (±)-9-desmethyltubulosine (87) has revealed that it is not identical with the alkaloid, supposedly of this structure, which has been isolated from *Alangium lamarckii*; this alkaloid, previously obtained by Popelak *et al.*,<sup>67b</sup> must therefore be the isomeric 10-desmethyltubulosine (88).

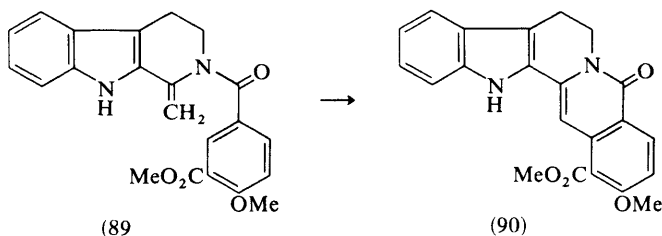
<sup>66</sup> T. Kametani, Y. Suzuki, and M. Ihara, (a) *Heterocycles*, 1978, **11**, 415; (b) *Can. J. Chem.*, 1979, **57**, 1679; (c) *Heterocycles*, 1979, **13**, 209.

<sup>67</sup> (a) M. Ohba, M. Hayashi, and T. Fujii, *Heterocycles*, 1980, **14**, 299; (b) A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Lett.*, 1966, 1081.

(87)  $R^1 = H, R^2 = Me$ (88)  $R^1 = Me, R^2 = H$ 

New synthetic work in the yohimbine series includes syntheses of dimethoxyhexadehydroyohimbane,<sup>68a</sup> yohimbane,<sup>68b</sup> and alloyohimbane.<sup>68b,68c</sup>

Photocyclization of the unstable enamide (89) affords a very low yield of the pentacyclic amide (90), which is an intermediate in an earlier synthesis of yohimbine;<sup>68d</sup> aside from the poor yield, the cyclization is not regiospecific, but efforts to overcome this problem have not yet proved successful.



(89)

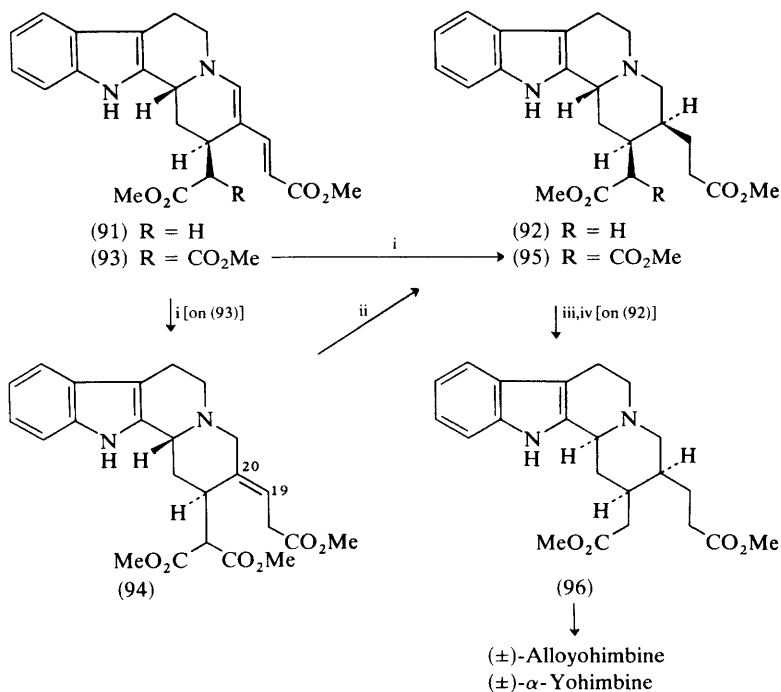
(90)

Details of Wenkert's synthesis<sup>69a</sup> of yohimbine and pseudoyohimbine have now been published,<sup>69b</sup> and the route has been modified to afford a new synthesis of alloyohimbine and  $\alpha$ -yohimbine. Hydrogenation of the diene ester (91) affords mainly the tetrahydro-ester of *pseudo* stereochemistry, from which pseudoyohimbine and yohimbine were synthesized. On a larger scale, some (<15%) tetrahydro-compound (92) of *epiallo* stereochemistry was obtained; however, an improved preparation of (92) was developed, in which the triester (93) was reduced with sodium cyanoborohydride. The product was a mixture of the *epiallo*-ester (95) and the unsaturated triester (94), together with some *pseudo*-isomer of (95). Hydrogenation of (94) gave more (95), which on hydrolysis, decarboxylation, and re-esterification gave the diester (92) in 35% overall yield from (83) (Scheme 12). Inversion of C-3 then gave the *allo*-isomer (96), which

<sup>68</sup> (a) G. D. Pandey and K. P. Tiwari, *Heterocycles*, 1979, **12**, 1483; (b) T. Suzuki, A. Tomino, K. Unno, and T. Kametani, *ibid.*, 1979, **13**, 301; (c) I. Ninomiya, Y. Tada, O. Miyata, and T. Naito, *ibid.*, 1980, **14**, 631; (d) T. Kametani, Y. Hirai, M. Kajiwar, T. Takahashi, and K. Fukumoto, *Chem. Pharm. Bull.*, 1975, **23**, 2634.

<sup>69</sup> (a) E. Wenkert, G. Kunesch, K. Orito, W. A. Temple, and J. S. Yadav, *J. Am. Chem. Soc.*, 1978, **100**, 4894; (b) E. Wenkert, T. D. J. Halls, G. Kunesch, K. Orito, R. L. Stephens, W. A. Temple, and J. S. Yadav, *ibid.*, 1979, **101**, 5370; (c) L. Töke, Z. Gombos, G. Blaskó, K. Honty, L. Szabó, J. Tamás, and C. Szántay, *J. Org. Chem.*, 1973, **38**, 2501.

had previously been converted into alloyohimbine and  $\alpha$ -yohimbine by Szántay and his collaborators.<sup>69c</sup>



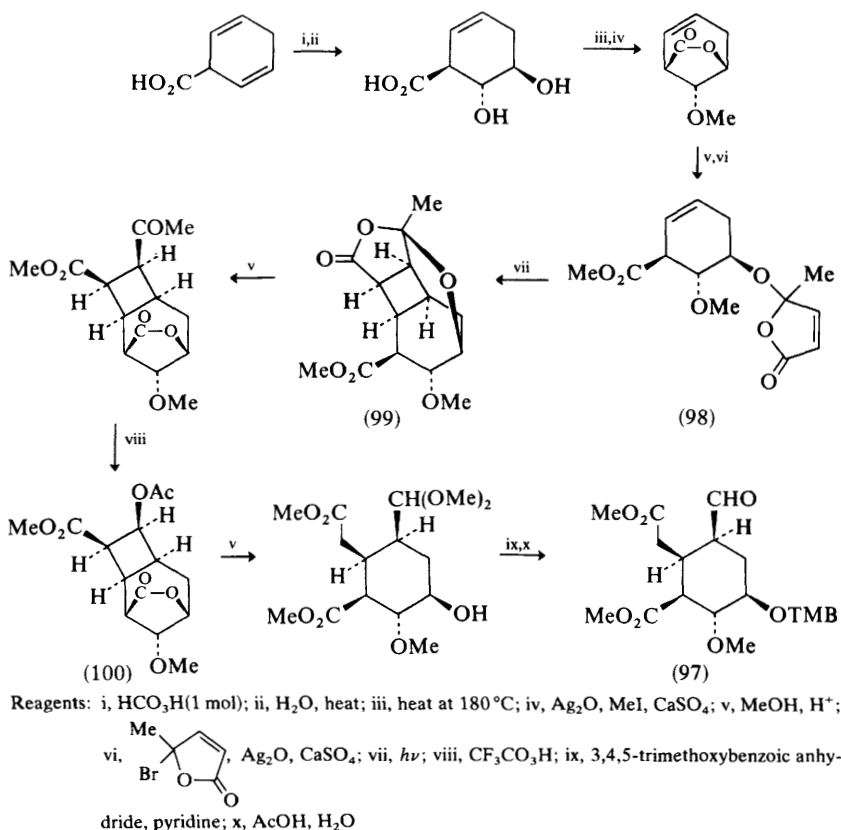
**Scheme 12**

An ingenious new method for the preparation of Woodward's intermediate (97) by Pearlman<sup>70</sup> constitutes another formal synthesis of reserpine. The essence of this new approach is an adaptation of the de Mayo reaction which allows the introduction of vicinal aldehyde and acetic ester functions on to a double-bond (Scheme 13). An internal  $[2\pi + 2\pi]$  photocyclization of the diene (98) gave the tetracyclic cyclobutane derivative (99), which was converted into the ester (100) by standard procedures. Methanolysis of the acetate function with concomitant retro-aldol fission completed the introduction of the vicinal aldehyde and acetic ester functions; obvious manipulation then gave the desired intermediate (97).

**Sarpagine-Ajmaline-Picraline Group.** Vincamajine and quebrachidine have been found to occur in the leaves and stem bark of *Alstonia odontophora*,<sup>59</sup> normacusine B occurs in *Strychnos rubiginosa*,<sup>58</sup> and vellosimine in *Rauwolfia vomitoria*.<sup>71a</sup> *R. volkensii* contains quaternine, nortetraphyllicine, peraksine,

<sup>70</sup> B. A. Pearlman, *J. Am. Chem. Soc.*, 1979, **101**, 6404.

<sup>71</sup> (a) A. Chatterjee and S. Bandyopadhyay, *Indian J. Chem., Sect. B*, 1979, **18**, 87; (b) J. Bruneton, A. Cavé, and C. Moretti, *Fitoterapia*, 1979, **50**, 123.



Scheme 13

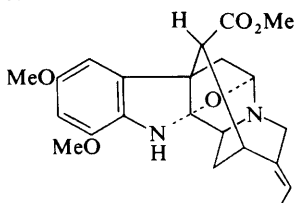
normacusine B, and a new alkaloid, volkensine, which is 10,11-dimethoxypicrinine.<sup>60</sup> Quebrachidine has also been isolated from the stems of *Tabernaemontana undulata* Vahl.<sup>71b</sup> Two new Malagasy *Hazunta* species have been extracted.<sup>72</sup> Of the alkaloids in this group, *H. modesta* ssp. *modesta* var. *divaricata* Mgf. and *H. modesta* ssp. *modesta* var. *brevituba* Mgf. contain vobasine, tabernaemontanine, dregamine, methuenine, isomethuenine, silicine, and 6-oxosilicine; the variety *divaricata* also contains polyneuridine, and the variety *brevituba* akuammidine and voacarpine.

The stems and leaves of Ghanaian *Tabernaemontana glandulosa* Stapf. contain<sup>73a</sup> tabernulosine (101), a new base of the picrinine type, which exhibits unusual substitution in the aromatic ring; however, details of its structure elucidation are not yet available.

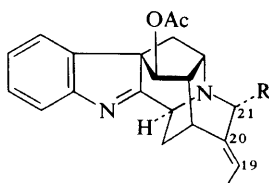
<sup>72</sup> A. M. Bui, P. Potier, M. Urrea, A. Clastres, D. Laurent, and M. M. Debray, *Phytochemistry*, 1979, **18**, 1329.

<sup>73</sup> (a) H. Achenbach and B. Raffelsberger, *Phytochemistry*, 1980, **19**, 716; (b) F. Libot, N. Kunesch, and J. Poisson, *ibid.*, p. 989; (c) G. Lewin, N. Kunesch, A. Cavé, T. Sevenet, and J. Poisson, *Phytochemistry*, 1975, **14**, 2067; G. Lewin, N. Kunesch, and J. Poisson, *C.R. Hebd. Seances Acad. Sci., Ser. C*, 1975, **280**, 987; (d) G. Lewin, N. Kunesch, J. Poisson, and T. Sevenet, *J. Indian Chem. Soc.*, 1978, **55**, 1096.

The leaves of four New Caledonian *Rauwolfia* species, namely *R. balansae* ssp. *balansae* Boiteau, *R. balansae* ssp. *schumanniana* var. *basicola* Boiteau, *R. spathulata* Boiteau, and *R. sevenetii* Boiteau, contain vomilenine (102a), *N*<sub>a</sub>-desmethyl-2-dehydrotetraphyllicine (102b), and raucaffrinoline (103), which have previously been encountered in other *Rauwolfia* species.<sup>73b</sup> The fourth alkaloid, 1-desmethyl-2-dehydro-17-acetyljmaline (104), has been prepared by the oxidation of ajmaline, but has not previously been isolated from a natural source.

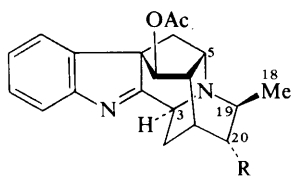


Tabernulosine (101)



Vomilenine (102a) R = OH

(102b) R = H

(104) R = OH; 19,20 $\alpha$ -dihydroRaucaffrinoline (103) R = CH<sub>2</sub>OH

Perakine (105) R = CHO

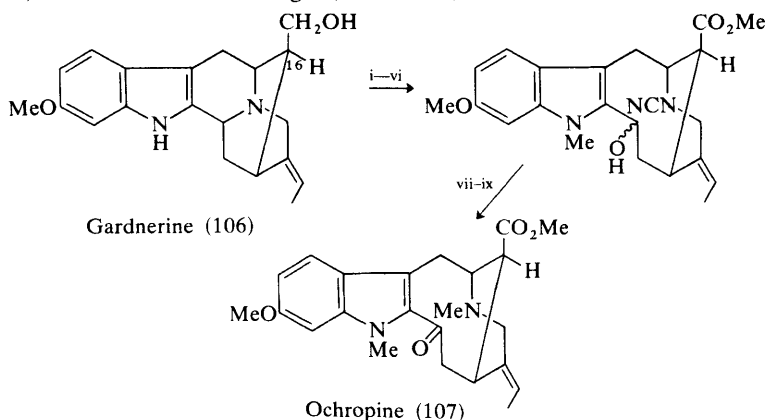
The structure of raucaffrinoline is not in doubt, but its complete stereochemistry was hitherto unknown. The conversion of vomilenine, by means of acid, into perakine (105), gentle reduction of which gives raucaffrinoline (103), establishes the stereochemistry at positions 3, 5, 15, 16, and 17, since vomilenine has earlier been related to ajmaline; this only leaves the stereochemistry at C-19 and C-20 uncertain. The stereochemistry at C-20 was elucidated by comparison of the <sup>13</sup>C n.m.r. spectra of (102a), (104), ajmaline, and isoajmaline [which has the opposite configuration at C-20 and at C-21 to (104)], from which it was concluded that raucaffrinoline has the isoajmaline configuration at C-21. A nuclear Overhauser enhancement of the signal due to the proton attached to C-5 on irradiation of the protons attached to C-18, but no observable effect on the signal of the proton at C-3, argues strongly in favour of the presence of a  $\beta$ -methyl group in raucaffrinoline, as shown in (103). The facile conversion of vomilenine into perakine (105) in acid medium suggests that the latter is an artefact, and this may be equally true of raucaffrinoline (103), which could conceivably be formed by a Cannizzaro reaction on perakine.<sup>73b</sup>

Details have been given of the isolation<sup>73c,d</sup> of lanciferine and of ten other alkaloids from the leaves and twigs of *Alstonia lanceolifera* S. Moore; in the last communication<sup>73d</sup> this plant is described as *A. boullindaensis* Boiteau.

A gas-chromatographic procedure for the qualitative determination of ajmaline in extracts of the root bark of *R. vomitoria* has been developed.<sup>74</sup>

<sup>74</sup> G. P. Forni, *J. Chromatogr.*, 1979, **176**, 129.

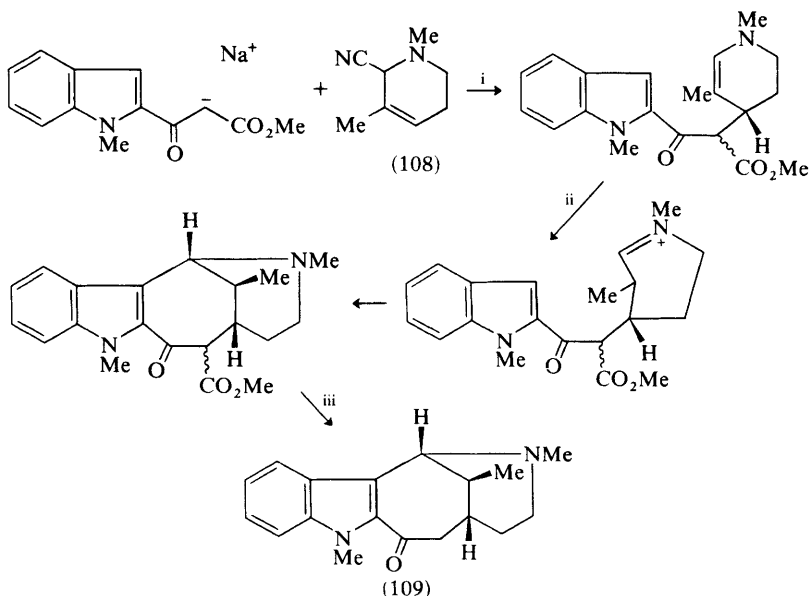
Gardnerine (106) has been converted into the 2-acylindole alkaloid ochropine (107) in nine conventional stages (Scheme 14).<sup>75</sup>



Reagents: i, *N*<sub>4</sub>-methylation; ii, *N*-chlorosuccinimide, Me<sub>2</sub>S, NEt<sub>3</sub>; iii, NH<sub>2</sub>OH; iv, Ac<sub>2</sub>O; v, MeOH, H<sub>2</sub>SO<sub>4</sub>, at 110 °C; vi, BrCN, Na<sub>2</sub>CO<sub>3</sub>, THF, H<sub>2</sub>O; vii, CrO<sub>3</sub>, pyridine, H<sub>2</sub>O; viii, NH<sub>4</sub>OAc, H<sub>2</sub>O, AcOH, heat; ix, CH<sub>2</sub>O, Pd/C, H<sub>2</sub>

**Scheme 14**

The first synthesis<sup>76</sup> of the ervitsine ring system (Scheme 15) has been achieved in a remarkably simple manner *via* two successive nucleophilic additions on a



Reagents: i, AgBF<sub>4</sub>, THF; ii, TsOH, PhMe, heat; iii, AcOH, H<sub>2</sub>O, H<sub>2</sub>SO<sub>4</sub>

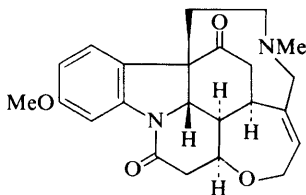
**Scheme 15**

<sup>75</sup> S. Sakai, Y. Yamamoto, and S. Hasegawa, *Heterocycles*, 1980, **14**, 85.

<sup>76</sup> M. Harris, D. S. Grierson, C. Riche, and H. P. Husson, *Tetrahedron Lett.*, 1980, **21**, 1957.

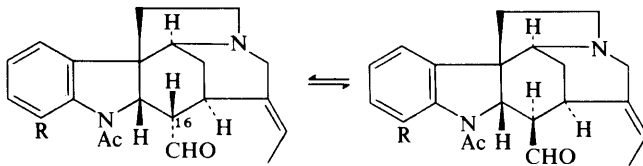
2-cyano- $\Delta^3$ -piperidine derivative (108). The relative stereochemistry of the final product (109) was confirmed by X-ray diffraction.

**Strychnine-Akuammicine-Ellipticine Group.** 11-Methoxyicajine (110)<sup>77</sup> and 15-hydroxystrychnine,<sup>78</sup> a new alkaloid, have been isolated from *Strychnos nuxvomica* seeds, and 11-methoxydiabolone from *S. rubiginosa*.<sup>58</sup> 10-Hydroxy-akuammicine (sewarine) occurs in the leaves of *Rauwolfia volkensii*,<sup>60</sup> and 11-methoxyakuammicine in *Alstonia odontophora*.<sup>59</sup>



11-Methoxyicajine (110)

The presence of isoretulinal (111) in the root bark of *Strychnos variabilis* de Wild. has been confirmed,<sup>79</sup> and it has also been shown that retulinal (112), with which it is very easily equilibrated, occurs in smaller amounts in the same extracts; both alkaloids exist in two forms, which are amide rotamers, according to their n.m.r. spectra. The 12-hydroxy-derivatives, (113) and (114), form a similar equilibrating pair of alkaloids, and were also isolated from this source. The occurrence of these easily interconvertible C-16 epimers explains the simultaneous occurrence of retuline and isoretuline derivatives in Nature, in both the monomeric and dimeric alkaloid series.



Retulinal (112) R = H

Isoretulinal (111) R = H

12-Hydroxyretulinal (114) R = OH

12-Hydroxyisoretulinal (113) R = OH

The first extractions of *Stremmeliopsis stremmelioides* K. Schum. (Family Apocynaceae), from Cuba, reveal that it is rich in alkaloids. The leaves and stem bark contain, amongst others, (+)-tubotaiwine and (+)-condylocarpine, and the stem bark also contains (–)-apparicine.<sup>80</sup> Apparicine (pericalline) also occurs, together with *O*-acetylvallesamine, 19,20-dihydrocondylocarpine, and eleven other alkaloids, in the wood and stem bark of *Ervatamia heyneana* (Wall.) T. Cooke,<sup>81</sup> and

<sup>77</sup> F. Rodriguez, J. Bernadou, and E. Stanislas, *Phytochemistry*, 1979, **18**, 2065.

<sup>78</sup> C. Galeffi, M. Nicoletti, I. Messina, and G. B. Marini-Bettòlo, *Tetrahedron*, 1979, **35**, 2545.

<sup>79</sup> M. Tits, L. Angenot, and D. Tavernier, *Tetrahedron Lett.*, 1980, **21**, 2439.

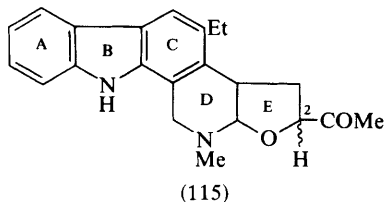
<sup>80</sup> A. Laguna, C. Dolejs, and L. Novotny, *Collect. Czech. Chem. Commun.*, 1980, **45**, 1419.

<sup>81</sup> S. P. Gunasekera, G. A. Cordell, and N. R. Farnsworth, *Phytochemistry*, 1980, **19**, 1213.



in *Hazunta modesta* ssp. *modesta* var. *divaricata* Mgf., together with 1,2-dihydroellipticine; this last base also occurs in the variety *brevituba*.<sup>72</sup> Ellipticine itself is the major alkaloid of the bark of *Strychnos dinklagei* Gilg., a liana from tropical West Africa which apparently enjoys wide use in popular medicine.<sup>82</sup>

The two D/E-*cis*-fused diastereoisomers of structure (115) have been synthesized,<sup>83a</sup> but neither proves to be identical with subincanine, which was earlier<sup>83b</sup> assigned the general structure (115), without stereochemistry. The available evidence indicates that subincanine is very unlikely to be a D/E-*trans*-fused isomer of (115); hence its structure remains obscure.



There has again been no dearth of synthetic activity aimed at ellipticine and its analogues; hence mention will be made here only of those investigations that have actually resulted in the preparation of ellipticine or a related alkaloid. Joule's brief synthesis (Scheme 16)<sup>84a</sup> makes use of the previously prepared intermediate (116), which, on oxidation and preferential protection of the methyl ketone carbonyl group, allowed the introduction of the final carbon atom by a Wittig reaction. Hydrogenation, release of the ketone carbonyl group, and cyclization then gave ellipticine (117).

A subsequent route by Joule and his collaborators<sup>84b</sup> made use of the primary alcohol (118) corresponding to (116). This was manipulated as shown, and cyclized to the quinone (119) before completion of the carbon skeleton, the cyclization stage being accompanied by spontaneous aerial oxidation of the initially formed hydroquinone derivative. Finally, the methyl groups were introduced by reaction with methyl-lithium, and the synthesis was completed by reduction (with NaBH<sub>4</sub>).

Snieckus' synthesis<sup>85</sup> involves an application of his ingenious tandem directed metallation reaction, which provides a one-step construction of the ellipticine ring system. Introduction of the remaining carbon atoms by the reaction of the quinone (120) with methyl-lithium, and removal of the protecting group, then gave ellipticine (119) in an overall yield of 40% (Scheme 16).

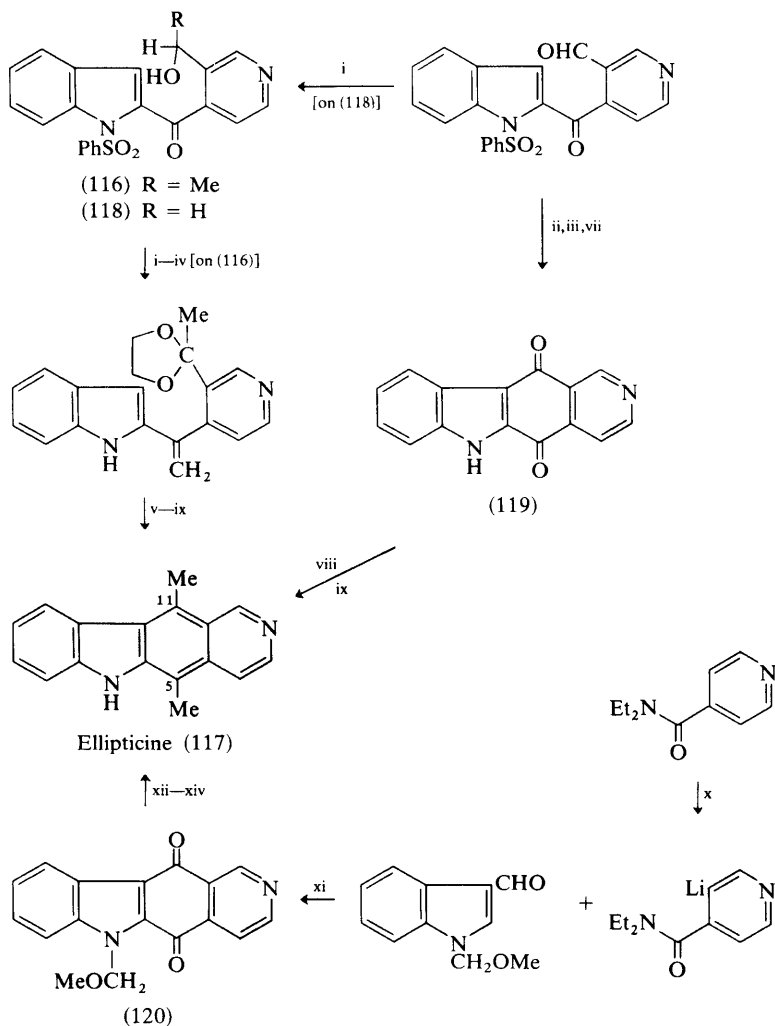
The versatility of all three syntheses lies in the opportunity to introduce substituents into positions 5 and 11, and into the indole ring, as desired.

<sup>82</sup> S. Michel, F. Tillequin, M. Koch, and L. A. Assi, *J. Nat. Prod.*, 1980, **43**, 294.

<sup>83</sup> (a) D. Cohlakakis, M. M. Baradarani, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1290; (b) A. J. Gaskell and J. A. Joule, *Tetrahedron Lett.*, 1970, 77.

<sup>84</sup> (a) D. A. Taylor and J. A. Joule, *J. Chem. Soc., Chem. Commun.*, 1979, 642; (b) D. A. Taylor, M. M. Baradarani, S. J. Martinez, and J. A. Joule, *J. Chem. Res.*, 1979, (S), 387; (M), 4801.

<sup>85</sup> M. Watanabe and V. A. Snieckus, *J. Am. Chem. Soc.*, 1980, **102**, 1457.



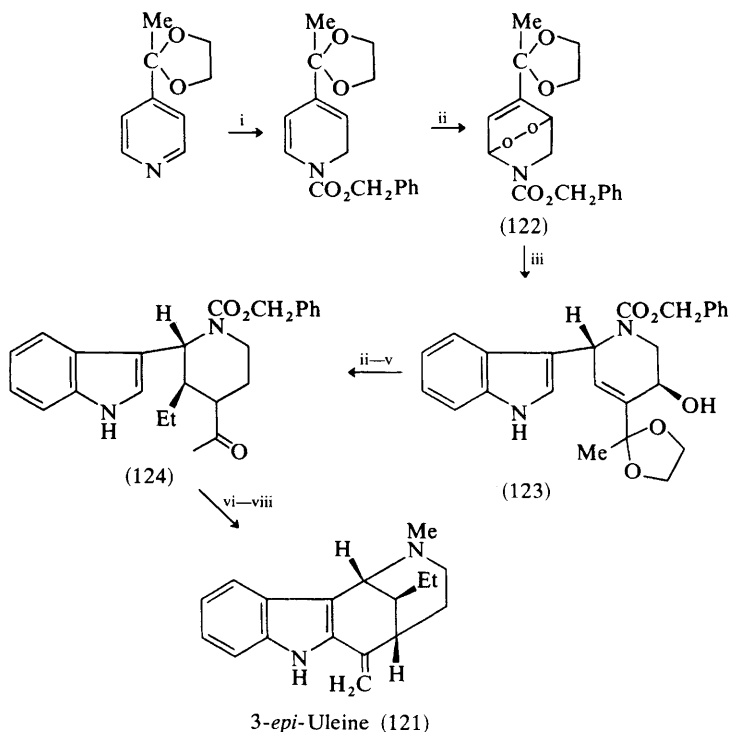
Reagents: i,  $\text{MnO}_2$ ,  $\text{CHCl}_3$ ; ii,  $(\text{CH}_2\text{OH})_2$ ,  $\text{TsOH}$ ,  $\text{CHCl}_3$ ; iii,  $\text{NaOH}$ ,  $\text{H}_2\text{O}$ ,  $\text{MeOH}$ ; iv,  $\text{Ph}_3\text{P}=\text{CH}_2$ ,  $\text{THF}$ ; v,  $\text{H}_2$ ,  $\text{Pt}$ ,  $\text{EtOH}$ , at  $60^\circ\text{C}$ ; vi,  $0.2\text{M-HCl}$ , reflux; vii,  $1\text{M-HCl}$ ; viii,  $\text{MeMgI}$ ; ix,  $\text{NaBH}_4$ ,  $\text{EtOH}$ ; x,  $\text{Bu}^t\text{Li}$ ,  $\text{TMEDA}$ ,  $\text{Et}_2\text{O}$ , at  $-78^\circ\text{C}$ ; xi,  $\text{Bu}^t\text{Li}$ ; xii,  $\text{MeLi}$ ; xiii, 47%  $\text{HI}$ ,  $\text{MeOH}$ ; xiv,  $\text{SnCl}_2$ ,  $\text{AcOH}$ ,  $\text{HCl}$ ,  $\text{THF}$

Scheme 16

A brief and elegant new synthesis<sup>86a</sup> of  $(\pm)$ -3-*epi*-uleine (121) employs the recently developed<sup>86b</sup> reaction of dihydropyridine endoperoxides [e.g. (122)] with stannous chloride in the presence of nucleophiles. With indole as nucleophile, ring-opening of the peroxide, alkylation with indole, and reduction afford

<sup>86</sup> (a) M. Natsume and Y. Kitagawa, *Tetrahedron Lett.*, 1980, **21**, 839; (b) M. Natsume, Y. Sekine, and M. Ogawa, *ibid.*, 1979, 3473.

the intermediate (123); the required carbon skeleton was then completed by the reaction of the corresponding enone with lithium diethylcuprate. The stereochemistry of the product (124) was established by an independent, but less direct, preparation, and the synthesis was completed by obvious stages (Scheme 17).



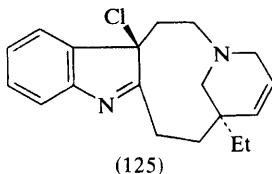
Reagents: i,  $\text{ClCO}_2\text{CH}_2\text{Ph}$ ,  $\text{NaBH}_4$ ; ii,  $^1\text{O}_2$ ; iii, indole,  $\text{SnCl}_2$ ; iv, acetone,  $\text{TsOH}$ ; v,  $\text{Et}_2\text{CuLi}$ , THF,  $\text{H}_2\text{O}$ ; vi,  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{MeOH}$ ,  $\text{CH}_2\text{O}$ ; vii,  $\text{NaOMe}$ ,  $\text{MeOH}$ ; viii,  $\text{TsOH}$ ,  $\text{CHCl}_3$ , reflux

**Scheme 17**

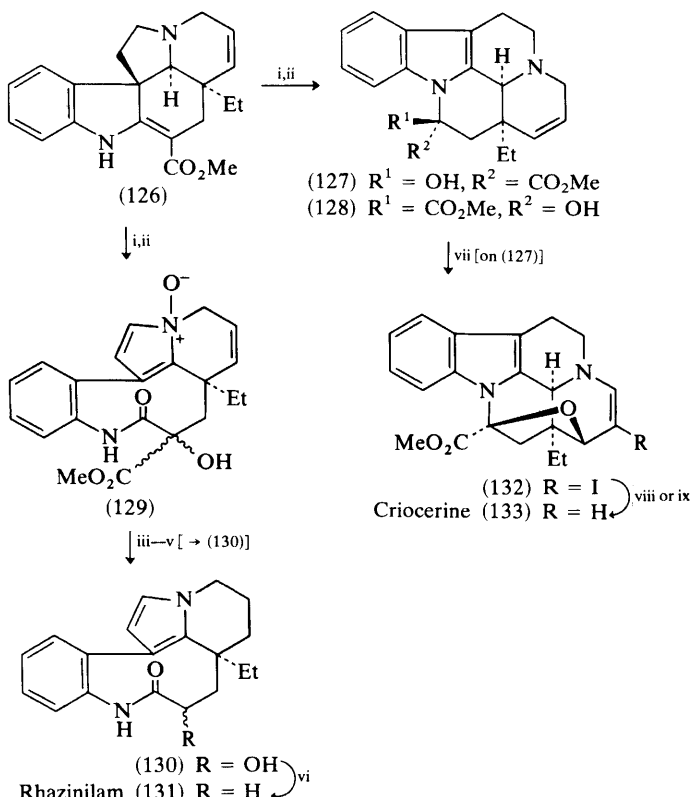
**Aspidospermine–Aspidofractine–Eburnamine Group.** Several of the alkaloids of *Strepeliopsis strepelioides* belong to the aspidospermine group.<sup>80</sup> Aspidospermine itself is the major alkaloid of the leaves and stem bark, which also contain (+)-desmethylassidospermine; (+)-desacetylassidospermine and (+)-vincadifformine are also found in the bark, and (–)-aspidosine, (–)-vallesine, and (+)-eburnamonine in the leaves. Tabersonine occurs in the seeds of *Tabernaemontana macrocalyx* M. Arg. (*Anacampta macrocalyx* Mgf.),<sup>71b</sup> voaphylline in *T. undulata*<sup>71b</sup> and *Hazunta modesta* ssp. *modesta* var. *divaricata*, and 10-hydroxy-11-methoxytabersonine in the variety *brevituba*.<sup>72</sup> Lochnericine has been isolated from the roots, and vindorosine from the leaves, of *Vinca pusilla*;<sup>87a</sup> lochnericine also occurs in *Petchia ceylonica* Wight.<sup>87b</sup>

<sup>87</sup> (a) A. Patra, A. K. Mukhopadhyay, and A. K. Mitra, *Indian J. Chem., Sect. B*, 1979, **17**, 175; (b) N. Kunesch, A. Cavé, E. W. Hagaman, and E. Wenkert, *Tetrahedron Lett.*, 1980, **21**, 1727.

On the basis of their  $^{13}\text{C}$  n.m.r. spectra, and in particular on the similarity of the C-5 and C-6 resonances, the 7-chloroindolenine derivatives of the cleavamines and quebrachamines have been concluded to have the same stereochemistry at C-7 as voaphylline hydroxyindolenine, whose configuration is known; 14,15-dehydroquebrachamine 7-chloroindolenine thus has the stereochemistry shown in (125).<sup>88</sup>



The c.d. spectra of vincamine and a number of close relatives have been discussed.<sup>89</sup>



Reagents: i, *m*- $\text{ClC}_6\text{H}_4\text{CO}_3\text{H}$ ,  $\text{PhH}$ ; ii,  $\text{Ph}_3\text{P}$ ,  $\text{AcOH}$ ; iii,  $\text{H}_2$ , Pt; iv,  $\text{KOH}$ ,  $\text{MeOH}$ ,  $\text{N}_2$ ; v,  $\text{H}_3\text{O}^+$ , heat; vi,  $\text{LiAlH}_4$ ; vii,  $\text{I}_2$ ,  $\text{KIO}_3$ ,  $\text{AcOH}$ ,  $\text{H}_2\text{O}$ ,  $\text{THF}$ ; viii,  $\text{HCl}$ ,  $\text{NH}_4\text{Cl}$ ; ix,  $\text{NaOAc}$ ,  $\text{AcOH}$

**Scheme 18**

<sup>88</sup> E. Wenkert, E. W. Hagaman, N. Wang, and N. Kunesch, *Heterocycles*, 1979, **12**, 1439.

<sup>89</sup> G. Tóth, O. Clauder, K. Gesztes, S. S. Yemul, and G. Snatzke, *J. Chem. Soc., Perkin Trans. 2*, 1980, 701.

Details of the oxidation and rearrangement of tabersonine (126) to (+)-14,15-dehydrovincamine (127) and (+)-14,15-dehydro-16-*epi*-vincamine (128), which were previously recorded only in the patent literature, have now been published.<sup>90</sup> A minor product in this sequence of reactions was formulated as (129), since hydrogenation, hydrolysis, and decarboxylation afford a hydroxy-amide (130), which can be reduced to rhazinilam (131) (Scheme 18). The reaction of 14,15-dehydrovincamine (127) with iodine and potassium iodate results in the formation of a dehydro-derivative (not isolated), followed by closure of the tetrahydrofuran ring. The product is the iodo-compound (132), which, as an iodo-enamine, loses its iodine when treated with acid, with formation of the alkaloid criocerine (133).<sup>90</sup>

The availability of the 19-iodotabersonines (134) by the reaction of vindoline with iodine in weakly alkaline solution has allowed the partial synthesis of several *Aspidosperma* alkaloids.<sup>91</sup> Thus, Kornblum oxidation of (134) under anhydrous conditions gives 19-oxotabersonine (135), which on hydrogenation of the 14,15 double-bond affords (–)-minovincine. In the presence of water, Kornblum oxidation gives some fragmentation product (136) [previously obtained by heating (134) in DMF–NaOAc] and some (19*S*)-hydroxytabersonine (137). Both (137) and the (19*R*)-epimer (138) are obtained on reduction of (135) with sodium borohydride, and are identical with two minor alkaloids of *Catharanthus ovalis* and *Melodinus celastroides*.<sup>92</sup> The absolute configuration of these epimers at C-19 was determined by application of Horeau's method; subsequent correlation of (137) with vincoline (139) and kitraline (140), and of (138) with kitramine (141), confirms the stereochemistry deduced earlier (Scheme 19).<sup>92b</sup> Hydrogenation of (19*R*)-hydroxytabersonine (138) was further found to give (–)-minovincine, thus confirming the earlier stereochemical assignment by Doepeke.

Minovincine (142) has previously been converted by aqueous acid into the hexacyclic base 19-oxoaspidofractinine (143), with loss of the ester function. It has now been shown<sup>91</sup> that, under anhydrous and carefully controlled acidic conditions, the ester group is retained, and the product is 16-*epi*-19-oxokopsinine (144); removal of the C-19 carbonyl group then gives 16-*epi*-kopsinine (145), also obtainable from venalstonine by hydrogenation of the 14,15 double-bond (→ kopsinine), followed by epimerization at C-16.

Full details of the syntheses<sup>93a</sup> of quebrachamine and tabersonine by Takano *et al.* have now been published.<sup>93b</sup>

The first enantioselective synthesis<sup>94</sup> of (+)-quebrachamine (146) has also been contributed by Takano's group, and in principle is an elegant adaptation of the Kutney route, the required aldehydo-acid (147) [with (*S*) configuration at the future C-20] being prepared from the lactone (148), itself obtained from L-glutamic acid. Alkylation of the anions from both (148) and (149) proceeded

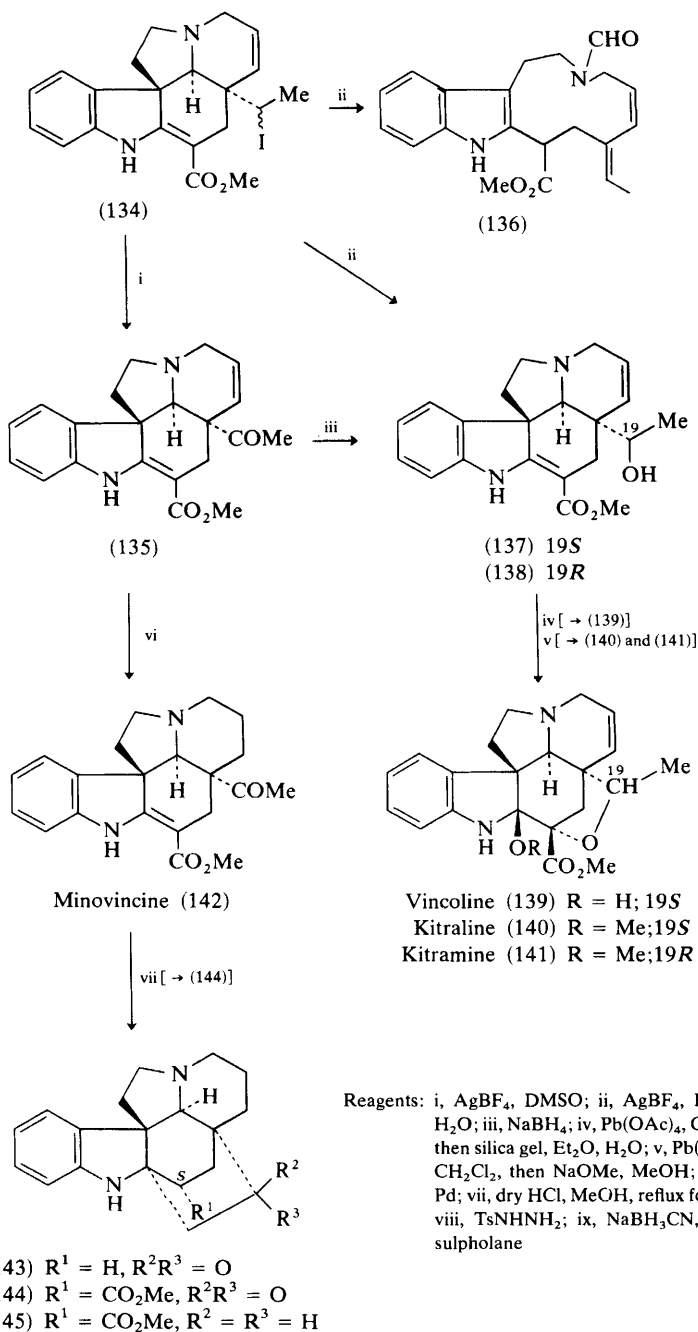
<sup>90</sup> G. Hugel, B. Gourdier, J. Lévy, and J. Le Men, *Tetrahedron*, 1980, **36**, 511.

<sup>91</sup> N. Langlois and R. Z. Andriamialisoa, *J. Org. Chem.*, 1979, **44**, 2468.

