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A Specialist Periodical Report

The Alkaloids

Volume 8

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Foreword

The intention of the eighth volume of *The Alkaloids* was once again to provide a comprehensive annual survey of the alkaloid literature. It has not been possible, however, to include chapters on the Tropane Alkaloids and on Miscellaneous Alkaloids, and certain aspects of the chemistry of isoquinoline alkaloids have been omitted; we expect to remedy these deficiencies by including a two-year coverage in Volume 9.

A number of our regular authors are not participating this year, and I would like to express my appreciation to Drs. Crout and McCorkindale for their contribution to Volumes 6 and 7 and in particular to Drs. Goutarel and Khuong-Huu for reviewing steroidal alkaloids of the Apocynaceae and Buxaceae since the inauguration of this series of Reports in 1971. In this Volume, all steroidal alkaloids are included in Chapter 14.

May I remind alkaloid chemists that comments on these Reports are welcome and that it is very helpful for authors to receive reprints of articles published in journals that are not generally accessible.

The untimely death of Professor S. M. Kupchan is referred to in Chapter 8. His important contributions to the chemistry of isoquinoline and steroidal alkaloids and his interest in anti-tumour alkaloids have been a regular feature of these reports.

April 1978 M. F. GRUNDON

Contents

1

Biosynthesis

BY R. B. HERBERT

1 Introduction

In order to facilitate access to material discussed in previous Reports in this series, the practice of listing them as the first references[1—7] is continued. This means that when new material is discussed the reference to material in, *e.g.*, Vol. 3 appears most simply as 'ref. 3' (and will do so in all Reports beginning with Vol. 6).

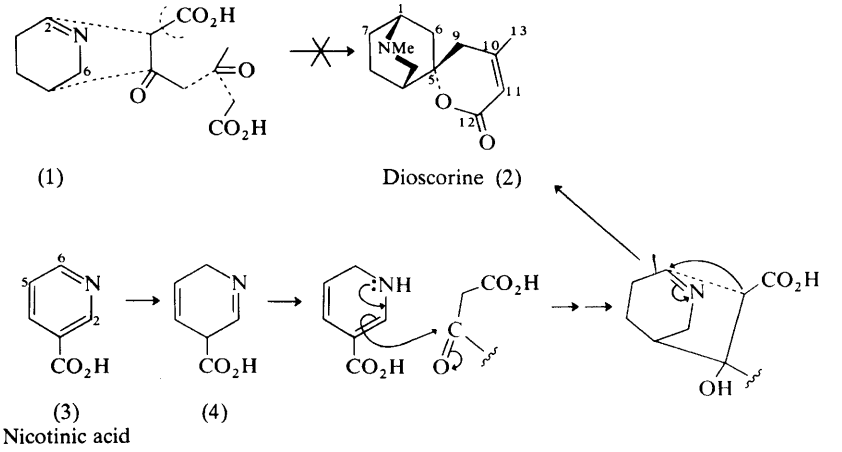
2 Piperidine, Pyridine, and Pyrrolidine Alkaloids

Dioscorine.—Labelling of C-5, C-10, and C-12 of dioscorine (2) by [1-^{14}C]acetic acid[8] indicates that C-5, C-6, C-9, C-10, C-11, C-12, and C-13 derive from acetate. This leaves a cyclic C_5N unit unaccounted for, which, from the wealth of evidence on the biosynthesis of similar systems (see previous Reports), one expects will arise from the amino-acid lysine *via* Δ^1-piperideine (1), an expectation not realized since neither compound is satisfactorily incorporated into dioscorine (2).[8]

The alkaloid anatabine (6) is exceptional in that its dehydropiperidine ring derives from nicotinic acid (3), rather than from lysine which is the source of the similar fragment in anabasine (7) (see below). Most interestingly it has been shown[9] that the related heterocyclic fragment (C_5N unit) of dioscorine also derives from nicotinic acid (3): [2-^{14}C]- and [5,6-$^{14}C_2$,$^{13}C_2$]-nicotinic acids were tested as precursors and in the latter case the dioscorine ^{13}C labelling was shown by ^{13}C n.m.r. to be of C-1 and C-7. 3,6-Dihydronicotinic acid (4) may be an important intermediate in the biosynthesis of nicotine and anabasine (7)[10] and of anatabine (6).