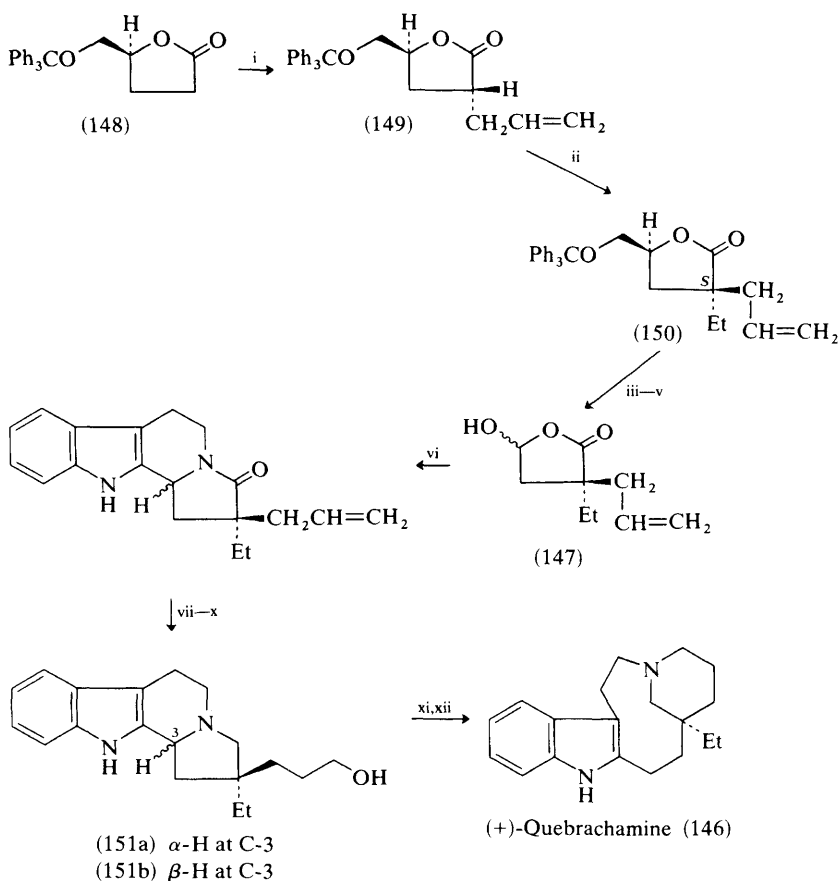
<sup>92</sup> (a) R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron Lett.*, 1976, 163; (b) A. Rabaron, M. H. Mehri, T. Sevenet, and M. M. Plat, *Phytochemistry*, 1978, **17**, 1452.

<sup>93</sup> S. Takano, S. Hatakeyama, and K. Ogasawara, (a) *J. Am. Chem. Soc.*, 1976, **98**, 3022; (b) *ibid.*, 1979, **101**, 6414.

<sup>94</sup> S. Takano, K. Chiba, M. Yonaga, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1980, 616.



Scheme 19



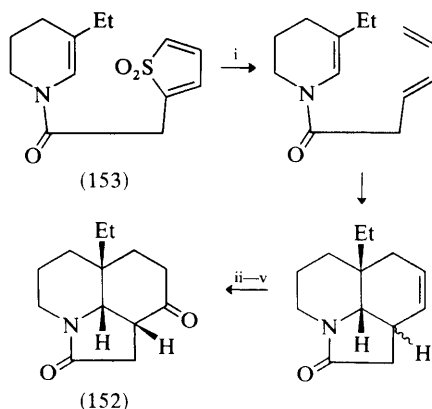
Reagents: i,  $\text{LiNPr}_2$ ,  $\text{H}_2\text{C}=\text{CHCH}_2\text{Br}$ , THF, at  $-78^\circ\text{C}$ ; ii,  $\text{LiNPr}_2$ ,  $\text{EtBr}$ , THF, at  $-78^\circ\text{C}$ ; iii,  $\text{HCl}$ ,  $\text{EtOH}$ ; iv,  $\text{NaOH}$ ,  $\text{H}_2\text{O}$ ,  $\text{MeOH}$ ; v,  $\text{NaIO}_4$ ; vi, tryptamine,  $\text{AcOH}$ , heat; vii,  $\text{B}_2\text{H}_6$ ,  $\text{DMS}$ , THF; viii,  $\text{NaOH}$ ,  $\text{H}_2\text{O}_2$ ,  $\text{H}_2\text{O}$ ; ix,  $\text{LiAlH}_4$ ; x, separation of diastereoisomers; xi,  $\text{MsCl}$ ; xii,  $\text{Na}$ ,  $\text{NH}_3$ ,  $\text{EtOH}$

### Scheme 20

preferentially at the less hindered side, with stereoselective formation of (149) and (150). The subsequent stages are conventional, and allowed the construction of both epimers of structure (151). These were separated, and the synthesis was completed according to the established procedures; both (151a) and (151b) afforded (+)-quebrachamine (146), as expected (Scheme 20).<sup>94</sup>

A further formal total synthesis<sup>95</sup> of aspidospermine is provided by a new preparation of Stork's tricyclic amido-ketone (152). The hydrolulolidine system in (152) was neatly constructed by cheletropic expulsion of sulphur dioxide from the amide-sulphone (153), followed by an internal Diels-Alder reaction.

<sup>95</sup> S. F. Martin, S. R. Desai, G. W. Phillips, and A. C. Miller, *J. Am. Chem. Soc.*, 1980, **102**, 3294.

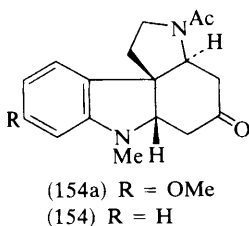


Reagents: i, heat at 600 °C; ii,  $\text{SeO}_2$ ,  $\text{AcOH}$ , at 100 °C; iii,  $\text{KOH}$ ,  $\text{H}_2\text{O}$ ,  $\text{EtOH}$ , at r.t.; iv, pyridinium chromate on silica gel; v,  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{EtOH}$

### Scheme 21

Subsequent adjustment of the functionality in the cyclohexene ring then gave (152) (Scheme 21), which has previously been converted into aspidospermine.

Details of Takano's synthesis<sup>96a</sup> of vindoline/vindorosine intermediates (154) have now been published.<sup>96b</sup>



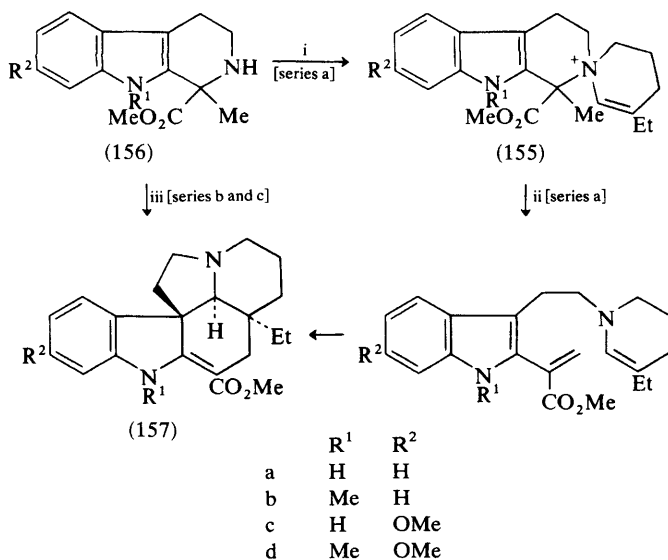
Kuehne *et al.*<sup>97</sup> have reported an improved version of their biomimetic synthesis of the vincadifformine group of alkaloids, in which the important secodine precursor is a spirocyclic tetrahydro- $\beta$ -carbolinium salt (155), rather than an indolo-azepine derivative. This leads to a much simpler synthesis, the starting materials (156) being obtained directly from the appropriate tryptamine and acetoacetic ester. By this route, ( $\pm$ )-vincadifformine (157a), ( $\pm$ )-minovine (157b), and ( $\pm$ )-ervinceine (157c) were synthesized in comparatively high yield, in essentially two stages from the starting tryptamine (Scheme 22). The  $N_\alpha$ -methyl-derivative (157d) of ( $\pm$ )-ervinceine, prepared by methylation of ( $\pm$ )-ervinceine, may be regarded as the relay in a formal total synthesis of ( $\pm$ )-vindoline, since the natural enantiomer, obtained by degradation of vindoline, has already been reconverted into vindoline.<sup>98a</sup>

<sup>96</sup> (a) S. Takano, K. Shishido, M. Sato, K. Yuta, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1978, 943; (b) S. Takano, K. Shishido, J. Matsuzaka, M. Sato, and K. Ogasawara, *Heterocycles*, 1979, **13**, 307.

<sup>97</sup> M. E. Kuehne, J. A. Huebner, and T. H. Matsko, *J. Org. Chem.*, 1979, **44**, 2477.

<sup>98</sup> J. E. Saxton, in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Royal Society of Chemistry, London, 1981, Vol. 10, (a) p. 181; (b) p. 191; (c) p. 196.





Reagents: i,  $\text{Cl}(\text{CH}_2)_3\text{CHEtCHO}$ , TsOH, PhMe, reflux; ii, DBU, heat; iii,  $\text{Cl}(\text{CH}_2)_3\text{CHEtCHO}$ , TsOH, PhMe, reflux in Dean-Stark water-trap with 3A molecular sieves, under  $\text{N}_2$

**Scheme 22**

In the eburnamine-vincamine sub-group, Takano *et al.* have given details<sup>99a</sup> of their synthesis of  $(\pm)$ -eburnamine.<sup>99b</sup> Other synthetic work reported includes further preparations of  $(\pm)$ -vincamone (eburnamone)<sup>100a</sup> and ethyl apovincamate,<sup>100b</sup> and a modification of Szántay's route to vincamine which was intended to result in an asymmetric synthesis of vincamine-5-carboxylic acid, since L-tryptophan was used as starting material. Unfortunately, racemization of C-5 occurred during the synthesis, so the final product was an ester of  $(\pm)$ -vincamine-5-carboxylic acid.<sup>101</sup>

**Catharanthine-Ibogamine-Cleavamine Group.** Ibogamine, heyneanine, and 19-*epi*-heyneanine have been isolated from *Hazunta modesta* ssp. *modesta* var. *divaricata*, and ibogamine from the variety *brevituba*.<sup>72</sup> Coronaridine, voacangine, and 19-*epi*-heyneanine are present in the stems of *Tabernaemontana undulata*, and coronaridine is present in the seeds of *T. macrocalyx*.<sup>71b</sup> The root bark of *T. divaricata* has yielded<sup>102</sup> nine indole alkaloids, of which coronaridine, coronaridine hydroxyindolenine, ibogamine, and 3-oxocoronaridine (158) are already known. The new bases are 5-oxocoronaridine (159), 6-oxocoronaridine (160), 5-hydroxy-6-oxocoronaridine (161), and  $(\pm)$ -19-hydroxycoronaridine

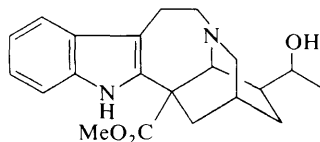
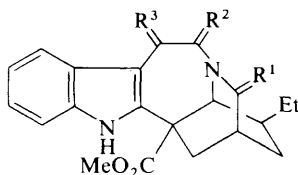
<sup>99</sup> S. Takano, S. Hatakeyama, and K. Ogasawara, (a) *J. Chem. Soc., Perkin Trans. 1*, 1980, 457; (b) *J. Chem. Soc., Chem. Commun.*, 1977, 68.

<sup>100</sup> (a) A. Buzas, J. P. Jacquet, and G. Lavielle, *J. Org. Chem.*, 1980, **45**, 32; (b) K. Ono, H. Kawakami, and J. Katsube, *Heterocycles*, 1980, **14**, 411.

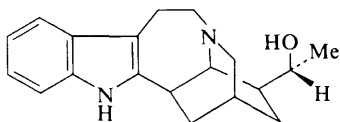
<sup>101</sup> L. Szabó, G. Kalaus, K. Nógrádi, and C. Szántay, *Acta Chim. Acad. Sci. Hung.*, 1979, **99**, 73.

<sup>102</sup> K. Rastogi, R. S. Kapil, and S. P. Popli, *Phytochemistry*, 1980, **19**, 1209.

(162). Both (159) and (161) were among the products obtained on oxidation of coronaridine by means of potassium permanganate.



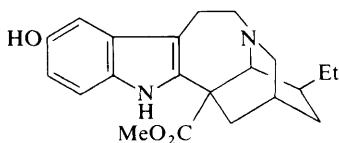
19-Hydroxycoronaridine (162)

(20*R*)-Hydroxyibogamine (163)

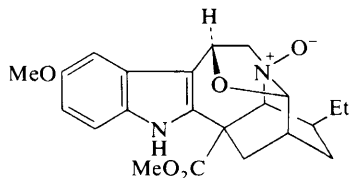
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
3-Oxocoronaridine (158)	O	H <sub>2</sub>	H <sub>2</sub>
5-Oxocoronaridine (159)	H <sub>2</sub>	O	H <sub>2</sub>
6-Oxocoronaridine (160)	H <sub>2</sub>	H <sub>2</sub>	O
5-Hydroxy-6-oxo-			
coronaridine (161)	H <sub>2</sub>	H, OH	O
3-Ethoxycoronaridine (164)	H, OEt	H <sub>2</sub>	H <sub>2</sub>

The roots of Peruvian *T. quadrangularis* contain fourteen alkaloids, all of which belong to this group; they are coronaridine, voacangine, ibogamine, ibogaine, heyneanine, 19-*epi*-heyneanine, 3-oxocoronaridine, 3-oxovoacangine, the hydroxyindolenines of coronaridine and voacangine, the pseudoindoxyls of coronaridine and ibogamine, and two new bases, *i.e.* (20*R*)-hydroxyibogamine (163) and the corresponding pseudoindoxyl derivative.<sup>103</sup> Another new coronaridine derivative is 3-ethoxycoronaridine (164), which has been isolated from the stems of *T. glandulosa*.<sup>73a</sup> This base may be partially synthesized by the reaction of coronaridine with iodine in benzene-ethanol solution; the available evidence seems to indicate that it is a genuine alkaloid, and not an artefact, in spite of the unusual feature of an ethoxy-group.

The alkaloids of the wood and stem bark of *Ervatamia heyneana* belong mainly to the coronaridine group and, in addition to the known bases coronaridine, voacangine, voacangine hydroxyindolenine, voacryptine, (19*S*)-heyneanine, and (19*S*)-voacangarine, they include three new bases, namely 10-hydroxycoronaridine (165), 10-methoxyeglandine *N*<sub>b</sub>-oxide (166), and (-)-heyneatine (167).<sup>81</sup> 10-Methoxyeglandine *N*<sub>b</sub>-oxide loses an oxygen atom in the mass spectrometer, and its subsequent fragmentation is similar to that observed for 11-methoxyeglandine. The presence of a carbinolamine ether grouping in (166) is confirmed by its n.m.r. spectrum, and this, together with the formation of voacanginol on reduction (by LiAlH<sub>4</sub>), establishes the structure (166).

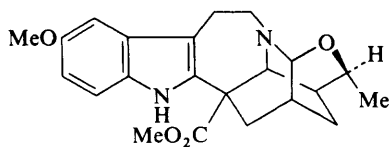


(165)

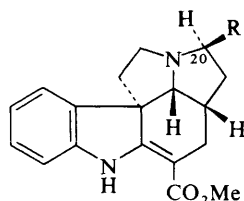


(166)

<sup>103</sup> H. Achenbach and B. Raffelsberger, *Z. Naturforsch., Teil. B*, 1980, **35**, 219.



(-)-Heyneatine (167)

20-*epi*-Ibophyllidine (168) R = Et  
Desethylibophyllidine (169) R = H

Heyneatine is a carbinolamine ether of a new type, in which the oxygen atom is situated between C-3 and C-19 (n.m.r. spectrum). Since reduction (with  $\text{LiAlH}_4$ ) gives rise to (19*S*)-voacangarinol or (with  $\text{NaBH}_4$ ) to (19*S*)-voacangarine, the complete structure of (-)-heyneatine must be (167).<sup>81</sup>

The trunk bark of *T. albiflora* (Miq.) Pull., from French Guyana, contains ibophyllidine, coronaridine, and two new alkaloids which prove to be 20-*epi*-ibophyllidine (168) and desethylibophyllidine (169).<sup>104</sup> The structures of (168) and (169) were determined largely by a complete analysis of their 400 MHz  $^1\text{H}$  n.m.r. spectra, and comparison with that of ibophyllidine. The very high dextrorotatory power of these alkaloids [*e.g.*, (168) exhibits  $[\alpha]_D^{20} + 518^\circ$ ] indicates that they belong to the same stereochemical series as (+)-vincadifformine. Desethylibophyllidine (169) has also been found recently in *Anacamptis disticha* (A. DC) Mgf.<sup>105</sup> This alkaloid is the first one in this group to be encountered which has lost the ethyl side-chain; this is probably connected with the contraction of the piperidine ring that occurs during the biosynthesis, the course of which remains to be elucidated.

Reference has been made above to the determination of the stereochemistry at C-7 of cleavamine 7-chloroindolenine.<sup>88</sup>

The Polonovski reaction on catharanthine *N*<sub>b</sub>-oxide (170) leads to fission of the 5,6-bond and re-cyclization with formation of (171);<sup>106</sup> in the presence of other nucleophiles (*e.g.* vindoline), this reaction forms the basis of the synthesis of the vinblastine group of alkaloids (*q.v.*). The formation of (171) is reversible in acid solution, and under appropriate conditions the methylene group (C-5) is lost as formaldehyde; re-cyclization by the Mannich reaction then gives 5-norcatharanthine (173) (Scheme 23).<sup>106b</sup>

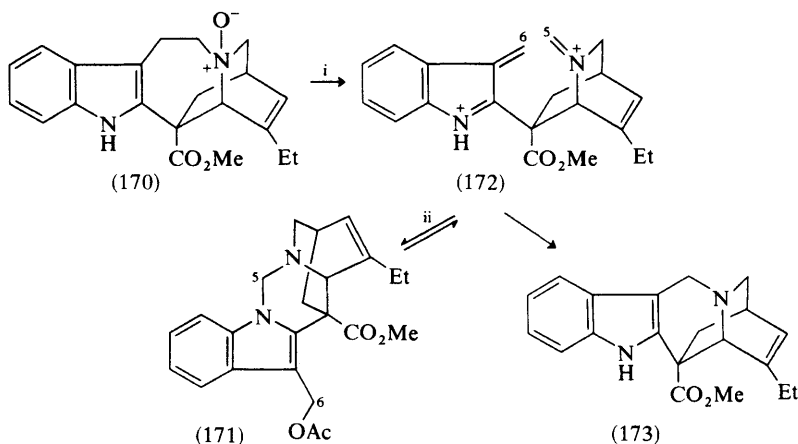
Details of the syntheses, by Harley-Mason and his collaborators, of (±)-16-hydroxydihydrocleavamine,<sup>107a</sup> (±)-α- and (±)-β-dihydrocleavamines, (±)-methoxycarbonyldihydrocleavamine, (±)-coronaridine, (±)-dihydrocatharanthine, (±)-ibogamine, (±)-*epi*-ibogamine, and (±)-catharanthine have now been published.<sup>107b</sup>

<sup>104</sup> C. Kan, H. P. Husson, H. Jacquemin, S. K. Kan, and M. Lounasmaa, *Tetrahedron Lett.*, 1980, **21**, 55.

<sup>105</sup> C. Miet, N. Kunesch, J. Poisson, and C. Moretti, *Communication au Colloque 'Substances Naturelles d'Intérêt Biologique du Pacifique'*, Nouméa (New Caledonia), August, 1979; quoted in ref. 104.

<sup>106</sup> (a) N. Langlois, F. Guéritte, Y. Langlois, and P. Potier, *Tetrahedron Lett.*, 1976, 1487; (b) R. Z. Andriamialisoa, N. Langlois, Y. Langlois, P. Potier, and P. Bladon, *Can. J. Chem.*, 1979, **57**, 2572.

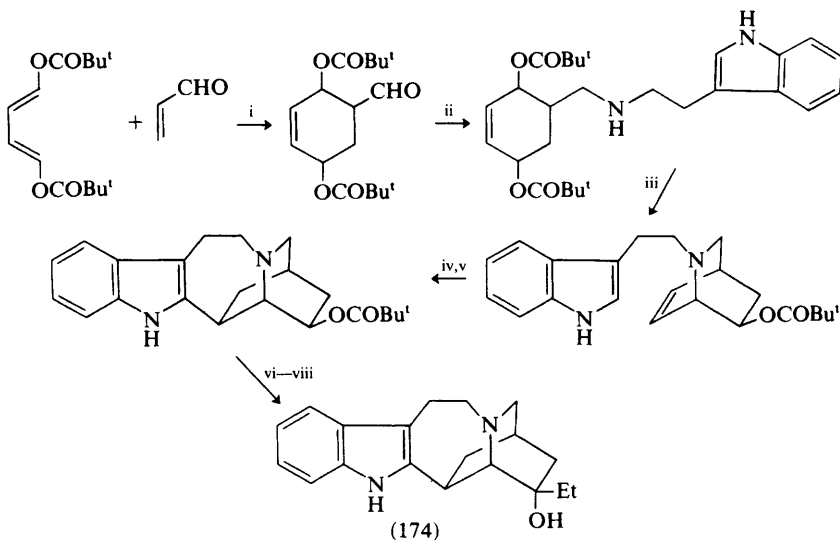
<sup>107</sup> (a) J. Harley-Mason and Atta-ur-Rahman, *Tetrahedron*, 1980, **36**, 1057; (b) Atta-ur-Rahman, J. A. Beisler, and J. Harley-Mason, *ibid.*, p. 1063.



Reagents: i, Ac<sub>2</sub>O; ii, 10% HCl, at 110 °C

**Scheme 23**

Trost has continued his remarkable series of palladium-catalysed syntheses in this area with a neat seven-stage synthesis of the catharanthine intermediate (174) (Scheme 24).<sup>108a</sup> Since (174) has already been converted into (±)-catharanthine by Büchi *et al.*,<sup>108b</sup> this constitutes a nine-step synthesis of (±)-catharanthine.



Reagents: i, PhMe, BF<sub>3</sub>·Et<sub>2</sub>O, at -30 to -10 °C; ii, tryptamine, PhMe, MgSO<sub>4</sub>, at -5 °C, then NaBH<sub>4</sub>, MeOH, at -5 °C; iii, [(Ph<sub>3</sub>P)<sub>4</sub>Pd], NEt<sub>3</sub>, MeCN, at 75 °C; iv, [(MeCN)<sub>2</sub>PdCl<sub>2</sub>], AgBF<sub>4</sub>, NEt<sub>3</sub>, MeCN, at 25 to 67 °C; v, NaBH<sub>4</sub>, MeOH, at 0 °C; vi, MeLi, Et<sub>2</sub>O, at r.t.; vii, pyridine·SO<sub>3</sub>, DMSO, NEt<sub>3</sub>, at r.t.; viii, EtMgBr, THF, Et<sub>2</sub>O, at -78 to -10 °C

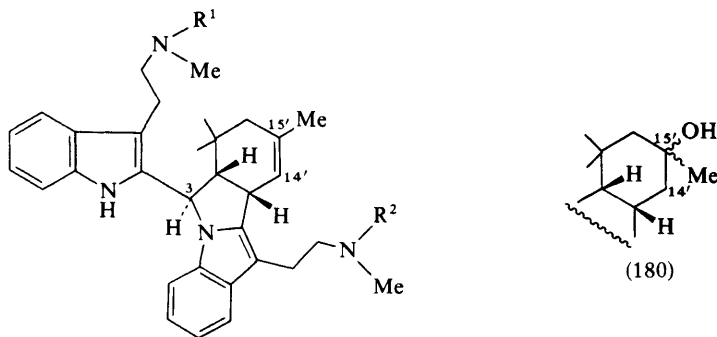
**Scheme 24**

<sup>108</sup> (a) B. M. Trost, S. A. Godleski, and J. L. Belletire, *J. Org. Chem.*, 1979, **44**, 2052; (b) G. Büchi, P. Kulsa, K. Ogasawara, and R. L. Rosati, *J. Am. Chem. Soc.*, 1970, **92**, 999.

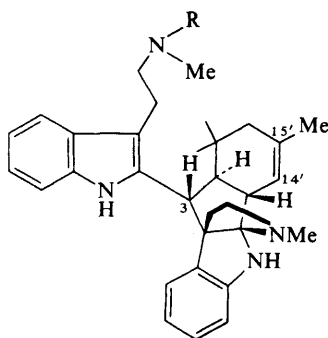
### 3 Bisindole Alkaloids

The application of infrared circular dichroism (IRCD) in the determination of absolute configurations has been discussed, with particular reference to calycanthine.<sup>109</sup>

The major alkaloids of *Flindersia fournieri* Panch. et Seb. are all dimers of borreverine (32a), or methylation products thereof. New alkaloids isolated from this source are 4,4'-dimethylisoborreverine (175), 4-methylborreverine (176), 4-methylisoborreverine (177),<sup>28a,110a</sup> 15'-hydroxy-14',15'-dihydroisoborreverine, and 15'-hydroxy-14',15'-dihydroborreverine.<sup>28a,110b</sup> The structure and stereochemistry of (175) and (176) were established by methylation (by CH<sub>2</sub>O, AcOH, and NaBH<sub>3</sub>CN) of isoborreverine (178) and borreverine (179), which gave (175) and (176) respectively. Similar methylation of 4'-methylisoborreverine (177) also gave (175).<sup>110a</sup> The structure of 15'-hydroxy-14',15'-dihydroisoborreverine [part-structure (180); remainder of molecule as in (178)] becomes clear from its



- 4,4'-Dimethylisoborreverine (175)  $R^1 = R^2 = \text{Me}$   
 4-Methylisoborreverine (177)  $R^1 = \text{Me}, R^2 = \text{H}$   
 Isoborreverine (178)  $R^1 = R^2 = \text{H}$



- 4-Methylborreverine (176)  $R = \text{Me}$   
 Borreverine (179)  $R = \text{H}$

<sup>109</sup> C. J. Barnett, A. F. Drake, and S. F. Mason, *Tetrahedron Lett.*, 1980, **21**, 391; S. F. Mason, *Bull. Soc. Chim. Belg.*, 1979, **88**, 853.

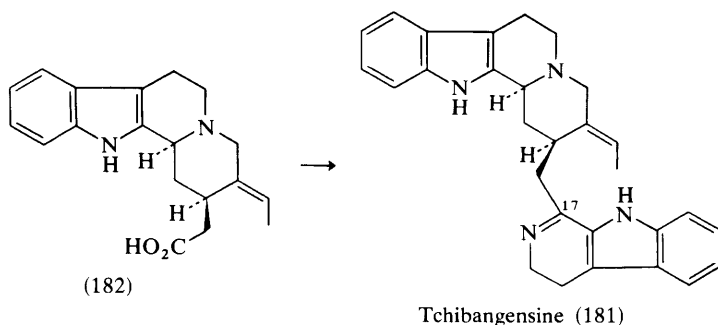
<sup>110</sup> F. Tillequin and M. Koch, (a) *Phytochemistry*, 1979, **18**, 1559; (b) *ibid.*, p. 2066.

spectrographic properties, and dehydration (by  $\text{CF}_3\text{CO}_2\text{H}$  and benzene) to isoborreverine (178); the configuration at C-15' remains unknown. The isomeric base, 15'-hydroxy-14',15'-dihydroborreverine [part-structure (180); remainder of molecule as in (179)], contains both indole and indoline chromophores (u.v. spectrum), an eserine-like structure (peak at  $m/z$  172 in the mass spectrum), and a hydroxy-group at C-15', as in (180) (n.m.r. spectrum). Its constitution as 15'-hydroxy-14',15'-borreverine was confirmed by dehydration with  $\text{CF}_3\text{CO}_2\text{H}$  in benzene; in the strongly acidic reaction conditions, the initially formed borreverine rearranges, as previously observed,<sup>98b</sup> and the final product is isoborreverine (178).<sup>110b</sup> Again the configuration at C-15' is unknown.

Roxburghine D and a hitherto unknown stereoisomer, roxburghine X, have been isolated from *Uncaria elliptica*; as yet, nothing is known about its stereochemistry.

Details of the X-ray determination of the structure of geissospermine have now been published,<sup>111a</sup> and the relative stereochemistry of the secamines, the presecamines, and their synthetic analogues has been discussed.<sup>111b</sup>

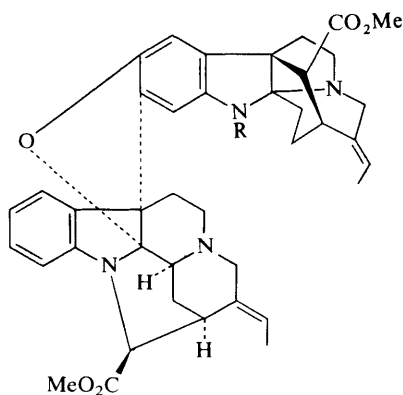
Tchibangensine (181) has been synthesized simply by condensation of tryptamine with geissoschizoic acid (182), followed by cyclization (by  $\text{POCl}_3$ ).<sup>111c</sup> Reduction with sodium borohydride gives two C-17 epimers, which on hydrogenation afford the *allo*-isomers ochrolifuanine C and ochrolifuanine D.



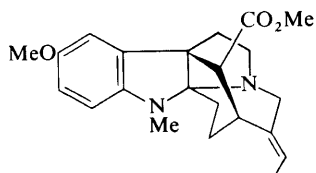
Among the alkaloids of the leaves and stem bark of *Alstonia odontophora* are pleiocorine (183), pleiocraline, and a new alkaloid which proves to be  $N_\alpha$ -desmethylpleiocorine (184), since on methylation (with  $\text{CH}_2\text{O}$ ,  $\text{NaBH}_3\text{CN}$ , and  $\text{AcOH}$ ) it yields pleiocorine (183).<sup>59</sup>

Three dimeric indole alkaloids of a new type, peceyline, peceylanine, and pelankine, have been isolated from a Sri Lankan apocynaceous plant, *Petchia ceylanica* Wight.<sup>87b</sup> The structures of these bases were determined mainly by n.m.r. spectroscopy. In their  $^1\text{H}$  spectra, all three alkaloids exhibit four aromatic singlets, one olefinic hydrogen multiplet, two methoxycarbonyl singlets, two *N*-methyl singlets, and two *C*-methyl doublets. One half of the non-aromatic carbon resonances in the  $^{13}\text{C}$  spectra show that one monomer unit is common to all three alkaloids, and inspection reveals that this unit must be based on vincorine

<sup>111</sup> (a) A. Chiaroni and C. Riche, *Acta Crystallogr., Sect. B*, 1979, **35**, 1820; (b) G. A. Cordell, G. F. Smith, and G. N. Smith, *J. Indian Chem. Soc.*, 1978, **55**, 1083; (c) C. Mirand-Richard, L. Le Men-Olivier, J. Lévy, and J. Le Men, *Heterocycles*, 1979, **12**, 1409.



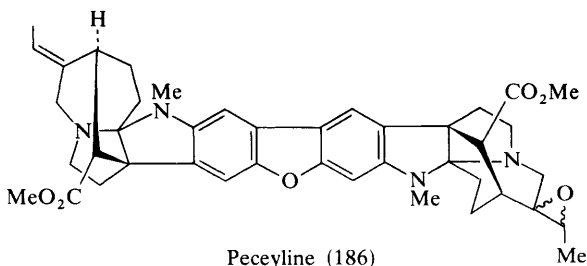
Pleiorcorine (183) R = Me

*N*<sub>a</sub>-Desmethylpleiocorine (184) R = H

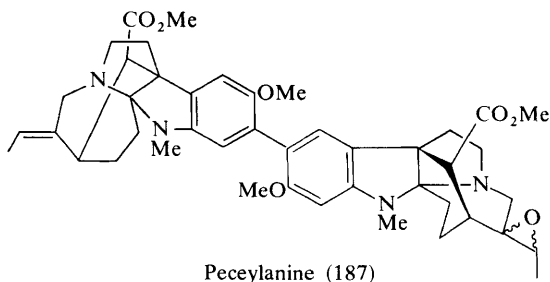
Vincorine (185)

(185), attached to the second component *via* C-11, to account for the <sup>1</sup>H aromatic singlets.

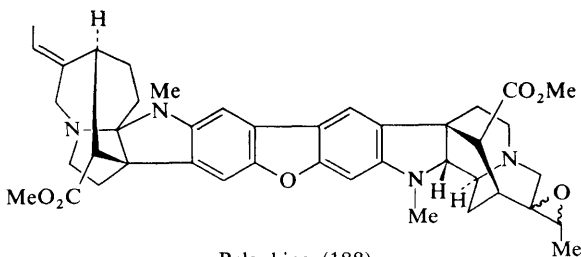
The non-aromatic portion of the second monomer unit in peceyline and peceylanine is also identical (<sup>13</sup>C spectra), and is based on vincorine epoxide. Since peceyline contains no methoxy-groups other than those in the ester functions, and its <sup>1</sup>H aromatic resonances are consistent with an unsymmetrical dibenzofuran system, a possible structure for peceyline is (186).



Peceylanine contains two aromatic methoxy-groups, and is also unsymmetrically substituted in the aromatic rings; on this basis, peceylanine could have the structure (187). Alternative structures for both peceyline and peceylanine are those in which the epoxide group and the double-bond are interchanged.

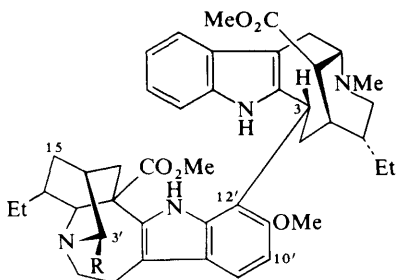


Half of the carbon resonances in the spectrum of peceyline are exactly reproduced in that of pelankine, which also contains an unsymmetrical dibenzofuran part-structure. The resonances of the second monomer unit differ, particularly those owing to carbons 2' and 3', and in fact are compatible with a structure based on desacetylidesformyl-*N*<sub>a</sub>-methyl-1,2*BH*-dihydroakuammiline. The complete structure deduced for pelankine is thus (188). In all three structures (186)–(188) the configuration of the epoxide function is unknown.<sup>87b</sup>



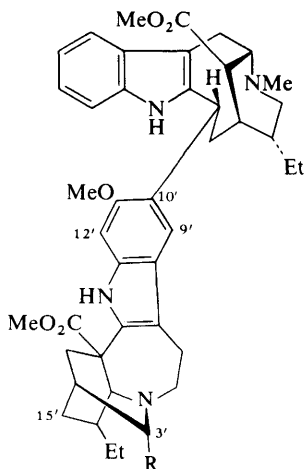
Pelankine (188)

Tabernaegantines C and D are two minor alkaloids of *Tabernaemontana elegans*; they are composed of dregaminol and isovoacangine units, attached *via* C-3 of dregaminol and C-12' (tabernaegantine C) (189a) or C-10' (tabernaegantine D) (190a) of isovoacangine.<sup>112a</sup> In both bases, a nitrile group is situated at C-3' (<sup>13</sup>C n.m.r. spectrum) of the isovoacangine component. In accordance with these conclusions, the nitrile group can be removed by Co<sup>II</sup> (or Ni<sup>II</sup>)-assisted reduction (by NaBH<sub>4</sub>), the products being tabernaegantine C (189b) [from (189a)] and tabernaegantine D (190b) [from (190a)]. The



Tabernaegantine C (189a) R = CN

Tabernaegantine C (189b) R = H



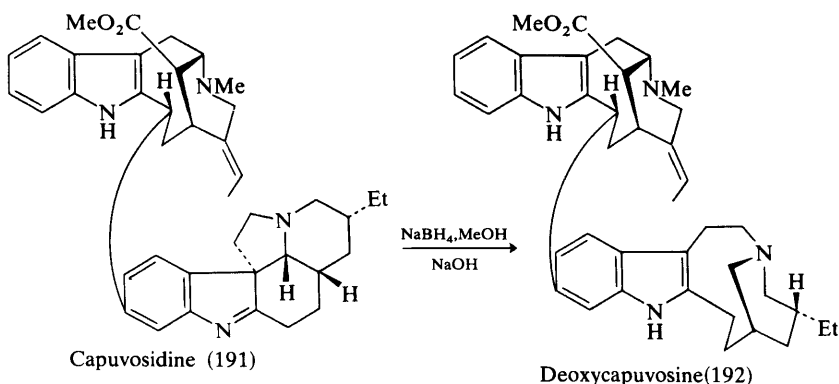
Tabernaegantine D (190a) R = CN

Tabernaegantine D (190b) R = H

<sup>112</sup> (a) B. Danieli, G. Palmisano, B. Gabetta, and E. M. Martinelli, *J. Chem. Soc., Perkin Trans. 1*, 1980, 601; (b) H. P. Hussen, I. Chardon-Loriaux, M. Andriantsiferana, and P. Potier, *J. Indian Chem. Soc.*, 1978, **55**, 1099.

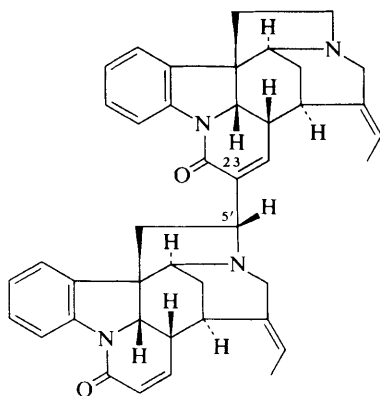


The reduction of capuvisidine (191) to an indole derivative by means of sodium borohydride in methanol solution<sup>98c</sup> has now been reported,<sup>112b</sup> and the product is indeed deoxycapuvosine (192); this completes the interconversion of the alkaloids of this group from *Pandaca boiteaui* and *Capuronetta elegans*. Further evidence in support of the 3'-11 attachment of the monomer units in these alkaloids has also been provided.<sup>112b</sup>

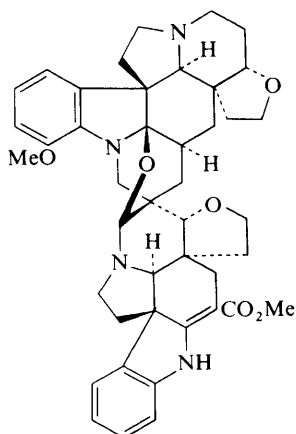


A new alkaloid of *Voacanga chalongana*,<sup>115</sup> 3 $\beta$ -hydroxyvobtusine (195), is identical with hydratoamatine, earlier<sup>54b</sup> postulated to be an intermediate in the conversion of amatine (194) into vobtusine (196). In consonance with the structure (195), reduction (by NaBH<sub>4</sub>) gives vobtusine (196), and dehydration gives amatine (194), this last reaction being accompanied by inversion of C-14, as previously noted.<sup>54b</sup>

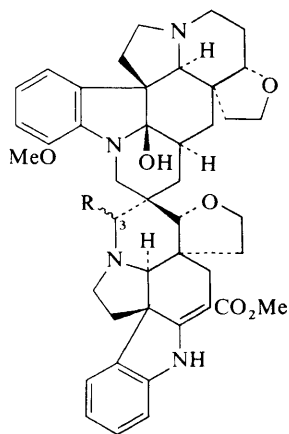
<sup>115</sup> B. Danieli, G. Lesma, G. Palmisano, and B. Gabetta, *Heterocycles*, 1980, **14**, 201.



Sungucine (193)



Amataine (Grandifoline) (194)



3ξ-Hydroxyvobtusine (195) R = OH

Vobtusine (196) R = H

A complete analysis of the 400 MHz  $^1\text{H}$  n.m.r. spectrum of ervafoline (197) should aid structure determination of new alkaloids in this group.<sup>116</sup>

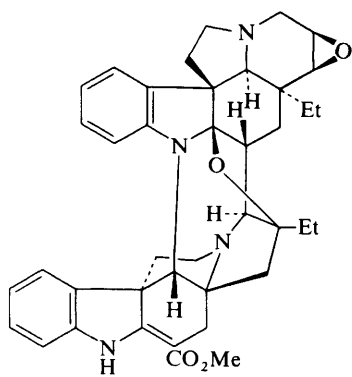
Vindolicine (vindoline 10,10'-dimer) and fourteen bisindole alkaloids of the vinblastine group have been isolated from the aerial parts of *Catharanthus ovalis*.<sup>117</sup> These include leurosine, 21'-hydroxyleurosine, vinblastine, 20'-deoxy-leurosine, 20'-deoxyvinblastine, pleurosine, catharine, catharinine, vincristine, and vincathicine. A new alkaloid is 21'-oxoleurosine (198), which has also been found recently in *Catharanthus roseus*.<sup>118</sup> The three remaining alkaloids are vincovaline (199) and vincovalinine (16'-desmethoxycarbonyl-leurosine), whose structures<sup>119</sup> have now been confirmed, and vincovalicine, which has

<sup>116</sup> A. Henriques, S. K. Kan, and M. Lounasmaa, *Acta Chem. Scand., Ser. B*, 1979, **33**, 775.

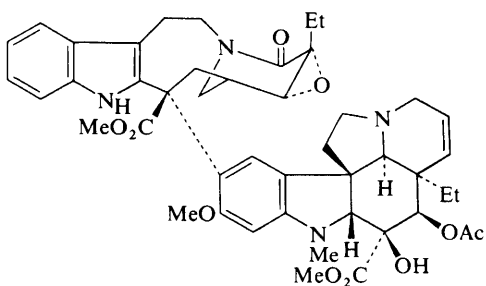
<sup>117</sup> N. Langlois, R. Z. Andriamialisoa, and N. Neuss, *Helv. Chim. Acta*, 1980, **63**, 793.

<sup>118</sup> A. El-Sayed, G. A. Handy, and G. A. Cordell, *J. Nat. Prod.*, 1980, **43**, 157.

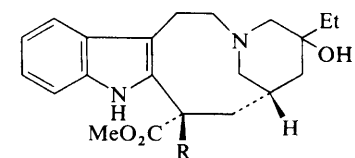
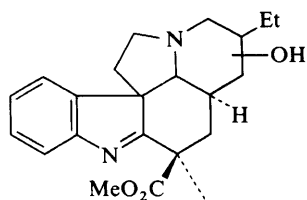
<sup>119</sup> R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron Lett.*, 1976, 2849.



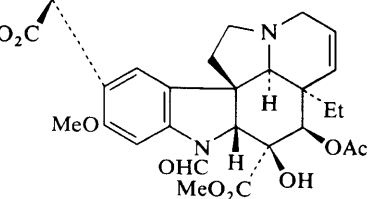
Ervafoline (197)



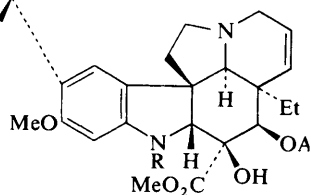
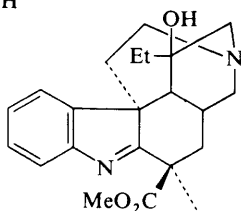
21'-Oxoleurosine (198)



Vincovaline (199) R = 10-Vindolinyloxy

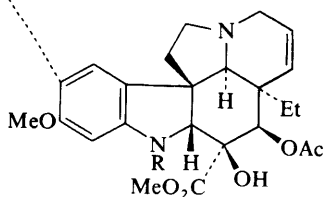
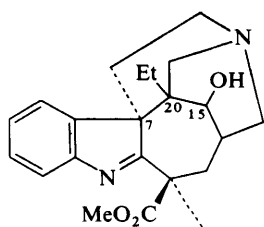


Vincovalicine (?) (200)



(201) R = CHO

(203) R = Me

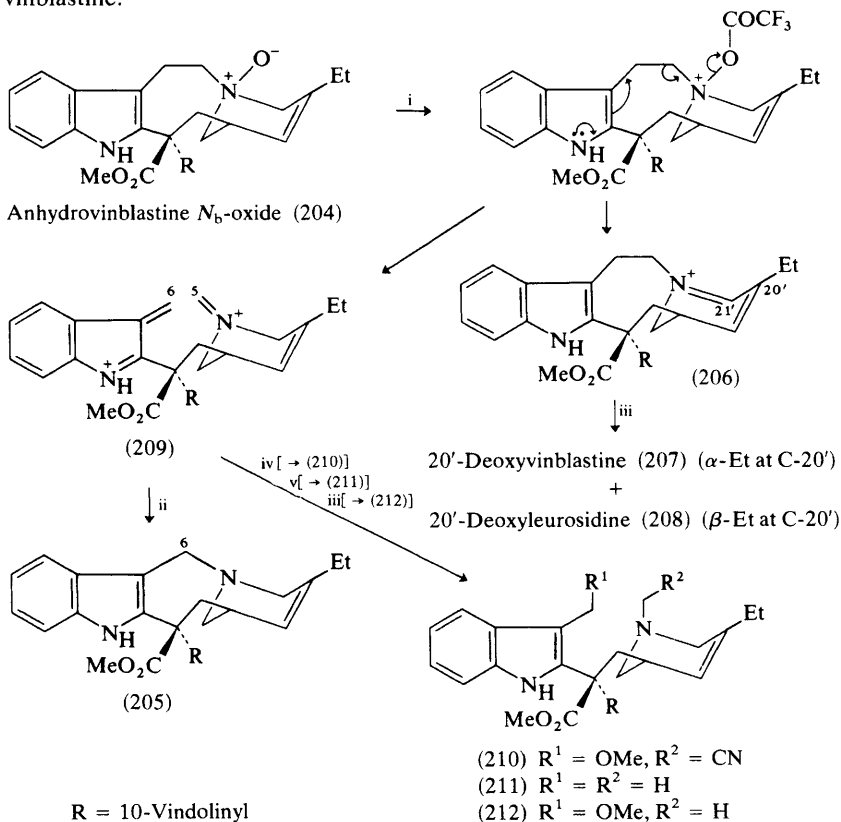


(202) R = CHO

provisionally been formulated as (200); lack of material has so far prevented a complete structure elucidation.<sup>117</sup>

In the course of this work, other structures which were considered for vincovalicine were  $N_a$ -desmethyl- $N_a$ -formylvincathicine (201) and  $N_a$ -desmethyl- $N_a$ -formylisovincathicine (202). The former was obtained by the Jones' oxidation of vincathicine (203), and the latter, together with (201), by the acid-induced rearrangement of leuroformine, which is the  $N_a$ -formyl analogue of leurosine; however, neither of these products proved to be identical with vincovalicine.<sup>117</sup>

Some of the earlier synthetic work in the vinblastine area, previously reported in brief, has now been published in detail. This includes syntheses of 16'-desmethoxycarbonyl-20'-deoxy-16'-*epi*-vinblastine,<sup>107a</sup> catharine, and vinamine,<sup>120</sup> and Potier has summarized the work which culminated in the synthesis of vinblastine.<sup>121</sup>



Reagents: i,  $(\text{CF}_3\text{CO})_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ , at  $0^\circ\text{C}$ ; ii,  $\text{H}_2\text{O}$ , THF; iii,  $\text{NaBH}_4$ , MeOH; iv, MeOH, KCN; v,  $\text{NaBH}_3\text{CN}$ , MeOH

Scheme 25

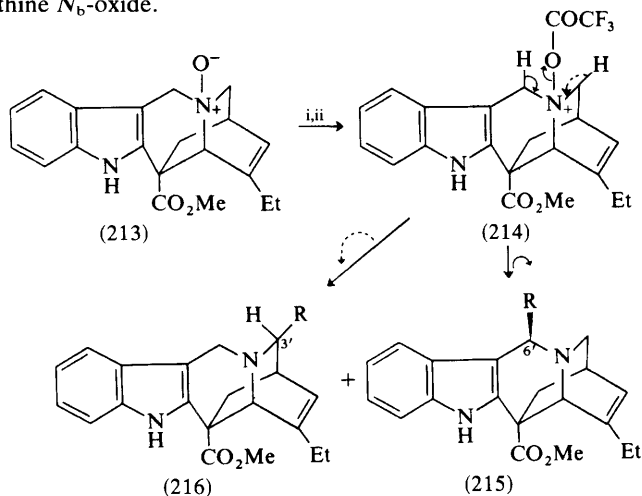
<sup>120</sup> J. P. Kutney, J. Balsevich, and B. R. Worth, *Can. J. Chem.*, 1979, **57**, 1682.

<sup>121</sup> P. Potier, *J. Nat. Prod.*, 1980, **43**, 72.

The diols (15'*R*)- and (15'*S*)-hydroxyleurosidine, and the four 15'-hydroxy-compounds derived from deoxyleurosidine and deoxyvinblastine, have been prepared by standard procedures from anhydrovinblastine for pharmacological evaluation.<sup>122</sup>

A new class of vinblastine derivatives has been prepared by applying the modified Polonovski reaction to anhydrovinblastine *N*<sub>b</sub>-oxide (204).<sup>123</sup> When the reaction mixture was treated with aqueous tetrahydrofuran, loss of C-5' occurred, and the product following re-closure by a Mannich reaction was 5'-noranhydrovinblastine (205). Some very polar material isolated from the reaction was presumably the conjugated immonium ion (206), formed by proton loss from C-21' instead of fragmentation, since reduction gave a mixture of 20'-deoxyvinblastine (207) and 20'-deoxyleurosidine (208).<sup>123a</sup> When the Polonovski reaction mixture was worked up with methanol and added nucleophile (*e.g.* CN<sup>-</sup>, BH<sub>3</sub>CN<sup>-</sup>, or BH<sub>4</sub><sup>-</sup>) the intermediate bis-immonium ion (209) was trapped, and the products were the 5',6'-seco-derivatives (210)–(212) (Scheme 25).<sup>123a,b</sup>

A second group of 5'-nor-derivatives has been obtained by the coupling of vindoline with 5-norcatharanthine (173), prepared as described above.<sup>106b</sup> Under the usual modified Polonovski reaction conditions, loss of a proton from C-6 or C-3 in the quaternary ion (214) derived from norcatharanthine *N*<sub>b</sub>-oxide (213) was followed by coupling with vindoline, with formation of the bis-indole bases (215) and (216) (Scheme 26). In this reaction, cleavage of the 16,21 bond in the norcatharanthine component is not observed, in contrast to the behaviour of catharanthine *N*<sub>b</sub>-oxide.



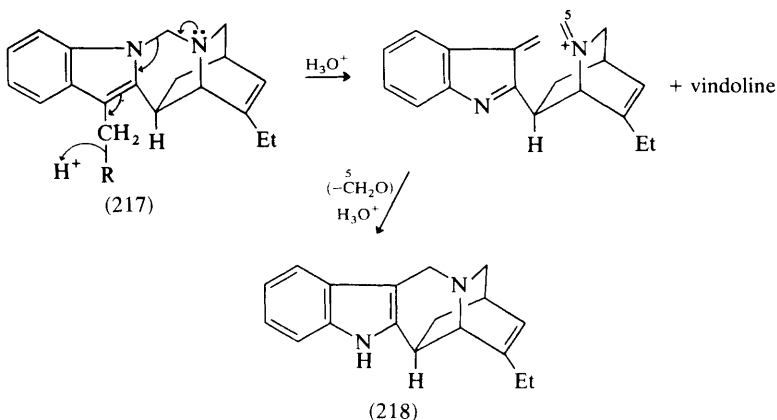
Reagents: i, (CF<sub>3</sub>CO)<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, at 0 °C, vindoline; ii, NaBH<sub>4</sub>, MeOH

**Scheme 26**

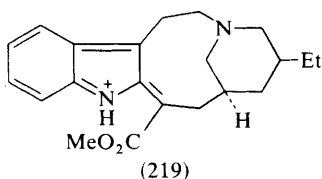
<sup>122</sup> J. P. Kutney, T. Honda, P. M. Kazmaier, N. J. Lewis, and B. R. Worth, *Helv. Chim. Acta*, 1980, **63**, 366.

<sup>123</sup> (a) P. Mangeney, R. Z. Andriamialisoa, J. Y. Lallemand, N. Langlois, Y. Langlois, and P. Potier, *Tetrahedron*, 1979, **35**, 2175; (b) P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *J. Org. Chem.*, 1979, **44**, 3765.

In an earlier study<sup>54c</sup> it was shown that the coupling of 16-desmethoxycarbonylcatharanthine  $N_b$ -oxide with vindoline gave a significant amount of bisindole base (217), in addition to products of vinblastine type. Further support for this structure comes from its cleavage with acid; loss of the vindoline component with concomitant fission of the  $N-CH_2-N$  grouping was followed by re-cyclization, with the formation of 16-desmethoxycarbonyl-5-norcatharanthine (218).<sup>106b</sup>

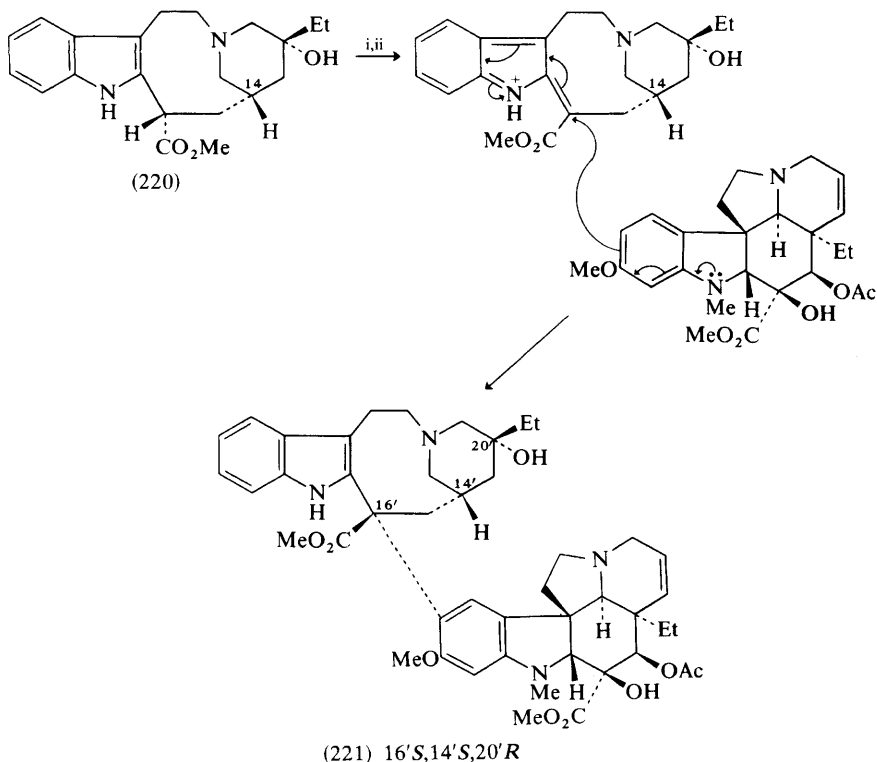


Earlier investigations had shown that the coupling of 7-chloroindolenine derivatives of velbanamine, cleavamine, and their relatives invariably gives products having the undesired ( $16'R$ ) configuration, presumably because the intermediate ion, *e.g.* (219), is attacked by nucleophile at its less hindered face.



Consequently, a substrate such as secopandoline (220), with opposite configuration at C-14, should lead to bisindole bases having the desired ( $16'S$ ) configuration, and since this configuration appears to be vital for pharmacological activity, such a reaction may well afford a route to new compounds of potential clinical use. The condensation of the chloroindolenine from (220) with vindoline gave, as expected, the vinblastine isomer (221) as shown in Scheme 27; it is of interest to note that this base is also isomeric with vincovaline (*vide supra*), but is not identical with it;<sup>124</sup> if the stereochemistry deduced for these bases is correct, vincovaline (199) is epimeric with the new base (221) at C-16' and possibly also at C-20'.

<sup>124</sup> N. Kunesch, P. L. Vaucamps, A. Cavé, J. Poisson, and E. Wenkert, *Tetrahedron Lett.*, 1979, 5073.



Reagents: i, Bu'OC1; ii, vindoline, HCl, DME

**Scheme 27**

Structure-activity relationships in the vinblastine group have been discussed.<sup>125</sup> As noted above, the (*S*) configuration at C-16' is essential for pharmacological activity, but the configuration at C-14', and the presence of an ester group at C-16', also seem to play an essential role in the determination of biological activity.

#### 4 Biogenetically Related Quinoline Alkaloids

**Cinchona Group.**—Details of Brown's partial synthesis<sup>54d</sup> of dihydro-meroquinene from secologanin have been published.<sup>126</sup>

A further example of the use of copolymers of acrylonitrile and *Cinchona* alkaloids in asymmetric synthesis has been reported;<sup>127</sup> thus these polymers catalyse the addition of benzyl mercaptan to  $\omega$ -nitrostyrene to give consistently an excess of the (+)-enantiomer of the adduct.

<sup>125</sup> P. Potier, D. Guenard, and F. Zavala, *Compt. Rend. Soc. Biol.*, 1979, **173**, 414.

<sup>126</sup> R. T. Brown and J. Leonard, *J. Indian Chem. Soc.*, 1978, **55**, 1092.

<sup>127</sup> N. Kobayashi and K. Iwai, *Tetrahedron Lett.*, 1980, **21**, 2167.

Procedures for the separation of *Cinchona* alkaloids by h.p.l.c. have been described,<sup>128</sup> and their separation by t.l.c. has been critically reviewed.<sup>129</sup>

**Camptothecin Group.**—Camptothecin and 9-methoxycamptothecin are two of the major cytotoxic alkaloids of the wood and stem bark of *Ervatamia heyneana*.<sup>81,130</sup>

Details of the synthesis<sup>131a</sup> of desethyl-desoxycamptothecin, by Walraven and Pandit, have been published.<sup>131b</sup>

Several camptothecin relatives have been prepared, either by total synthesis or from natural 10-hydroxycamptothecin, for pharmacological evaluation.<sup>132</sup>

<sup>128</sup> (a) S. E. Barrow, A. A. Taylor, E. C. Horning, and M. G. Horning, *J. Chromatogr.*, 1980, **181**, 219; (b) M. Bauer and G. Untz, *ibid.*, 1980, **192**, 479.

<sup>129</sup> R. Verpoorte, T. Mulder-Krieger, J. J. Troost, and A. B. Svendsen, *J. Chromatogr.*, 1980, **184**, 79.

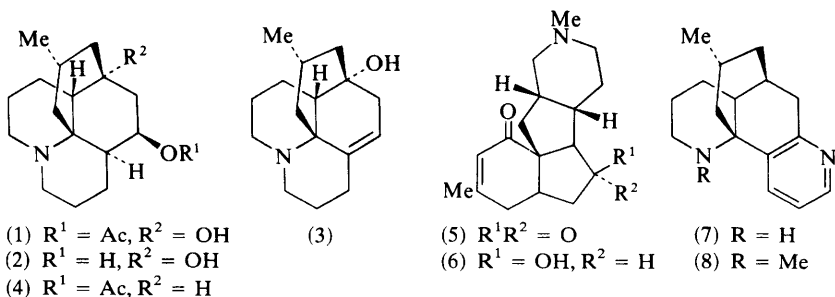
<sup>130</sup> S. P. Gunasekera, M. M. Badawi, G. A. Cordell, N. R. Farnsworth, and M. Chitnis, *J. Nat. Prod.*, 1979, **42**, 475.

<sup>131</sup> H. G. M. Walraven and U. K. Pandit, (a) *Tetrahedron Lett.*, 1975, 4507; (b) *Tetrahedron*, 1980, **36**, 321.

<sup>132</sup> M. C. Wani, P. E. Ronman, J. T. Lindley, and M. E. Wall, *J. Med. Chem.*, 1980, **23**, 544.



The structures of three previously reported<sup>1</sup> alkaloids from *Lycopodium paniculatum* have appeared.<sup>2</sup> Paniculine (1), previously called alkaloid P<sub>2</sub>, is the first lycopodine-type alkaloid bearing a hydroxyl group at the C-7 bridgehead position. The diol (2) obtained by hydrolysis of (1) is also a naturally occurring compound. Dehydration (by SOCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>) of (2) provides the olefin (3), identical with previously reported<sup>1</sup> alkaloid P<sub>5</sub>. Alkaloid P<sub>4</sub> was shown to be identical with desacetyl-lycoclavine.<sup>3</sup> Lycoclavine<sup>3</sup> and flabellidine were also isolated from *L. paniculatum*.<sup>2</sup> Treatment of paniculine (1) with PCl<sub>5</sub>, followed by catalytic hydrogenation of the product, gave acetyldihydrolycopodine (4). The alkaloids of *L. magellanicum*<sup>4</sup> have been further investigated and a new alkaloid, magellaninone (5), has been reported.<sup>5</sup> Oxidative correlation with magellanine (6) established the structure of magellaninone (5). The absolute stereochemistry of these alkaloids and of the related compound paniculatine<sup>1</sup> was determined using the Horeau method, Brewster's benzoate method, and o.r.d. studies.<sup>5</sup> The presence of lycodine (7) and *N*-methyl-lycodine (8) in *L. magellanicum* is noted.<sup>5</sup>



An interesting transformation of lycopodine into [9-<sup>14</sup>C]lycopodine, which is potentially useful in biosynthetic studies, has been described.<sup>6</sup> The *N*-formyl

<sup>1</sup> M. Castillo, G. Morales, L. A. Loyola, I. Singh, C. Crispo, H. L. Holland, and D. B. MacLean, *Can. J. Chem.*, 1976, **54**, 2900.

<sup>2</sup> G. Morales, L. A. Loyola, and M. Castillo, *Phytochemistry*, 1979, **18**, 1719.

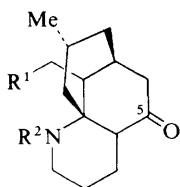
<sup>3</sup> W. A. Ayer and D. A. Law, *Can. J. Chem.*, 1962, **40**, 2088.

<sup>4</sup> S. N. Alam, K. A. H. Adams, and D. B. MacLean, *Can. J. Chem.*, 1964, **42**, 2456.

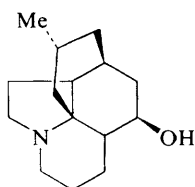
<sup>5</sup> L. A. Loyola, G. Morales, and M. Castillo, *Phytochemistry*, 1979, **18**, 1721.

<sup>6</sup> W. D. Marshall and D. B. MacLean, *Pol. J. Chem.*, 1979, **53**, 13.

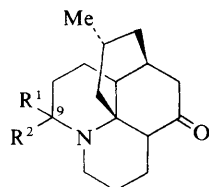
acid (9), available by oxidation of lycopodine with aqueous potassium permanganate, was transformed by hydrolysis, cyclization (using DCC in pyridine), and reduction (by  $\text{LiAlH}_4$ ) to the A-norlycopodine (10). Cleavage of (10) with cyanogen bromide gave the bromide (11; 5-OH), which was allowed to react with NaCN to give the dicyano-compound and was oxidized to the ketone (12). Vigorous hydrolysis of (12), followed by cyclization of the resulting acid (13), provided lycopodine- $\alpha$ -lactam (14). Reduction of (14) with  $\text{NaBH}_4$  in the presence of triethyloxonium fluoroborate gave lycopodine (15). The use of  $\text{Na}^{14}\text{CN}$  in the sequence yields the 9-labelled lycopodine.<sup>6</sup>



(9)  $\text{R}^1 = \text{CO}_2\text{H}$ ,  $\text{R}^2 = \text{CHO}$



(10)



(14)  $\text{R}^1\text{R}^2 = \text{O}$

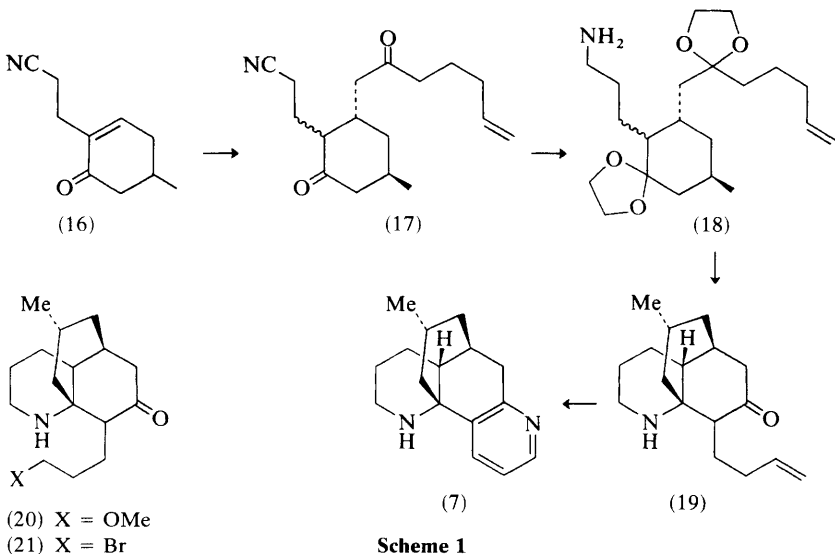
(15)  $\text{R}^1 = \text{R}^2 = \text{H}$

(11)  $\text{R}^1 = \text{CH}_2\text{Br}$ ,  $\text{R}^2 = \text{CN}$

(12)  $\text{R}^1 = \text{CH}_2\text{CN}$ ,  $\text{R}^2 = \text{CN}$

(13)  $\text{R}^1 = \text{CH}_2\text{CO}_2\text{H}$ ,  $\text{R}^2 = \text{H}$

Heathcock has extended his elegant approach to the synthesis of the *Lycopodium* alkaloids, reviewed last year (*cf.* Vol. 10, p. 207) in the case of lycopodine (15),<sup>7</sup> to provide the first total synthesis of lycodine (7).<sup>8</sup> The synthesis (Scheme 1) proceeds from the previously described cyano-enone (16) in just

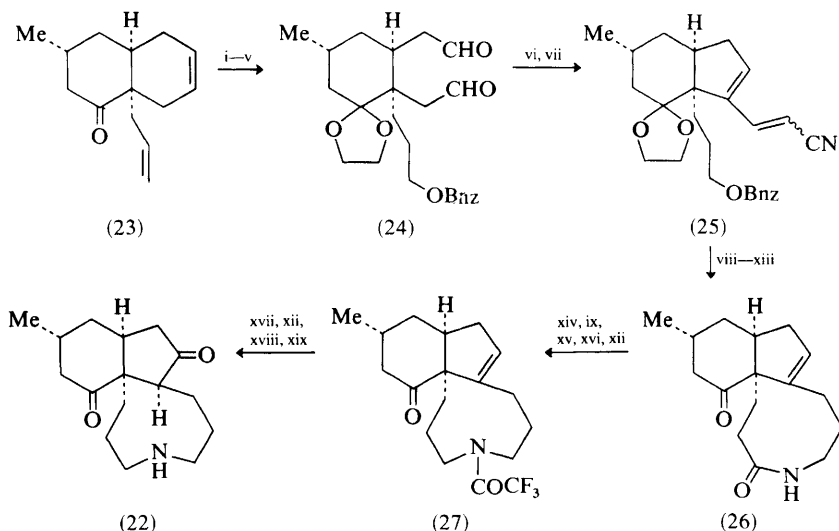


<sup>7</sup> For an excellent account of the lycopodine synthesis, see C. H. Heathcock, E. Kleinman, and E. S. Binkley, *Int. Congr. Ser.-Excerpta Medica*, 1979, **457**, 71.

<sup>8</sup> E. Kleinman and C. H. Heathcock, *Tetrahedron Lett.*, 1979, 4125.

five steps to give ( $\pm$ )-lycodine in 22% overall yield. Addition of the cuprate derived from the lithium enolate of hept-6-en-2-one dimethylhydrazone affords, after hydrolysis, the cyano-dione (17). Ketalization of (17), followed by reduction with  $\text{LiAlH}_4$ , provides the amine (18). Treatment of (18) with  $\text{HCl}$  in methanol at reflux for seven days gives the tricyclic amino-ketone (19) directly, as a single stereoisomer. Lycodine (7) is then produced in a 'one-pot' process involving first ozonolysis and treatment with hydroxylamine, then heating in the presence of dimethyl sulphide.<sup>8</sup> An adaptation of this sequence, utilizing the dimethylhydrazone of 6-methoxy-2-hexanone instead of the olefinic hydrazone, gives the tricyclic intermediate (20). When this compound is treated with  $\text{HBr}$  in acetic acid, followed by alkaline work-up, ( $\pm$ )-lycopodine (15) is obtained in 20.5% overall yield from (16). Presumably the intermediate bromo-compound (21) cyclizes spontaneously during the alkaline work-up.<sup>8</sup>

Another highlight of the period under review is the report of the total synthesis of the tricyclic alkaloid fawcettimine (22) (Scheme 2).<sup>9</sup> Lewis-acid-catalysed Diels-Alder addition of butadiene to 2-allyl-5-methylcyclohex-2-enone provided the *cis*-octalone (23), which was modified as indicated to give the dialdehyde (24). After considerable experimentation, conditions were defined which led to regioselective ring-closure in the desired direction. The unsaturated aldehyde was treated directly with the Wadsworth-Emmons reagent to provide

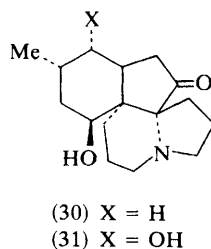
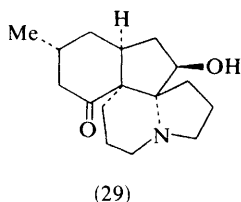
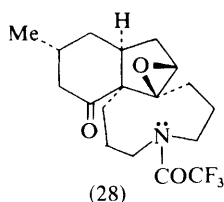


Reagents: i,  $\text{HOCH}_2\text{CH}_2\text{OH}$ ,  $\text{H}^+$ ; ii, disiamylborane,  $\text{H}_2\text{O}_2$ ,  $\text{OH}^-$ ; iii,  $\text{NaH}$ ,  $\text{PhCH}_2\text{Br}$ ; iv,  $\text{OsO}_4$ ; v,  $\text{HIO}_4$ ; vi, morpholine-camphoric acid, ether-HMPA; vii,  $(\text{EtO})_2\text{POCH}_2\text{CN}$ ; viii,  $\text{H}_2$ ,  $[(\text{Ph}_3\text{P})_3\text{RhCl}]$ ; ix,  $\text{LiAlH}_4$ ; x,  $\text{N}_3\text{CO}_2\text{Bu}^+$ ; xi,  $\text{Li}$ , in liquid  $\text{NH}_3$ ; xii, Jones' reagent; xiii, *N*-hydroxysuccinimide,  $\text{DCC}$ ,  $\text{CF}_3\text{CO}_2\text{H}$ ,  $\text{Bu}^+\text{N}$ ,  $\text{MeCN}$ ; xiv,  $\text{NaBH}_4$ ; xv,  $(\text{CF}_3\text{CO})_2\text{O}$ , pyridine; xvi,  $\text{OH}^-$ ; xvii, MCPBA; xviii,  $\text{H}_2$ ,  $\text{Pd/C}$ ; xix,  $\text{KOH-MeOH}$

Scheme 2

<sup>9</sup> T. Harayama, M. Takatani, and Y. Inubushi, *Tetrahedron Lett.*, 1979, 4307.

the nitrile (25). Transformation of the  $\alpha\beta$ -unsaturated nitrile into the saturated amine, and conversion of the protected primary hydroxyl into a carboxylic acid group, followed by high-dilution formation of a lactam, gave (26). Reduction of (26) with  $\text{NaBH}_4$  gave epimeric alcohols, both of which were transformed into the keto-amide (27). Oxidation of (27) with peracid gave epimeric epoxides. The  $\alpha$ -epoxide was transformed into ( $\pm$ )-fawcettimine (22) as indicated in Scheme 2. When the trifluoroacetyl protecting group of the corresponding  $\beta$ -epoxide (28) was removed, ring-closure occurred to give the tetracyclic compound (29). Oxidation of (29) to the diketone, followed by selective reduction of the carbonyl group of the cyclohexane ring, provided ( $\pm$ )-8-deoxyserratinine (30), previously prepared from naturally occurring serratinine (31).<sup>9</sup>



An interesting account of the early synthetic studies on the *Lycopodium* alkaloids has appeared.<sup>10</sup>

<sup>10</sup> R. V. Stevens, in 'The Total Synthesis of Natural Products', ed. J. ApSimon, Wiley, New York, Vol. 3, 1977, pp. 489—515.

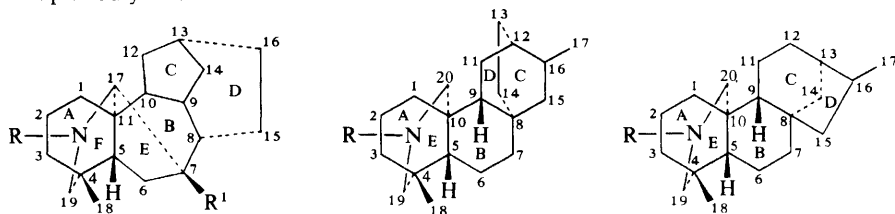
## 1 Introduction

The chemistry of the diterpenoid alkaloids, rather than their structure elucidation by physical methods, has attracted more interest during the year covered by this Report. While several new alkaloids have been reported, most of the research on these polycyclic, polyfunctional bases has involved chemical conversions and synthetic methods. Most notably, Wiesner's group at New Brunswick, Canada, has reported a fourth-generation synthesis of the delphinine-type alkaloids. That this marvel of 'synthetic engineering' accomplishes the stated goals<sup>1</sup> of a highly efficient, fully regio- and stereo-specific synthesis of these complex natural products is abundantly clear.

Two new alkaloids from *Daphniphyllum gracile* Gage have been reported.<sup>2</sup> Plants of the related species *Daphniphyllum humile* Maxim have been implicated in cattle poisonings in Hokkaido, Japan.<sup>3</sup>

Surveys of recent developments in the chemistry of C<sub>20</sub> diterpenoid alkaloids,<sup>4</sup> of the alkaloids of *Consolida ambigua*,<sup>5</sup> and of the synthesis of diterpenoid alkaloids by thermolysis<sup>6</sup> have appeared.

The numbering systems for the aconitine, lycoctonine, atisine, and veatchine skeletons are presented in structures A, B, C, and D, respectively. This Report surveys the work reported in the literature that was available in our libraries up to July 1980.



(A) Aconitine skeleton,  $R^1 = H$  (C) Antisine skeleton  
(B) Lycoctonine skeleton,  $R^1 = OR^2$

(D) Veatchine skeleton

<sup>1</sup> K. Wiesner, *Chem. Soc. Rev.*, 1977, **6**, 413.

<sup>2</sup> S. Yamamura, J. A. Lambertson, M. Niwa, K. Endo, and Y. Hirata, *Chem. Lett.*, 1980, 393.

<sup>3</sup> M. Sonoda, M. Tasaka, K. Takahashi, M. Koiwa, S. Minami, M. Iwase, and K. Yashiro, *J. Jpn. Vet. Med. Assoc.*, 1978, **31**, 140.

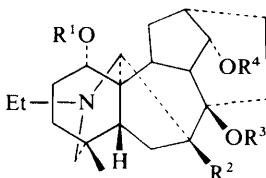
<sup>4</sup> S. W. Pelletier and N. V. Mody, *J. Nat. Prod.*, 1980, **43**, 41.

<sup>5</sup> S. W. Pelletier, R. S. Sawhney, H. K. Desai, and N. V. Mody, *J. Nat. Prod.*, 1980, **43**, 395.

<sup>6</sup> T. Kametani, *Pure Appl. Chem.*, 1979, **51**, 747.

## 2 C<sub>19</sub> Diterpenoid Alkaloids

**Alkaloids of *Delphinium cardiopetalum* DC (syn. *D. verdunense* Balbis).**—The structures of two new minor alkaloids from plants of *D. cardiopetalum* collected in León, Spain, have been determined by spectral and X-ray crystallographic analysis.<sup>7</sup> Cardiopetaline (1) [C<sub>21</sub>H<sub>33</sub>NO<sub>3</sub>; m.pt 179—181 °C] formed a diacetate (2) when treated with Ac<sub>2</sub>O in pyridine and a triacetate (3) when treated with Ac<sub>2</sub>O and TsOH. Cardiopetalidine (4) [C<sub>21</sub>H<sub>33</sub>NO<sub>4</sub>; m.pt 223—227 °C] formed a diacetate (5) when treated with Ac<sub>2</sub>O in pyridine. The X-ray crystal structures of (1) and (4) were determined by direct methods, the final agreement factors being  $R = 0.097$  and  $0.131$ , respectively. These are the first C<sub>19</sub> diterpenoid alkaloids without an oxygen function at C-16 to be reported.



- Cardiopetaline (1)  $R^1 = R^2 = R^3 = R^4 = H$   
 (2)  $R^1 = R^4 = Ac, R^2 = R^3 = H$   
 (3)  $R^1 = R^3 = R^4 = Ac, R^2 = H$   
 Cardiopetalidine (4)  $R^1 = R^3 = R^4 = H, R^2 = OH$   
 (5)  $R^1 = R^4 = Ac, R^2 = OH, R^3 = H$

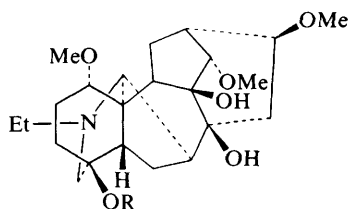
**Alkaloids of *Delphinium cashmirianum* Royle.**—A recent study<sup>8</sup> of the alkaloids from plants of *Delphinium cashmirianum* Royle collected in Kashmir, Pakistan, has demonstrated the presence of six known diterpenoid alkaloids. Lappaconitine (6), *N*-desacetyl-lappaconitine (7), anthranoyl-lycoctonine (8), avadharidine (9), lyaconitine (10), and cashmiradelphine (septentriodine) (11) were isolated from ethanol extracts of the roots of these plants by chromatography, using a column of silica gel. This is the first reported isolation of (6) and (7) from a *Delphinium* species. Prior to the appearance of this publication, (11) had been reported from plants of *Aconitum septentrionale* Koelle and named septentriodine (*cf.* Vol. 10, p. 215).<sup>9</sup> Treatment of anthranoyl-lycoctonine (8) with monomethylsuccinic acid chloride for 16 hours at room temperature afforded cashmiradelphine (septentriodine) (11). Oxidation of lycoctonine (12), which is the hydrolysis product of (8), with pyridinium chlorochromate in CH<sub>2</sub>Cl<sub>2</sub> gave lycoctonal (13).

Studies of the arrhythmogenic effects and the effects on heart rate of aconitine (14), *N*-desacetyl-lappaconitine (7), lappaconitine (6), lycoctonal (13), lycoctonine (12), lappaconine (15), avadharidine (9), lyaconitine (10), anthranoyl-lycoctonine (8), and cashmiradelphine (septentriodine) (11) were also reported.<sup>8</sup> The alkaloids (6), (7), and (15) were found to be arrhythmogenic

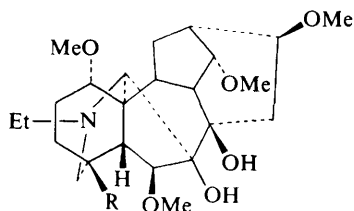
<sup>7</sup> A. G. González, G. de la Fuente, M. Reina, V. Zabel, and W. H. Watson, *Tetrahedron Lett.*, 1980, **21**, 1155.

<sup>8</sup> M. Shamma, P. Chinnasamy, G. A. Miana, A. Khan, M. Bashir, M. Salazar, P. Patil, and J. L. Beal, *J. Nat. Prod.*, 1979, **42**, 615.

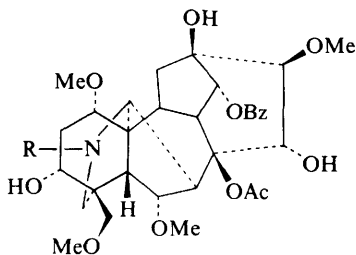
<sup>9</sup> S. W. Pelletier, R. S. Sawhney, and A. J. Aasen, *Heterocycles*, 1979, **12**, 377.



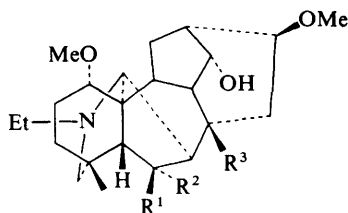
- Lappaconitine (6)  $R = \text{COC}_6\text{H}_4\text{-2-NHAc}$   
*N*-Desacetyl-lappaconitine (7)  $R = \text{COC}_6\text{H}_4\text{-2-NH}_2$   
 Lappaconine (15)  $R = \text{H}$



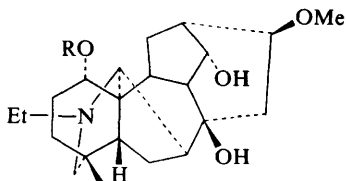
- Anthranoyl-lycoctonine (8)  $R = \text{CH}_2\text{OCOC}_6\text{H}_4\text{-2-NH}_2$   
 Avadharidine (9)  $R = \text{CH}_2\text{OCOC}_6\text{H}_4\text{-2-NHCO(CH}_2)_2\text{CONH}_2$   
 Lyaconitine (10)  $R = \text{CH}_2\text{OCOC}_6\text{H}_4\text{-2-(N-succinimidyl)}$   
 Septentriodine (Cashmiradelphine) (11)  $R = \text{CH}_2\text{OCOC}_6\text{H}_4\text{-2-NHCO(CH}_2)_2\text{CO}_2\text{Me}$   
 Lycoctonine (12)  $R = \text{CH}_2\text{OH}$   
 Lycoctonal (13)  $R = \text{CHO}$



- Aconitine (14)  $R = \text{Et}$   
 Mesaconitine (24)  $R = \text{Me}$



- (16)  $R^1, R^2 = \text{OMe, H}; R^3 = \text{OAc}$   
 (17)  $R^1, R^2 = \text{OH, H}; R^3 = \text{OH}$   
 (18)  $R^1 = \text{H}; R^2 = \text{OAc}; R^3 = \text{OMe}$   
 (19)  $R^1 = \text{H}; R^2 = R^3 = \text{OH}$   
 Alkaloid A (20)  $R^1 = \text{OAc}; R^2 = \text{H}; R^3 = \text{OMe}$   
 Alkaloid B (21)  $R^1 = R^3 = \text{OH}; R^2 = \text{H}$



- Karakoline (Vilmorrianine B) (22)  $R = \text{H}$   
 Vilmorrianine D (23)  $R = \text{Me}$

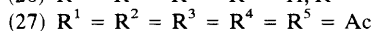
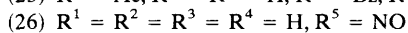
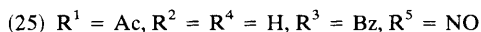
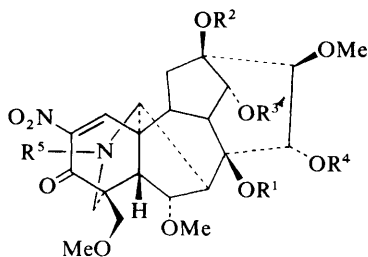
substances, although they were about 100 times less potent than aconitine. Lappaconitine (6) was active at concentrations of  $10^{-4} \text{ mol l}^{-1}$ , and, in contrast to aconitine, it did not increase the heart rate.

**Alkaloids of *Delphinium bicolor* Nutt.**—The structures of alkaloids A and B have been established by an X-ray crystallographic analysis of the hydroiodide salt of alkaloid A and its chemical conversion into alkaloid B.<sup>10</sup> These compounds were originally assigned structures (16) and (17), respectively.<sup>11</sup> On the basis of extensive  $^{13}\text{C}$  n.m.r. studies,<sup>12</sup> the structures of these compounds were revised to (18) and (19), respectively. However, the X-ray crystallographic structure determination of the hydroiodide of alkaloid A revealed that it is the 6 $\beta$ -epimer of (18), i.e. (20).<sup>10</sup> The incorrect assignment from the n.m.r. data resulted from an incorrectly drawn structure for the compounds with which the  $^{13}\text{C}$  n.m.r. signals had been correlated.

On heating alkaloid A (20) with 3M sulphuric acid on a steam bath overnight, alkaloid B (21) was obtained.

**Alkaloids from Plants in the Peoples Republic of China.**—In a report for which the original paper was not available for review, Chinese researchers<sup>13</sup> have determined that vilmorrianine B corresponds to the previously reported karakoline (22). The base vilmorrianine D was identified as (23) from the mass-spectral and  $^{13}\text{C}$  n.m.r. data. From the substantial number of unknown alkaloids previously isolated from Chinese species,<sup>14</sup> the structure elucidation of more of these bases will hopefully be reported in the near future.

**The Structure of Nitro-*N*-nitrosoaconitinic Acid.**—Oxidation of aconitine (14), mesaconitine (24), and their derivatives with nitric acid was reported to yield



[(24) appears with structure (14)]

<sup>10</sup> P. W. Coddington, K. A. Kerr, M. H. Benn, A. J. Jones, S. W. Pelletier, and N. V. Mody, *Tetrahedron Lett.*, 1980, **21**, 127.

<sup>11</sup> A. J. Jones and M. H. Benn, *Can. J. Chem.*, 1973, **51**, 486.

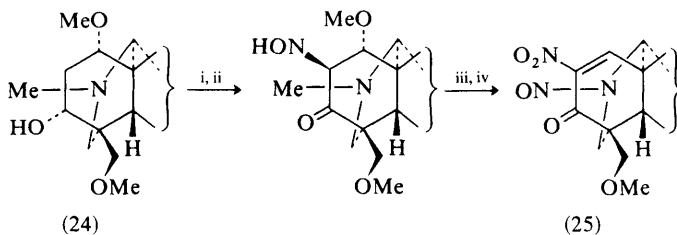
<sup>12</sup> S. W. Pelletier, N. V. Mody, A. J. Jones, and M. H. Benn, *Tetrahedron Lett.*, 1976, 3025.

<sup>13</sup> T.-R. Yang, X.-J. Hao, and J. Chow, *Yun-nan Chih Wu Yen Chin*, 1979, **1**, 41 (*Chem. Abstr.*, 1980, **93**, 46 909).

<sup>14</sup> S. W. Pelletier and L. H. Kieth, in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1970, Vol. 12, Ch. 1, p. 120.



nitro-*N*-nitroso-derivatives as early as 1913.<sup>15</sup> Several subsequent investigations<sup>16</sup> failed in assigning structures for these products. Recent work,<sup>17,18</sup> employing i.r., u.v., mass, and <sup>1</sup>H and <sup>13</sup>C n.m.r. analysis, has enabled Japanese workers to propose structure (25) for this product. Alkaline hydrolysis of (25) gave (26). Acetylation of (26) with acetyl chloride afforded (27). Correlation of the <sup>13</sup>C n.m.r. signals of (25), (26), and (27) with those of aconitine and related alkaloids<sup>19</sup> greatly facilitated the structural assignments. Since (25) could also be obtained from (24)<sup>20</sup> as indicated in Scheme 1, the location of the nitro-group at C-2 could be confirmed.



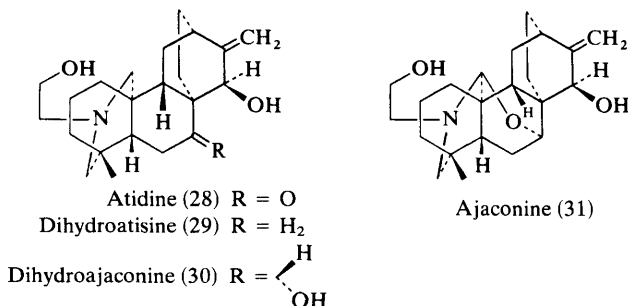
Reagents: i, CrO<sub>3</sub>; ii, C<sub>5</sub>H<sub>11</sub>ONO; iii, N<sub>2</sub>O<sub>3</sub>; iv, HNO<sub>3</sub>

Scheme 1

This novel 2-nitrocyclohex-2-en-1-one system has a p*K*<sub>a</sub> value comparable to those of carboxylic acids.

### 3 C<sub>20</sub> Diterpenoid Alkaloids

**The Structure of Atidine.**—An X-ray crystallographic analysis of atidine [C<sub>22</sub>H<sub>33</sub>NO<sub>3</sub>; m.pt 182.3—183.5 °C] has been reported.<sup>21</sup> This compound has been isolated from plants of *Aconitum heterophyllum* Wall. Its structure was solved by direct phasing methods and refined to a final *R* of 0.045. Since atidine



<sup>15</sup> O. L. Brady, *J. Chem. Soc.*, 1913, **103**, 1821.

<sup>16</sup> cf. E. S. Stern, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1954, Vol. 4, Ch. 37, p. 303.

<sup>17</sup> T. Amiya, Y. Kanaiwa, H. Bando, N. Nakano, and H. Sugimoto, *Chem. Lett.*, 1979, 1163.