[1] R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1.
[2] J. Staunton, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1972, Vol. 2.
[3] R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3.
[4] R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4.
[5] R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1975, Vol. 5.
[6] R. B. Herbert, in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6.
[7] R. B. Herbert, in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London,, 1977, Vol. 7.
[8] E. Leete and A. R. Pinder, *Phytochemistry*, 1972, **11**, 3219; R. B. Herbert, in ref. 4, p. 3.
[9] E. Leete, *J. Amer. Chem. Soc.*, 1977, **99**, 648.
[10] E. Leete and Y.-Y. Liu, *Phytochemistry*, 1973, **12**, 593; R. B. Herbert, in ref. 4, p. 7.

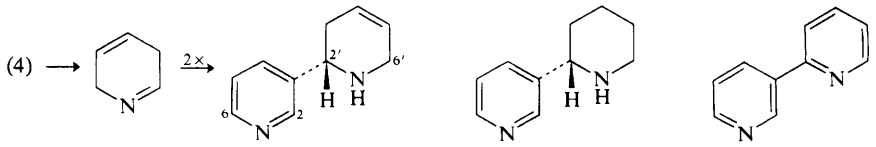
The evidence for dioscorine biosynthesis is consistent likewise with the intermediacy of (4) (see Scheme 1). The sequences of saturation and condensation leading to dioscorine, and also anatabine, cannot yet be specified, but are clearly well worth exploring. Of interest too, in the case of dioscorine, is the way in which the branched acetate chain originates (stepwise introduction of acetoacetate units in the course of the biosynthesis of the alkaloid?).



Scheme 1

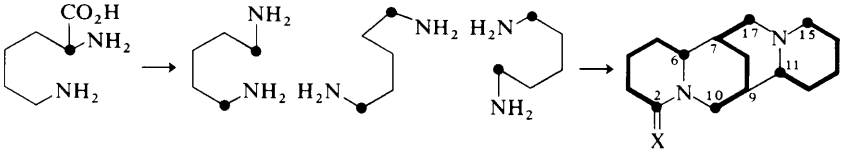
Anatabine.—A study of the biosynthesis of anatabine (6), which has been published in preliminary form and reviewed,[11] is now available in a full paper.[12] The incorporation of [2-^{14}C]nicotinic acid equally into C-2 and C-2′ of anatabine (6) provides essentially the only new information. This result complements that obtained with [6-^{14}C]nicotinic acid, *i.e.* labelling of C-6 and C-6′. Nicotinic acid was equally incorporated into both halves of (6) regardless of the length of the feeding experiment, which argues for alkaloid formation from two identical fragments [as (5)] rather than from (4) and (5), which might be formed from pools of material of different size and thus be dependent upon the length of the experiment.

In these experiments radioactive α,β-bipyridyl (8) was isolated and it appears from degradation studies that both rings of the alkaloid arise from nicotinic acid, so (8) can arise from anatabine (6) but not from anabasine (7), in which only one ring originates from nicotinic acid.



[11] E. Leete, *J.C.S. Chem. Comm.*, 1975, 9; R. B. Herbert, in ref. 6, p. 2.
[12] E. Leete and S. A. Slattery, *J. Amer. Chem. Soc.*, 1976, **98**, 6326.

Lupin Alkaloids.—The C_{15} lupin alkaloids, *e.g.* sparteine (9) and lupanine (10), are biosynthesized from three C_5 units derived (as shown in Scheme 2) from lysine and