<sup>18</sup> T. Amiya, Y. Kanaiwa, H. Bando, N. Nakano, T. Mori, and H. Sugimoto, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1381.

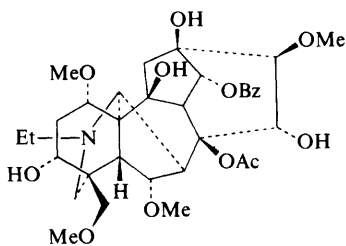
<sup>19</sup> S. W. Pelletier and Z. Djarmati, *J. Am. Chem. Soc.*, 1976, **98**, 2626.

<sup>20</sup> R. Majima and K. Tamura, *Liebigs Ann. Chem.*, 1940, **545**, 1.

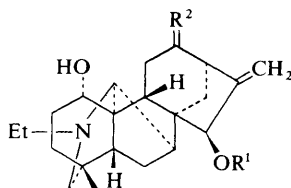
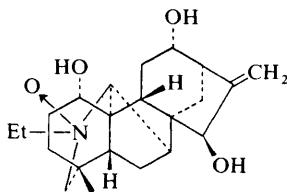
<sup>21</sup> J. Finer-Moore, N. V. Mody, R. S. Sawhney, and S. W. Pelletier, *Cryst. Struct. Commun.*, 1979, **8**, 649.

(28) had been correlated with dihydroatisine (29), it has the absolute configuration previously determined for (29).<sup>22</sup> From the correlations of atidine with dihydroajaconine (30) and ajaconine (31),<sup>23</sup> this structure determination serves to confirm the structures of these alkaloids.

**Alkaloids of *Aconitum karakolicum*.**—Soviet workers at Tashkent have reported a study of the dynamics of the accumulation of alkaloids in the epigeal parts of plants of *Aconitum karakolicum* collected in the Kirghiz S.S.R.<sup>24</sup> The percentages of total alkaloids by dry weight were 1.13 for the early period (May 12), 0.26 for the budding period (July 10), 0.22 for the flowering period (August 5), and 0.17 for the seed-ripening period (August 25). Aconitine (14), aconifine (32), 12-acetylnapelline (33), songorine (34), napelline (35), napelline *N*-oxide (36), and the aporphine alkaloid isoboldine were isolated from plants collected



Aconifine (32)

12-Acetylnapelline (33)  $R^1 = \text{Ac}$ ,  $R^2 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}$ Songorine (34)  $R^1 = \text{H}$ ,  $R^2 = \text{O}$ Napelline (35)  $R^1 = \text{H}$ ,  $R^2 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}$ Napelline *N*-oxide (36)

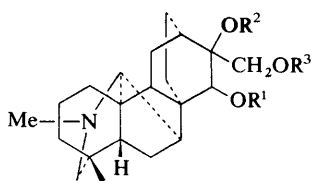
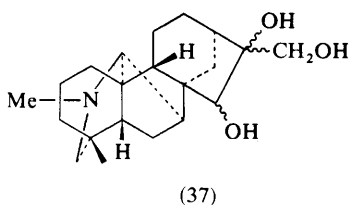
during the early period. This is the first report of the isolation of the *N*-oxide of napelline from plant material. The structure of this base was determined by i.r., n.m.r., and mass-spectral analyses and by its conversion into napelline (35) by reduction with  $\text{FeSO}_4$ . These same alkaloids, with the exception of aconifine (32), were isolated during the budding phase. The largest amounts of (33), (34), and (35) were observed in the early period. As the plants developed, the quantities of napelline *N*-oxide (36) increased as the quantities of napelline (35) decreased.

<sup>22</sup> S. W. Pelletier, W. H. DeCamp, and N. V. Mody, *J. Am. Chem. Soc.*, 1978, **100**, 7976.

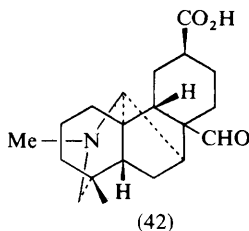
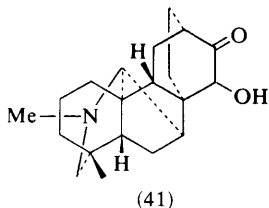
<sup>23</sup> D. Dvornik and O. E. Edwards, *Tetrahedron*, 1961, **14**, 54.

<sup>24</sup> M. N. Sultankhodzhaev, L. V. Beshitashvili, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Priro. Soedin.*, 1979, 826.

**Alkaloids of *Delphinium dictyocarpum* DC.**—Dictysine [ $C_{21}H_{33}NO_3$ ; m.pt 184—186 °C] has been assigned structure (37) on the basis of chemical and spectroscopic studies.<sup>25a</sup> An unpublished X-ray analysis<sup>25b</sup> demonstrates that (37) is incorrect and that the structure should be as shown in (37a). Derivatives of dictysine (38)—(42) are shown here as the corrected structures. This alkaloid was isolated from the epigeal parts of *Delphinium dictyocarpum* DC.<sup>26</sup> On acetylation of dictysine with acetyl chloride, the triacetate (38) and the two diacetates, (39) and (40), were obtained. The reaction of dictysine with one molar equivalent of periodic acid for three hours gave the  $\alpha$ -hydroxy-ketone (41), while treatment with excess periodic acid for three days yielded the aldehyde carboxylic acid (42). These structures were supported by mass-spectral, i.r., and  $^1H$  and  $^{13}C$  n.m.r. analyses. This is the first example of a  $C_{20}$  diterpenoid alkaloid which contains hydroxyl groups at C-16 and C-17.



Dictysine (37a)  $R^1 = R^2 = R^3 = H$   
 (38)  $R^1 = R^2 = R^3 = Ac$   
 (39)  $R^1 = R^3 = Ac, R^2 = H$   
 (40)  $R^1 = H, R^2 = R^3 = Ac$



**Revision of the Structure of Cuauchichicine.**—Cuauchichicine, a minor alkaloidal constituent of the leaves and bark of *Garra ovata* var. *lindheimeri*, had been assigned structure (43) on the basis of a chemical correlation with (–)- $\beta'$ -dihydrokaurene (44).<sup>27</sup> On the basis of  $^{13}C$  n.m.r. spectral studies and an X-ray crystallographic analysis, cuauchichicine has been determined to be the C-16 and C-20 epimer (45) of the originally assigned structure.<sup>28</sup>

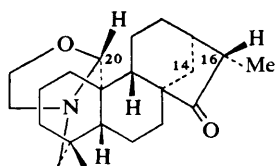
Comparison of the  $^1H$  and  $^{13}C$  n.m.r. data of cuauchichicine and related diterpenoids indicates that cuauchichicine exists as a single C-20 epimer, with the proton at C-20 in the  $\alpha$ -configuration. To establish the stereochemistry at

<sup>25</sup> (a) B. T. Salimov, M. S. Yunusov, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1979, 812; (b) M. S. Yunusov, personal communication, received 31 December 1980.

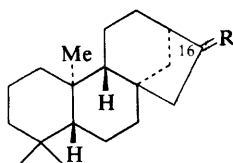
<sup>26</sup> B. T. Salimov, N. D. Abdullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1978, 235.

<sup>27</sup> H. Vorbruegggen and C. Djerassi, *J. Am. Chem. Soc.*, 1962, **84**, 2990.

<sup>28</sup> S. W. Pelletier, H. K. Desai, J. Finer-Moore, and N. V. Mody, *J. Am. Chem. Soc.*, 1979, **101**, 6741.

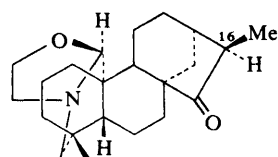


(43)

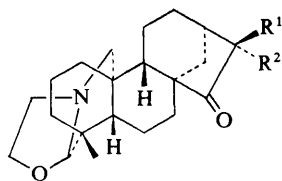


(-)-β'-Dihydrokaurene (44)  $R = \begin{array}{c} \text{H} \\ \diagup \\ \text{Me} \end{array}$

(-)-α'-Dihydrokaurene (50)  $R = \begin{array}{c} \text{Me} \\ \diagup \\ \text{H} \end{array}$

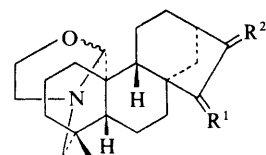


Cuauchichicine (45)



Isocuauchichicine (46)  $R^1 = \text{Me}, R^2 = \text{H}$

(47)  $R^1 = \text{H}, R^2 = \text{Me}$



Veatchine (48)  $R^1 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}, R^2 = \text{CH}_2$

Garryfoline (51)  $R^1 = \begin{array}{c} \text{H} \\ \diagup \\ \text{OH} \end{array}, R^2 = \text{CH}_2$

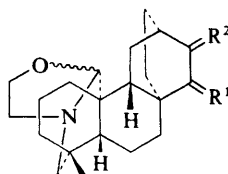
Veatchinone (53)  $R^1 = \text{O}, R^2 = \text{CH}_2$

(80)  $R^1 = \begin{array}{c} \text{H} \\ \diagup \\ \text{OH} \end{array}, R^2 = \begin{array}{c} \text{H} \\ \diagup \\ \text{Me} \end{array}$

(82)  $R^1 = \begin{array}{c} \text{H} \\ \diagup \\ \text{OH} \end{array}, R^2 = \begin{array}{c} \text{Me} \\ \diagup \\ \text{H} \end{array}$

(84)  $R^1 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}, R^2 = \begin{array}{c} \text{Me} \\ \diagup \\ \text{H} \end{array}$

Ovatine (89)  $R^1 = \begin{array}{c} \text{OAc} \\ \diagup \\ \text{H} \end{array}, R^2 = \text{CH}_2$



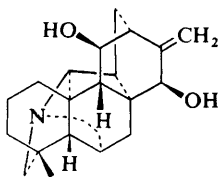
Atisine (49)  $R^1 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}, R^2 = \text{CH}_2$

(77)  $R^1 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}, R^2 = \begin{array}{c} \text{Me} \\ \diagup \\ \text{H} \end{array}$

(78)  $R^1 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}, R^2 = \begin{array}{c} \text{H} \\ \diagup \\ \text{Me} \end{array}$

(79)  $R^1 = \text{O}, R^2 = \begin{array}{c} \text{Me} \\ \diagup \\ \text{H} \end{array}$

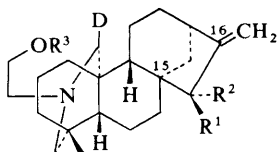
Atisinone (87)  $R^1 = \text{O}, R^2 = \text{CH}_2$



Kobusine (52)

C-16 by n.m.r. methods, isocuauchichicine (46) and its C-16 epimer (47) were prepared. From spectral comparisons and molecular-model considerations, the 16-methyl group in cuauchichicine was assigned the  $\beta$ -configuration. These structural assignments were confirmed by a single-crystal *X*-ray analysis (final  $R = 0.071$ ), using direct phasing methods. One of the protons attached to C-14 is much closer to the  $\alpha$ -side of C-20 in (45) than in veatchine (48) (which exists as C-20 epimers). This close contact may prevent the ring-closure to the other cuauchichicine epimer during isolation from its ternary iminium salt. Since veatchine (48) has been correlated with cuauchichicine and with atisine (49), cuauchichicine has the same absolute configuration as determined for atisine.

The structural studies of cuauchichicine indicate that either the structure assigned to  $(-)\text{-}\beta'$ -dihydrokaurene (44) is incorrect, or epimerization at C-16 had occurred during the correlation sequence. To distinguish between these alternatives, and since almost 100 compounds had been correlated with  $(-)\text{-}\beta'$ -dihydrokaurene (44), further structural investigations of this compound were carried out.

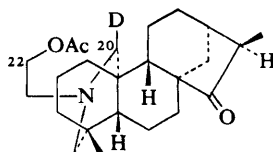


(54)  $R^1 = OD, R^2 = D, R^3 = H(D)$

(55)  $R^1 = D, R^2 = OD, R^3 = H(D)$

(56)  $R^1 = OAc, R^2 = D, R^3 = Ac$

(57)  $R^1 = D, R^2 = OAc, R^3 = Ac$



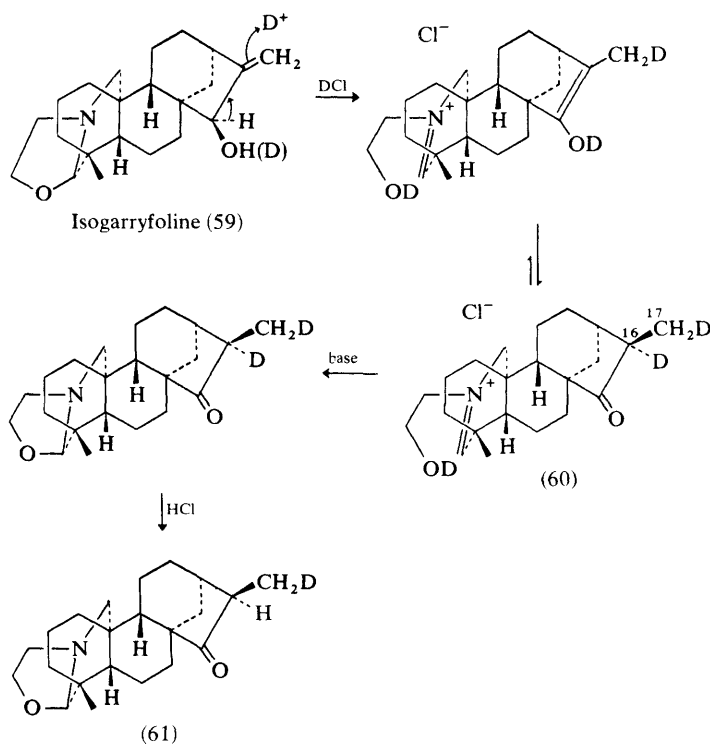
(58)

Hydrogenation of *ent*-kaurene gave  $(-)\text{-}\alpha'$ -dihydrokaurene (50) as the major product and the  $(-)\text{-}\beta'$ -isomer (44) in a yield that was too small to permit its isolation. An *X*-ray crystallographic analysis of crystals of  $(-)\text{-}\alpha'$ -dihydrokaurene determined that its structure is (50) ( $R = 0.054$ ). Therefore, the structure of  $(-)\text{-}\beta'$ -dihydrokaurene (44) is as originally assigned. The epimerization at C-16 most probably occurs during the Wolff-Kishner reduction of the intermediate ketone in the degradation of cuauchichicine to (44). From these data, the previously assigned<sup>27</sup> stereochemistry of the 16-methyl group for the degradation products of cuauchichicine (45), garryfoline (51), and veatchine must be revised.

**The Mechanism of the Garryfoline-Cuauchichicine Rearrangement.**—The acid-catalysed rearrangement of garryfoline (51) and of other  $C_{20}$  diterpenoid

alkaloids with a  $15\beta$ -ol substituent, *e.g.* atisine (49), kobusine (52), or napelline (35), to the corresponding 15-one-16 $\beta$ -methyl compounds has attracted considerable mechanistic interest since it was first reported in 1955.<sup>29</sup> The  $15\alpha$ -ol isomers, *e.g.* veatchine (48), are stable even on heating in dilute hydrochloric acid. Non-classical carbonium ion<sup>30</sup> and 1,2-hydride-shift<sup>31</sup> mechanisms have been proposed. Recent studies, including  $^{13}\text{C}$  n.m.r. spectral analysis, have provided strong evidence in support of a mechanism involving enolization, followed by *exo*-protonation of the enol.<sup>32</sup>

Oxidation of veatchine (48) with Sarett reagent gave veatchinone (53), which, when reduced with  $\text{NaBD}_4$  in  $\text{CH}_3\text{OH}$ , afforded an epimeric mixture of (54) and (55). This mixture was acetylated with acetic anhydride in pyridine and the acetates, (56) and (57), were separated by preparative-scale t.l.c. Treatment of (56) with 10%  $\text{HCl}$  and re-acetylation gave (58). The  $^{13}\text{C}$  n.m.r. data indicated that there was no deuterium present at C-16 in (58); therefore, this rearrangement did not take place by a  $15 \rightarrow 16$  hydride shift.



**Scheme 2**

<sup>29</sup> C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor, and J. Herran, *J. Am. Chem. Soc.*, 1955, **77**, 4801, 6633.

<sup>30</sup> K. Wiesner and Z. Valenta, *Fortschr. Chem. Org. Naturstoffe*, 1958, **16**, 26.

<sup>31</sup> M. F. Barnes and J. MacMillan, *J. Chem. Soc., C*, 1967, 361.

<sup>32</sup> S. W. Pelletier, H. K. Desai, and N. V. Mody, *Heterocycles*, 1979, **13**, 277.

Treatment of isogarryfoline (59) with 10% DCl in D<sub>2</sub>O gave (60). The n.m.r. spectra of (60) revealed deuterium substitution at C-16 and C-17. The mechanism outlined in Scheme 2 accounts for this observation and explains the stereochemistry observed; *i.e.*, D<sup>+</sup> is transferred from the less-hindered *exo* side during ketonization. When (60) was treated with dilute HCl, no deuterium exchange by hydrogen was observed in 24 hours. However, after 96 hours, (61) was obtained. This result further supports an enol-ketone mechanism.

**Conversions of the Oxazolidine Rings in C<sub>20</sub> Diterpenoid Alkaloids.**—Several studies of the formation and opening of the oxazolidine ring system in the C<sub>20</sub> diterpenoid alkaloids have been reported.<sup>33—35</sup>

The formation of the 'iso-type' of oxazolidine ring, *e.g.* in isoatisine (69), was accomplished by the reaction of compounds that contained the *N*-CH<sub>2</sub>CH<sub>2</sub>OH group with silver oxide in 75% ethanol or methanol.<sup>33</sup> The yields of this cyclization reaction are shown in Table 1. No 'normal-type' [C(20)—O—] oxazolidines were detected as cyclization products. For formation of both the 'iso' and 'normal' oxazolidine ring systems from the *N*-CH<sub>2</sub>CH<sub>2</sub>OH compounds, an efficient method utilizing alkaline potassium ferricyanide has been developed.<sup>34</sup> The ratios of products and yields are shown in Table 1. The products could be separated by column chromatography on alumina or by pH extraction. Both silver oxide and potassium ferricyanide failed to cyclize *N*-piperidine-ethanol. This result was attributed to the requirement of a conformationally rigid system with a geometry that is favourable for ring-closure.

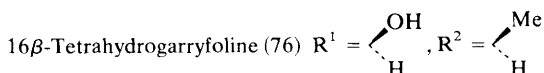
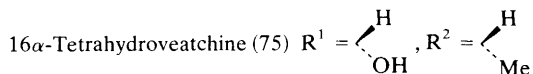
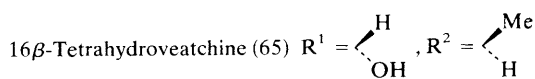
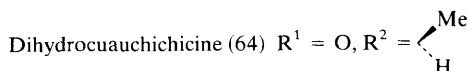
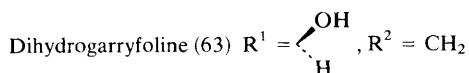
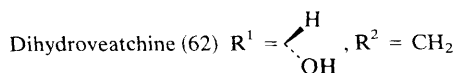
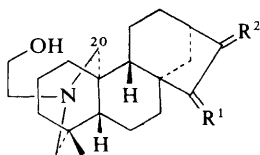
**Table 1** Comparison of the yields of 'iso' and 'normal' types of oxazolidine ring when alkaloids are oxidized with silver oxide and with potassium ferricyanide

Substrate	Ag <sub>2</sub> O (ref. 33)	K <sub>3</sub> [Fe(CN) <sub>6</sub> ] (ref. 34)	
	Yield of 'iso'-compound	'Normal': 'Iso'	Total yield
Dihydroveatchine (62)	78% of (70)	54:46 [(48), (70)]	95%
Dihydrogarryfoline (63)	76% of (59)	46:53 [(51), (59)]	83%
Dihydroatisine (29)	90% of (69)	51:49 [(49), (69)]	82%
Dihydrocuauchichicine (64)	76% of (46)	35:65 [(45), (46)]	60%
'α'-Tetrahydroatisine (67)	72% of (73)	45:55 [(77), (73)]	72%
'β'-Tetrahydroatisine (68)	72% of (74)	49:51 [(78), (74)]	91%
15-Ketotetrahydroatisine (66)	83% of (72)	45:55 [(79), (72)]	76%
16α-Tetrahydroveatchine (75)	—	48:52 [(80), (81)]	74%
16β-Tetrahydroveatchine (65)	79% of (71)	56:44 [(82), (71)]	72%
16β-Tetrahydrogarryfoline (76)	—	55:45 [(84), (85)]	83%

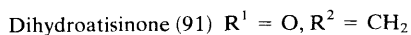
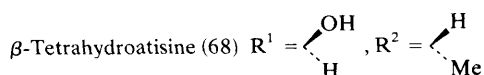
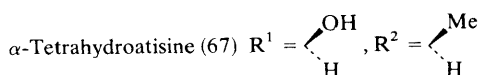
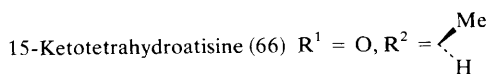
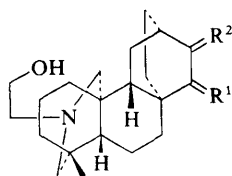
The selective reduction of the oxazolidine ring to the *N*-CH<sub>2</sub>CH<sub>2</sub>OH group in the presence of the αβ-unsaturated ketone in compounds such as veatchinone (53) had presented considerable synthetic difficulties. This conversion has now

<sup>33</sup> S. W. Pelletier, A.-M. M. Ateya, N. V. Mody, and L. C. Schramm, *Heterocycles*, 1980, **14**, 1155.

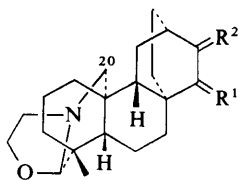
<sup>34</sup> S. W. Pelletier, A.-M. M. Ateya, N. V. Mody, H. K. Desai, and L. C. Schramm, *Tetrahedron Lett.*, 1980, **21**, 3647.



[(77)—(79) are with (49); (80) is with (48)]







Isoatisine (69)  $R^1 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}$ ,  $R^2 = \text{CH}_2$

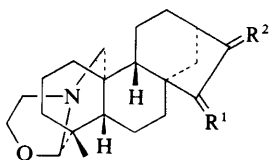
(72)  $R^1 = \text{O}$ ,  $R^2 = \begin{array}{c} \text{Me} \\ \diagup \\ \text{H} \end{array}$

(73)  $R^1 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}$ ,  $R^2 = \begin{array}{c} \text{Me} \\ \diagup \\ \text{H} \end{array}$

(74)  $R^1 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}$ ,  $R^2 = \begin{array}{c} \text{H} \\ \diagup \\ \text{Me} \end{array}$

Isoatisinone (88)  $R^1 = \text{O}$ ,  $R^2 = \text{CH}_2$

[(89) is with structure (48)]



Garryine (70)  $R^1 = \begin{array}{c} \text{H} \\ \diagup \\ \text{OH} \end{array}$ ,  $R^2 = \text{CH}_2$

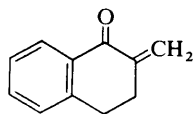
(71)  $R^1 = \begin{array}{c} \text{H} \\ \diagup \\ \text{OH} \end{array}$ ,  $R^2 = \begin{array}{c} \text{Me} \\ \diagup \\ \text{H} \end{array}$

(81)  $R^1 = \begin{array}{c} \text{H} \\ \diagup \\ \text{OH} \end{array}$ ,  $R^2 = \begin{array}{c} \text{H} \\ \diagup \\ \text{Me} \end{array}$

(85)  $R^1 = \begin{array}{c} \text{OH} \\ \diagup \\ \text{H} \end{array}$ ,  $R^2 = \begin{array}{c} \text{Me} \\ \diagup \\ \text{H} \end{array}$

Garryinone (86)  $R^1 = \text{O}$ ,  $R^2 = \text{CH}_2$

[(82) is with (48); (87) is with (49)]

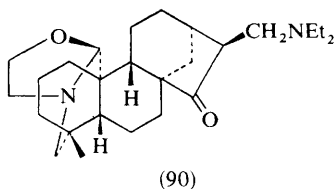


(83)

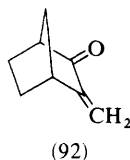
[(84) is with structure (48)]

been accomplished from both the 'iso' and 'normal' compounds, using sodium cyanoborohydride in methanol at 25 °C and maintaining the pH at 6–7 with 10% HCl.<sup>35</sup> Veatchinone (53), garryinone (86), atisinone (87), isoatsinone (88), cuauchichicine (45), isocuauchichicine (46), and ovatine (89) were reduced to the corresponding dihydro-derivatives in essentially quantitative yields.

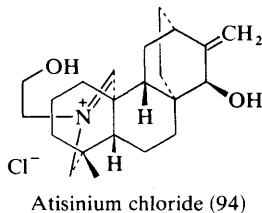
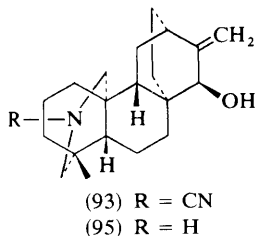
**Michael Addition of Secondary Amines to Atisinone and Other Exocyclic  $\alpha\beta$ -Unsaturated Ketones.**—During investigation of the chemistry of the C<sub>20</sub> diterpenoid alkaloids, an alumina-catalysed Michael addition (using alumina of activity III) of diethylamine to veatchinone (53), giving (90) in quantitative yield, was observed.<sup>36</sup> This reaction did not proceed in the absence of alumina or with alumina of activity I. The structure of (90) was established by mass-spectral and by i.r. and <sup>1</sup>H and <sup>13</sup>C n.m.r. spectroscopic studies, and was confirmed by an X-ray crystallographic analysis. While the addition of secondary amines to  $\alpha\beta$ -unsaturated compounds in general proceeds without catalyst, in the case of exocyclic  $\alpha\beta$ -unsaturated ketones this reaction either gives low yields or does not occur in the absence of a catalyst. Analogous products and yields were obtained from atisinone (87), dihydroatsinone (91), 2-methylene-1-tetralone (83), and 3-methylenenorbornanone (92). From these and from studies with other secondary amines, this reaction appears to be of general scope.



[(91) is with structure (66)]



**The von Braun Reaction with Dihydroatsinine.**—Indian researchers<sup>37</sup> have reported a study of the von Braun reaction of dihydroatsinine (29) and a mass spectral analysis of the resulting product, the *N*-nitrile (93). Reduction of atisinium chloride (94) with sodium borohydride gave dihydroatsinine (29). The reaction of the latter with cyanogen bromide in anhydrous ether at room temperature for 24 hours gave (93) [m.pt 265 °C] in a yield of 86%. Acid hydrolysis of (93) with 10% HCl afforded compound (95).



<sup>35</sup> S. W. Pelletier, N. V. Mody, A. P. Venkov, and H. K. Desai, *Tetrahedron Lett.*, 1979, 4939.

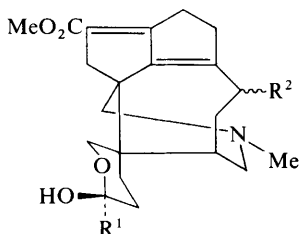
<sup>36</sup> S. W. Pelletier, A. P. Venkov, J. Finer-Moore, and N. V. Mody, *Tetrahedron Lett.*, 1980, **21**, 809.

<sup>37</sup> M. Rai and A. Singh, *J. Indian Chem. Soc.*, 1979, **56**, 433.

**Quantitation of Napelline.**—The pharmacological activity of napelline (35)<sup>38</sup> has prompted the development of a method for the quantitation of this alkaloid in raw plant materials.<sup>39</sup> This method consists of the extraction of the total alkaloids, chromatographic separation, and a micro-scale acid–base titration of the napelline eluate in a non-aqueous medium. The total alkaloids were exhaustively extracted from a sodium carbonate suspension with chloroform. This extract was concentrated, dissolved in acetone, and chromatographed on silica-gel plates, with a standard reference of napelline as a marker. The appropriate bands were quantitatively removed and extracted, and the extracts were concentrated to dryness. These residues were dissolved in glacial acetic acid and titrated with 0.01N perchloric acid. The standard deviation of this method was  $\pm 3.39 \times 10^{-3}$ . No limits of detection are reported.

#### 4 *Daphniphyllum* Alkaloids

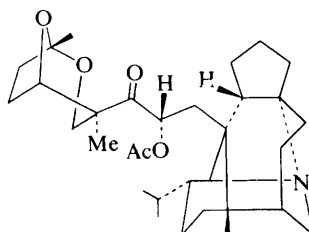
**Alkaloids of *Daphniphyllum gracile* Gage.**—Three new alkaloids have been isolated from the bark of plants of *Daphniphyllum gracile* Gage growing in New Guinea.<sup>2</sup> The structures of daphgracine (96), daphgraciline (97), and hydroxydaphgraciline (98) were assigned from the spectral data. The overall yields of these compounds (calculated from the dry weight of the bark) were 0.00009, 0.0003, and 0.00008%, respectively. The known alkaloids daphniphylline (99)



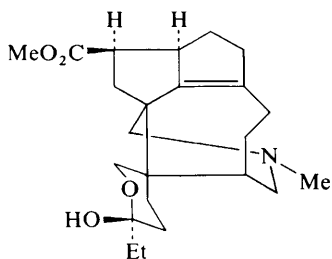
Daphgracine (96)  $R^1 = \text{Pr}^i$ ,  $R^2 = \text{H}$

Daphgraciline (97)  $R^1 = \text{Et}$ ,  $R^2 = \text{H}$

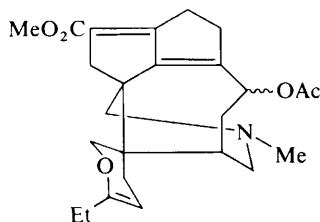
Hydroxydaphgraciline (98)  $R^1 = \text{Et}$ ,  $R^2 = \text{OH}$



Daphniphylline (99)



Daphnigraciline (100)

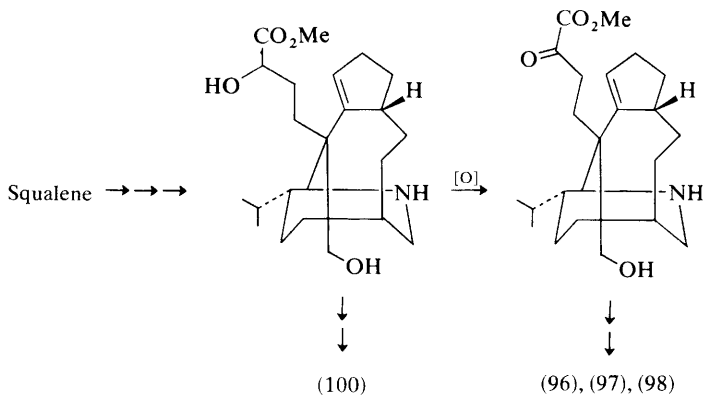


(101)

<sup>38</sup> F. N. Dzhakhangirov and F. S. Sadritdinov, *Dokl. Akad. Nauk Uzb. SSR*, 1977, 3.

<sup>39</sup> L. V. Beshitaishvili, D. A. Rakhimova, E. K. Dobronravova, T. T. Shakirov, and M. S. Yunusov, *Khim. Pri. Soedin.*, 1979, 872.

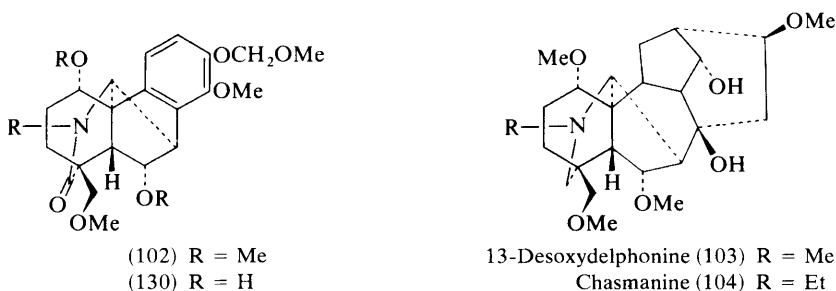
and daphnigraciline (100) were isolated from the bark in overall yields of 0.0001 and 0.00009%, respectively. Treatment of hydroxydaphnigraciline (98) with acetic anhydride and acetic acid afforded a dehydrated monoacetate (101). A biosynthetic route for the formation of (96), (97), and (98) from squalene has been proposed (Scheme 3).



Scheme 3

## 5 Synthetic Studies

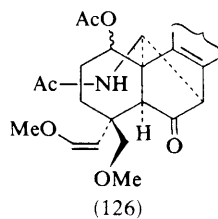
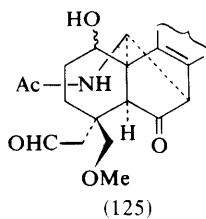
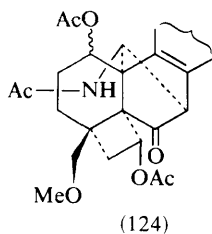
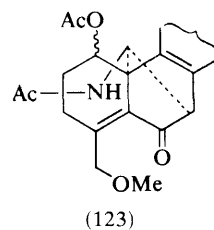
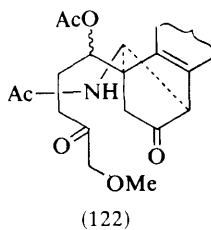
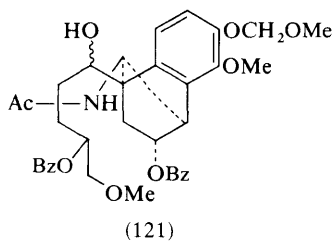
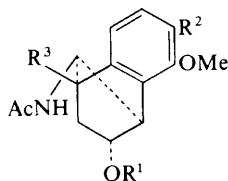
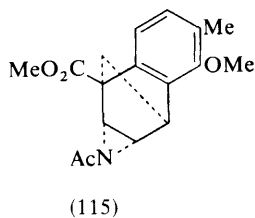
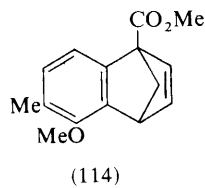
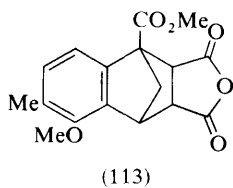
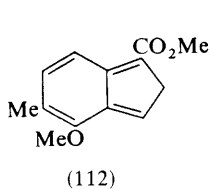
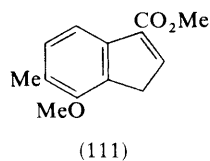
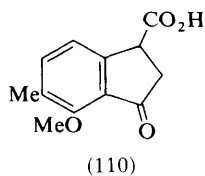
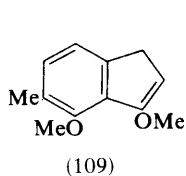
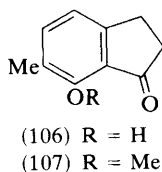
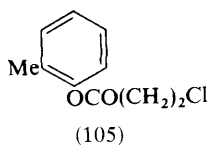
**An Improved Synthesis of 13-Desoxydelphonine and Chasmanine.**—Wiesner and co-workers<sup>40,41</sup> have reported a more efficient synthesis of (102). This intermediate (102) has been used in the synthesis of 13-desoxydelphonine (103)

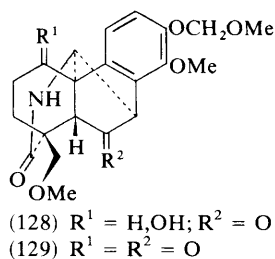
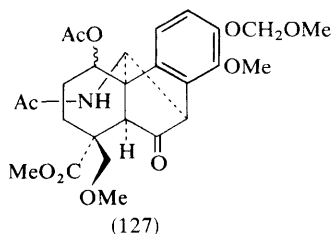


and chasmanine (104). Cresol was converted into (105) by treatment with 3-chloropropionyl chloride in benzene. The reaction of (105) with  $\text{AlCl}_3$  gave (106). This indanone was methylated with dimethyl sulphate and  $\text{K}_2\text{CO}_3$  to yield (107). Conversion of (107) into the dimethyl acetal (108) with trimethyl orthoformate and Rexyn 101, followed by pyrolytic elimination in refluxing *o*-xylene, gave (109). Treatment of (109) with *n*-butyl-lithium and  $\text{CO}_2$  in THF, followed by hydrolysis, afforded the keto-acid (110). Reduction of (110) with borohydride, followed by dehydration with phosphoric acid and esterification, gave (111).

<sup>40</sup> T. Y. R. Tsai, K. P. Nambiar, D. Krikorian, M. Botta, R. Marini-Bettolo, and K. Wiesner, *Can. J. Chem.*, 1979, **57**, 2124.

<sup>41</sup> K. Wiesner, *Pure Appl. Chem.*, 1979, **51**, 689.





[(130) is with structure (102)]

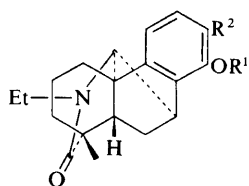
Addition of maleic anhydride to the thermal tautomer (112) of (111) yielded the adduct (113). This compound was decarboxylated to the tricyclic olefin (114) with bis(triphenylphosphine)nickel dicarbonyl in diglyme. The acetylaziridine (115) was prepared from (114) by treatment with trimethylsilyl azide followed by acetic anhydride and acetic acid. This aziridine rearranged *in situ* to (116) when heated at 85 °C for several days. Oxidation of (116) with ceric ammonium nitrate gave the aldehyde (117). Methanolysis of (117), followed by benzylation, yielded the benzyl ether (118). The aldehyde group in (118) was converted into the phenol (119) by treatment with *m*-chloroperoxybenzoic acid and methanolysis of the resulting formate ester. Protection of this phenol (119) with chloromethyl methyl ether and conversion of the carbomethoxyl group by reduction with borohydride and re-oxidation with DMSO and DCC gave (120). Treatment of (120) with excess 3-benzyloxy-4-methoxy-*n*-butylmagnesium bromide furnished a mixture of the epimeric alcohols (121). Acetylation of (121), followed by hydrogenolysis and then oxidation with the  $\text{CrO}_3$ -pyridine complex in  $\text{CH}_2\text{Cl}_2$ , afforded the epimeric diketones (122). Heating (122) in  $\text{K}_2\text{CO}_3$  produced the  $\alpha\beta$ -unsaturated ketone (123) in 90% yield. The photoaddition of vinyl acetate to (123) gave the epimers (124). Basic hydrolysis of (124) was accompanied by a retro-aldol cleavage to yield (125). Conversion of (125) into the dimethyl acetal, acetylation, and heating in a mixture of *o*-xylene and pyridine gave (126). Oxidation of (126) with permanganate and periodate and esterification of the resulting acid with diazomethane yielded (127). Refluxing (127) with dilute methanolic sodium methoxide gave the lactam (128) with the desired *trans* A/B-ring junction. Oxidation of (128) with the  $\text{CrO}_3$ -pyridine complex in  $\text{CH}_2\text{Cl}_2$  gave the diketo-lactam (129). This compound was reduced with *t*-butoxyaluminum hydride and the resulting diol (130) was then methylated with sodium hydride and methyl iodide to afford (102). This compound was identical with the same intermediate obtained from vanillin<sup>42</sup> (*cf.* Vol. 9, p. 233).

**The Total Synthesis of Diacetyloxodenudatine.**—Wiesner and co-workers<sup>43</sup> have reported the conversion of (131) into racemic diacetyloxodenudatine (132). This phenol (131) had been prepared previously by the aziridine synthesis<sup>44</sup> (*cf.* Vol. 4, p. 342).

<sup>42</sup> K. Wiesner, T. Y. R. Tsai, and K. P. Nambiar, *Can. J. Chem.*, 1978, **56**, 1451.

<sup>43</sup> S. P. Sethi, R. Sterzycki, W. H. Sy, R. Marini-Bettolo, T. Y. R. Tsai, and K. Wiesner, *Heterocycles*, 1980, **14**, 23.

<sup>44</sup> K. Wiesner, *Chem. Soc. Rev.*, 1977, **6**, 413.



(131)  $R^1 = R^2 = H$

(133)  $R^1 = CH_2CH=CH_2$ ,  $R^2 = H$

(134)  $R^1 = H$ ,  $R^2 = CH_2CH=CH_2$

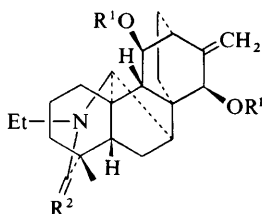
(135)  $R^1 = CH_2CO_2Me$ ,  $R^2 = CH_2CH=CH_2$

(136)  $R^1 = CH_2CO_2Me$ ,  $R^2 = CH=CH\sim Me$

(137)  $R^1 = CH_2CO_2Me$ ,  $R^2 = CHO$

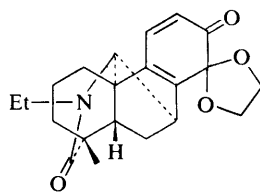
(138)  $R^1 = CH_2CO_2Me$ ,  $R^2 = OCHO$

(139)  $R^1 = CH_2CH_2OH$ ,  $R^2 = OH$

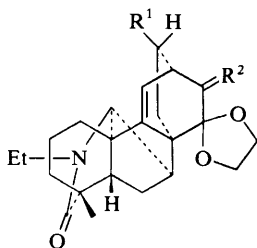


Diacetyloxodenudatine (132)  $R^1 = Ac$ ,  $R^2 = O$

Denudatine (149)  $R^1 = H$ ,  $R^2 = H_2$



(140)

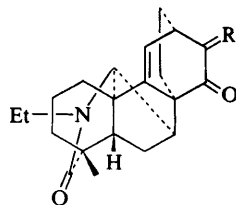


(141)  $R^1 = SEt$ ;  $R^2 = O$

(142)  $R^1 = H$ ;  $R^2 = H, OH$

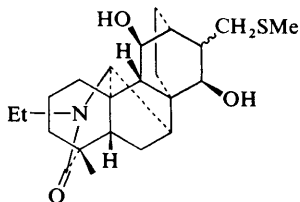
(143)  $R^1 = H$ ;  $R^2 = O$

(144)  $R^1 = H$ ;  $R^2 = OH, CHSiMe_3$

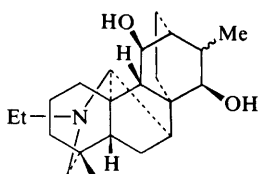


(145)  $R = CH_2$

(146)  $R = H, CH_2SMe$



(147)

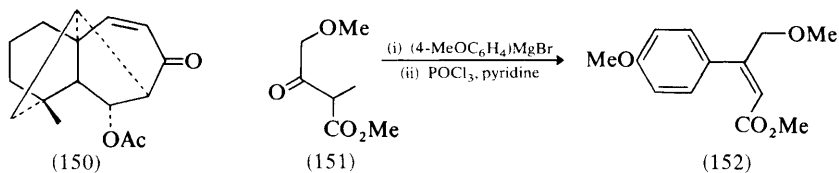


(148)

[(149) is with structure (132)]

Treatment of (131) with allyl bromide in dry acetone with  $K_2CO_3$  and 18-crown-6 gave the allyl ether (133). When heated at 200 °C in *NN*-dimethylaniline for 48 hours, (133) underwent a Claisen rearrangement to (134). This phenol was alkylated with methyl bromoacetate to afford the ester (135). Isomerization of the latter with  $[(PhCN)_2PdCl_2]$  in refluxing benzene gave a mixture of *cis*- and *trans*-olefins (136). Oxidation of (136) with osmium tetroxide in aqueous dioxan gave the aldehyde (137). Oxidation of (137) with *m*-chloroperbenzoic acid in  $CH_2Cl_2$  (Baeyer–Villiger) yielded the unstable formate (138), which was immediately reduced with  $LiBH_4$  in THF to the phenol-alcohol (139). Oxidation of (139) with  $Tl(NO_3)_3$  and  $CaCO_3$  in dry THF at 0 °C gave the *ortho*-quinone acetal (140). Treatment of (140) with excess ethyl vinyl thioether for 20 hours at 40 °C gave, after isolation by preparative t.l.c., the adduct (141). Reduction of (141) with sodium borohydride, followed by desulphurization with Raney nickel, afforded (142). Oxidation of (142) with the  $CrO_3$ –pyridine complex in  $CH_2Cl_2$  gave the keto-acetal (143), which was reduced with excess  $Me_3SiCH_2MgCl$  in THF to give (144). Treatment of (144) with  $HClO_4$  in THF yielded the dienone (145). This compound was converted into the thioether (146) when treated with  $MeSH$  and  $Na_3BO_3$  in aqueous THF. Hydroboration of (146) with excess  $B_2H_6$ , followed by oxidation with  $H_2O_2$ , gave, after isolation by preparative t.l.c., the diol (147). Acetylation of (147), oxidation to the sulphoxide with  $NaIO_4$ , and pyrolysis in refluxing *o*-xylene for 24 hours gave the racemate (132). This compound was spectrally and chromatographically identical with the optically active material prepared from denudatine by acetylation and oxidation with the  $CrO_3$ –pyridine complex. Unfortunately, reduction of (132) with  $LiAlH_4$  gave the dihydrodenudatine (148), and there was an insufficient quantity of (147) available to repeat the sequence. The authors suggested that reduction of (147) with hydride, followed by pyrolysis, might yield denudatine (149) as the final product.

**Synthetic Studies directed toward the Diterpenoid Alkaloids.**—In studies directed toward the synthesis of the C<sub>19</sub> diterpenoid alkaloids, Chatterjee has reported<sup>45</sup> the preparation of intermediate (150) by a very unusual synthetic sequence.

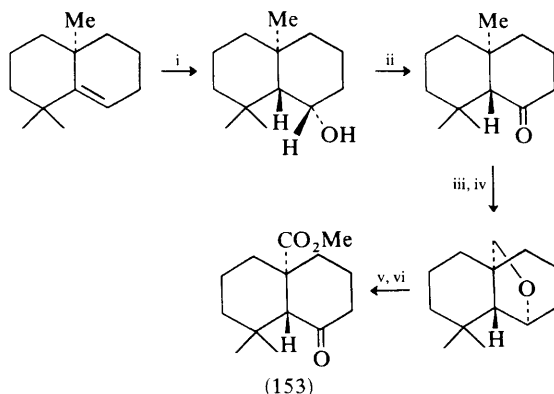


Cornforth<sup>46</sup> has severely criticized this scheme and stated that all claims in this paper should be accepted as fact after, but not before, verification by independent experiment. Amongst other points, he noted that the conversion of (151) into (152) requires: (a) an abnormal reaction of a  $\beta$ -keto-ester with a Grignard reagent, and (b) a so-called dehydration involving the wholly unexplained disappearance of a C-methyl group.

<sup>46</sup> J. Cornforth, *Tetrahedron Lett.*, 1980, **21**, 709.



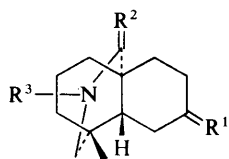
A new approach to the synthesis of the angularly substituted ester (153) as outlined in Scheme 4 has been reported.<sup>47</sup> This ester was converted into the



Reagents: i,  $\text{B}_2\text{H}_6$ ; ii,  $\text{CrO}_3$ , HMPT; iii,  $\text{LiAlH}_4$ ; iv,  $\text{Pb}(\text{OAc})_4$ ,  $\text{I}_2$ ,  $h\nu$ ; v,  $\text{CrO}_3$ ,  $\text{AcOH}$ ; vi,  $\text{Me}_3\text{O}^+ \text{BF}_4^-$

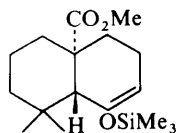
**Scheme 4**

lactam (154). Treatment of the enolate of (153) (generated by lithium diisopropylamide in 1,2-dimethoxyethane) with trimethylsilyl chloride gave predominantly (155). The reaction of this enol ether with *m*-chloroperoxybenzoic acid, followed by hydrolysis with  $\text{HCl}$  in ether, afforded (156), in 50% yield. Methylation of this hydroxy-ketone with  $\text{MeI}$  and  $\text{NaH}$ , and then Clemmensen reduction, yielded (157). Demethylation of (157) with boron triamide, followed

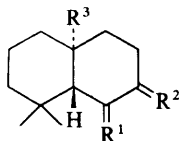


(154)  $\text{R}^1 = \text{R}^2 = \text{O}$ ,  $\text{R}^3 = \text{H}$

(160)  $\text{R}^1 = \text{O}$ ,  $\text{R}^2 = \text{H}_2$ ,  $\text{R}^3 = \text{Ms}$



(155)

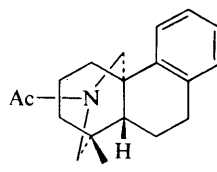


(156)  $\text{R}^1 = \text{O}$ ;  $\text{R}^2 = \text{H, OH}$ ;  $\text{R}^3 = \text{CO}_2\text{Me}$

(157)  $\text{R}^1 = \text{H}_2$ ;  $\text{R}^2 = \text{H, OMe}$ ;  $\text{R}^3 = \text{CO}_2\text{Me}$

(158)  $\text{R}^1 = \text{H}_2$ ;  $\text{R}^2 = \text{O}$ ;  $\text{R}^3 = \text{CO}_2\text{Me}$

(159)  $\text{R}^1 = \text{H}_2$ ;  $\text{R}^2 = 2\text{-dioxolanyl}$ ;  $\text{R}^3 = \text{CON}_3$



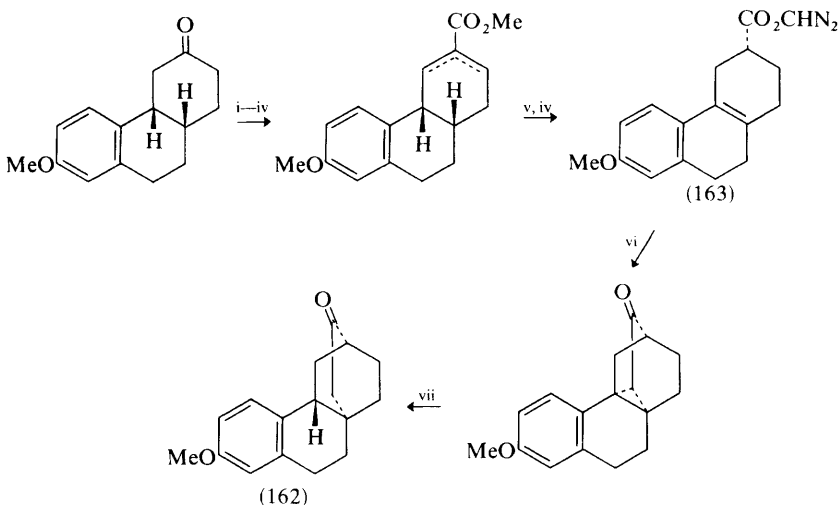
(161)

<sup>47</sup> A. K. Banerjee, P. C. Caraballo, H. E. Hurtado, and M. C. Carrasco, *Heterocycles*, 1980, **14**, 315.

by Jones oxidation, afforded (158). The azide (159) was prepared by sequential ketalization of (158), hydrolysis of the product with chlorotrimethylsilane and NaI in MeCN, treatment of the resulting acid with oxalyl chloride, and reaction of the acid chloride with hydrazoic acid in pyridine and toluene. Photolysis of the azide (159) in benzene, followed by deketalization with toluene-*p*-sulphonic acid, gave the desired lactam (154) in 7.8% yield. Reduction of (154) with excess  $\text{LiAlH}_4$  in dioxan, oxidation with pyridinium chlorochromate, and treatment with mesityl chloride in pyridine afforded (160).

Methods reported by Meyer and co-workers<sup>48</sup> (*cf.* Vol. 9, p. 235) could be used for the conversion of compound (160) into (161), which has previously been formally converted into atisine, veatchine, and garryine.

Ghatak and co-workers<sup>49</sup> have reported further progress on their synthetic elaboration of the atisane system, as outlined in Scheme 5. A key step in the synthesis of the tetracyclic compound (162) was the CuO-catalysed intermolecular alkylation of the diazoacetyl compound (163).



Reagents: i, KCN, DMSO, EtOH; ii,  $\text{POCl}_3$ ; iii, KOH, MeOH,  $\text{H}_2\text{O}$ ; iv,  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ ; v,  $\text{ClCOCOCl}$ ; vi, CuO; vii, Pd/C

**Scheme 5**

**Acknowledgment:** The authors express their appreciation to Dr. Naresh V. Mody for reviewing the manuscript and making several helpful suggestions.

<sup>48</sup> W. L. Meyer, T. E. Goodwin, R. J. Hoff, and C. W. Sigel, *J. Org. Chem.*, 1977, **42**, 2761.

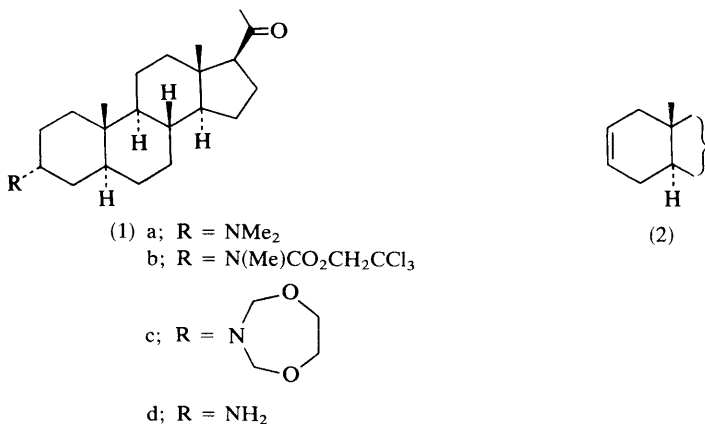
<sup>49</sup> S. C. Roy, M. Sarkar, and U. R. Ghatak, *Indian J. Chem., Sect. B.*, 1980, **19**, 305.

Steroidal alkaloids are discussed in reviews dealing primarily with the isoprenoid alkaloids,<sup>1</sup> the photochemistry of alkaloids,<sup>2</sup> and the liquid chromatography of steroids.<sup>3</sup>

### 1 Alkaloids of the Apocynaceae

It has been reported that the reaction of *NN*-dimethylfuntumine (1a) with trichloroethoxycarbonyl chloride gave the elimination product (2), in high yield, rather than the expected urethane (1b).<sup>4</sup> Under the same reaction conditions the epimeric dimethylamino-pregnane derivatives (3a) and (3b) both gave the olefin (4), accompanied by minor amounts of the expected urethanes (3c) and (3d) respectively. The reaction of conessine (5a) with  $\text{Cl}_3\text{CCH}_2\text{OCOCl}$  yielded only the urethane (5b).<sup>4</sup>

The dioxazepine (1c) was formed when funtumine (1d) was treated with formaldehyde and ethane-1,2-diol in benzene. Under similar conditions, epiholafebrine (3e) furnished the dioxazepine (3f).<sup>5</sup>



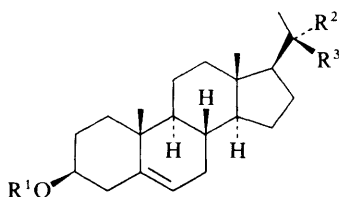
<sup>1</sup> J. G. Roddick, *Encycl. Plant Physiol., New Ser.*, 1980, **8** (Secondary Plant Products), p. 167.

<sup>2</sup> S. P. Singh, V. I. Stenberg, and S. S. Parmar, *Chem. Rev.*, 1980, **80**, 269.

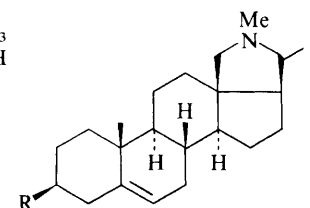
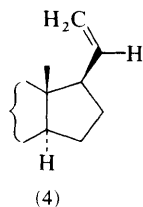
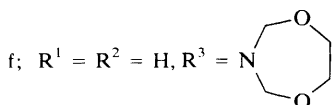
<sup>3</sup> E. Heftmann, *J. Liq. Chromatogr.*, 1979, **2**, 1137.

<sup>4</sup> H. Kapnang and G. Charles, *Tetrahedron Lett.*, 1980, **21**, 2951.

<sup>5</sup> H. Kapnang and G. Charles, *Tetrahedron Lett.*, 1980, **21**, 2949.



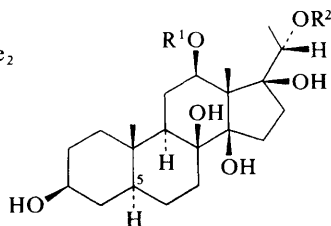
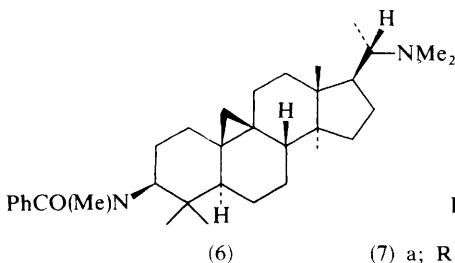
- (3) a;  $R^1 = \text{Ac}, R^2 = \text{H}, R^3 = \text{NMe}_2$   
 b;  $R^1 = \text{Ac}, R^2 = \text{NMe}_2, R^3 = \text{H}$   
 c;  $R^1 = \text{Ac}, R^2 = \text{H}, R^3 = \text{N(Me)CO}_2\text{CH}_2\text{CCl}_3$   
 d;  $R^1 = \text{Ac}, R^2 = \text{N(Me)CO}_2\text{CH}_2\text{CCl}_3, R^3 = \text{H}$   
 e;  $R^1 = R^2 = \text{H}, R^3 = \text{NH}_2$



- (5) a;  $R = \text{NMe}_2$   
 b;  $R = \text{N(Me)CO}_2\text{CH}_2\text{CCl}_3$

## 2 *Buxus* Alkaloids

Recent work on the *Buxus* alkaloids has been reviewed.<sup>6</sup> Cyclobuxines B and D, cycloprotobuxine D, cyclovirobuxine D, and two new alkaloids have been isolated from *B. sempervirens*. It was suggested that one of the new bases possessed the structure *N*-benzoyl-cycloprotobuxine C (6).<sup>7</sup>



- (7) a;  $R^1 = o\text{-MeNHC}_6\text{H}_4\text{CO}, R^2 = \text{Ac}$   
 b;  $R^1 = \text{PhCH}=\text{CHCO}, R^2 = \text{nicotinoyl}$   
 c;  $R^1 = R^2 = \text{H}$   
 d;  $R^1 = \text{PhCH}=\text{CHCO}, R^2 = \text{nicotinoyl}; \Delta^5$

## 3 Alkaloids of the Asclepiadaceae

The structures of the major alkaloids of *Stephanotis japonica* were reported earlier.<sup>8</sup> Two minor alkaloids, stephanthraniline B (7a) and dihydrogagaminin

<sup>6</sup> J. Tomko and Z. Voticky, *IUPAC Int. Symp. Chem. Nat. Prod.*, 1978, 4 (Part 1), 260 (*Chem. Abstr.*, 1980, **92**, 6792).

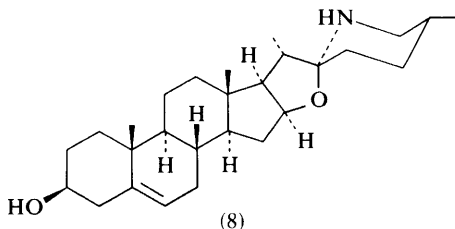
<sup>7</sup> B. U. Khodzhaev, R. Shakirov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1980, 130 (*Chem. Abstr.*, 1980, **92**, 177 459).

<sup>8</sup> (a) S. Terada, K. Hayashi, and H. Mitsuhashi, *Tetrahedron Lett.*, 1978, 1995; *Chem. Pharm. Bull.*, 1977, **25**, 2802 (*Chem. Abstr.*, 1977, **87**, 65 331); (b) D. M. Harrison, in 'The Alkaloids', ed. M. F. Grondon, (Specialist Periodical Reports), The Chemical Society, London, 1979, Vol. 9, p. 241.

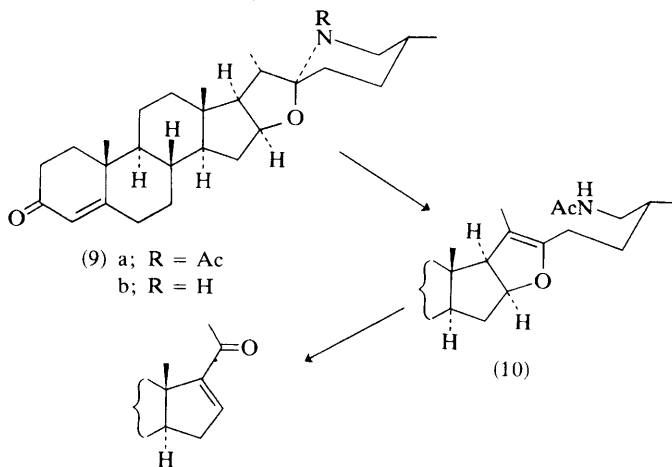
(7b), both gave dihydrosarcostine (7c) on alkaline hydrolysis, and they were assigned the structures that are indicated here mainly on the basis of spectroscopic studies.<sup>9</sup> Ambiguities in the placement of the ester functions of the two new alkaloids were resolved by biosynthetic considerations. The known base gagaminin (7d) was also isolated from *S. japonica*.<sup>9</sup>

#### 4 *Solanum* Alkaloids

The *Solanum* steroidal alkaloids<sup>10</sup> and the distribution of alkaloids in Australian *Solanum* species<sup>11</sup> have been reviewed. A review on the constituents of tomatoes includes discussion on the tomato glyco-alkaloids.<sup>12</sup>



The aglycon solasodine (8) is becoming increasingly important as a starting material for the synthesis of steroids in the pharmaceutical industry,<sup>13</sup> and aspects of the isolation and chemistry of solasodine have been reviewed in this light.<sup>14</sup>



<sup>9</sup> S. Terada and H. Mitsuhashi, *Chem. Pharm. Bull.*, 1979, **27**, 2304 (*Chem. Abstr.*, 1980, **92**, 72 674); S. Terada, K. Hayashi, and H. Mitsuhashi, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, 21st, 1978, 614 (*Chem. Abstr.*, 1979, **91**, 39 722).

<sup>10</sup> K. Schreiber, *Linn. Soc. Symp. Ser.*, 1979, **7** (Biology and Taxonomy of the Solanaceae), p. 193 (*Chem. Abstr.*, 1979, **91**, 171 613).

<sup>11</sup> V. Bradley, D. J. Collins, F. W. Eastwood, M. C. Irvine, and D. E. Symon, *Linn. Soc. Symp. Ser.*, 1979, **7** (Biology and Taxonomy of the Solanaceae), p. 203 (*Chem. Abstr.*, 1979, **91**, 171 715).

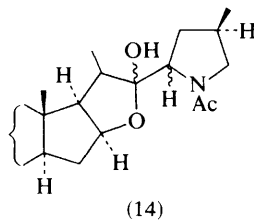
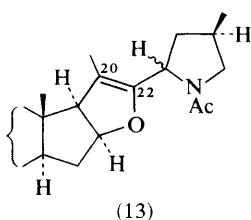
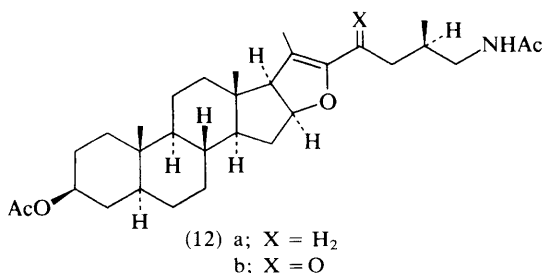
<sup>12</sup> K. Herrmann, *Z. Lebensm.-Unters. Forsch.*, 1979, **169**, 179 (*Chem. Abstr.*, 1979, **91**, 171 590).

<sup>13</sup> J. Kloosterman, *Chem. N.Z.*, 1979, **43**, 146 (*Chem. Abstr.*, 1980, **92**, 111 209).

<sup>14</sup> J. D. Mann, *Adv. Agron.*, 1978, **30**, 207 (*Chem. Abstr.*, 1979, **91**, 44 430).

The industrial isolation of solasodine from its glycosides is normally achieved *via* acid-catalysed hydrolysis of the latter. A microbiological alternative was investigated by feeding the crude glyco-alkaloids of *S. eleagnifolium* to the fungus *Aspergillus niger*. The resultant fungal mycelium was rich in solasodine that was suitable for further conversion into 16-dehydropregnenolone acetate.<sup>15</sup> A recent patent describes the conversion of *N*-acetylsolasodenone (9a) into the pseudosolasodine analogue (10) and thence into 16-dehydropregesterone (11).<sup>16</sup>

*N,O*-Diacetyldihydropseudosolasodine (12a) gave the epimeric pyrrolidines (13) on treatment with bromine. When *N*-bromosuccinimide was used as oxidant, the ketone (12b) and the pyrrolidine (14) were also formed.<sup>17</sup> The Wolff-Kishner reductions of solasodenone (9b) and of the epimeric 4,5 $\xi$ -dihydro-analogues have been reported.<sup>18</sup> Solasodine gave the expected 5 $\alpha$ ,6-epoxide on treatment with perbenzoic acid.<sup>19</sup> The preparation of an intermediate in the synthesis of the solanidine alkaloids has been reviewed.<sup>20</sup>



Solasodine (0.01%), tomatidenol (0.001%), and a new *Solanum* alkaloid, solanaviol (0.05%), have been isolated from dried leaves of *S. aviculare*.<sup>21</sup> Solanaviol was assigned the structure 12 $\beta$ -hydroxysolasodine (15a) on the basis of mass-spectral and <sup>1</sup>H and <sup>13</sup>C n.m.r. studies and the conversion of solanaviol

<sup>15</sup> J. Rodriguez, R. Segovia, E. Guerreiro, F. Ferretti, G. Z. De Sosa, and R. Ertola, *J. Chem. Technol. Biotechnol.*, 1979, **29**, 525 (*Chem. Abstr.*, 1980, **92**, 59 105).

<sup>16</sup> G. Adam, H. T. Huong, and M. Lischewski, Ger. (East) P. 132 437 (*Chem. Abstr.*, 1979, **91**, 91 840).

<sup>17</sup> G. G. Malanina, L. I. Klimova, L. M. Morozovskaya, and G. S. Grinenko, *Khim. Farm. Zh.*, 1979, **13**, No. 10, p. 72 (*Chem. Abstr.*, 1980, **92**, 111 225).

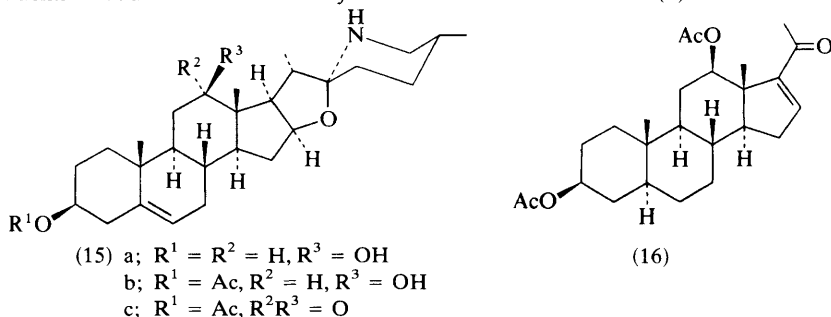
<sup>18</sup> M. P. Irismetov, M. I. Goryaev, and V. V. Kuril'skaya, *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.*, 1979, No. 3, p. 58 (*Chem. Abstr.*, 1979, **91**, 211 671).

<sup>19</sup> M. P. Irismetov, V. V. Kuril'skaya, M. I. Goryaev, and V. S. Bazalitskaya, *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.*, 1979, **29**, No. 1, p. 35 (*Chem. Abstr.*, 1979, **91**, 74 777).

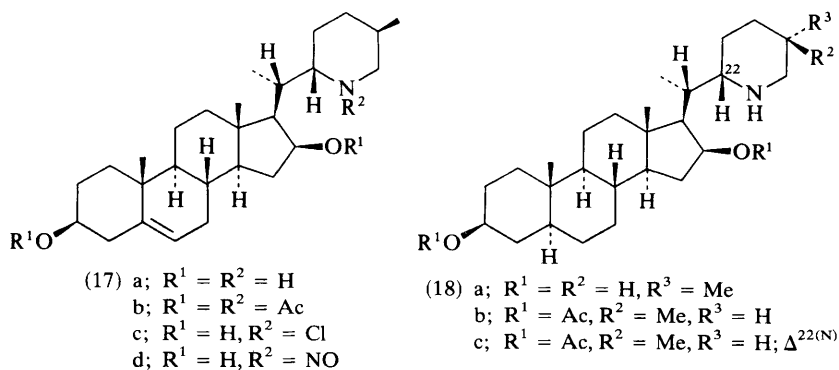
<sup>20</sup> D. Miljkovic and K. Gasi, *11th IUPAC Int. Symp. Chem. Nat. Prod.*, 1978, **3**, 123 (*Chem. Abstr.*, 1979, **91**, 211 647).

<sup>21</sup> K. Kaneko, K. Niitsu, N. Yoshida, and H. Mitsuhashi, *Phytochemistry*, 1980, **19**, 299.

into the known pregnane derivative (16). Additional evidence for the structure proposed for solanaviol was gathered by sequential monoacetylation (by AcOH and HCl), which gave the 3-*O*-acetyl derivative (15b), and oxidation (by CrO<sub>3</sub> and AcOH) of the latter derivative to yield the acetoxy-ketone (15c). Wolff-Kishner reduction of the acetoxy-ketone furnished solasodine (8).<sup>21</sup>



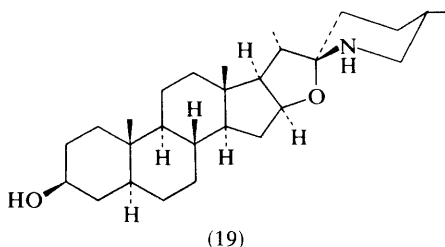
A new aglycon, solaverbascine, has been isolated in 0.01% yield from dried leaves of *S. verbascifolium* grown in Vietnam.<sup>22</sup> Solaverbascine (17a) was shown to possess the 22,26-epiminocholestane structure, indicated mainly on the basis of spectroscopic studies on the alkaloid and its derivatives (17b), (17c), and (17d). This structural proposal was confirmed by direct comparison with authentic (17a) that had been prepared by reductive ring-opening of solasodine.<sup>22</sup> The major aglycons of the leaves of the Vietnamese plant were solasodine (0.26%) and tomatidine (0.05%),<sup>22</sup> in contrast to the isolation only of solasodine, solafioridine, and tomatidenol from the same species when it had been grown in Cuba.<sup>23</sup> Solaverbascine (17a) and the related 22,26-epiminocholestane (18a) are oxidized by manganese dioxide to furnish solasodine (8) and tomatidine (19) respectively, in excellent yield.<sup>24</sup> These reactions occur *via* oxidative formation of a  $\Delta^{22(N)}$  double-bond followed by spontaneous cyclization to form the observed



<sup>22</sup> G. Adam, H. Th. Huong, and N. H. Khoi, *Phytochemistry*, 1980, **19**, 1002.

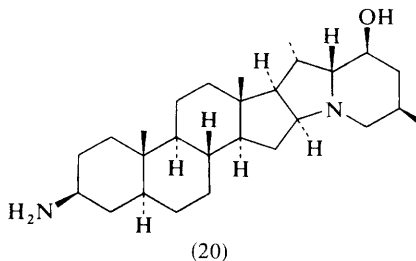
<sup>23</sup> W. Doeppke, J. L. Mola, and U. Hess, *Pharmazie*, 1976, **31**, 656.

<sup>24</sup> G. Adam and H. Th. Huong, *Tetrahedron Lett.*, 1980, **21**, 1931.



spiro-amino-ketal products. In keeping with this suggestion, the  $16\beta$ -acetoxy-compound (18b) gave only the azine (18c) when treated with manganese dioxide. It is anticipated that such one-step oxidative cyclization reactions will replace traditional methods for the conversion of  $16\beta$ -hydroxy-22,25-epiminocholestane derivatives into spiro-amino-ketals *via* *N*-chloro or *N*-nitroso intermediates.<sup>24,25</sup>

The isolation of the  $3\beta$ -amino-steroid solanogantine (20) from leaves of *S. giganteum* was earlier the subject of a preliminary communication.<sup>26</sup> Experimental details of this work are now available, together with the description of two new alkaloids, solanogantamine (21a) and isosolanogantamine (22a), which were isolated from the same source.<sup>27</sup> The new alkaloids were both isomeric with solanogantine, and they were assigned the structures that are indicated here mainly on the basis of the evidence summarized below.



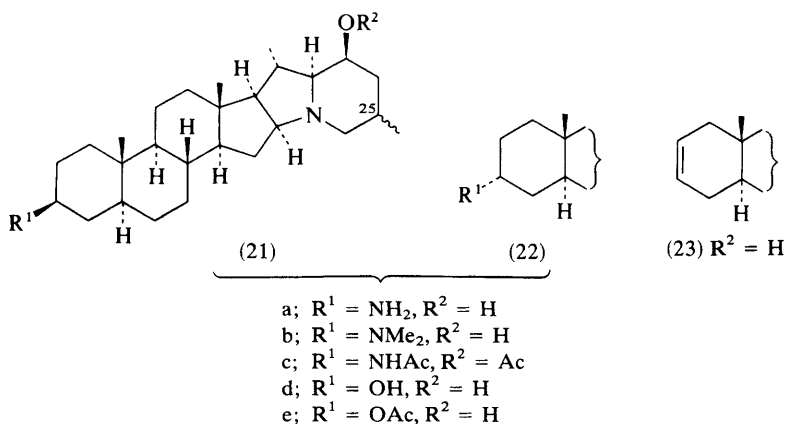
The mass spectra of solanogantamine, isosolanogantamine, their *NN*-dimethyl derivatives (21b) and (22b) respectively, and their *N,O*-diacetyl derivatives (21c) and (22c) respectively were almost identical to those of solanogantine (20) or the appropriate derivative, which suggested that the new alkaloids were stereoisomers of solanogantine. In particular, the mass spectrum of the *NN*-dimethyl derivatives showed fragment ions with  $m/z$  84 and 110 (which are appropriate for a 3-dimethylamino-cholestane),  $m/z$  166 and 220 (which are characteristic of a solanidine derivative with a hydroxy-group in ring E or F),

<sup>25</sup> K. Schreiber, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1968, Vol. 10, p. 1, and references therein.

<sup>26</sup> (a) S. C. Pakrashi, A. K. Chakravarty, and E. Ali, *Tetrahedron Lett.*, 1977, 645, 814; (b) D. M. Harrison, in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London, 1978, Vol. 8, p. 253.

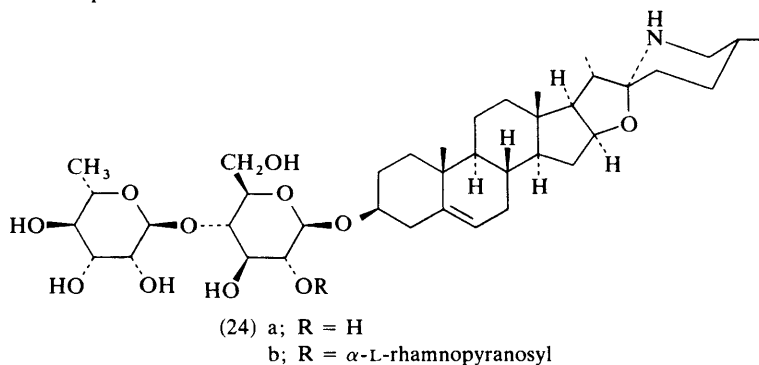
<sup>27</sup> S. C. Pakrashi, A. K. Chakravarty, E. Ali, T. K. Dhar, and S. Dan, *J. Indian Chem. Soc.*, 1978, **55**, 1109 (*Chem. Abstr.*, 1980, **92**, 6806).





and  $m/z$  343 and 370 (in support of the 23-hydroxy-solanidine structures indicated). The deamination of alkaloids (21a) and (22a) with nitrous acid in aqueous acetic acid was most revealing. In particular, solanogantamine (21a) gave the diol (21d) together with minor quantities of the acetate (21e) and the olefin (23) while isosolanogantamine gave the olefin (23) as the major product. Hence the alkaloids differed only in their configurations at C-3, and solanogantamine was assigned the  $3\beta$ -amino structure shown. The detailed stereochemistry of rings E and F was deduced from the results of a high-resolution n.m.r. study. The configuration of the 25-methyl group in (21a) and (22a) remains unknown.<sup>27</sup>

The isolation of solasodenone (9b) from leaves and roots of *S. hainanense* has been reported.<sup>28</sup>



A new glyco-alkaloid, khasianine (24a), has been isolated, together with solamargine (24b) and solasonine, from berries of *S. khasianum*.<sup>29</sup> Khasianine

<sup>28</sup> G. Adam, H. T. Huong, M. Lischewski, and N. H. Khoi, *Pharmazie*, 1979, **34**, 362; G. Adam, H. T. Huong, N. H. Khoi, and M. Lischewski, *11th IUPAC Int. Symp. Chem. Nat. Prod.*, 1978, **2**, 330 (*Chem. Abstr.*, 1979, **91**, 193 497); G. Adam, M. Lischewski, H. T. Huong, and N. H. Khoi, *Tap San Hoa Hoc*, 1978, **16**, No. 4, p. 28 (*Chem. Abstr.*, 1980, **92**, 55 067); cf. G. Adam, H. T. Huong, M. Lischewski, and N. H. Khoi, *Phytochemistry*, 1978, **17**, 1070; D. M. Harrison, in ref. 8b, p. 244.

<sup>29</sup> S. B. Mahato, N. P. Sahu, A. N. Ganguly, R. Kasai, and O. Tanaka, *Phytochemistry*, 1980, **19**, 2017.

is identical to  $\beta$ -solamargine, which is a degradation product of solamargine. The structure elucidation of khasianine relied heavily on  $^{13}\text{C}$  n.m.r. studies, in the course of which some n.m.r. assignments that had been made by other workers<sup>30</sup> for the carbohydrate portion of solasonine were revised.<sup>29</sup>

High-performance liquid chromatography has been used to follow the kinetics and the sequence of cleavages which occur during the acid-catalysed hydrolysis of the solasodine glycosides.<sup>31</sup> Further study has been reported on the known ability of  $\alpha$ -tomatine and of the potato glyco-alkaloids to form complexes with  $3\beta$ -hydroxy-steroids such as cholesterol.<sup>32</sup> Methods for the determination of glyco-alkaloids in tomato cultivars<sup>33</sup> and potato tubers<sup>34</sup> have been reported. New reagents have been recommended for the detection of steroidal glyco-alkaloids during thin-layer chromatography.<sup>35</sup>

Studies have been reported on the distribution of the glycosides of solasodine in various parts of the plants *S. americanum*,<sup>36</sup> *S. indicum*,<sup>37</sup> and *S. acculeatissimum*.<sup>38</sup> Solasodine was isolated in 0.4% yield from ripe fruits of the latter plant,<sup>39</sup> and in 0.15% yield from ripe fruits of *S. grandiflorum*.<sup>40</sup> Fruits and leaves of thirty-one *Solanum* species have been assayed for their solasodine content. The best sources of the aglycon were *S. khasianum*, *S. eleagnifolium*, *S. auriculatum*, and *S. giganteum*.<sup>41</sup> *S. aviculare* had a particularly high solasodine content (2.7%) in the leaves.<sup>42</sup> The large-scale isolation of solasodine from fruits of *S. mammosum* and *S. khasianum* has been described.<sup>43</sup> Studies have been reported on the influence of environmental factors on the solasodine content of *S. khasianum*<sup>44</sup> and on the course of production of solasodine by the same species.<sup>45</sup> The seasonal variations of production of solasodine in *S. khasianum* var. *chatterjeeanum* and *S. laciniatum* have been studied<sup>46</sup> and the factors affecting the alkaloid composition of *S. dulcamara* have been reviewed.<sup>47</sup>

<sup>30</sup> R. J. Weston, E. Gottlieb, E. W. Hagaman, and E. Wenkert, *Aust. J. Chem.*, 1977, **30**, 917.

<sup>31</sup> P. G. Crabbe and C. Fryer, *Chem. Eng. Commun.*, 1980, **4**, 135 (*Chem. Abstr.*, 1980, **93**, 8451).

<sup>32</sup> J. G. Roddick, *Phytochemistry*, 1979, **18**, 1467.

<sup>33</sup> E. Simekova and V. Horcin, *J. Food Sci.*, 1980, **45**, 386.

<sup>34</sup> D. T. Coxon, K. R. Price, and P. G. Jones, *J. Sci. Food Agric.*, 1979, **30**, 1043.

<sup>35</sup> R. Jellema, E. T. Elema, and T. M. Malingre, *J. Chromatogr.*, 1980, **189**, 406.

<sup>36</sup> I. Mathe Jnr., H. van Mai, and I. Mathe, *11th IUPAC Int. Symp. Chem. Nat. Prod.*, 1978, **2**, 379 (*Chem. Abstr.*, 1979, **91**, 189 813).

<sup>37</sup> A. K. Rathore, K. P. Sharma, and G. L. Sharma, *Bangladesh Pharm. J.*, 1978, **7**, No. 4, p. 10 (*Chem. Abstr.*, 1980, **92**, 55 119).

<sup>38</sup> P. G. Kadkade, J. A. Recinos, and T. R. Madrid, *Planta Med.*, 1979, **37**, 70.

<sup>39</sup> A. K. Rathore and R. Kamal, *Pharmazie*, 1979, **34**, 250 (*Chem. Abstr.*, 1979, **91**, 87 365).

<sup>40</sup> G. Indrayanto, E. Sundrawati, and Sutarjadi, *Bull. ISFI Jatim*, 1979, **11**, 17 (*Chem. Abstr.*, 1980, **92**, 160 519).

<sup>41</sup> P. C. Maiti, S. Mookherjee, R. Mathew, and S. S. Dan, *Econ. Bot.*, 1979, **33**, 75 (*Chem. Abstr.*, 1980, **92**, 90 906).

<sup>42</sup> E. I. Korneva, L. I. Pikova, and L. F. Matveencko, *Khim. Farm. Zh.*, 1979, **13**, No. 5, p. 77 (*Chem. Abstr.*, 1979, **91**, 52 730).

<sup>43</sup> L. Telek, *Planta Med.*, 1979, **37**, 92.

<sup>44</sup> R. K. Chaudhuri and S. K. Chatterjee, *Indian J. Pharm. Sci.*, 1979, **41**, 76 (*Chem. Abstr.*, 1979, **91**, 16 724).

<sup>45</sup> S. Varghese, N. S. Sharma, J. D. Desai, and J. J. Chinoy, *Indian J. Pharm. Sci.*, 1979, **41**, 198 (*Chem. Abstr.*, 1980, **92**, 160 680).

<sup>46</sup> L. M. F. Miller and M. E. Davies, *Linn. Soc. Symp. Ser.* 1979, **7** (Biology and Taxonomy of the Solanaceae), p. 231 (*Chem. Abstr.*, 1979, **91**, 171 717).

<sup>47</sup> I. Mathe, Jnr., and I. Mathe, *Linn. Soc. Symp. Ser.*, 1979, **7** (Biology and Taxonomy of the Solanaceae), p. 211 (*Chem. Abstr.*, 1979, **91**, 171 614).

A study has been reported on the effect of auxins on the solasodine content of *S. platanifolium*.<sup>48</sup>

A recent patent describes the isolation of tomatidenol from leaves of *S. trilobatum*.<sup>49</sup>

The subcellular distributions of the steroidal glyco-alkaloids of *S. tuberosum* and *Lycopersicon esculentum* have been studied.<sup>50</sup>

Tissue cultures of *S. khasianum*,<sup>51</sup> *S. laciniatum*,<sup>52</sup> and *S. surattense*<sup>53</sup> have been studied as sources of solasodine and glyco-alkaloids.

The possible relationship between the glyco-alkaloid content of the potato and the resistance to the potato cyst nematode has been studied, with some conflicting results being obtained.<sup>54</sup> A study on the effect of glyco-alkaloids on the potato leafhopper has been reported.<sup>55</sup>

The hydrolysis of tomatine by an inducible extracellular enzyme from *Fusarium oxysporum* f. sp. *lycopersici* has been described.<sup>56</sup>

### 5 *Veratrum* and *Fritillaria* Alkaloids

Methods have been reported for the conversion of jervine into C-nor-D-homo-steroids that are functionalized at C-18.<sup>57,58</sup> The key intermediate, aldehyde (27a), was prepared from 11-deoxojervine (25a) via the hexahydro-derivative (26a), as summarized in Scheme 1.<sup>57</sup> Alternatively, *N,O*-diacetyl-11-deoxojervine (25b) was reduced sequentially with Pt/H<sub>2</sub> and with Rh/Pt/H<sub>2</sub> and the product (26b) was converted into the aldehyde (27b) by irradiation of a solution of (26b) in benzene, in the presence of mercuric oxide and iodine.<sup>58</sup> Further studies have been reported on the chemistry of C-nor-D-homo-steroids that are derived from jervine.<sup>59</sup> Details of the formal conversion of jervine into testosterone have been published.<sup>60</sup>

Several biogenetically important alkaloids have been isolated from *Veratrum grandiflorum* plants that had been grown in the presence of light.<sup>61</sup> This system

<sup>48</sup> R. K. Puri and D. C. Shukla, *Planta Med.*, 1979, **36**, 142.

<sup>49</sup> K. K. Purushothaman and V. Narayanaswami, *Indian P.* 140 381 (*Chem. Abstr.*, 1980, **92**, 72 965).

<sup>50</sup> J. G. Roddick, *Linn. Soc. Symp. Ser.*, 1979, **7** (Biology and Taxonomy of the Solanaceae), p. 223 (*Chem. Abstr.*, 1979, **91**, 171 716).

<sup>51</sup> C. K. Kokate and S. S. Radwan, *Z. Naturforsch., Teil. C*, 1979, **34**, 634 (*Chem. Abstr.*, 1979, **91**, 154 371); A. Uddin and H. C. Chaturvedi, *Planta Med.*, 1979, **37**, 90.

<sup>52</sup> H. Hosoda and M. Yatazawa, *Agric. Biol. Chem.*, 1979, **43**, 821 (*Chem. Abstr.*, 1979, **91**, 2626); H. Hosoda, H. Ito, and M. Yatazawa, *ibid.*, p. 1745 (*Chem. Abstr.*, 1979, **91**, 154 500).

<sup>53</sup> A. R. Chowdhury, R. N. Prasad, and A. Uddin, *Q. J. Crude Drug Res.*, 1979, **17**, 137 (*Chem. Abstr.*, 1980, **92**, 107 405).

<sup>54</sup> V. A. Voinilo and I. Ya. Ponin, *Vestsi Akad. Navuk B. SSR, Ser. Biyal. Navuk*, 1979, No. 4, p. 73 (*Chem. Abstr.*, 1979, **91**, 171 812); J. M. S. Forrest and D. T. Coxon, *Ann. Appl. Biol.*, 1980, **94**, 265 (*Chem. Abstr.*, 1980, **92**, 177 571).

<sup>55</sup> K. V. Raman, W. M. Tingey, and P. Gregory, *J. Econ. Entomol.*, 1979, **72**, 337 (*Chem. Abstr.*, 1979, **91**, 72 043).

<sup>56</sup> J. E. Ford, D. J. McCance, and R. B. Drysdale, *Linn. Soc. Symp. Ser.*, 1979, **7** (Biology and Taxonomy of the Solanaceae), p. 237 (*Chem. Abstr.*, 1979, **91**, 189 911).