Lysine Cadaverine Sparteine (9) X = H_2
Lupanine (10) X = O

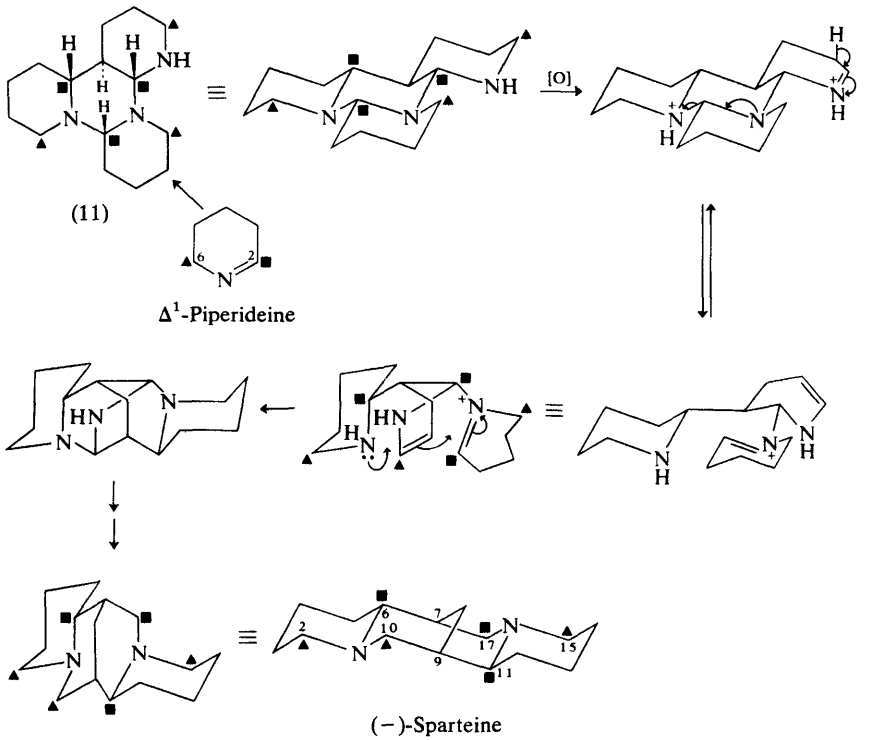
Scheme 2

cadaverine,[13,14] the two nitrogen atoms also arising from lysine.[14,15] Although the later stages of biosynthesis of these and related alkaloids are fairly clear,[16—18] the steps which lie between cadaverine and the alkaloids are obscure, the available hypotheses not being supported by experimental results. Recent results, however, support in a preliminary way an attractive new hypothesis, *i.e.* that these C_{15} alkaloids are modified trimers of Δ^1-piperideine (1)[19] (which is an important intermediate in the biosynthesis of many alkaloids derived from lysine). One of these trimers is isotripiperidine (11), shown with the favoured all-*trans* stereochemistry. Modification of (11) as shown for (−)-sparteine (Scheme 3) leads to lupin alkaloids with the same relevant stereochemistry as (11), *i.e.* 6*R*, 7*S*, 9*S*; those with 6*S*, 7*R*, 9*R*-stereochemistry may be derived from the enantiomer of (11). (−)-β-Isosparteine is the only alkaloid with 6*R*, 7*R*, 9*R*-stereochemistry and it is suggested that it arises from another stereoisomer of (11).

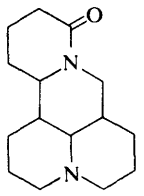
The Δ^1-piperideine trimer hypothesis is supported initially by the equal incorporation of lysine and cadaverine into all three alkaloid fragments[13,14] but more significantly by the incorporation of three molecules of Δ^1-piperideine (1) into lupanine (10) and by the manner of this incorporation: label from C-6 appeared at C-2, C-15, and, by inference, C-10, whereas C-2 label appeared at C-17, C-11, and, by inference, C-6, consistent with the hypothesis (see Scheme 3).[19] Further, approximately a third of the label was located at each of the determined sites.