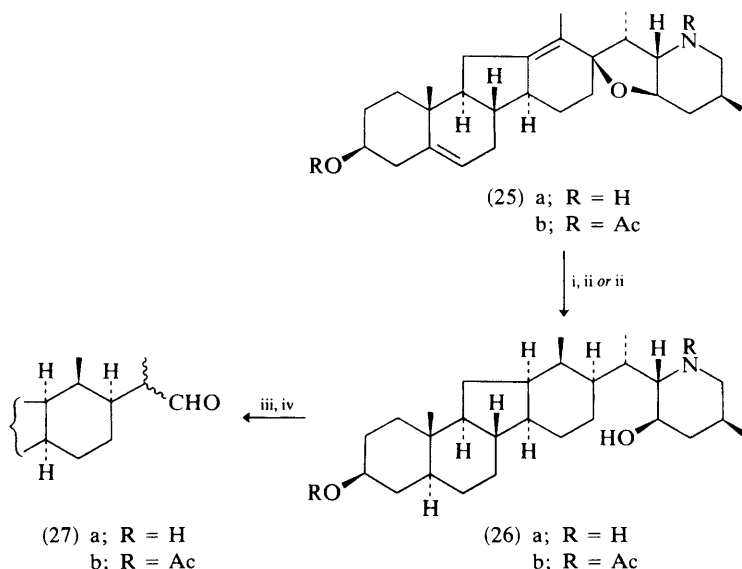
<sup>57</sup> H. Sugimoto, N. Sato, and T. Masamune, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3043.

<sup>58</sup> H. Sugimoto, N. Yonekura, and T. Masamune, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 210.

<sup>59</sup> A. Murai, N. Iwasa, M. Takeda, and T. Masamune, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 243; A. Murai, H. Sasamori, and T. Masamune, *ibid.*, p. 254.

<sup>60</sup> A. Murai, N. Iwasa, and T. Masamune, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 259.

<sup>61</sup> K. Kaneko, N. Kawamura, M. Tanaka, and H. Mitsuhashi, *Koen Yoshishu-Tennen Yuki Kagobutsu Toronkai*, 22nd, 1979, 55 (*Chem. Abstr.*, 1980, **93**, 8387); cf. K. Kaneko, N. Kawamura, T. Kuribayashi, M. Tanaka, and H. Mitsuhashi, *Tetrahedron Lett.*, 1978, 4801.



Reagents: i, Pt, H<sub>2</sub>; ii, Pt, Rh, H<sub>2</sub>; iii, *N*-chlorosuccinimide, THF; iv, NaOMe, MeOH

**Scheme 1**

has now yielded two new alkaloids, *i.e.* hosukinidine (28) from the rhizomes and epirubijervine (29) from aerial parts of the plant.<sup>62</sup> The structure of hosukinidine was deduced in part from the <sup>1</sup>H n.m.r. spectrum, which showed, *inter alia*, singlet methyl resonances at  $\delta$  0.98 and 1.56 (assigned to protons attached to C-19 and C-18 respectively), a multiplet at  $\delta$  5.38 (proton at C-6), and a multiplet at  $\delta$  3.48 which moved downfield to  $\delta$  4.64 on acetylation (3 $\alpha$ -proton). The mass spectrum of hosukinidine displayed a molecular ion, together with important fragment ions with *m/z* 125 and 98, the latter suggesting the presence of a methylpiperidyl side-chain. The structure (28) suggested for hosukinidine was confirmed by single-crystal X-ray analysis on the hydrochloride salt. Hosukinidine is the first plant steroid which has the (20*R*) stereochemistry depicted.<sup>62</sup>

The structure (29) of epirubijervine was deduced mainly on the basis of <sup>1</sup>H and <sup>13</sup>C n.m.r. data, and was confirmed by direct comparison with authentic material.<sup>62</sup>

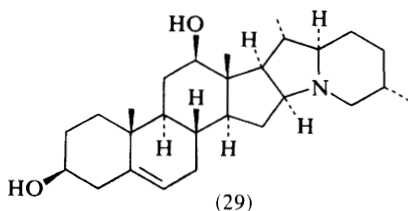
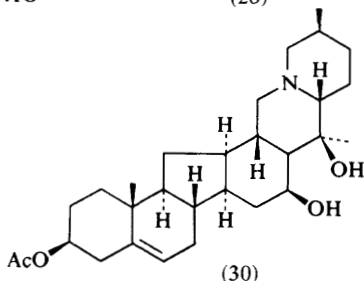
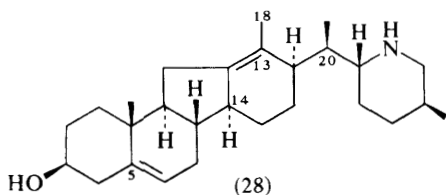
The crystal structure of 3-*O*-acetylveramarine (30) has been reported.<sup>63</sup>

Pseudojervine, veratrosine, veratramine, jervine, and a new alkaloid, verdine, have been isolated from *V. dahuricum*. It was suggested that the new alkaloid possesses the jervanine skeleton.<sup>64</sup> Underground parts of *V. nigrum* have yielded

<sup>62</sup> K. Kaneko, N. Kawamura, H. Mitsuhashi, and K. Ohsaki, *Chem. Pharm. Bull.*, 1979, **27**, 2534 (*Chem. Abstr.*, 1980, **92**, 72 676).

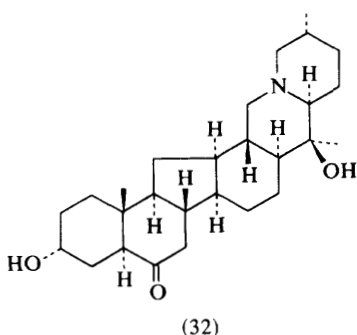
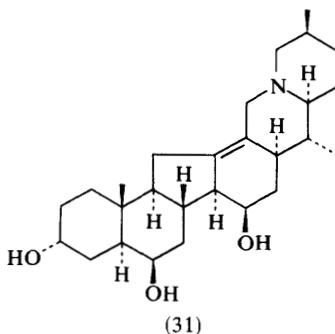
<sup>63</sup> F. Pavelčík and J. Tomko, *Acta Crystallogr., Sect. B*, 1979, **35**, 1790; *Tetrahedron Lett.*, 1979, 887.

<sup>64</sup> I. Nakhatov, R. Shakirov, E. M. Taskhanova, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1980, 131 (*Chem. Abstr.*, 1980, **92**, 194 475).



protoveratrine A, didesacetylprotoveratrine A, veramarine, germidine, and verazine.<sup>65</sup> Underground parts of the latter species grown in Czechoslovakia furnished jervine and veratroylzygadenine.<sup>66</sup> The variations in alkaloid composition of *V. lobelianum* during the life cycle of the plant have been studied.<sup>67</sup>

Edpetisidinine (31), isolated from *Petilium eduardi* (*Fritillaria* sp.), has been assigned the structure and stereochemistry indicated, on the basis of spectroscopic studies on the alkaloid and its derivatives.<sup>68</sup>



A new base, sevelin, has been isolated from *Korolkowia sewerzowi*. The cevanine-based structure (32) was assigned to sevelin on the basis of spectroscopic studies on the alkaloid and its simple derivatives.<sup>69</sup>

<sup>65</sup> N. V. Bondarenko, *Khim. Priro. Soedin.*, 1979, 105 and 415 (*Chem. Abstr.*, 1979, **91**, 16 719 and 207 412).

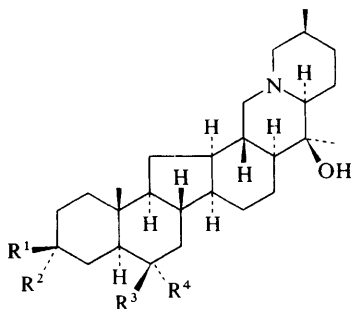
<sup>66</sup> D. Grancai, J. Mlckova, V. Suchy, and J. Tomko, *Chem. Zvesti*, 1979, **33**, 547 (*Chem. Abstr.*, 1980, **92**, 72 733).

<sup>67</sup> T. P. Antsupova and E. M. Taskhanova, Deposited Document, 1978, VINITI 1348, p. 35 (*Chem. Abstr.*, 1979, **91**, 137 146).

<sup>68</sup> P. Shakirov, A. Nabiev, and S. Yu. Yunusov, *Khim. Priro. Soedin.*, 1979, 584 (*Chem. Abstr.*, 1980, **92**, 147 002).

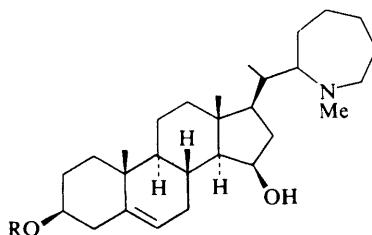
<sup>69</sup> K. Samikov, D. U. Abdullaeva, R. Shakirov, and S. Yu. Yunusov, *Khim. Priro. Soedin.*, 1979, 529 (*Chem. Abstr.*, 1980, **92**, 215 589).

Solanidine and hapepunine have been isolated from *Fritillaria verticillata*, together with two new alkaloids, baimonidine (33a) and isovorticine (33b). The structures indicated were assigned mainly on the basis of the  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectra of the new alkaloids and were confirmed by the preparation of these alkaloids from vorticinone (33c) by standard methods.<sup>70</sup> The  $^{13}\text{C}$  n.m.r. spectra of a number of other cevanine derivatives have been reported.<sup>70</sup> Fritillarine and a new alkaloid,  $\text{C}_{27}\text{H}_{43}\text{O}_3\text{N}$ , have been isolated from *F. karelinii*.<sup>71</sup>



- (33) a;  $\text{R}^1 = \text{R}^4 = \text{H}, \text{R}^2 = \text{R}^3 = \text{OH}$   
 b;  $\text{R}^1 = \text{R}^3 = \text{OH}, \text{R}^2 = \text{R}^4 = \text{H}$   
 c;  $\text{R}^1 = \text{OH}, \text{R}^2 = \text{H}, \text{R}^3\text{R}^4 = \text{O}$

Extraction of aerial parts of *Rhinopetalum bucharicum* yielded solanidine, imperialine, and two new glyco-alkaloids, rhinoline<sup>72</sup> and rhinoline.<sup>73</sup> Acid-catalysed hydrolysis of rhinoline gave D-glucose and a new aglycon, rhinolidine (1:1 molar ratio). This aglycon formed an *OO*-diacetyl derivative and a digitonide. On the basis of  $^1\text{H}$  n.m.r., i.r., and mass-spectral data it was suggested that rhinolidine possessed the structure (34a) and that rhinoline was the glucoside (34b).<sup>72</sup> Rhinoline also gave D-glucose and rhinolidine (2:1 molar ratio) on



- (34) a;  $\text{R} = \text{H}$   
 b;  $\text{R} = \beta\text{-D-glucopyranosyl}$   
 c;  $\text{R} = 4\text{-O}-(\beta\text{-D-glucopyranosyl})\text{-}\beta\text{-D-glucopyranosyl}$

<sup>70</sup> K. Kaneko, M. Tanaka, K. Haruki, N. Naruse, and H. Mitsuhashi, *Tetrahedron Lett.*, 1979, 3737.

<sup>71</sup> Hsiu-Fu Pan and Tse-Ching Chu, *K'o Hsueh T'ung Pao*, 1980, **25**, 186 (*Chem. Abstr.*, 1980, **92**, 194 503).

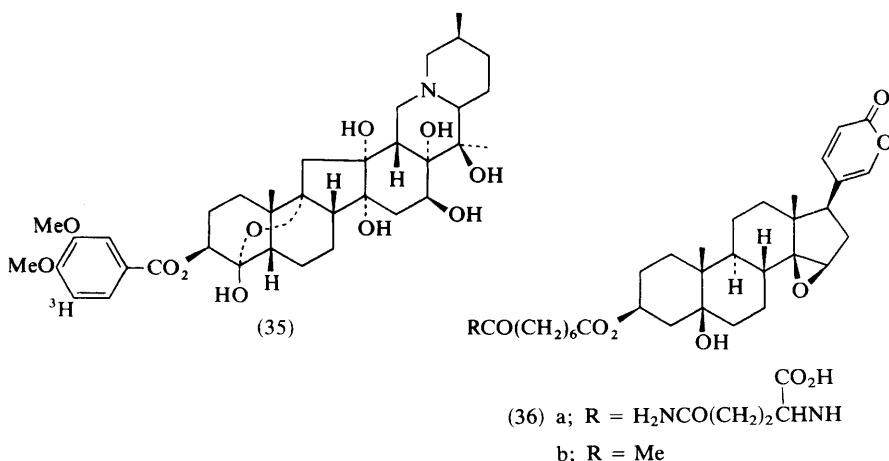
<sup>72</sup> K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1978, 815 (*Chem. Abstr.*, 1979, **91**, 16 668).

<sup>73</sup> K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1979, 350 (*Chem. Abstr.*, 1979, **91**, 207 406).

acid-catalysed hydrolysis. The glycoside was shown to be a derivative of cellobiose by examination of the products of permethylation followed by acid-catalysed hydrolysis. The structure indicated for rhinoline (34c) was suggested on the basis of spectroscopic studies on the glycoside and on its derivatives.<sup>73</sup> The structures proposed for rhinolidine and its glycosides, like those proposed for edpetilidine<sup>74</sup> and sevcornine<sup>75</sup> by the same authors, must be considered to be provisional in the absence of definitive evidence for the unusual side-chain suggested in each case.

The *Veratrum*<sup>6,76</sup> and *Fritillaria*<sup>76,77</sup> alkaloids and steroidal alkaloid teratogens<sup>78</sup> have been reviewed.

Tritium-labelled veratridine (35) has been prepared, with high specific activity, by condensation of veracevine with 3-bromo-4,5-dimethoxybenzoyl chloride followed by catalytic reduction with tritium gas.<sup>79</sup>



## 6 Miscellaneous Steroidal Alkaloids

A new toxic alkaloid, marinobufagin 3-suberoyl-L-glutamine ester (36a), has been isolated from the skin of the poison toad (*Bufo americanus*). The partial synthesis of the toxin from the ester (36b) was also reported.<sup>80</sup>

<sup>74</sup> R. N. Nuriddinov and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1969, 601 (*Chem. Abstr.*, 1970, **73**, 15 098).

<sup>75</sup> K. Samikov, R. Shakirov, D. U. Abdullaeva, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1976, 269 (*Chem. Abstr.*, 1976, **85**, 108 928); D. M. Harrison, in ref. 26b, p. 263.

<sup>76</sup> R. Shakirov and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1980, 3 (*Chem. Abstr.*, 1980, **92**, 177 373).  
<sup>77</sup> Jse-Tsin Chu, *Hua Hsueh Tung Pao*, 1979, 302 (*Chem. Abstr.*, 1979, **91**, 171 581).

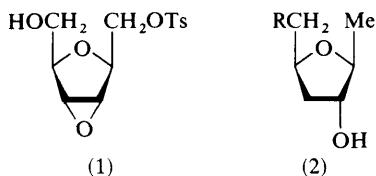
<sup>78</sup> R. F. Keeler, in 'Effects of Poisonous Plants on Livestock, [Proceedings of the Joint U.S.-Australian Symposium on Poisonous Plants], ed. R. F. Keeler, K. R. Van Kampen, and L. F. James, Academic Press, New York, 1977 (publ. 1978), p. 397 (*Chem. Abstr.*, 1979, **91**, 84 358); D. Brown, *ibid.*, p. 409 (*Chem. Abstr.*, 1979, **91**, 84 359).

<sup>79</sup> H. L. Tripathi and G. A. Yost, *J. Labelled Compd. Radiopharm.*, 1978, **15** (Suppl.), p. 619 (*Chem. Abstr.*, 1979, **91**, 20 902).

<sup>80</sup> K. Shimada and T. Nambara, *Tetrahedron Lett.*, 1979, 163.

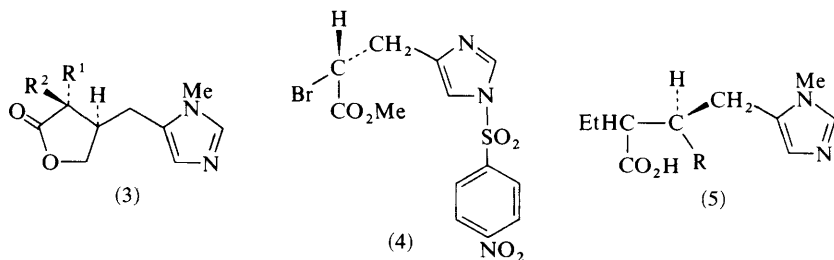
### 1 Muscarine Alkaloids

An elegant stereospecific synthesis of (+)-muscarine (2;  $R = \text{NMe}_3^+$ ) has been achieved by reduction of the epoxide (1) (easily produced from D-mannitol) with sodium bis-(2-methoxyethoxy)aluminium hydride to give predominantly (2;  $R = \text{OH}$ ); on monotosylation, this forms (2;  $R = \text{OTs}$ ). Chromatographic resolution and treatment with trimethylamine yielded (+)-muscarine (2;  $R = \text{NMe}_3^+$ ).<sup>1</sup>



### 2 Imidazole Alkaloids

(+)-Pilocarpine (3;  $R^1 = \text{H}, R^2 = \text{Et}$ ) and (+)-isopilocarpine (3;  $R^1 = \text{Et}, R^2 = \text{H}$ ) can be prepared from L-histidine by conversion into (S)-2-hydroxy-3-(5-imidazolyl)propionic acid; on esterification, sulphonation, and bromination, this gave the (R)-bromopropionate (4) with ~75% optical purity. Methylation of (4) with  $\text{Me}_3\text{O}^+\text{BF}_4^-$  and substitution with  $\text{NaC}(\text{Et})(\text{CO}_2\text{CH}_2\text{Ph})_2$  gave the benzyl ester, which upon debenzylation and decarboxylation gave the diastereoisomeric imidazole derivative (5;  $R = \text{CO}_2\text{Me}$ ). Reduction of this ester to the carbinol and concomitant cyclization gave a mixture of the pilocarpines.<sup>2</sup>



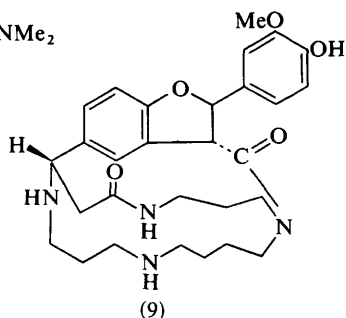
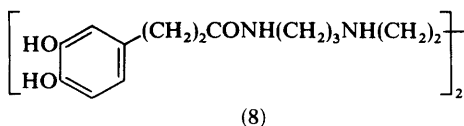
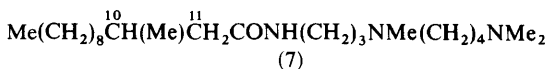
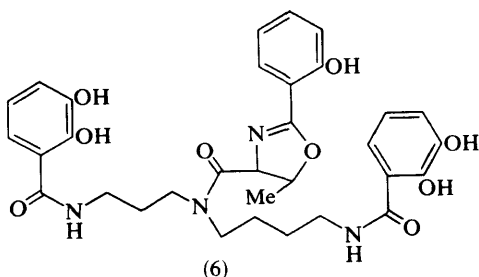
<sup>1</sup> A. M. Mubarak and D. M. Brown, *Tetrahedron Lett.*, 1980, **21**, 2453.

<sup>2</sup> A. Noordam, L. Maat, and H. C. Beyerman, *Recl. Trav. Chim. Pays-Bas*, 1979, **98**, 467.



### 3 Peptide Alkaloids

A revised structure for the catecholamide spermidine siderophore obtained from *Paracoccus denitrificans* has been proposed; the new structure contains a centrally located oxazole ring (6).<sup>3</sup> The soft coral *Sinularia brongersmai* contains two spermidine derivatives, *i.e.* (7) and its 10,11-dehydro-derivative [(10*E*)], both of which show cytotoxic activity.<sup>4</sup> The hypotensive principle of the root bark of *Lycium chinense* has been isolated as an amorphous alkaloid called kukoamine A.<sup>5</sup> Acid hydrolysis of the alkaloid produced only spermine and dihydrocaffeic acid, which, in association with its n.m.r. spectrum, indicated the structure (8). Another hypotensive principle, ephedradine B (9), has been obtained from *Ephedra* roots.<sup>6</sup>



Study continues on the extractives of the Celastraceae, *Maytenus* species being of particular importance due to the current interest in the antileukaemic alkaloid maytansine (*cf.* Vol. 10, p. 245). *Maytenus buxifolia*<sup>7</sup> contains mayfoline (10), which is another variant of the spermidine group, and *Maytenus mossambicensis*<sup>8</sup> the isomeric bicyclic alkaloids cyclocelabenzene (11) and isocyclocelabenzene (12). The first total synthesis of a natural maytansinoid has been reported by Meyers<sup>9</sup> and co-workers. Maysine (13) was assembled by

<sup>3</sup> T. Peterson and J. B. Neilands, *Tetrahedron Lett.*, 1979, 4805.

<sup>4</sup> F. J. Schmitz, K. H. Hollenbeak, and A. S. Prasad, *Tetrahedron Lett.*, 1979, 3387.

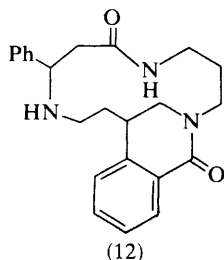
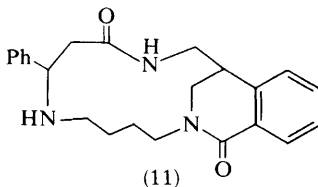
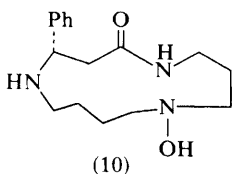
<sup>5</sup> S. Funayama, K. Yoshida, C. Konno, and H. Hikino, *Tetrahedron Lett.*, 1980, **21**, 1355.

<sup>6</sup> M. Tamada, K. Endo, and H. Hikino, *Heterocycles*, 1979, **12**, 783.

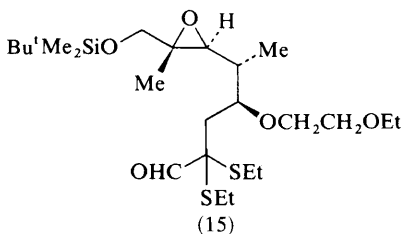
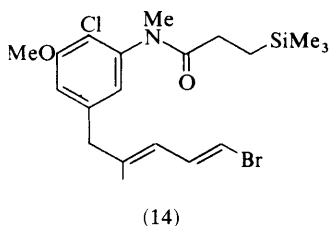
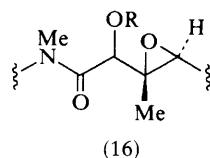
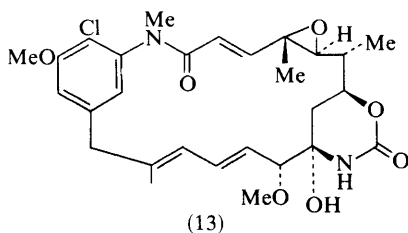
<sup>7</sup> H. Ripperger, *Phytochemistry*, 1980, **19**, 162.

<sup>8</sup> H. Wagner, J. Burghart, and W. E. Hull, *Tetrahedron Lett.*, 1978, 3893.

<sup>9</sup> A. I. Meyers, D. L. Comins, D. M. Roland, R. Henning, and K. Shimizu, *J. Am. Chem. Soc.*, 1979, **101**, 7104.



combination of (14) with stereochemically pure (15) and subsequent elaboration to (13). Corey has reported a new and better synthesis of ( $\pm$ )-*N*-methylmaytensine<sup>10</sup> (*cf.* Vol. 10, p. 245) as has Meyers.<sup>11</sup> A patent has been issued covering the conversion of maytansinol (the parent alcohol of the maytansinoid group of pharmacologically active compounds) into ansamitocins; *e.g.*, of P-3 (16; R = H) into (16; R = CHMe<sub>2</sub>CO), using the appropriate acid, DCC, and 4-(dimethylamino)pyridine.<sup>12</sup> Aryl *O*-demethylation of maytansinoids can be accomplished by incubation with *Bacillus megaterium*.<sup>13</sup> The structure of naphthomycin has been shown by degradation studies to be (17), the OH group being *peri*, as originally suggested by Reinhart.<sup>14</sup> Two metabolites of the sponge *Iathella basta*, possessing antimicrobial activity and named bastadin-1 and bastadin-2, have the peptide tyrosinyl structures (18; R = H) and (18; R = Br) respectively.<sup>15</sup>



<sup>10</sup> E. J. Corey, L. O. Weigel, A. R. Chamberlin, and B. Lipshutz, *J. Am. Chem. Soc.*, 1980, **102**, 1439.

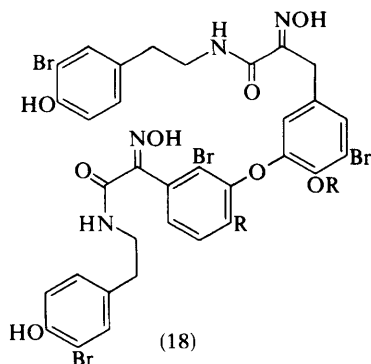
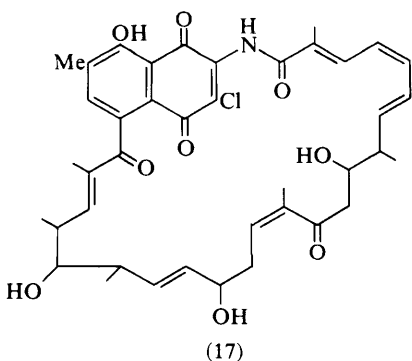
<sup>11</sup> A. I. Meyers, D. M. Roland, D. L. Comins, R. Henning, M. P. Fleming, and K. Shimizu, *J. Am. Chem. Soc.*, 1979, **101**, 4732.

<sup>12</sup> N. Hashimoto and T. Kishi, Ger. Offen. 2 911 248 (*Chem. Abstr.*, 1980, **92**, 94 449).

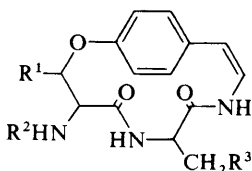
<sup>13</sup> A. Mitsuko, N. Kazuo, and I. Motowa, Eur. Pat. Appl. 4466 (*Chem. Abstr.*, 1980, **92**, 111 076).

<sup>14</sup> M. Brufani, L. Cellai, and W. Keller-Schierlein, *J. Antibiot.*, 1979, **32**, 167.

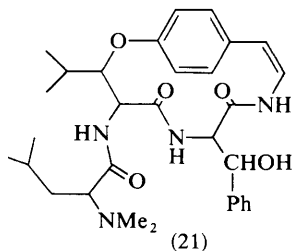
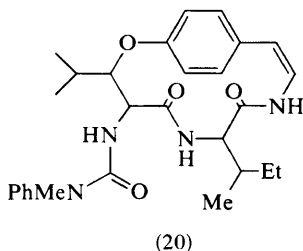
<sup>15</sup> R. Kazlauskas, R. O. Lidgard, P. T. Murphy, and R. J. Wells, *Tetrahedron Lett.*, 1980, **21**, 2277.



The four new cyclopeptide alkaloids (19a)—(19d) isolated from the shrub *Ceanothus integerrimus* contain a *para*-bridged fourteen-membered-ring nucleus (19), for which the name phencyclopeptine has been proposed.<sup>16</sup> The crude alkaloidal extract from *Ceanothus sanguineus*<sup>17</sup> showed the presence of five major components on composite field-desorption mass spectrometry. H.p.l.c., however, yielded six alkaloids, two of which were isomeric and one of which was a new alkaloid (20). The bark of *Scutia buxifolia* contains five scutianine alkaloids (B, C, D, E, and H); H is new, and is (21).<sup>18</sup> Two new cyclopeptides, sativanines A and B, have been identified as (22) and (23) by m.s.—n.m.r. study.<sup>19</sup>



- (19) a;  $R^1 = \text{Ph}$ ,  $R^2 = \text{MeVal}$ ,  $R^3 = 3\text{-indolyl}$   
 b;  $R^1 = \text{CHMe}_2$ ,  $R^2 = \text{Me}_2\text{Val}$ ,  $R^3 = 3\text{-indolyl}$   
 c;  $R^1 = \text{Ph}$ ,  $R^2 = \text{Me}_2\text{Ile}$ ,  $R^3 = \text{CH}_2\text{Ph}$   
 d;  $R^1 = \text{Ph}$ ,  $R^2 = \text{Melle}$ ,  $R^3 = \text{CH}_2\text{CHMe}_2$

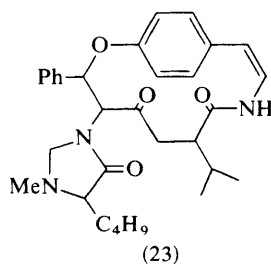
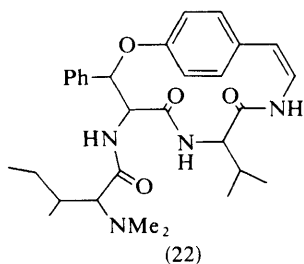


<sup>16</sup> J. C. Lagarias, D. Goff, F. K. Klein, and H. Rapoport, *J. Nat. Prod.*, 1979, **42**, 220.

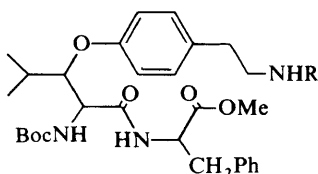
<sup>17</sup> J. C. Lagarias, D. Goff, and H. Rapoport, *J. Nat. Prod.*, 1979, **42**, 663.

<sup>18</sup> A. F. Morel, R. van Fossen Bravo, F. de A. M. Reis, and E. A. Ruveda, *Phytochemistry*, 1979, **18**, 473.

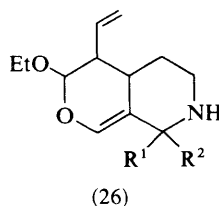
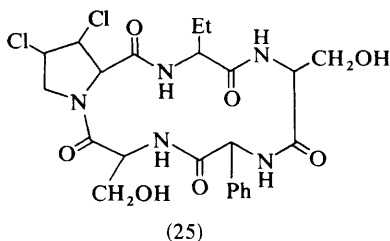
<sup>19</sup> R. Tschesche, A. H. Shah, and G. Eckhardt, *Phytochemistry*, 1979, **18**, 702.



The first and second papers in a series on medicinal plants of Pakistan report the presence of thirteen-membered cyclopeptide alkaloids in the leaves of *Cocculus villosus*<sup>20</sup> and in their stems.<sup>21</sup> A study on the cyclization of 'ansapeptides', e.g. (24), has shown that the fourteen-membered ring was not obtained from (24; R = H) but that fifteen-, sixteen-, and seventeen-membered rings were produced from (24; R = COCH<sub>2</sub>NH<sub>2</sub>).<sup>22</sup>



A potent toxin produced by *Penicillium islandicum* has been characterized<sup>23</sup> by mass spectroscopy combined with partial acid hydrolysis, and shown to possess structure (25). Three alkaloids isolated from the Egyptian plant *Centaurium spicatum* (which is used for the treatment of hypertension) are (26; R<sup>1</sup>R<sup>2</sup> = O), its methoxy-acetal (26; R<sup>1</sup> = OH, R<sup>2</sup> = OMe), and spicatine.<sup>24</sup>



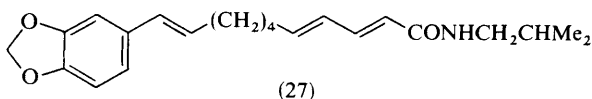
<sup>20</sup> M. I. D. Chughtai, I. Khokhar, A. Ahmad, U. Ghani and M. Anwar, *Pak. J. Sci. Res.*, 1979, **31**, 79 (*Chem. Abstr.*, 1980, **92**, 90 933).

<sup>21</sup> M. I. D. Chughtai, I. Khokhar, A. Ahmad, I. Ahmad, and A. Rehman, *Pak. J. Sci. Res.*, 1979, **31**, 237 (*Chem. Abstr.*, 1980, **92**, 90 949).

<sup>22</sup> F. Rocchicciolo, F.-X. Jarreau, and M. Païs, *Tetrahedron*, 1978, **34**, 2917.

<sup>23</sup> R. J. Anderegg, K. Biemann, A. Manmade, and A. C. Ghosh, *Biomed. Mass Spectrom.*, 1979, **6**, 129.

<sup>24</sup> D. W. Bishay, S. A. Ross, and P. J. Hylands, *Planta Med.*, 1979, **37**, 253.



A new Piperaceae amide, pipericide (27), obtained from the fruits of *Piper nigrum*, shows insecticidal activity against the adzuki bean weevil.<sup>25</sup> New pungent compounds of the capsaicinoid group have been isolated from the fruits of *Capsicum annuum* var. *annuum*.<sup>26</sup>

#### 4 Alkaloid-containing Plants and Unclassified Alkaloids

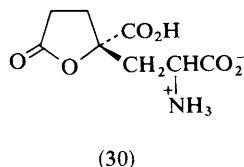
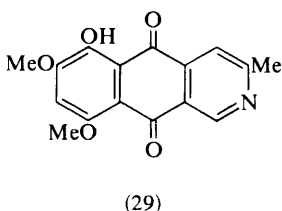
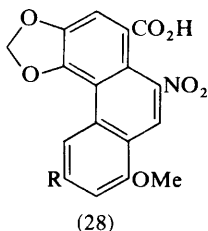
A review of isoxazole compounds (covering the period 1963—1977) discusses their synthesis, reactivity, and physiological and physicochemical properties; naturally occurring and biologically active isoxazoles are included.<sup>27</sup> Some Saudi Arabian plants have been screened for alkaloids.<sup>28</sup> Aristolochic acids I (28: R = H) and D (28: R = OH), which are cytotoxic to mammalian systems, are also cytotoxic to non-tumorous plant cells.<sup>29</sup>

##### *Fusarium moniliforme*

This fungal parasite of the Gramineae contains four dark-red pigments;<sup>30</sup> they are the naphthaquinones javanicin, solaniol, and fusarubin together with the structurally related alkaloid 8-*O*-methylbostrycoidin (29).

##### *Lycoperdon perlatum*

Lycoperdic acid (30), as well as its ring-opened compound  $\text{HO}_2\text{C}(\text{CH}_2)_2\text{C}(\text{OH})-(\text{CO}_2\text{H})\text{CH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$ , have been isolated from this common forest mushroom.<sup>31</sup>



<sup>25</sup> M. Miyakado, I. Nakayama, H. Yoshioka, and N. Nakatani, *Agric. Biol. Chem.*, 1979, **43**, 1609 (*Chem. Abstr.*, 1979, **91**, 154 269).

<sup>26</sup> J. Jurenitsch, M. David, F. Heresch, and W. Kubelka, *Planta Med.*, 1979, **36**, 61.

<sup>27</sup> B. J. Wakefield and D. J. Weight, *Adv. Heterocycl. Chem.*, 1979, **25**, 148.

<sup>28</sup> W. S. Woo, H. J. Chi, and H. S. Yun, *Saengyak Hakhoe Chi (Han'guk Saengyak Hakhoe)*, 1977, **8**, 109 (*Chem. Abstr.*, 1980, **92**, 107 337).

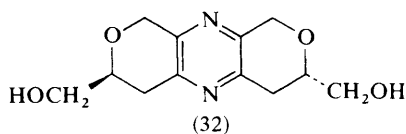
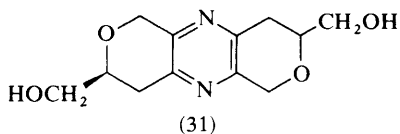
<sup>29</sup> C. Moretti, M. Rideau, J. C. Chenieux, and C. Viel, *Planta Med.*, 1979, **35**, 360.

<sup>30</sup> P. S. Steyn, P. L. Wessels, and W. F. O. Marasas, *Tetrahedron*, 1979, **35**, 1551.

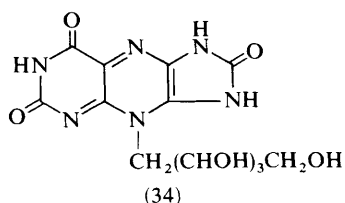
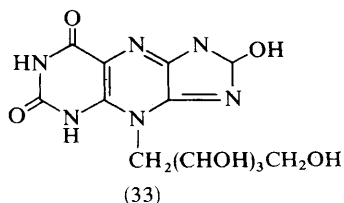
<sup>31</sup> N. Rhugenda-Banga, A. Welter, J. Jadot, and J. Casimir, *Phytochemistry*, 1979, **18**, 482.

*Palythoa tuberculosa*

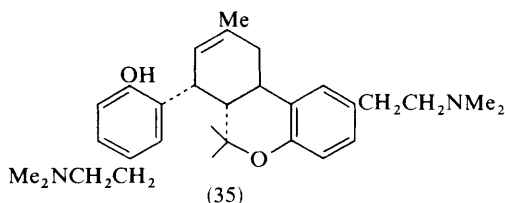
Two isomeric compounds possessing a pyrazine ring system, palythazine (31), and isopalythazine (32), have been obtained from this zoanthid, which is native to Japan.<sup>32</sup>

*Russula* species

Five yellow pigments have been obtained from a species of this fungus; two, named RP-yellow<sub>I</sub> and RP-yellow<sub>IV</sub>, are the lumazine derivatives (33) and (34) respectively.<sup>33</sup>

*Zanthoxylum punctatum*

A new alkaloid, which is structurally related to the cannabinoids and named alfileramine (35), has been obtained from the leaves of this Rutaceous plant.<sup>34</sup>



<sup>32</sup> D. Uemura, Y. Toya, I. Watanabe, and Y. Hirata, *Chem. Lett.*, 1979, 1481.

<sup>33</sup> P. X. Iten, H. Maerki-Danzig, and C. H. Eugster, *Dev. Biochem.*, 1978, **4**, 105 (*Chem. Abstr.*, 1979, **91**, 52 712).

<sup>34</sup> M. A. Caolo and F. R. Stermitz, *Tetrahedron*, 1979, **35**, 1487.