This trimer hypothesis may be extended to related alkaloids, *e.g.* matrine (12).[19] Attractive though this is, it is argued against by the unequal utilization of Δ^1-piperideine (1) units in the construction of this alkaloid skeleton.[20]

[13] H. R. Schütte, F. Bohlmann, and W. Reusche, *Arch. Pharm.*, 1961, **294**, 610; H. R. Schütte, E. Nowacki, and Ch. Schäfer, *ibid.*, 1962, **295**, 20; H. R. Schütte and Ch. Schäfer, *Naturwiss.*, 1961, **48**, 669; H. R. Schütte and H. Hindorf, *Annalen.*, 1965, **685**, 187.
[14] H. R. Schütte, H. Hindorf, K. Mothes, and G. Hübner, *Annalen*, 1964, **680**, 93.
[15] H. R. Schütte and G. Seelig, *Annalen*, 1968, **711**, 221.
[16] H. R. Schütte, in 'Biosynthese der Alkaloide', ed. K. Mothes and H. R. Schütte, VEB Deutscher Verlag der Wissenschaften, Berlin, 1969, p. 324.
[17] I. D. Spenser, in 'Comprehensive Biochemistry', ed. M. Florkin and E. H. Stotz, Elsevier, Amsterdam, 1968, Vol. 20, p. 262.
[18] R. B. Herbert, in ref. 3, p. 30; in ref. 4, p. 12; in ref., 5, p. 10; in ref. 6, p. 6; J. Staunton, in ref. 2, p. 26.
[19] W. M. Golebiewski and I. D. Spenser, *J. Amer. Chem. Soc.*, 1976, **98**, 6726.
[20] S. Shibata and U. Sankawa, *Chem. and Ind.*, 1963, 1161.



Scheme 3

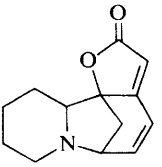


(12)

Securinine.—Further details of one group's study of the biosynthesis of securinine (13) have been published.[21] The origins of this alkaloid are well defined,[22] and information which adds to this definition is that tyrosine is incorporated without loss of tritium from the carbon atoms flanking the phenolic hydroxy-group.[21]

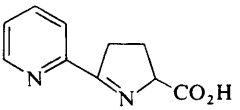
[21] U. Sankawa, Y. Ebizuka, and K. Yamasaki, *Phytochemistry*, 1977, **16**, 561.

[22] R. J. Parry, *Tetrahedron Letters*, 1974, 307; *J.C.S. Chem. Comm.*, 1975, 144; U. Sankawa, K. Yamasaki, and Y. Ebizuka, *Tetrahedron Letters*, 1974, 1867; W. M. Golebiewski, P. Horsewood, and I. D. Spenser, *J.C.S. Chem. Comm.*, 1976, 217; R. B. Herbert, in ref. 5, p. 10; in ref. 6, p. 40; in ref. 7 p. 2.



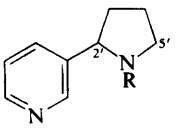
Securinine (13)

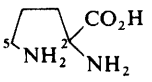
Proferrorosamine A.—Further information[23] on the biosynthesis of the bacterial metabolite proferrorosamine A (14), which is known to derive from picolinic acid,[24] is that [1-^{14}C]glycerol is more extensively incorporated into the pyrrolidine than the pyridine fragment of (14).

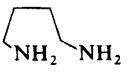


(14)

Nicotine.—[2-^{14}C]Ornithine is incorporated[25,26] into the pyrrolidine ring of nicotine (15) with equal labelling of C-2′ and C-5′. This requires passage of the amino-acid through a symmetrical intermediate, which combined evidence from experiments with labelled compounds[27] and enzymes[28] strongly indicates is putrescine. The intermediacy of a symmetrical compound (putrescine) in biosynthesis is supported by the results of one set of experiments[29] with $^{14}CO_2$, but inconsistent with another.[26,30] In this latter case the conclusion is that the pyrrolidine ring of nicotine derives partially *via* a symmetrical intermediate and partially without the intervention of such a compound. Re-examination of [2-^{14}C]ornithine and