# Author Index

---

- Aasen, A. A., 52  
 Aasen, A. J., 204  
 Aasen, A. O., 112  
 Abalina, N. S., 82  
 Abbott, B. J., 139  
 Abd El Rahman, A. E. R., 90  
 Abdullaev, N. D., 209  
 Abdullah, N. P., 58  
 Abdullaeva, D. U., 235, 237  
 Abdullaeva, Kh. A., 71  
 Abdullah, M. I., 137  
 Abdusamatov, A., 132  
 Abe, M., 22, 157  
 Aboul-Enein, M. N., 78  
 Achenbach, H., 171, 184  
 Acheson, R. M., 35  
 Achimov, D. L., 34  
 Ackermann, R. F., 108  
 Acklin, W., 24, 146  
 Acocella, M., 107  
 Adam, G., 228, 229, 231  
 Adams, K. A. H., 199  
 Adams, R. J., 96, 114  
 Adamska, M., 40  
 Adanin, V. M., 157  
 Aggarwal, N. D., 42  
 Aghajanian, G. K., 78  
 Agyemang, N. O., 101, 119  
 Ahmad, A., 242  
 Ahmad, I., 95, 242  
 Ahmad, R., 125  
 Ahmad, V. U., 138  
 Aikat, B. K., 56  
 Akasu, M., 124  
 Akbarov, Z. S., 95  
 Akgun, S., 116  
 Akhter, M. A., 94  
 Akinloye, B. A., 166  
 Akinniyi, J. A., 30  
 Akiyama, T., 158  
 Akramov, S. T., 58  
 Alam, S. N., 199  
 Albonico, S., 114  
 Albonico, S. M., 44  
 Alder, M. W., 110  
 Alder, R. W., 3  
 Aldrete, J. A., 109  
 Aleixandre, A., 110  
 Ali, E., 99, 230  
 Ali, S. A., 60  
 Aliiev, Kh. U., 95  
 Allen, D. R., 106  
 Allen, J. K., 21  
 Altomani, L., 78  
 Al-Yahya, M. A. I., 36  
 Ames, M. M., 57  
 Amin, A. F., 76  
 Amir, S., 111  
 Amit, Z., 111  
 Amiya, T., 207  
 Ampofo, S. A., 85  
 Anderegg, R. J., 242  
 Anderson, J. A., 22  
 Ando, K., 88  
 Andriamialisoa, R. Z., 179, 185, 192, 195  
 Andriantsiferana, M., 190  
 Andu, K., 42  
 Angenot, L., 174, 191  
 Anisimov, Yu. Z., 110  
 Anita, J., 80  
 Anokhina, I. P., 108  
 Antonio, R. P., 85  
 Antsupova, T. P., 235  
 Anwar, M., 242  
 Arata, Y., 95  
 Archer, S., 105  
 Ardentova, N. N., 112  
 Arguelles, J. E., 109  
 Arigoni, D., 24, 146  
 Arinbasarov, M. U., 157  
 Aripov, T. F., 67  
 Arndt, J. O., 111  
 Arnold, E., 148  
 Arnold, E. V., 23, 160  
 Arnsten, A. T., 111  
 Asharobi, R. B., 85  
 Ashcroft, S. B., 112  
 Ashcroft, W. R., 167  
 Assem, E. M., 114  
 Assi, L. A., 175  
 Atal, C. K., 31, 53, 58, 76  
 Atanakovic, D., 109  
 Ateya, A.-M. M., 101, 119, 213  
 Atta-ur-Rahman, 185  
 Aulakh, O. S., 42  
 Avendano, C., 40  
 Awazi, N., 82  
 Ayafor, J. F., 71  
 Ayer, W. A., 199  
 Ayim, J. S. K., 101, 119  
 Aylsworth, C. F., 111  
 Aynechi, Y., 87  
 Azari, J., 57  
 Azov, R., 109  
 Bac, N. V., 19  
 Bacharach, U., 110  
 Bachtet, B., 145  
 Backer, R. C., 107  
 Bacon, C. W., 159  
 Bacotti, A., 109  
 Badawi, M. M., 198  
 Bagley, J. R., 42  
 Balakrishnan, V., 88  
 Baldessarini, R. J., 117  
 Baldino, F., 110  
 Baldwin, J. E., 28  
 Balestrieri, B., 43  
 Balkon, J., 108  
 Ballesteros, P., 40  
 Balsevich, J., 194  
 Bando, H., 207  
 Bandyopadhyay, S., 170  
 Banerjee, A. K., 223  
 Banfi, D., 80  
 Banholzer, R., 43  
 Bannister, S. J., 100  
 Baoua, M., 33  
 Baradarani, M. M., 175  
 Barakat, I. E., 137  
 Baranov, A. G., 82  
 Barnes, M. F., 212  
 Barnett, C. J., 187  
 Barr, G. A., 78  
 Barrow, K. D., 21  
 Barrow, S. E., 198  
 Basharova, L. A., 110  
 Bashir, M., 204  
 Batcho, A. D., 149  
 Bates, H. A., 39  
 Batra, V. K., 112  
 Bauer, M., 198  
 Baum, M. J., 111  
 Bauman, J., 112  
 Baumgartner, A. M., 108  
 Baumgartner, W. A., 108  
 Baxter, R. L., 33  
 Baytop, T., 94  
 Bazalitskaya, V. S., 228  
 Beal, J. L., 78, 83, 84, 119, 129, 204  
 Beani, L., 110  
 Beaton, J. M., 109  
 Beaumier, P. L., 106  
 Beaumont, D., 80  
 Beck, A. B., 63  
 Beckman, A. L., 110  
 Beebe, D. C., 116  
 Beijersbergen van Henegouwen, G. M. J., 100  
 Beisler, J. A., 185  
 Bell, E. A., 33, 54  
 Bell, K. L., 60

- Belenky, G. L., 111  
 Belleau, B. R., 113  
 Belletire, J. L., 186  
 Bellodi, L., 112  
 Beloyartsev, F. F., 109  
 Belzecki, C. M., 23  
 Benages, I. A., 114  
 Benalal, D., 110  
 Bender, K. I., 110, 112  
 Benn, M. H., 53, 206  
 Bennett, G. J., 108  
 Bentley, K. W., 101, 102  
 Beran, M., 160  
 Berchtold, G. A., 34  
 Berenyi, S., 101  
 Bergenthal, D., 145  
 Berghem, L., 42  
 Bergman, U., 42  
 Berka, C., 112  
 Berkman, K., 110  
 Berkowitz, B. A., 108  
 Berkowitz, D. S., 106  
 Bernadou, J., 174  
 Bernath, J., 101  
 Berndt, W. O., 109  
 Bernston, G. G., 112  
 Bert, M., 153  
 Beshitaishvili, L. V., 208, 217  
 Bessiere, J.-M., 33  
 Besselièvre, R., 167  
 Bessho, N., 114  
 Besson, J. M., 108, 111  
 Bessonova, I. A., 71  
 Bevalot, F., 87  
 Beyerman, H. C., 101, 238  
 Bezanson, G. S., 28  
 Bhacca, N. S., 79, 119  
 Bhakuni, D. S., 10, 11, 14, 138  
 Bhatia, M. L., 56  
 Bhatt, H. V., 85  
 Bhattacharya, S. K., 79, 117  
 Bhaumik, P. K., 79, 119  
 Bhide, M. B., 85  
 Bhide, N. K., 94  
 Bhise, S. B., 85  
 Bian, C. F., 43  
 Bianchine, J., 79  
 Bick, I. R. C., 20, 29, 82, 160, 161  
 Bidanset, J. H., 108  
 Biemann, K., 242  
 Binkley, E. S., 200  
 Birbaeva, G. N., 32  
 Birecka, H., 52  
 Birkhahan, J., 109  
 Bishay, D. W., 242  
 Black, C. T., 108  
 Blade-Font, A., 115  
 Bladon, P., 185  
 Blair, R., 111  
 Blake, P. A., 129  
 Blanchette-Mackie, E. J., 116  
 Blaskó, G., 169  
 Blau, S., 116  
 Blomster, R. N., 129  
 Blount, J. F., 149  
 Blum, K., 79  
 Blum, M. S., 30  
 Bobbitt, J. M., 14  
 Bobkiewicz, T., 94, 114  
 Bobkova, V. M., 109  
 Bodem, G. B., 31  
 Bodnar, R. J., 108, 111  
 Bodycote, I. J., 112  
 Boekkamp, C. L., 109  
 Boeva, A., 53  
 Boeyens, J. C. A., 158  
 Bognar, R., 80, 95, 101  
 Bohlmann, F., 47, 53  
 Boizard, F., 110  
 Bond, R. F., 158  
 Bondarenko, N. V., 235  
 Bonetti, S., 52  
 Boppré, M., 54  
 Borges, J., 166  
 Borisov, M. M., 110  
 Borka, L., 53  
 Born, C. K., 110  
 Bornstein, J., 110  
 Borrell, J., 110  
 Borrell, S., 110  
 Bose, R., 79, 117  
 Boss, J. H., 115  
 Botta, M., 218  
 Bottaro, J. C., 34  
 Bourgeois, J., 63  
 Bowen, I. H., 71  
 Boyman, R., 109  
 Bradley, V., 227  
 Bradshaw, D., 115  
 Brady, O. L., 207  
 Brambilla, F., 112  
 Brands, B., 111  
 Brandt, S., 140  
 Brassy, C., 145  
 Bratek-Wiewiórska, M. D., 64, 65  
 Brazdovicova, B., 128  
 Brazile, J., 85  
 Brenner, M., 116  
 Brenner, R. C., 71  
 Brettell, T. A., 108  
 Brice, J. E. H., 111  
 Bridger, W. H., 78  
 Broch-Due, A. I., 52  
 Broquist, H. P., 7  
 Brossi, A., 79, 80, 86, 115, 120  
 Brous, M., 108  
 Brown, D. M., 238  
 Brown, D. R., 111  
 Brown, J. J., 101  
 Brown, K. D., 116  
 Brown, R. T., 99, 162, 165, 167, 197  
 Brufani, M., 76, 240  
 Bruinvels, J., 110  
 Bruneton, J., 170  
 Bruni, J. F., 108, 109  
 Brunner, R., 158  
 Buckett, W. R., 112  
 Buckland, P. R., 26  
 Budd, R. D., 107  
 Budzikiewicz, H., 59, 71  
 Büchi, G., 152, 186  
 Bugsch, L. A., 109  
 Bui, A. M., 171  
 Bulaev, V. M., 110  
 Bull, L. B., 50  
 Burghart, J., 239  
 Burks, T. F., 108, 112  
 Burrow, B. F., 37  
 Bush, L. P., 2  
 Buzas, A., 183  
 Byng, G. S., 25  
 Byrd, L. D., 42  
 Cabelli, M. D., 16  
 Cabral, J. R. P., 57  
 Cahill, R., 2  
 Cain, P. A., 115  
 Campbell, H. F., 37  
 Campos Neves, A. da S., 36  
 Campos Neves, M. T., 36  
 Caolo, M. A., 71, 244  
 Capasso, F., 43  
 Capasso, L., 43  
 Caplan, Y. H., 107  
 Capps, T. M., 12  
 Capraro, H. G., 115  
 Caraballo, P. C., 223  
 Cardellino, J. H., 145  
 Carlé, J. S., 153  
 Carlson, E. C., 116  
 Carmody, J. J., 112  
 Carrasco, M. A., 112  
 Carrasco, M. C., 223  
 Carrol, P. R., 112  
 Carson, D. L., 113  
 Caruso, T. P., 113  
 Casagrande, C., 117  
 Cashaw, J. L., 82  
 Casimir, J., 243  
 Cassels, B. K., 82, 125, 129  
 Castaldo, S., 43  
 Castedo, L., 128  
 Castellano, C., 78, 112  
 Castillo, M., 199  
 Castonguay, A., 35  
 Cava, M. P., 130  
 Cavé, A., 86, 87, 117, 125, 166, 170, 171, 177, 196  
 Cavillo, O., 109  
 Cazzullo, C. L., 112  
 Cellai, L., 240  
 Cerrera, K. V., 108  
 Chai, C. Y., 112  
 Chaichit, N., 160  
 Chakraborty, D. P., 75, 145  
 Chakravarty, A. K., 230



- Chamberlin, A. R., 240  
 Chan, S. H. H., 110  
 Chan, V., 112  
 Chance, W. T., 108  
 Chang, C. C., 24  
 Chang, C. J., 78  
 Chang, M. N. T., 15  
 Chang, T. C., 37  
 Channon, R. T., 121  
 Chardon-Loriaux, I., 190  
 Charles, G., 225  
 Charuzi, I., 115  
 Chaskes, M. J., 52  
 Chatterjee, A., 170, 191  
 Chatterjee, S., 222  
 Chatterjee, S. K., 232  
 Chatterjee, N., 101  
 Chattopadhyay, S. C., 41  
 Chatson, K. B., 19  
 Chaturvedi, H. C., 233  
 Chaturvedi, R., 10  
 Chaudhuri, R. K., 232  
 Chen, C.-H., 85, 86  
 Chen, C. M., 120  
 Chen, H.-I., 86  
 Chen, H. T., 108, 109  
 Chen, X.-L., 112  
 Cheng, L.-J., 22  
 Cheng, Y.-C., 88  
 Chenieux, J. C., 243  
 Cheon, Y. S., 111  
 Cheshier, G. B., 112  
 Chhuttani, P. N., 56  
 Chi, H. J., 243  
 Chiang, H.-C., 88  
 Chiaroni, A., 87, 188  
 Chiba, K., 179  
 Chinnasamy, P., 93, 204  
 Chinoy, J. J., 232  
 Chitnis, M., 198  
 Cho, D., 112  
 Choi, L. S. L., 19  
 Chow, J., 206  
 Chowdhury, A. R., 233  
 Chowdhury, B. K., 76  
 Christian, J. C., 43  
 Christian, J. J., 112  
 Christophersen, C., 153  
 Chu, J., 237  
 Chu, T., 236  
 Chughtai, M. I. D., 242  
 Chun, Y. T., 94  
 Chvapil, M., 116  
 Ciardetti, A., 107  
 Cionga, E., 33  
 Clardy, J., 23, 24, 146, 147, 148, 160  
 Clark, W. C., 108  
 Clark, W. G., 117  
 Clarke, D. D., 101  
 Clarke, M., 51  
 Clarke, P. J., 148  
 Clastres, A., 171  
 Clauder, O., 178  
 Clausen, T., 141  
 Clement-Cormier, Y. C., 94  
 Clevenstone, E. C., 7  
 Clingbine, G., 116  
 Clouet, D. H., 109  
 Cloyd, J. C., 28  
 Codding, P. W., 206  
 Coggon, P., 139  
 Cohen, I., 85  
 Cohen, J. F., 4  
 Cohylakis, D., 175  
 Colapret, J. A., 31  
 Colau, B., 32  
 Cole, R. J., 147  
 Colegate, S. M., 59  
 Collins, D. J., 227  
 Collins, J. P., 42  
 Collins, M. A., 79  
 Colombo, M., 115  
 Comer, F., 4  
 Comins, D. L., 239, 240  
 Cone, E. J., 107  
 Connolly, J. D., 30  
 Constabel, F., 19  
 Contz, O., 33  
 Cools, A. R., 109  
 Cordell, G. A., 174, 188, 192, 198  
 Córdova B., H. E., 148  
 Corey, E. J., 240  
 Cormier, R. A., 40  
 Cornforth, J., 222  
 Cosson, J. P., 167  
 Costall, B., 117  
 Costentin, J., 109  
 Court, W. E., 166, 167  
 Coutts, I. G. C., 14  
 Cowan, A., 110  
 Cox, B., 110  
 Cox, R. H., 151  
 Coxon, D. T., 232, 233  
 Crabb, T. A., 43  
 Crabbé, P. G., 232  
 Craig, C. C., 43  
 Creagan, E. T., 57  
 Creasey, W. A., 94  
 Cremaschi, D., 116  
 Crespi-Perellino, N., 23  
 Crispo, C., 199  
 Critchley, S. R., 35  
 Crombie, L., 33  
 Crombie, W. M. L., 33  
 Crossley, A. W. A., 108  
 Crout, D. H. G., 2, 48  
 Croxatto, R., 109  
 Crumley, F. G., 151  
 Csendes, I. G., 48  
 Cubbedu-Ximenez, L., 82  
 Culvenor, C. C. J., 44, 50, 51  
 Cutler, H. G., 151  
 Dadisch, G. L., 107  
 Dafeldecker, W. P., 117  
 Dafny, N., 108, 109  
 Dagan, L. A., 42  
 Daily, A., 63  
 Dalton, D. R., 29  
 Daly, J. W., 60  
 Dalzell, H. C., 102  
 Dan, S., 230  
 Dan, S. S., 232  
 Dang, J. F., 43  
 Danieli, B., 190, 191  
 Danishefsky, S., 135  
 Darling, D. S., 24  
 Darwin, W. D., 107  
 Das, B. C., 167  
 Das, N. V., 26  
 Dasgupta, S., 31, 79, 95, 96, 117  
 Datta, D. V., 56  
 David, M., 243  
 Davidson, D., 116  
 Davies, M. E., 232  
 Davis, M., 108  
 Davis, N. D., 157  
 Davis, V. E., 82, 94  
 Davis, W. M., 111  
 Deacon, R. M. J., 111  
 Deadwyler, S. A., 110  
 DeBoer, C., 55  
 Debray, M. M., 171  
 DeCamp, W. H., 208  
 De Groot, J. A., 101  
 de Kok, A. J., 63, 65  
 De La Baume, S., 109  
 de la Fuente, G., 204  
 Delaveau, P., 165  
 Delfel, N. S., 16  
 De Lima, R. A., 148  
 Della Casa de Marcano, D. P., 139  
 De Maio, D., 112  
 Demetriou, S., 111  
 Demuth, T. P., 34  
 Desai, H. K., 203, 209, 212, 213, 216  
 Desai, J. D., 232  
 Desai, S. R., 181  
 DeShong, P. R., 152  
 De Silva, S. O., 95  
 De Sosa, G. Z., 228  
 Despreaux, C. W., 167  
 Dettmar, P. W., 110  
 Dewey, W. L., 111  
 Dews, P. B., 42  
 Dhar, K. L., 31, 76  
 Dhar, T. K., 230  
 Dias, R. D., 112  
 Dick, A. T., 50  
 Dideberg, O., 191  
 Diener, U. L., 157  
 Dime, D., 97  
 Dimenna, G. P., 55  
 Di Miceo, J. A., 96  
 Dinnendahl, V., 111  
 Djarmati, Z., 207  
 Djerassi, C., 37, 209, 212

- Djura, P., 148  
 Dobremenez, J. F., 63  
 Dobronravova, E. K., 95, 217  
 Doepke, W., 131, 132, 229  
 Dolak, L. A., 55  
 Dolan, R., 40  
 Dolejs, C., 174  
 Dolejs, L., 86, 94, 95  
 Dominguez, D., 128  
 Domino, E. F., 111  
 Donzanti, B. A., 109  
 Dorling, P. R., 59  
 Dornbush, R., 112  
 Doskotch, R. W., 78, 83, 84, 119, 129  
 Dostalova, K., 43  
 Downs, D. A., 112  
 Drake, A. F., 187  
 Dreyer, D. L., 71  
 Drost-Karbowska, K., 94  
 Drozdovskaya, L. N., 100  
 Drysdale, R. B., 233  
 Dubick, M. A., 100  
 Dudar, J. D., 43  
 Dufresne, R. F., 16  
 Duka, T., 109  
 Duke, P. C., 109  
 Dum, J., 108  
 Duncalf, D., 112  
 Duncalf, R. M., 112  
 Dupont, L., 191  
 Duquette, P. H., 107  
 Durgeat, M., 145  
 Dutshevskaya, Kh., 63  
 Dvořáčková, S., 53  
 Dvornik, D., 208  
 Dwoskin, L. P., 112  
 Dwuma-Badu, D., 85, 101, 119  
 Dyke, S. F., 80, 129  
 Dykstra, L., 109  
 Dzhakhangirov, F. N., 217  
  
 Eargle, D., 78  
 Easler, M. E., 42  
 Eastwood, F. W., 227  
 Eckhardt, G., 241  
 Edelman, N. H., 109  
 Edgar, J. A., 50, 51, 54, 57  
 Edwards, O. E., 37, 208  
 Edwards, W. B., 34  
 Eggers, N. J., 59  
 Eggert, J. H., 28  
 Eid, A. I., 78  
 Eikelboom, R., 111  
 Eisenstein, D., 57  
 El Azizi, M. M., 85, 101, 119  
 Elder, J. W., 37  
 Elema, E. T., 232  
 Elguero, J., 115  
 El-Hossary, G., 54  
 Ellingboe, J., 112  
 Elliott, M. L., 78  
  
 Ellman, S. J., 108  
 Elmaleh, D. R., 106, 123  
 El-Menshaw, B., 54  
 El-Sayed, A., 192  
 Endo, K., 203, 239  
 Endoh, M., 82  
 Engler, J., 80  
 Englert, L. F., 42  
 Enomoto, Y., 82  
 Epe, B., 140, 141  
 Epe, M., 140, 141  
 Ermes-Busio, M. E. C., 111  
 Eroglu, L., 108  
 Ertel, N. H., 116  
 Ertola, R., 228  
 Eshbaev, F. Sh., 68  
 Esposito, R. V., 108  
 Estevez, V. S., 42  
 Etherington, T., 24  
 Etienne, J. P., 32  
 Eugster, C. H., 244  
 Eustace, D. C., 25  
 Evans, D. A., 115  
 Evans, J. V., 55, 126  
 Evans, W. C., 36  
 Everett, E. H., 42  
 Evstigneeva, R. P., 80  
 Extein, I., 111  
  
 Faber, L., 59  
 Faden, A. I., 111  
 Fajardo, V., 82  
 Fales, H. M., 30  
 Fan, S.-G., 112  
 Farnsworth, N. R., 129, 174, 198  
 Farnum, S. A., 115  
 Faugeras, G., 63  
 Faulkner, D. J., 148  
 Fauré, R., 115  
 Feagans, D. E., 116  
 Fedeli, W., 76  
 Feeney, J., 41  
 Felby, S., 108  
 Fellows, L. E., 33  
 Ferrari, G., 117, 148  
 Ferreira, S. H., 111  
 Ferretti, F., 228  
 Ferris, M. J., 35  
 Fertel, R. H., 79  
 Fields, H. L., 110  
 Figdor, S. K., 212  
 Filer, C. N., 121, 126  
 Findlay, J. W. A., 108  
 Finer, J., 146  
 Finer-Moore, J., 207, 209, 216  
 Fink, A. D., 108  
 Finnerty, E. P., 110  
 Fischer, C., 140, 141  
 Fischman, M. W., 42  
 Flieger, M., 160  
 Fleischhacker, W., 104, 105  
 Fleming, M. P., 240  
  
 Flood, M. E., 25  
 Floss, H. G., 22, 23, 160  
 Fodor, G., 39, 41  
 Foldes, F., 112  
 Ford, D. H., 109  
 Ford, J. E., 233  
 Formaniak, M., 108  
 Forn, G. P., 172  
 Forrest, G., 34  
 Forrest, J. M. S., 233  
 Fortune, D. N., 117  
 Foster, R., 41  
 Foxman, B. M., 15  
 Foy, J. E., 82  
 Frahn, J. L., 51  
 Franatovic, Y., 109  
 Francis, M. M., 26  
 Frank, G. B., 111  
 Franko, J. B., 30  
 Freer, A., 102  
 French, E. D., 108, 109  
 Frenk, H., 112  
 Frensch, K., 106  
 Frey, A. J., 158  
 Frey, G. A., 43  
 Frey, L. G., 109  
 Freze, E., 111  
 Friberg, U., 116  
 Frid, M., 112  
 Friedkin, M., 116  
 Friedler, G., 109  
 Fries, D. S., 113  
 Frisse, M., 53  
 Frohlich, M. W., 52  
 Fryer, C., 232  
 Fuganti, C., 156  
 Fuji, K., 32  
 Fujii, H., 73  
 Fujii, M., 56  
 Fujii, S., 114  
 Fujii, T., 99, 168  
 Fujimoto, H., 158  
 Fujita, E., 32  
 Fujiwara, T., 60, 114  
 Fukaya, C., 62  
 Fukumoto, K., 82, 169  
 Fukushima, S., 31  
 Fulmore, W., 101  
 Funayama, S., 239  
 Furukawa, H., 118, 139  
 Furukawa, T., 42  
 Furuya, T., 56  
 Fushimi, T., 133  
  
 Gaal, G., 95  
 Gabetta, B., 190, 191  
 Gafurova, Sh. M., 63  
 Gaiduk, R. I., 57  
 Gainsford, G. J., 50  
 Gairola, C., 26  
 Galeffi, C., 165, 174  
 Gallagher, R. T., 24, 146, 158, 161  
 Gallup, G. G., 111

- Games, D. E., 137  
 Gammill, R., 135  
 Ganguly, A. N., 231  
 Garcia, J. F., 108  
 Garia de Jalon, P. D., 110  
 Garrett, E. R., 108  
 Gasheva, A. Ya, 32  
 Gasi, K., 228  
 Gaskell, A. J., 175  
 Gatehouse, B. M., 160  
 Gaston, J. L., 74  
 Gatti, G., 156  
 Gawróński, J., 67  
 Gaylord, J. C., 108  
 Gazdag, M., 160  
 Gdaniec, M., 63  
 Geber, G. L., 96  
 Geissman, T. A., 46  
 Gelbaum, L., 52  
 Gellert, E., 129  
 Genc, E. C., 110  
 Genenah, A. A., 62  
 George, R., 108, 109  
 Geran, R. I., 139  
 Gerecke, M., 120  
 Gerhard, A., 76  
 Gerrans, G. C., 62  
 Gerritsma, K. W., 100  
 Gesma, D., 116  
 Gessa, G. L., 111, 112  
 Gesztes, K., 178  
 Geyer, M. A., 78  
 Gfeller, J. C., 43  
 Ghanbarpour, A., 95  
 Ghani, U., 242  
 Ghatak, U. R., 224  
 Ghoneim, K. M., 78  
 Ghoneim, M. M., 43  
 Ghosh, A. C., 242  
 Ghosh, B., 42  
 Gibbons, J. L., 78  
 Giesbrecht, A. M., 148  
 Gillard, J. W., 29  
 Gillis, R. A., 96  
 Girotra, N. N., 34  
 Giroud, J. P., 115  
 Gitterman, A., 16  
 Glennon, R. A., 78  
 Glusman, M., 111  
 Gnevkovskaya, T. V., 82  
 Godleski, S. A., 186  
 Goertzen, P., 109  
 Gössinger, E., 63  
 Goethert, M., 110  
 Goff, D., 241  
 Gokhale, A. M., 73  
 Gold, M. S., 111  
 Goldberg, L. I., 106  
 Goldspink, B. H., 63  
 Golebiewski, W. M., 4  
 Gombos, Z., 169  
 González, A. G., 204  
 Goodwin, T. E., 224  
 Gopichand, Y., 145  
 Gordon, M. M., 52  
 Gorelick, D. A., 78  
 Gorodetsky, W. C., 107  
 Goryaev, M. I., 228  
 Gossinger, E., 40  
 Goto, T., 157  
 Gottlieb, E., 232  
 Gottlieb, H. E., 148  
 Gottlieb, O. R., 148  
 Gough, A. N., 94  
 Goulart, M. O. F., 148  
 Gould, S. J., 24  
 Gourdiér, B., 179  
 Governo, T. F., 108  
 Gowdey, C. W., 111  
 Grambal, F., 94  
 Gramsch, C., 109  
 Grancai, D., 235  
 Granchelli, F. E., 106, 120, 121, 123, 126  
 Greco, M. N., 147  
 Gregory, P., 233  
 Green, J. F., 126  
 Greenberg, N. H., 139  
 Greenstein, R., 111  
 Greenwald, J. E., 79  
 Grierson, D. S., 173  
 Griffith, R. L., 43  
 Grinenko, G. S., 228  
 Grodetetskaya, N. S., 82  
 Gronostaj, K., 94, 114  
 Grout, R. J., 36  
 Grundon, M. F., 21, 73, 74  
 Guaza, C., 110  
 Guenard, D., 197  
 Guéritte, F., 19, 185  
 Guerreiro, E., 228  
 Guerrero, M., 108, 111  
 Guerrero-Munoz, F., 108, 111  
 Guest, I. G., 102  
 Guha, D., 85  
 Guha, R., 145  
 Guicciardi, A., 23  
 Guilhem, J., 33  
 Guinaudeau, H., 117  
 Guldborg, H., 82  
 Gumulka, S. W., 111  
 Gunasekera, S. P., 174, 198  
 Gungor, M., 110  
 Gupta, A. D., 56  
 Gupta, O. P., 31, 58  
 Gupta, R. C., 42  
 Gupta, R. K., 76  
 Gupta, R. N., 3  
 Gupta, S. C., 31  
 Gupta, Y. P., 120  
 Guseinov, D. Ya, 57  
 Gutsche, D. C., 37  
 Gutzwiller, J., 167  
 Guyda, H., 111  
 Guyot, M., 145  
 Haack, E., 168  
 Haarmann, L., 109  
 Habermehl, G. G., 62  
 Hadley, W. M., 41  
 Haga, M., 56  
 Hagaman, E. W., 177, 178, 232  
 Hahn, R. G., 57  
 Hai, M. A., 20, 160, 161  
 Halls, T. D. J., 169  
 Halsall, T. G., 139  
 Ham, J., 85  
 Hamada, M., 55  
 Hamaguchi, H., 88  
 Hamblin, M. R., 14, 21  
 Hamilton, M. G., 79  
 Han, J.-S., 112  
 Hanaoka, M., 92, 93, 94, 95, 96  
 Handa, K. L., 40  
 Handa, V. K., 31  
 Handy, G. A., 192  
 Hannigan, J. J., 79, 82  
 Hansford, G. S., 25  
 Hao, X.-J., 206  
 Hara, H., 88, 113  
 Haranath, P. S. R. K., 85  
 Harayama, T., 201  
 Hardy, D. G., 101  
 Hardy, R. A., 101  
 Harley-Mason, J., 185  
 Harrigan, S. E., 112  
 Harrington, S. M., 108  
 Harris, M., 173  
 Harris, T. M., 7  
 Harrison, D. M., 21, 226, 230, 231, 237  
 Harry, G. J., 112  
 Hart, D. J., 115  
 Hartenstein, J., 101, 123  
 Hartmann, T., 5, 6, 63  
 Haruki, K., 236  
 Haruna, M., 139, 140  
 Hasegawa, S., 173  
 Hashiba, M., 73  
 Hashimoto, N., 240  
 Hatakeyama, S., 100, 179, 183  
 Hatfield, G. M., 63  
 Hatoum, N. S., 111  
 Hayashi, K., 226, 227  
 Hayashi, M., 159, 168  
 Hayashi, Y., 57  
 Heading, C. E., 116  
 Heathcock, C. H., 200  
 Hecht, A., 109  
 Heftmann, E., 225  
 Heinstein, P., 19, 162  
 Heinz, G., 109  
 Heitz, S., 145  
 Helquist, P., 140  
 Hemscheidt, T., 17  
 Hengartner, U., 149  
 Henning, R., 239, 240  
 Henriques, A., 192  
 Henry, J. L., 109

- Herath, W. H. W. M., 166  
 Herbert, R. B., 1, 4, 20, 24, 25, 26  
 Heresch, F., 243  
 Herlihy, P., 102  
 Herran, J., 212  
 Herrmann, E.-G., 59  
 Herrmann, K., 227  
 Herscheid, J. D. M., 28  
 Herz, A., 108, 109, 111  
 Hess, U., 229  
 Hesse, M., 161  
 Heyndrickx, A., 78  
 Highet, R. J., 60  
 Hikichi, M., 56  
 Hikino, H., 239  
 Hindenlang, D. M., 91  
 Hinshaw, W. B., jun., 126  
 Hinz, H., 55  
 Hirai, Y., 169  
 Hirano, A., 158  
 Hirata, T., 19, 167  
 Hirata, Y., 203, 244  
 Hirobe, M., 101, 107  
 Hirono, I., 56  
 Hiroshi, H., 124  
 Hirotsu, K., 24, 146  
 Hirst, M., 111  
 Hitchcock, M. J. M., 26  
 Hite, G. J., 41, 42  
 Hladon, B., 94, 114  
 Ho, B. T., 42  
 Ho, I. K., 109, 111  
 Ho, W. K. K., 110  
 Hocquemiller, R., 86  
 Hodson, C. A., 111  
 Hoeck, P. G., jun., 85  
 Höfle, G., 19  
 Hölldobler, B., 30  
 Hoeltt, V., 108, 109  
 Hoff, R. J., 224  
 Hoffmann, I. S., 82  
 Hofmann, A., 158  
 Hogg, G. G., 57  
 Hohlbrugger, R., 97, 98  
 Holaday, J. W., 111  
 Holcslaw, T. L., 41  
 Holland, H. L., 12, 95, 199  
 Hollander, W., 115  
 Hollenbeak, K. H., 239  
 Holliman, F. G., 24, 25, 26  
 Holst-Larsen, H. H., 112  
 Holtzman, J. L., 107  
 Holzman, S. G., 111  
 Holubek, J., 160  
 Holzapfel, C. W., 158  
 Honda, G., 76  
 Honda, T., 195  
 Honma, M., 82  
 Honor, D. P., 28  
 Honty, K., 169  
 Hootel , C., 32, 68  
 Horcin, V., 232  
 Horii, Z., 117  
 Horio, Y., 42  
 Horiuchi, Y., 55  
 Hornemann, U., 28  
 Horning, E. C., 198  
 Horning, M. G., 198  
 Horsewood, P., 3, 4, 102  
 Hosaka, M., 88  
 Hosaka, S., 56  
 Hoser, A., 65  
 Hosino, O., 88, 113, 122, 124, 133  
 Hosoda, H., 233  
 Hoss, W., 108  
 Hosztafi, S., 101  
 Hotellier, F., 165  
 Howard, A. S., 62  
 Howell, C. F., 101  
 Howes, J. F., 101  
 Hrbek, J., 43  
 Huber, C. S., 41  
 Huebner, J. A., 182  
 Huen, J. M., 43  
 Hugel, G., 179  
 Huidobro, F., 109  
 Huidobro-Toro, J. P., 109  
 Huizing, H. J., 55  
 Hull, L., 52  
 Hull, W. E., 239  
 Humphrey, D. W., 127  
 Huong, H. Th., 228, 229, 231  
 Hurdnall, S. D., 78  
 Hurley, L. H., 26  
 Hurst, M., 79  
 Hurtado, H. E., 223  
 Hussain, S. F., 117  
 Husson, H.-P., 17, 162, 167, 173, 185, 190  
 Hutchinson, A. J., 154  
 Huxtable, C. R., 59  
 Huxtable, R., 57  
 Hylands, P. J., 165, 242  
 Ibberson, P. N., 24  
 Ibragimov, B. T., 67  
 Ibrahim, Y. A., 78  
 Ichikawa, K., 32  
 Ieiri, T., 108, 109  
 Ignatov, Yu. D., 110  
 Ihara, M., 87, 99, 117, 122, 154, 168  
 Itaka, Y., 31, 113, 132, 158  
 Ikeda, D., 55  
 Ikeda, M., 108  
 Ikeda, T., 55  
 Ikram, M., 127  
 Ikuta, H., 133  
 Imanishi, T., 92, 93, 94, 96  
 Indrayanto, G., 232  
 Inturrisi, C. E., 110  
 Inubushi, Y., 201  
 Invernizzi, R., 109  
 Irie, H., 34, 133  
 Irismetov, M. P., 228  
 Irvine, M. C., 227  
 Isaacson, H. V., 35  
 Ishbaev, A. I., 63  
 Ishida, T., 107  
 Ishii, H., 159  
 Islamov, B. I., 109  
 Isogai, A., 156  
 Isquierdo, I., 110  
 Israilov, I. A., 97, 117, 118, 128  
 Itaka, Y., 55  
 Iten, P. X., 244  
 Ito, H., 233  
 Ito, K., 139, 140  
 Iversen, S. D., 109  
 Iwai, K., 197  
 Iwai, Y., 158  
 Iwasa, K., 113, 114  
 Iwasa, N., 233  
 Iwashita, T., 45, 62  
 Iwase, M., 203  
 Iwata, C., 117  
 Iwatsubo, K., 110  
 Iwu, M. M., 167  
 Izquierdo, I., 112  
 Jackler, F., 108  
 Jackman, L. M., 125  
 Jackson, A. H., 137  
 Jackson, A. J., 108  
 Jacquemin, H., 86, 185  
 Jacquet, J. P., 183  
 Jadot, J., 243  
 Jaerbe, T. U. C., 112  
 Jago, M. V., 51  
 Jain, S., 10, 11, 14, 138  
 James, B., 112  
 James, K. J., 74  
 Janicki, P., 112  
 Janot, M.-M., 33  
 Jao, M. Y., 112  
 Jaouni, T., 30  
 Jarreau, F.-X., 242  
 Jeffs, P. W., 12  
 Jellema, R., 232  
 Jensen, R. A., 25  
 Jeretin, S., 113  
 Jewers, K., 148  
 Jham, G. N., 126  
 Jhamandes, K., 109  
 Jin, S. J., 43  
 Johns, C. H., 109  
 Johnson, J., 109  
 Jones, A. J., 21, 50, 206  
 Jones, E. C., 108  
 Jones, H. F., 148  
 Jones, P. F., 108  
 Jones, P. G., 232  
 Jones, R. L., 94  
 Jones, T. H., 30  
 Joule, J. A., 167, 175  
 Joyce, E. M., 109  
 Judis, J., 108  
 Juneau, J. P., 79, 119

- Jurenitsch, J., 243  
 Jurna, I., 109
- Kachroo, P. L., 31  
 Kadkade, P. G., 232  
 Kadry, A. M., 78  
 Kadyrov, C. S., 58  
 Kadyrov, Kh. A., 131, 132  
 Kaiko, R. F., 110  
 Kajiware, M., 169  
 Kakisawa, H., 45, 62  
 Kalas, G., 183  
 Kallman, M. J., 108  
 Kaluski, Z., 65  
 Kamal, R., 232  
 Kambu, K., 191  
 Kameji, R., 57  
 Kametani, T., 82, 87, 99, 100,  
 117, 122, 154, 168, 169,  
 203  
 Kamigauchi, M., 114  
 Kan, C., 185  
 Kan, S. K., 167, 185, 192  
 Kanaïwa, Y., 207  
 Kanaya, N., 154  
 Kaneda, M., 132  
 Kaneko, C., 73  
 Kaneko, K., 228, 233, 234,  
 236  
 Kan-Fan, C., 17, 162  
 Kao, L. C., 112  
 Kapil, R. S., 71, 183  
 Kapnang, H., 225  
 Karamzina, N. M., 82  
 Karim, A., 115  
 Karimova, S. U., 117, 118,  
 128  
 Karle, I. L., 60  
 Karlsson, E. M., 63  
 Kasai, R., 231  
 Kashiara, Y., 48  
 Kasturi, T. E., 56  
 Kasymov, A. K., 68  
 Kato, N., 71  
 Kato, R., 108  
 Katrusiak, A., 65  
 Katsube, J., 183  
 Katsumura, S., 152  
 Katz, E., 26  
 Katz, R. J., 112  
 Kaul, P. N., 144  
 Kawakami, H., 183  
 Kawamura, N., 233, 234  
 Kawasaki, T., 158  
 Kazlauskas, R., 240  
 Kazmaier, P. M., 195  
 Kazuo, N., 240  
 Keber, G., 109  
 Keck, G. E., 46  
 Keeler, R. F., 237  
 Kelleher, R. T., 42  
 Keller, W. J., 8, 63  
 Keller-Schierlein, W., 76, 240
- Kelly, D. D., 111  
 Kende, A. S., 34  
 Keogh, R. G., 158  
 Kerekes, P., 80, 95  
 Kerr, K. A., 206  
 Kessar, S. V., 120  
 Keyer-Uysal, M., 110  
 Khaidarov, K. Kh., 82  
 Khaitbaev, Kh., 63  
 Khalifa, M., 78  
 Khalikov, D. S., 57  
 Khamidkhodzhaev, S. A., 131  
 Khan, A., 204  
 Khatri, N. A., 62  
 Khmelevskii, V. I., 32  
 Khodzhaev, B. U., 226  
 Khodzhimatov, M., 52  
 Khoi, N. H., 229, 231  
 Khokhar, I., 242  
 Khoroshilov, N. V., 82  
 Khristolyubova, N. A., 108  
 Khuong-Huu, Q., 32  
 Kier, L. B., 78  
 Kieth, L. H., 206  
 Kiguchi, T., 114, 160  
 Kihara, M., 133  
 Kilber, M. M., 42  
 King, G. S., 160  
 Kinghorn, A. D., 63, 148  
 Kinsman, R. G., 80  
 Kirby, G. W., 27, 46, 102,  
 121, 147  
 Kirby, M. L., 110  
 Kirfel, A., 53  
 Kirkpatrick, B., 115  
 Kirksey, J. W., 147  
 Kirkup, M. P., 145  
 Kishi, T., 240  
 Kishi, Y., 154  
 Kisin, I., 109  
 Kit, V. I., 57  
 Kitagawa, Y., 176  
 Klásek, A., 53  
 Kleber, H. D., 111  
 Klein, F. K., 241  
 Kleinman, E., 200  
 Klemm, W. R., 108  
 Klimentjev, N. I., 20  
 Klimova, L. I., 228  
 Klivenyi, P., 80  
 Kloetzer, W., 97, 98  
 Kloosterman, J., 227  
 Klose, W., 47  
 Kloster, G., 106  
 Knapp, J. E., 85, 101, 119  
 Knoll, J., 113  
 Knox, J. R., 63  
 Kobayashi, N., 197  
 Kobayashi, S., 133  
 Koch, M., 71, 153, 175, 187  
 Kocherga, S. I., 55  
 Koelsch, P. M., 115  
 Koenig, J. I., 108  
 Körösi, J., 71
- Koga, K., 34  
 Kogan, B. M., 108  
 Koiwa, M., 203  
 Kokate, C. K., 233  
 Kolesnik, T. E., 109  
 Kolodziejczyk, P., 19  
 Kolt, R. J., 37  
 Koltai, E., 80  
 Komenda, S., 43  
 Komendantova, M. V., 110  
 Kondo, S., 55  
 Kondo, Y., 110  
 Kong, Y. C., 94  
 Konno, C., 239  
 Koo, S. H., 3  
 Koomen, G.-J., 34  
 Korczyn, A. D., 109  
 Kornetsky, C., 108  
 Korneva, E. I., 232  
 Korth, H., 71  
 Kostalova, D., 128  
 Kosturkiewicz, Z., 63  
 Kotick, M. P., 101  
 Kovach, J. S., 57  
 Kovacic, B., 111  
 Kovalev, I. E., 110  
 Koyama, J., 34  
 Koyuncuoglu, H., 110  
 Kowalewski, Z., 94, 114  
 Kozello, I. A., 32  
 Kozikowski, A. P., 147  
 Koziol, A. E., 63  
 Kozlovskii, A. G., 157  
 Krajčiček, A., 158  
 Kramer, W., 116  
 Krasgenor, N. A., 42  
 Kravetz, T. M., 90  
 Krebs, H. A., 107  
 Křepelka, J., 160  
 Krick, T. P., 53, 55  
 Krikorian, D., 218  
 Krivut, B. A., 55  
 Kruhlich, L., 108  
 Krushovska, D., 53  
 Kryger, A. C., 148  
 Kubelka, W., 243  
 Kuchkarov, S., 63, 67, 68  
 Kuehne, M. E., 182  
 Kuehnle, J. C., 112  
 Kula, N. S., 117  
 Kulics, A. T., 109  
 Kuls, P., 186  
 Kunesch, G., 169  
 Kunesch, N., 87, 171, 177,  
 178, 185, 196  
 Kunitomo, J., 95, 120, 124  
 Kupchikov, V. V., 110  
 Kuribayashi, T., 233  
 Kurilska, V. V., 228  
 Kurz, W. G. W., 19  
 Kushmuradov, Yu. K., 63, 67,  
 68  
 Kusumi, T., 45, 62  
 Kutney, J. P., 19, 194, 195

- Kuzhelyuk, T. S., 90  
 Kuz'mina, L. G., 97  
 Kyburz, R., 161  
  
 Laan, J., 41  
 La Bella, F. S., 112  
 Lagarias, J. C., 241  
 Laguna, A., 174  
 Lajevardi, S., 95  
 Lakin, V. V., 110  
 Lalezari, I., 95  
 Lallemand, J. Y., 195  
 Lallimant, A. M., 42  
 Lambardi, F., 107  
 Lamberton, J. A., 203  
 Lamotte, J., 191  
 Lancaster, L. E., 101  
 Langlois, N., 179, 185, 192, 195  
 Langlois, Y., 19, 185, 195  
 Lanigan, G. W., 57  
 Larionov, N. G., 55  
 Larsheid, M. E., 149  
 Lashford, A. G., 99  
 Lasskaya, O. E., 114  
 Lasswell, W. L., 26  
 Lastra, L., 110  
 Latch, G. C. M., 158  
 Lau, K. L., 94  
 Laurent, D., 171  
 Lavielle, G., 183  
 Law, D. A., 199  
 Law, S.-J., 117, 126  
 Lazer, E. S., 42  
 Lazur'evskii, G. V., 20, 148  
 Le Bars, D., 108, 111  
 Leboeuf, M., 87, 117, 125  
 Lee, A. W. M., 63  
 Lee, G. E., 45  
 Lee, H. K., 112  
 Lee, S.-L., 19, 167  
 Lee, T.-F., 110  
 Lee, Y. Y., 48  
 Leete, E., 1, 19, 20, 31, 35, 37, 150  
 Legg, R. F., 57  
 Lehman, T. M., 112  
 Leimgruber, W., 149  
 Leitner, E., 105  
 Leland, D. L., 101  
 Le Men, J., 165, 179, 188  
 Le Men-Olivier, L., 165, 188  
 Leonard, J., 162, 167, 197  
 Leon, H.-M., 29, 82  
 Lesma, G., 191  
 Lesse, H., 42  
 Leung, A., 110  
 Leung, W. J., 107  
 Leutwiler, A., 146  
 Lévy, J., 165, 179, 188  
 Lewin, G., 171  
 Lewis, J. R., 71  
 Lewis, N. J., 195  
 Lewis, R. L., 167  
  
 Libich, J., 112  
 Libot, F., 171  
 Lidgard, R. O., 240  
 Liebeskind, J. C., 109  
 Ligia de Paula Ramos, A., 56  
 Ligumsky, M., 82  
 Liljequist, R., 43  
 Lin, C.-N., 88  
 Lind, M. D., 111  
 Lindley, J. T., 198  
 Lineberry, C. G., 109  
 Lipp, C., 116  
 Lippman, A. E., 212  
 Lippmann, M., 113  
 Lipshutz, B., 240  
 Lischewski, M., 228, 231  
 Litvinchuk, M. T., 57  
 Liu, J.-C., 88  
 Loew, G. H., 106  
 Login, I. S., 108  
 Logue, J. N. D., 21  
 Loh, H. M., 111  
 Loman, P., 112  
 Lorenz, R. R., 123  
 Lounasmaa, M., 167, 185, 192  
 Lovkova, M. Ya., 20  
 Loyola, L. A., 199  
 Ludden, T. M., 112  
 Ludgate, P., 137  
 Luethy, J., 53  
 Lynch, V. D., 108  
 Lynn, D. G., 33  
  
 Maat, L., 101, 238  
 Macakova, J., 43  
 McCabe, T., 24, 146  
 McCance, D. J., 233  
 McCann, S. M., 108  
 McCarthy, D. A., 112  
 McClurg, J. E., 82  
 Macdonald, M. M., 139  
 MacDonald, T. L., 40, 62  
 McGaw, B. A., 1  
 MacGillavry, C. H., 41  
 McGivern, R., 112  
 McGrath, J. A., 21  
 Machata, G., 107  
 McInnes, A. G., 7  
 McKenna, M. O., 42  
 Mackulla, H. J., 106  
 McLaughlin, J. L., 78  
 MacLean, D. B., 12, 96, 199  
 MacLean, D. M., 95  
 McLean, S., 97, 108  
 Macleod, R. M., 108  
 MacMillan, J., 212  
 McMurtrey, K. D., 82  
 McNutt, R. W., 144  
 McPhail, A. T., 139  
 Madaminov, G. N., 109  
 Madrid, T. R., 232  
 Madsen, K., 116  
  
 Maebayashi, Y., 151  
 Maerki-Danzig, H., 244  
 Maguire, M., 21  
 Mahato, S. B., 231  
 Mahran, G., 54  
 Maiti, P. C., 232  
 Majima, R., 207  
 Makino, T., 108  
 Makleit, S., 80, 101  
 Makriannis, A., 41  
 Malanina, G. G., 228  
 Malhotra, R. K., 26  
 Mali, R. S., 73  
 Malichova, V., 115  
 Malik, J. K., 42  
 Malingré, T. M., 55, 232  
 Mallari, C. G., 108  
 Mallya, A., 112  
 Mamedova, K. T., 57  
 Manavalan, R., 58  
 Manchanda, S. C., 56  
 Mandava, N., 41  
 Mandell, B., 115  
 Mangeney, P., 195  
 Manikumar, G., 117  
 Manmade, A., 242  
 Mann, J. D., 227  
 Manresa, M. T., 166  
 Mantle, P. G., 160  
 Manura, J., 108  
 Marasas, W. F. O., 243  
 Marcais, H., 109  
 Marfat, A., 140  
 Margolin, D. L., 111  
 Marini-Bettolo, G. B., 165, 174, 218, 220  
 Marino, J. P., 120  
 Markiewicz, M., 66  
 Markiewicz, W., 109  
 Marques, E. K., 56  
 Marshall, R. J., 85  
 Marshall, W. D., 199  
 Martin, J. B., 111  
 Martin, M. I., 110  
 Martin, S. F., 31, 181  
 Martinelli, E. M., 190  
 Martinez, S. J., 175  
 Marton, S., 82  
 Marwaha, J., 111  
 Masamune, T., 233  
 Masashi, O., 124  
 Mashelkar, U. C., 79  
 Masiello, S., 43  
 Mason, S. F., 187  
 Masood, M., 80, 138, 148  
 Massey, S. R., 121  
 Massiot, G., 165  
 Masuma, R., 158  
 Mathe, I., jun., 232  
 Mathew, R., 232  
 Mathis, D. F., 107  
 Matsko, T. H., 182  
 Matsubara, N., 56  
 Matsumoto, T., 48

- Matsushima, T., 56  
 Matsuura, S., 56  
 Matsuzaka, J., 182  
 Matteo, R. S., 85  
 Matter, B. E., 116  
 Mattila, M. J., 43  
 Mattocks, A. R., 57  
 Matveenko, L. F., 232  
 Mavraganis, V. G., 137  
 May, D., 78  
 Mayer, D. J., 108  
 Mayfield, M. A., 108  
 Mazza, F., 76  
 Medvedeva, T. N., 157  
 Meerholz, C. A., 62  
 Mehri, M. H., 179  
 Mehta, J., 115  
 Meijer, D. K. F., 85  
 Meites, J., 108, 109, 111  
 Melik-Guseinov, V. V., 94  
 Menachery, M. D., 130  
 Mendelson, J. H., 112  
 Mendoza, R., 62  
 Menon, M. K., 117  
 Merrick, A., 41  
 Merrien, M. A., 157  
 Merriman, V. J., 111  
 Merz, G., 85  
 Merz, H., 106  
 Messana, I., 165, 174  
 Mester, I., 71, 145  
 Meszaros, Z., 80  
 Metkalova, S., 110  
 Mewaldt, S. P., 43  
 Meyer, G., 108  
 Meyer, W. L., 224  
 Meyers, A. I., 239, 240  
 Meyerson, L. R., 82, 94  
 Miana, G. A., 82, 138, 127, 204  
 Michael, J. P., 62  
 Michel, S., 175  
 Miet, C., 185  
 Mikolajczak, K. L., 142  
 Miljkovic, D., 228  
 Miller, A. C., 181  
 Miller, L. M. F., 232  
 Miller, R. D., 85  
 Miller, R. W., 139  
 Milosevic, M., 43  
 Min, K. R., 115  
 Minami, S., 203  
 Minamikawa, J., 79  
 Minar, A., 101  
 Minard, R. D., 82  
 Minker, E., 80  
 Mino, Y., 63  
 Miranda, F., 109  
 Mirand-Richard, C., 188  
 Mirzaabdullaev, A. B., 63  
 Misawa, T., 110  
 Misra, A. L., 42  
 Mitchell, M. B., 2  
 Mitra, A. K., 177  
 Mitsuhashi, H., 226, 227, 228, 233, 234, 236  
 Mitsuko, A., 240  
 Miura, I., 33  
 Miura, K., 55  
 Miyakado, M., 243  
 Miyase, T., 31  
 Miyata, N., 101, 107  
 Miyata, O., 169  
 Miyazaki, H., 157  
 Mioshi, M., 120  
 Mizukami, H., 19  
 Mizuno, C., 115  
 Mlckova, J., 235  
 Mnatsakanyan, V. A., 94  
 Mody, N. V., 203, 206, 207, 208, 209, 212, 213, 216  
 Moertel, C. G., 57  
 Mohamed, Y. A. H., 78  
 Mohammad, T., 120  
 Mohr, S., 141  
 Mohri, K., 149  
 Mok, M. S., 113  
 Mola, J. L., 229  
 Moleman, P., 110  
 Mollov, N., 79, 124  
 Molnar, L., 107  
 Monder, H., 112  
 Mondon, A., 140, 141  
 Moniot, J. L., 90, 91, 125, 127  
 Mookherjee, S., 232  
 Moon, B. H., 111  
 Moore, A. M., 43  
 Moore, R. E., 145  
 Morales, G., 199  
 Moreau, S., 157  
 Morel, A. F., 241  
 Moreland, T. A., 111  
 Moretti, C., 170, 185, 243  
 Morgans, D., 112  
 Morgans, D. J., 134  
 Mori, K., 133  
 Mori, T., 207  
 Mori, Y., 118  
 Moriyama, Y., 32  
 Morozova, A. S., 110  
 Morozovskaya, L. M., 228  
 Morris, J., 135  
 Morrison, B. E., 112  
 Morton, D., 116  
 Morton, G. O., 101  
 Moskalewski, S., 116  
 Motowa, I., 240  
 Mrozikiewicz, A., 94  
 Mubarak, A. M., 238  
 Müller, U. S., 2  
 Mukai, C., 92, 95  
 Mukherjee, B., 79, 119  
 Mukherjee, R., 79, 119  
 Mukhopadhyay, A. K., 177  
 Mulder-Krieger, T., 198  
 Mullen, G., 135  
 Muller, R., 115  
 Munakata, K., 71, 73  
 Murai, A., 233  
 Murakami, Y., 95, 124  
 Muraki, T., 108  
 Muramo, T., 112  
 Muramoto, K., 110  
 Murata, H., 118  
 Murav'eva, D. A., 94  
 Murphy, P. T., 240  
 Murugesan, N., 88, 117  
 Musson, D., 100  
 Myers, B. M., 111  
 Mynderse, J. S., 145  
 Nabiev, A., 235  
 Nagai, S. H., 108  
 Nagakura, N., 17  
 Nagami, K., 94, 96  
 Nagao, M., 56  
 Nagarajan, K., 81  
 Nagasawa, H., 156  
 Nagashima, H., 112  
 Nagayama, H., 95  
 Naghaway, J., 85  
 Nagraj, S., 115  
 Nahin, R. L., 109  
 Naik, N. R., 76  
 Naito, T., 73, 114, 160, 169  
 Najam, N., 109  
 Najami, K., 93  
 Najmus-Saqib, Q., 138  
 Nakadachi, K., 133  
 Nakadate, H., 108  
 Nakahara, Y., 159  
 Nakamura, H., 55  
 Nakamura, M., 111  
 Nakanishi, K., 33  
 Nakano, N., 207  
 Nakashita, Y., 117  
 Nakatani, N., 243  
 Nakatsuka, S., 157  
 Nakayama, I., 243  
 Nakayama, M., 56  
 Nakhatov, I., 234  
 Nakova, E. P., 80  
 Nalliah, B. C., 95  
 Nambara, T., 237  
 Nambiar, K. P., 218, 220  
 Narasimhan, N. S., 73  
 Narayanaswami, V., 233  
 Narula, M., 120  
 Naruse, N., 236  
 Nasirov, S. M., 97  
 Natarajan, S., 81  
 Natsume, M., 32, 176  
 Nau, M. E., 116  
 Navratil, J., 43  
 Naylor, R. J., 117  
 Neilands, J. B., 239  
 Nelson, W. T., 108  
 Nemeckova, A., 95  
 Nestler, H. J., 141  
 Netzel, D. A., 62  
 Neuman, R. S., 109

- Neumeyer, J. L., 106, 117,  
120, 121, 123, 126  
Neuss, N., 192  
Ngadjui, B., 71  
Nicholson, J., 24, 146  
Nickell, D. G., 46  
Nickisch, K., 47  
Nicoletti, M., 165, 174  
Nieforth, K. A., 42  
Nielsen, C. J., 55  
Niitsu, K., 228  
Ninomiya, I., 114, 160, 169  
Nishimura, T., 110  
Nishino, H., 110, 112  
Nishitatenko, K., 108  
Nivard, R. J. F., 28  
Niwa, M., 203  
Niwaguchi, T., 159  
Noble, R. G., 110  
Nógrádi, K., 183  
Nohria, V., 117  
Noordam, A., 238  
Noro, T., 31  
Northway, M. G., 112  
Nossin, P. M. M., 47  
Novotny, L., 174  
Nuriddinov, R. N., 237  
  
O'Brien, C. P., 111  
Ogasawara, K., 100, 179, 182,  
183, 186  
Ogawa, M., 32, 176  
Oguma, K., 157  
Oguri, K., 107  
Ōhashi, T., 22, 157  
Ohba, M., 99, 168  
Ohomo, S., 157  
Ohmoto, S., 22  
Ohsaki, K., 234  
Ohtani, M., 122  
Oikawa, Y., 149  
Ojewole, J. A. O., 85  
Okajima, K., 93  
Okayasu, T., 115  
Okumura, K., 108  
Okuyama, E., 151  
Olaniyi, A. A., 165  
Oliveras, J. L., 111  
Olofson, R. A., 101  
Omura, S., 158  
Onda, M., 114  
Ono, K., 183  
Ono, T., 110  
Onshuus, I., 53  
Oomura, Y., 110  
Orakhovats, A., 129  
Orito, K., 169  
Orsini, F., 148  
Osei-Gyimak, P., 105  
Osgood, P. F., 101  
O'Shea, S., 110  
Ostrander, J. M., 26  
Ostrowski, N. L., 110, 111  
Ota, N., 63  
  
Otsuka, H., 22, 23, 57, 160  
Ott, H., 158  
Otteneheim, H. C. J., 28  
Overberger, C. G., 37  
Overman, L. E., 60, 62  
  
Paalzow, G., 112  
Paalzow, L., 112  
Paddock, J., 115  
Padgett, H. C., 48  
Paglietti, E., 111  
Pai, B. R., 81  
País, M., 242  
Pakrashi, S. C., 99, 230  
Pal, S. R., 56  
Palmisano, G., 190, 191  
Pan, H., 236  
Pandey, G. D., 78, 87, 169  
Pandey, V. B., 95, 96  
Pandit, U. K., 34, 198  
Pandit, V. L., 56  
Panksepp, J., 109  
Parady, E. D., 123  
Parfitt, R. T., 107  
Paris, R. R., 63  
Paris, V. B., 82  
Parks, D. E., 115  
Parmar, S. S., 29, 115, 225  
Parry, R., 26  
Parry, R. J., 15, 16  
Partridge, J. J., 167  
Pascard, C., 157  
Pasch, T., 109  
Pascual, C., 166  
Pashuk, L. K., 110  
Pass, D. A., 57  
Pastewka, U., 52  
Patchett, A. A., 34  
Patel, M. P., 100  
Patel, R. B., 42  
Patel, S. R., 76  
Patey, G., 109  
Pathania, A. G. S., 56  
Patil, B. B., 52  
Patil, P., 204  
Patra, A., 177  
Pateva, O. G., 58  
Paul, B. S., 42  
Paulig, G., 108  
Pavelčík, F., 234  
Pavliades, C., 111  
Peacock, E. E., 116  
Pearl, J., 126  
Pearlman, B. A., 170  
Pellegrini-Quarantotti, B., 111  
Pelletier, S. W., 203, 204,  
206, 207, 208, 209, 212,  
213, 216  
Pellizzoni, F., 148  
Peña, C. A., 148  
Penchas, S., 115  
Peng, A., 55  
Pepe, J. P., 101  
Perdue, G. P., 129  
  
Perera, K. P. W. C., 71  
Perrollaz, F. F., 59  
Perrson, S., 109  
Peta, M., 111  
Peter, H. W., 63  
Petersen, L. R., 78  
Petersen, R. C., 43  
Peterson, G. K., 112  
Peterson, J. E., 51  
Peterson, J. F., 57  
Peterson, T., 239  
Petlichnaya, L. I., 90  
Petrún, M., 113  
Pevenik, J., 112  
Pezzorno, M. T., 44  
Pfitzner, A., 19  
Pharmar, S. S., 41  
Philbin, D. M., 85  
Philipov, S., 124  
Phillips, A. G., 109  
Phillips, G. W., 181  
Phillips, H., 94  
Pierson, S. L., 82  
Pikova, L. I., 232  
Pilbeam, D. J., 54  
Pilkiewicz, F., 33  
Pinsky, C., 109, 112  
Piper, E. A., 41  
Pitner, T. P., 34  
Pizzolato, G., 167  
Plat, M. M., 179  
Poisson, J., 171, 185, 196  
Pokhmelnina, S. A., 55  
Polazzi, J. O., 101  
Polevaya, O. Yu., 110  
Polhill, R. M., 54  
Polonsky, J., 157  
Polskii, V. I., 82  
Ponin, I. Ya., 233  
Pootakahm, K., 87  
Popelak, A., 168  
Popli, S. P., 71, 183  
Porter, J. K., 159  
Portlock, D. E., 102  
Portoghese, P. S., 113  
Post, R. M., 43  
Potesilova, H., 115  
Potier, P., 19, 171, 179, 185,  
190, 192, 194, 195, 197  
Pottash, A. L. C., 111  
Pousset, J. L., 165  
Poutani, R. B., 42  
Powell, R. G., 139, 144  
Powis, G., 57  
Pradhan, S. N., 42, 85  
Prager, M. J., 108  
Prange, T., 157  
Prasad, A. S., 239  
Prasad, R. N., 233  
Pratt, S. B., 99, 165  
Preininger, V., 86, 94, 95, 115  
Preston, N. W., 20, 160, 161  
Price, K. R., 232  
Proska, B., 107



- Protais, J., 109  
 Pruess, D. L., 167  
 Pryakhin, O. R., 55  
 Przewlocki, R., 109  
 Pucci, B., 33  
 Puckette, T. A., 31  
 Pulverer, G., 71  
 Puri, R. K., 233  
 Purushothaman, K. K., 30, 233  
 Putek, J., 107  
 Pyati, P., 112  
  
 Quevauviller, A., 110  
 Quigley, F. R., 23  
  
 Rachmilewitz, D., 82  
 Rabaron, A., 179  
 Radema, M. H., 63, 65  
 Radwan, S. S., 233  
 Raffelsberger, B., 171, 184  
 Rahman, H., 85  
 Rai, M., 216  
 Rajani, M., 56  
 Rajaraman, R., 81  
 Rakhimova, D. A., 95, 217  
 Raman, K. V., 233  
 Ramón, J. L. M., 166  
 Rankin, J. M., 63  
 Rao, N. V. R., 43  
 Rao, P. R., 40  
 Rao, R. S., 85  
 Rapoport, H., 39, 48, 241  
 Rashkes, Ya. V., 209  
 Rasmusson, D. D., 43  
 Rastogi, K., 183  
 Rathod, S. P., 100  
 Rathore, A. K., 232  
 Ratnayake, V. U., 137  
 Ratner, M., 109  
 Ray, A. B., 31, 36, 79, 95, 96, 117  
 Razakova, D. M., 71  
 Razdan, R. K., 101, 102  
 Reches, A., 110  
 Recinos, J. A., 232  
 Reden, J., 86  
 Redmond, D. E., 111  
 Reed, D., 108  
 Řeháček, Z., 158, 160  
 Rehman, A., 242  
 Reid, L. D., 110, 111  
 Reina, M., 204  
 Reiner, R. K., 114  
 Reis, F. de A. M., 80, 241  
 Reisch, J., 71, 145  
 Reker, D., 112  
 Resch, K., 116  
 Reshetilova, T. A., 157  
 Reuland, D. J., 107  
 Reuning, R. H., 112  
 Reuse-Blom, S., 82  
 Rexford, O., 119  
  
 Rhines, R. K., 109  
 Rhugenda-Banga, N., 243  
 Rice, K. C., 80, 86  
 Rice, P. E., 111  
 Richards, M. J., 82  
 Riche, C., 87, 173, 188  
 Richter, B., 104, 105  
 Rideau, M., 243  
 Riemer, R. K., 96  
 Riffée, W. H., 127  
 Rigaud, J.-P., 33  
 Rigor, B. M., 108  
 Rikard-Bell, L., 57  
 Riley, D. J., 109  
 Riley, T. N., 42  
 Ripka, W. C., 86  
 Ripperger, H., 33, 119, 239  
 Ritchie, R., 154  
 Robbers, J. E., 22, 23, 160  
 Robbins, J. D., 159  
 Roberts, J. D., 24  
 Roberts, J. T., 85  
 Robins, D. J., 27, 44, 48, 49, 147  
 Robinson, J. H., 110  
 Roblot, F., 86  
 Rocchiccioli, F., 242  
 Roch-Arveiller, M., 115  
 Roddick, J. G., 225, 232, 233  
 Rodgers, R. J., 111  
 Rodrigo, R., 95  
 Rodriguez, F., 174  
 Rodriguez, J., 228  
 Roeder, E., 52, 53, 106  
 Roensch, H., 98, 100  
 Roesner, H., 85  
 Roland, D. M., 239, 240  
 Rolfsen, W. N. A., 165  
 Romers, C., 63, 65  
 Rominger, K. L., 39  
 Romo-Salas, F., 109  
 Ronman, P. E., 198  
 Rosati, R. L., 186  
 Rose, G. J., 78  
 Rosen, J. B., 112  
 Rosenberg, D., 115  
 Rosencrans, J. A., 112, 108  
 Rosenfeld, G. C., 108  
 Rosenfeld, J. P., 111  
 Rosenmund, P., 149  
 Rosic, N., 43  
 Ross, S. A., 242  
 Rostogi, K., 71  
 Roush, W. R., 31  
 Rousselet, R., 153  
 Roy, S. C., 145, 224  
 Rozengurt, E., 116  
 Rucker, G., 43  
 Rueffer, M., 17, 162  
 Ruffing, D., 111  
 Rugstad, H. E., 112  
 Rumero, A., 166  
 Russell, G. B., 50  
 Russell, R. G., 57  
  
 Ruveda, E. A., 80, 241  
 Rychlewska, U., 65  
  
 Saá, J. M., 128  
 Sabir, M., 94  
 Sadikov, A. S., 95  
 Sadikov, T., 95  
 Sadri, E., 149  
 Sadritdinov, F. S., 58, 217  
 Sadykov, A. S., 67  
 Sadykov, Yu. D., 52  
 Saeed, A., 54  
 Saferstein, R., 108  
 Saha, A. K., 41  
 Sahai, M., 36  
 Sahu, N. P., 231  
 Saiki, Y., 31  
 St. John, A. B., 110  
 Saitoh, Y., 32  
 Sakai, S., 173  
 Sakanashi, M., 42  
 Sakdarat, S., 44, 49  
 Sakharovskii, V. G., 157  
 Salamy, J. G., 109  
 Salazar, M., 204  
 Salgo, P., 126  
 Salimov, B. T., 209  
 Samanin, R., 109  
 Samikov, K., 235, 236, 237  
 Sams, R. A., 112  
 Sandman, C. A., 112  
 Sands, S. F., 109  
 Sanforo, R. E., 43  
 Sankawa, U., 94, 158  
 Sano, T., 132  
 Santiago, T. V., 109  
 Šant'ana, A. E. G., 148  
 Šantaný, F., 53, 115  
 Sarada, A., 30  
 Sariyar, G., 94  
 Sarkar, M., 75, 224  
 Sarto, G., 110  
 Sasaki, K., 110  
 Sasamori, H., 233  
 Sashida, H., 133  
 Sastre, A., 40  
 Sato, M., 182  
 Sato, N., 233  
 Satzinger, G., 101, 123  
 Saunders, J. W., 2  
 Savarese, J. J., 85  
 Sawaki, S., 133  
 Sawhney, R. S., 203, 204, 207  
 Saxton, J. E., 154, 162, 182  
 Sayre, L. M., 113  
 Sbordone, R. J., 78  
 Scaf, A. H. J., 85  
 Schade, W., 100  
 Schaller, U., 71  
 Schiebel, H.-M., 5, 63  
 Schiff, P. L., jun., 85, 101, 119  
 Schildt, B., 42

- Schimmel, G. T., 78  
 Schioerring, E., 109  
 Schlatter, C., 53  
 Schlunegger, U. P., 59  
 Schmitz, F. J., 145, 239  
 Schneider, D., 54  
 Schoemaker, H., 33  
 Schoenhoefer, P. S., 111  
 Schöpp, E., 161  
 Schramm, L. C., 213  
 Schreiber, K., 227, 230  
 Schreiber, R. A., 111  
 Schütte, H. R., 12  
 Schuijt, C., 100  
 Schultz, R., 109, 111  
 Schultz, W., 43  
 Schumacher, A. M., 139  
 Schuster, C. R., 42  
 Schut, R. N., 101  
 Schwab, J. M., 15  
 Schwartz, A., 120  
 Schwartz, M. A., 107  
 Schwarz, J. C., 109  
 Schwarz, R., 79  
 Scott, A. I., 19, 167  
 Scott, J. W., 149  
 Scott, P. M., 157  
 Scully, F. E., jun., 35  
 Secor, H. V., 34  
 Sedmera, P., 53, 115, 158  
 Seeman, J. I., 34  
 Seeman, P., 117  
 Seff, K., 145  
 Sefton, M. A., 27, 147  
 Segal, D. S., 111  
 Segall, H. T., 53, 55  
 Segovia, R., 228  
 Segretti, A., 111  
 Sehgal, C. K., 31  
 Sehgal, S., 56  
 Seidel, E. R., 109  
 Sekine, Y., 176  
 Semonský, M., 160  
 Seth, K. K., 95  
 Sethi, P. D., 36  
 Sethi, S. P., 220  
 Sevenet, T., 71, 153, 165, 171, 179  
 Severinica, G., 117  
 Severson, A., 116  
 Sewell, G. J., 107  
 Sewerin, E., 132  
 Shaath, N. A., 85  
 Shabana, M. M., 62  
 Shafiee, A., 95  
 Shah, A. H., 241  
 Shah, D. S., 100  
 Shah, N. S., 78  
 Shah, S. A. H., 95  
 Shakidoyatov, K. M., 58  
 Shakirov, R., 226, 234, 235, 236, 237  
 Shakirov, T. T., 95, 217  
 Shaller, D. A., 115  
 Shami, A., 52  
 Shamma, M., 82, 88, 90, 91, 93, 117, 125, 127, 204  
 Shani, J., 109  
 Sharipov, F. Kh., 82  
 Sharipov, I. N., 148  
 Sharma, G. L., 232  
 Sharma, K. P., 232  
 Sharma, N. S., 232  
 Sharma, P. N., 71  
 Sharma, R. L., 31, 76  
 Sheiner, L. B., 85  
 Sheridan, J. B., 24  
 Sherstnev, V. V., 110  
 Shifter, L., 109  
 Shimada, K., 237  
 Shimizu, K., 239, 240  
 Shin, M. S., 111  
 Shingu, T., 133  
 Shirai, A., 56  
 Shishido, K., 182  
 Shiwaku, Y., 112  
 Shoeb, A., 71  
 Shono, T., 88  
 Shringarpure, J., 62  
 Shukla, D. C., 233  
 Shulgin, A. T., 78  
 Shuster, C. R., 42  
 Shvetsov, I. M., 109  
 Siddiqi, M. A., 53, 58  
 Siddiqui, M. T., 117  
 Siefen, E., 114  
 Siegel, J. A., 40  
 Sigel, C. W., 224  
 Sim, G. A., 102  
 Simanek, V., 86, 94, 95  
 Simchowitz, L., 115  
 Simekova, E., 232  
 Simmonds, D. J., 33  
 Simmonds, M. A., 96  
 Simmons, C. J., 145  
 Simpson, S. T., 85  
 Sinatra, R. S., 109  
 Sinclair, N. M., 35  
 Singer, G., 112  
 Singh, A., 216  
 Singh, A. N., 11  
 Singh, G. B., 58  
 Singh, I., 199  
 Singh, N. J., 43  
 Singh, R. S., 138  
 Singh, S., 31, 102  
 Singh, S. P., 29, 41, 115, 225  
 Singh, T., 40  
 Siniscalchi, A., 110  
 Siroka, A., 43  
 Sistare Noguera, J., 101  
 Sitaram, N., 43  
 Siwon, J., 119  
 Skolnik, S., 41  
 Slater, P., 108  
 Slatkin, D. J., 85, 101, 119  
 Slavik, J., 86, 87, 118  
 Slavikova, L., 86, 87, 118  
 Sleigh, S. K., 19  
 Slosse, P., 68  
 Smith, A. C. B., 102  
 Smith, A. F., 108  
 Smith, C. R., jun., 139, 142, 144, 212  
 Smith, D. G., 7  
 Smith, G. F., 188  
 Smith, G. N., 188  
 Smith, L. W., 51  
 Smith, R. L., 113  
 Smith, R. V., 126, 127  
 Smolenski, S. J., 63, 148  
 Smysl, B., 86  
 Snatzke, G., 178  
 Snieckus, V. A., 95, 175  
 Soares, F., 109  
 Soerbo, B., 42  
 Sohar, P., 80  
 Soine, T. O., 85  
 Soine, W. H., 126  
 Soloway, A. H., 121, 126  
 Somei, M., 73  
 Sondengam, B. L., 71  
 Sonderegger, T., 110  
 Sonnet, P. E., 62  
 Sonoda, M., 203  
 Soper, C. J., 107  
 Souza, D. O., 112  
 Spáčil, J., 158  
 Sparber, S. B., 112  
 Sparlein, M. T., 108  
 Spealman, R. D., 42  
 Speckamp, W. N., 33, 47  
 Spector, S., 108  
 Spencer, R. M., 108  
 Spenser, I. D., 3, 4  
 Spiaggia, A., 111  
 Spiehler, V. R. O., 112  
 Spilberg, I., 115  
 Spingler, H., 168  
 Springer, J. P., 146, 147, 151, 152  
 Sprague, G. L., 108, 112  
 Squillace, K. M., 43  
 Squillacote, M., 24  
 Stadler, P. A., 158  
 Stajic, M., 107  
 Stanislas, E., 174  
 Stanski, D. R., 85  
 Stapleton, J. M., 110, 111  
 Steen, S. N., 113  
 Stefanova-Gateva, B., 53  
 Stefek, M., 107  
 Steinbronn, K., 116  
 Steiner, S. S., 108  
 Stenberg, V. I., 29, 41, 115, 225  
 Stephens, R. L., 125, 169  
 Stephens, R. V., 63  
 Stermitz, F. R., 71, 119, 244  
 Stern, E. S., 207  
 Sternbach, D. D., 16  
 Sternson, L. A., 100

- Sterzycki, R., 220  
 Stevens, J., 100  
 Stevens, R. V., 202  
 Stewart, J., 111  
 Steyn, P. S., 155, 158, 243  
 Stierle, D. B., 148  
 Stockhaus, K., 106  
 Stöckigt, J., 17, 19, 162  
 Stoeckli-Evans, H., 56  
 Stolc, V., 116  
 Stork, G., 134  
 Strauss, H. F., 31  
 Struchkov, Yu. T., 97  
 Stuart, K. L., 19  
 Stütz, P. L., 158  
 Suau, R., 128  
 Suchy, V., 235  
 Sugimura, T., 56  
 Sugimura, Y., 152  
 Suginome, H., 207, 233  
 Sugita, T., 34  
 Sugiyama, S., 118  
 Suguna, H., 81  
 Suinonic, A., 109  
 Sulcova, A., 96  
 Sullivan, B., 148  
 Sultanbawa, M. U. S., 166  
 Sultankhodzhaev, M. N., 208  
 Sun, S.-W., 86  
 Sundarsanam, V., 81  
 Sundrawati, E., 232  
 Suri, K. A., 53, 58  
 Suri, O. P., 53, 58  
 Susan, S. M., 96  
 Sutarjadi, 232  
 Suzuki, A., 156  
 Suzuki, F., 140  
 Suzuki, K., 158  
 Suzuki, M., 62  
 Suzuki, T., 169  
 Suzuki, Y., 99, 168  
 Suzuta, Y., 34  
 Svelto, M., 116  
 Svendsen, A. B., 119, 198  
 Svoboda, K. S., 148  
 Swaminathan, C. S., 81  
 Swaynok, J., 109, 112  
 Swedberg, M. D. B., 112  
 Swinehart, J. A., 71, 119  
 Sy, W. H., 220  
 Sylvester, P. W., 109  
 Symon, D. E., 227  
 Szabó, L., 169, 183  
 Szántay, C., 169, 183  
 Szczyrbak, C. A., 160  
 Szendrei, K., 33, 71  
 Szentmiklósi, P., 82  
 Szepesi, G., 160  
  
 Tabata, M., 76  
 Tada, Y., 169  
 Taha, A. M., 43  
 Takahashi, K., 82, 203  
 Takahashi, T., 32, 169  
 Takahashi, M., 48  
 Takahashi, Y., 100  
 Takanashi, H., 56  
 Takano, S., 100, 179, 182, 183  
 Takao, N., 113, 114  
 Takatani, M., 201  
 Takeda, H., 110  
 Takeda, M., 233  
 Takemori, A. E., 108, 112, 113  
 Takekoshi, T., 37  
 Takeuchi, T., 55  
 Talekar, R. R., 27, 147  
 Talipov, S. A., 67  
 Tallman, J. F., 43  
 Tamada, M., 239  
 Tamás, J., 169  
 Tampier, L., 112  
 Tamura, K., 207  
 Tamura, S., 156  
 Tanaka, M., 233, 236  
 Tanaka, O., 231  
 Tanaka, R., 108  
 Tandon, R. K., 56  
 Taneja, S. C., 31  
 Tang, J., 112  
 Tasaka, M., 203  
 Tashkhodzhaev, B., 55  
 Taskhanova, E. M., 234, 235  
 Tavernier, D., 174  
 Taylor, A. A., 198  
 Taylor, D. A., 175  
 Taylor, D. L., 42  
 Taylor, H. L., 139  
 Taylor, R. E., 82  
 Teague, R. S., 109  
 Tegdes, A., 101  
 Tei, K., 158  
 Telek, L., 232  
 Telezhenetskaya, M. V., 55  
 Temple, W. A., 169  
 Tence, I. M., 57  
 Tereda, S., 226, 227  
 Terdy, L., 160  
 Terent'eva, I. V., 148  
 Teresawa, H., 99  
 Ternes, J., 111  
 Tetenyi, P., 101  
 Thevenin, J. P., 43  
 Thielke, D., 167  
 Thielking, W. H., 123  
 Thompson, B. C., 107  
 Thompson, T., 111  
 Thornhill, J. A., 111  
 Thureau, O., 62  
 Thyberg, J., 116  
 Tjhuis, M. W., 28  
 Till, G., 116  
 Tillequin, F., 71, 153, 175, 187  
 Tingey, W. M., 233  
 Tinley, E. J., 14  
  
 Tishchenko, G. N., 67  
 Titeler, M., 117  
 Tits, M., 174  
 Tittel, G., 55  
 Tiwari, K. P., 78, 80, 87, 138, 148, 169  
 Toda, J., 132  
 Töke, L., 169  
 Tokunaga, Y., 108  
 Tokuyama, T., 60  
 Tolis, G., 111  
 Tolkachev, O. N., 80, 114  
 Tomino, A., 169  
 Tomioka, K., 34  
 Tomita, K., 114  
 Tomko, J., 128, 226, 234, 235  
 Torrellas, A., 110  
 Tóth, G., 178  
 Toth, J., 39  
 Toya, Y., 244  
 Trehan, I. R., 31  
 Treimer, J. F., 17  
 Trewella, J. C., 125  
 Trifonov, L. S., 129  
 Trigo, G. G., 40  
 Trim, C., 85  
 Trimino, Z., 131, 132  
 Trinkler, W. A., 107  
 Tripathi, H. L., 237  
 Troost, J. J., 198  
 Troost, T., 26  
 Trost, B. M., 186  
 Trtik, B., 158  
 Tsai, T. Y. R., 218, 220  
 Tschertter, H., 158  
 Tschesche, R., 241  
 Tsuchimoto, T., 116  
 Tsuda, Y., 132  
 Tsurufuji, S., 115  
 Tufariello, J. J., 29, 45, 60  
 Turkevich, N. M., 90  
 Turner, S., 102  
 Tyce, G. M., 109  
  
 Uba, K., 101, 107  
 Uchida, E., 56  
 Uddin, A., 233  
 Uemura, D., 244  
 Ueno, A., 31  
 Ueno, I., 56  
 Ul'yankina, T. I., 110  
 Ul'yanov, M. I., 110  
 Umeda, M., 56  
 Umezawa, B., 88, 113, 122, 124, 133  
 Umezawa, H., 55  
 Unno, K., 169  
 Untz, G., 198  
 Urakov, A. L., 82  
 Urca, G., 109  
 Urrea, M., 171  
 Urzua, A., 82, 125, 129  
 Usgaonkar, R. N., 79

- Uskoković, M. R., 167  
 Usmanghani, K., 138  
 Usui, Y., 88  
 Uyeo, S., 133
- Vadlamani, N. L., 42  
 Vale, J., 110  
 Valenta, Z., 212  
 Van der Bercken, J., 111  
 Van der Kloot, W. G., 85  
 Van Derveer, D. G., 52  
 Van der Wende, C., 108  
 Van Eijk, J. L., 63, 65  
 van Essen, G. F. A., 119  
 van Fossen Bravo, R., 241  
 van Mai, H., 232  
 van Peteghem, C., 78  
 Van Vugt, D. A., 108, 109  
 van Zele, W., 78  
 Varghese, S., 232  
 Vasquez, S., 109  
 Vaucamps, P. L., 196  
 Vdoviko, E. A., 55  
 Vecchietti, V., 117, 148  
 Venera, G., 33  
 Venkov, A. P., 79, 216  
 Vercauteren, J., 165  
 Vermeer, G. A., 85  
 Vermin, W. J., 63, 65  
 Verpoorte, R., 119, 198  
 Viel, C., 243  
 Vig, O. P., 31  
 Vilhuber, H. G., 140, 141  
 Villareal, J. E., 101  
 Vincent, E. J., 115  
 Vincze, I., 39  
 Vining, L. C., 7, 28  
 Vinkler, E., 80  
 Viswanathan, N., 88  
 Vleggaar, R., 22, 155, 157  
 Vocci, F. J., 111  
 Voegtle, F., 106  
 Voinilo, V. A., 233  
 Vokoun, J., 53, 158  
 Volavka, J., 112  
 Vofford, J., 80  
 Vorbrueggen, H., 209  
 Votický, Z., 107, 226  
 Vourois, P., 126  
 Vunakis, H. V., 35
- Wada, A., 92  
 Wagener, R. E., 157  
 Wagner, H., 55, 239  
 Waigh, R. D., 80  
 Waight, E. S., 160  
 Weiss, A. C., 46  
 Wakefield, B. J., 243  
 Waldman, S. D., 85  
 Walker, C. M. M., 111  
 Walker, J. M., 112  
 Wall, M. E., 139, 198  
 Wallace, R. A., 107
- Wallenstein, M. C., 109  
 Wallnau, L. B., 111  
 Walraven, H. G. M., 198  
 Walter, J. A., 7  
 Walter, P., 7  
 Walterova, D., 95  
 Walther, G., 43  
 Wan, T. S., 28  
 Wang, C., 112  
 Wang, N., 178  
 Wang, S.-D., 56  
 Wani, M. C., 139, 198  
 Wanner, M. J., 34  
 Wannigama, G. P., 166  
 Warshawsky, H., 115  
 Warwick, R. O., 109  
 Wassel, G., 54  
 Wasserman, M. A., 43  
 Watanabe, H., 108  
 Watanabe, I., 244  
 Watanabe, K., 101, 107, 108  
 Watanabe, M., 175  
 Waterman, P. G., 87  
 Watkin, D. J., 35  
 Watson, W. H., 125, 204  
 Way, E. L., 108, 111  
 Wayner, M. J., 112  
 Wegener, J., 167  
 Wehking, E., 110  
 Weibel, F., 24, 146  
 Weigel, L. O., 240  
 Weight, D. J., 243  
 Weigle, W. O., 115  
 Weiner, C., 79  
 Weinreb, S. M., 62  
 Weinstein, S. H., 108  
 Weisleder, D., 144  
 Weissman, B. A., 109  
 Weitering, J. G., 85  
 Welch, R. M., 108  
 Wells, J. M., 147  
 Wells, R. J., 240  
 Welter, A., 243  
 Wendler, N. L., 34  
 Wenger, G. R., 42  
 Wenkert, E., 125, 148, 169,  
 177, 178, 196, 232  
 Wessels, P. L., 22, 157, 243  
 Westlake, D. W., 26  
 Weston, R. J., 232  
 Wheeler, H. S., 109  
 Whidby, J. F., 34  
 White, A. T., 108  
 White, B. J., 24  
 White, M., 108  
 Whiting, D. A., 33  
 Wick, H., 43  
 Wiechers, A., 31  
 Wiedenfeld, H., 52, 53  
 Wiegrobe, W., 59  
 Wiesner, K., 203, 212, 218,  
 220  
 Wiewiórski, M., 65, 66  
 Wilcox, R. E., 127
- Wiley, J. N., 112  
 Will, G., 53  
 Williams, C. H., 85  
 Wilson, B. J., 24, 146  
 Wilson, P. R., 110  
 Wilson, W. D., 94  
 Wingard, J. A., 78  
 Wink, M., 5, 6, 63  
 Winter, J. C., 109  
 Winterfeldt, E., 167  
 Withers, S. F., 85, 101, 119  
 Witkop, B., 40  
 Witte, L., 6, 63  
 Wolff, C., 140, 141  
 Wolińska-Mocydlarz, J., 65  
 Wolverton, W., 42  
 Wong, L., 79  
 Woo, W. S., 243  
 Woods, I., 111  
 Woody, G. E., 111  
 Woolley, J. G., 1  
 Worth, B. R., 19, 194, 195  
 Wouters, W., 111  
 Wright, J. L. C., 7  
 Wrobel, J. T., 4  
 Wu, J., 83, 84, 85  
 Wu, W.-N., 78, 119, 129  
 Wueter, M., 109, 111  
 Wurst, M., 160  
 Wysocka, W., 66, 67
- Xing, S. H., 43
- Yadav, J. S., 169  
 Yadav, V. S., 120  
 Yagudaev, M. R., 55, 167  
 Yajima, T., 71  
 Yaksh, Th., 109  
 Yaksh, T. L., 110  
 Yakubovskii, A. K., 110  
 Yakushijin, K., 118  
 Yamaguchi, H., 114  
 Yamamoto, O., 114  
 Yamamoto, Y., 173  
 Yamamura, S., 203  
 Yamanaka, H., 56  
 Yamazaki, M., 151, 158  
 Yanagida, T., 42  
 Yanagiura, S., 110  
 Yang, T. H., 120  
 Yang, T.-R., 206  
 Yang, W. C. T., 100  
 Yano, I., 110, 112  
 Yao, S. Y., 127  
 Yashiro, K., 203  
 Yasnetsov, V. V., 110  
 Yasuda, S., 92, 93  
 Yasukawa, Y., 112  
 Yatazawa, M., 233  
 Yates, J., 78  
 Yazima, T., 73  
 Yeh, S. Y., 107  
 Yemul, S. S., 178  
 Yeung, R. T. T., 112

Yip, T. T., 94  
 Yoge, E., 120  
 Yonaga, M., 179  
 Yonekura, N., 233  
 Yonemitsu, O., 149  
 Yoshida, K., 88, 239  
 Yoshida, N., 228  
 Yoshifuji, S., 99  
 Yoshimura, H., 107  
 Yoshioka, H., 243  
 Yoshioka, T., 149  
 Yost, G. A., 237  
 Young, A. M., 111  
 Young, J. C., 108

Yu, M.-L., 1  
 Yun, H. S., 243  
 Yunusov, M. S., 97, 117, 118,  
 128, 208, 209, 217  
 Yunusov, S. Yu., 55, 71, 97,  
 118, 128, 132, 167, 208,  
 209, 226, 234, 235, 236,  
 237  
 Yuta, K., 182  
 Yuzbashinskaya, P. A., 57  
  
 Zabel, V., 125, 204  
 Zalkow, L. H., 52  
 Zamboni, A., 112

Zanboni-Muciaccia, W., 112  
 Zarembo, J. E., 43  
 Zavala, F., 197  
 Zbierska, J., 114  
 Zeile, K., 43  
 Zenk, M. H., 17, 162  
 Zhai, Q.-Z., 112  
 Ziesche, J., 53  
 Zimmerman, E., 110  
 Zimmerman, S. B., 34  
 Zor, U., 82  
 Zoryan, E. V., 110  
 Zweifel, U., 53



Complement your SPECIALIST  
PERIODICAL REPORT with

# C A Selects

C A Selects appear once every two weeks and contain titles, bibliographies, details and abstracts of recently published papers, reports, patents, conference proceedings etc., in broad areas in chemical sciences.

Just some of the titles covered by C A Selects are:

ATOMIC SPECTROSCOPY  
CARBON AND HETEROATOM NMR  
CHEMICAL INSTRUMENTATION  
ELECTRON AND AUGER SPECTROSCOPY  
GAS CHROMATOGRAPHY  
GEL PERMEATION CHROMATOGRAPHY  
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY  
INFRARED SPECTROSCOPY (ORGANIC ASPECTS)  
MASS SPECTROMETRY  
PAPER AND THIN-LAYER CHROMATOGRAPHY  
ULTRAVIOLET AND VISIBLE SPECTROSCOPY  
X-RAY ANALYSIS AND SPECTROSCOPY

For details contact:

THE ROYAL SOCIETY OF CHEMISTRY,  
THE UNIVERSITY,  
NOTTINGHAM NG7 2RD  
ENGLAND

# Royal Society of Chemistry

## Specialist Periodical Reports

A series of reviews by leading specialists in their fields which gives systematic and comprehensive coverage of the progress in major areas of research. Titles of interest to those working in the borderlands of chemistry and biology include:

### Biosynthesis Vol. 6

Senior Reporter: J. D. Bu'Lock

The sixth volume in the series reviews the literature published during 1977 and 1978.

#### Brief Contents:

Biosynthesis of Polyketides; Phenolic Compounds derived from Shikimate; The Biosynthesis of  $C_5$ – $C_{20}$  Terpenoid Compounds; Triterpenoids, Steroids, and Carotenoids; Non-protein Amino-acids; Cyanogenic Glycosides, and Glucosinolates; Biosynthesis of Alkaloids.

"The authors have succeeded in providing a volume which should be invaluable to those chemists or biochemists who study biosynthesis".

— *British Book News*, reviewing Vol. 4

Hardcover 305pp 0 85186 990 4

### Environmental Chemistry Vol. 1

Senior Reporter: G. Eglinton

The first volume in a series which will review the progress in this area. The first volume covers organic aspects and future volumes will cover inorganic and other aspects of environmental chemistry.

Hardcover 210pp 0 85186 755 3

### Carbohydrate Chemistry Vol. 12

Senior Reporters: J. F. Kennedy and N. R. Williams

This volume reviews the literature published during 1978.

#### Brief Contents:

Part I: Mono-, Di-, and Tri-saccharides and their Derivatives; Part II: Macromolecules.

"The Senior Reporter and six other reporters have again accomplished the difficult task of providing a comprehensive coverage of literature in the field. Over 3,000 articles are cited, and the reporters have done a superb job of abstracting their important points".

— *Journal of Medicinal Chemistry*, reviewing Vol. 10

Hardcover 639pp 0 85186 940 8

### Foreign Compound Metabolism in Mammals Vol. 6

Senior Reporter: D. E. Hathway

This volume reviews the literature published during 1978 and 1979.

#### Brief Contents:

Drug Kinetics; Enzymic Mechanisms of Oxidation, Reduction, and Hydrolysis; Species, Strain, and Sex Differences in Metabolism; Mechanisms of Chemical Carcinogenesis; Drugs Acting on the Central Nervous System; Cardiovascular Drugs; Biotransformation of Sympathomimetic Agents and Bronchodilators; Anti-infective Agents; Steroids and Anthrormones; Food Additives; Agricultural Chemicals; Industrial Chemicals and Miscellaneous Organic Compounds; Cancer Chemotherapeutic Agents.

"Overall, this volume is recommended highly as an organised source of metabolism-pharmacokinetics literature on important xenobiotics of many kinds".

— *Journal of Pharmaceutical Sciences*, reviewing Vol. 5

Hardcover 406pp 0 85186 058 3

### Terpenoids and Steroids Vol. 10

Senior Reporter: J. R. Hanson

A review of the literature published between September 1978 and August 1979.

#### Brief Contents:

Terpenoids; Sesquiterpenoids; Diterpenoids; Triterpenoids; Carotenoids and Polyterpenoids; Steroids; Physical Methods; Steroid Reactions and Partial Synthesis.

"The high level of reporting in this well established series needs no further recommendation to all who work in the field of terpenoids and steroids or have an interest in general alicyclic chemistry".

— *Chemistry in Britain*, reviewing Vol. 9.

Hardcover 296pp 0 85186 336 1

Further information on any of these publications may be obtained from: **The Royal Society of Chemistry, Marketing Department, Burlington House, London W1V 0BN**