Nicotine (15) R = Me
(16) R = H

Ornithine

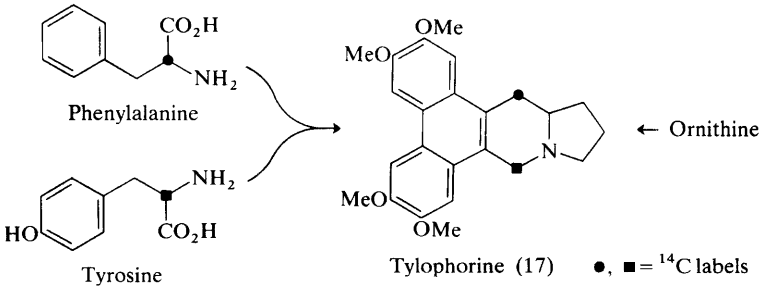
Putrescine

[23] A. M. Helbling and M. Viscontini, *Helv. Chim. Acta*, 1976, **59**, 2284.
[24] M. Pouteau-Thouvenot, J. Padikkala, M. Barbier, A. Helbling, and M. Viscontini, *Helv. Chim. Acta*, 1972, **55**, 2295; R. B. Herbert, in ref. 4, p. 9; see also ref. 5, p. 11.
[25] E. Leete and K. J. Siegfried, *J. Amer. Chem. Soc.*, 1957, **79**, 4529; B. L. Lamberts, L. J. Dewey, and R. U. Byerrum, *Biochim. Biophys. Acta*, 1959, **33**, 22.
[26] A. A. Liebman, B. P. Mundy, and H. Rapoport, *J. Amer. Chem. Soc.*, 1967, **89**, 664.
[27] E. Leete, *J. Amer. Chem. Soc.*, 1967, **89**, 7081; H. R. Schütte, W. Maier, and K. Mothes, *Acta Biochim. Polon.*, 1966, **13**, 401.
[28] S. Mizusaki, Y. Tanabe, M. Noguchi, and E. Tamaki, *Phytochemistry*, 1972, **11**, 2757; *Plant Cell Physiol.*, 1971, **12**, 633; *ibid.*, 1973, **14**, 103; R. B. Herbert, in ref. 4, p. 7.
[29] H. R. Zielke, R. U. Byerrum, R. M. O'Neal, L. C. Burns, and R. E. Koeppe, *J. Biol. Chem.*, 1968, **243**, 4757.
[30] M. L. Rueppel, B. P. Mundy, and H. Rapoport, *Phytochemistry*, 1974, **13**, 141; W. L. Alworth, A. A. Liebman, and J. Rapoport, *J. Amer. Chem. Soc.*, 1964, **86**, 3375; A. A. Liebman, F. Morsingh, and H. Rapoport, *ibid.*, 1965, **87**, 4399; R. B. Herbert, in ref. 5, p. 14.

$^{14}CO_2/^{13}CO_2$ incorporation, in association with a new degradation sequence, has led to a reaffirmation of the conclusion that both precursors are incorporated exclusively *via* a symmetrical intermediate.[31] It must be noted, however, that the results from examining $^{13}CO_2$ incorporation by n.m.r.,[32] in contrast to those obtained by degradation[31] ($^{14}CO_2$), are less unequivocal.

It had been noted earlier[33] that nornicotine (16) formed from [2-^{14}C]ornithine in an excised root culture of *Nicotiana rustica* was apparently unequally labelled at C-2′ and C-5′, arguing for partial incorporation of the amino-acid without intervention of a symmetrical intermediate. The validity of this conclusion is seriously questioned by the recent observation that, in *N. glutinosa* plants, ornithine was incorporated into nornicotine (16) in the same way as into nicotine (15), *i.e.* symmetrically.[31]

Phenanthroindolizidine Alkaloids.—These alkaloids, which may be exemplified by tylophorine (17), have been shown to have their genesis in tyrosine,[34] phenylalanine,[35] and probably ornithine,[35,36] as shown in Scheme 4; the phenylalanine is



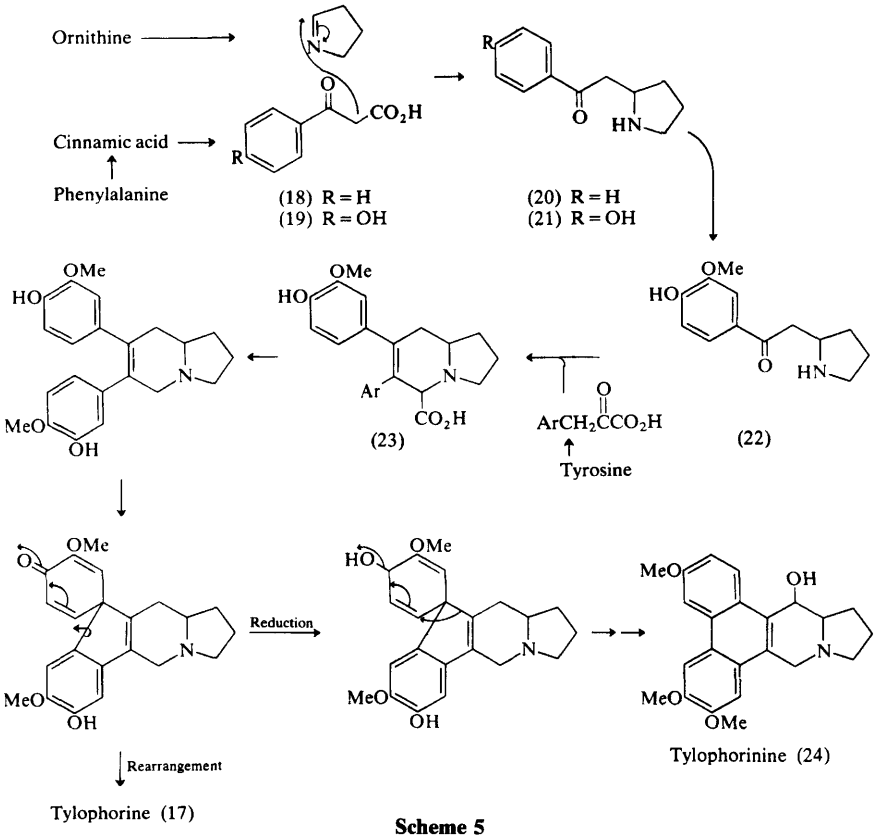
Scheme 4

utilized by way of cinnamic acid.[37] This latter observation is consistent with a normal pathway for phenylalanine incorporation in which benzoylacetic acid is an intermediate.[38] Accordingly, incorporations of this acid (18), and also its monohydroxy-derivative (19), have been recorded; (25) was not incorporated.[39] More importantly for the biosynthesis of phenanthroindolizidine alkaloids, the phenacylpyrrolidines [as (20)], which are analogous to many alkaloids with a

[31] E. Leete, *J. Org. Chem.*, 1976, **41**, 3438.
[32] C. R. Hutchinson, M.-T. S. Hsia, and R. A. Carver, *J. Amer. Chem. Soc.*, 1976, **98**, 6006.
[33] S. Mizusaki, T. Kisaki, and E. Tamaki, *Agric. and Biol. Chem. (Japan)*, 1965, **29**, 714.
[34] N. B. Mulchandani, S. S. Iyer, and L. P. Badheka, *Phytochemistry*, 1969, **8**, 1931; R. B. Herbert, in ref. 1, p. 15.
[35] N. B. Mulchandani, S. S. Iyer, and L. P. Badheka, *Phytochemistry*, 1971, **10**, 1047; J. Staunton, in ref, 2, p. 27.
[36] R. B. Herbert, unpublished results, quoted in ref. 39.
[37] N. B. Mulchandani, S. S. Iyer, and L. P. Badheka, *Phytochemistry*, 1976, **15**, 1697.
[38] *Cf.* M. H. Zenk, in 'Biosynthesis of Aromatic Compounds', Proceedings of the 2nd meeting of F.E.B.S., ed. G. Billek, Pergamon Press, Oxford, Vol. 3, 1966, p. 45; M. H. Zenk, in 'Pharmacognosy and Phytochemistry', ed. H. Wagner and L. Hörhammer, Springer-Verlag, Berlin, 1971, p. 314; R. N. Gupta and I. D. Spenser, *Canad. J. Chem.*, 1967, **45**, 1275; D. G. O'Donovan, D. J. Long, E. Forde, and P. Geary, *J.C.S. Perkin I*, 1975, 415; R. B. Herbert, in ref. 6, p. 3.
[39] R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J.C.S. Chem. Comm.*, 1976, 865.

pyrrolidine or piperidine ring, are defined as key intermediates.[39] Thus the compounds (20), (21), and (22), doubly labelled, were incorporated intact into tylophorinine (24). The results obtained with these phenacylpyrrolidines and the keto-acids, when combined, lead to the early part of the pathway shown in Scheme 5; the incorporation of both (19) and (20) indicates that aromatic hydroxylation may occur before as well as after phenacylpyrrolidine formation.

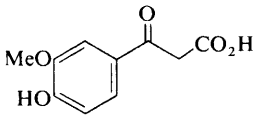
Later steps of biosynthesis follow as the joining together of (22) with a tyrosine-derived molecule to give the amino-acid (23), analogues of which are involved in isoquinoline biosynthesis.[40] Appropriate oxidative phenol coupling[41] and subsequent steps as indicated (Scheme 5) could afford tylophorine (17) and tylophorinine (24).[39]



Scheme 5

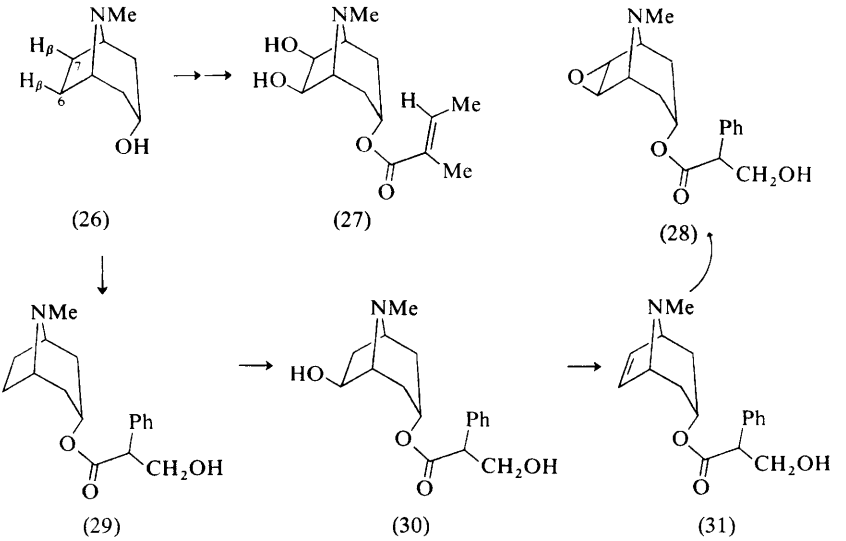
[40] G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Fayez, Y. N. Vaishnav, and H. M. Fales, *J. Amer. Chem. Soc.*, 1970, **92**, 6943; M. L. Wilson and C. J. Coscia, *J. Amer. Chem. Soc.*, 1975, **97**, 431; A. R. Battersby, R. C. F. Jones, and R. Kazlauskas, *Tetrahedron Letters*, 1975, 1873; J. Staunton, in ref. 2, p. 10; R. B. Herbert, in ref. 6, p. 17.

[41] D. H. R. Barton and T. Cohen, in 'Festschrift Dr. A. Stoll', Birkhäuser, Basel, 1957, p. 117; A. R. Battersby, in 'Oxidative Coupling of Phenols', ed. W. I. Taylor and A. R. Battersby, Arnold, London, 1967, p. 119.



(25)

Tropane Alkaloids.—It is known that tropine (26) is a precursor for meteloidine (27),[42] and its close relative hyoscyamine (29) is a precursor for scopolamine (28).[43] Experiments with samples of (26) labelled with β-tritium at C-6 and C-7 show that entry of the two β-hydroxy-groups in (27) must occur with normal retention of configuration since almost complete loss of tritium occurred.[44] Tritium was again lost almost completely on formation of scopolamine (28). On the assumption that early conclusions[45] on the sequential intermediacy of (30) and (31) in the biosynthesis of (28) are correct, formation of (30) involves normal retention of configuration (loss of half the tritium) and *cis*-dehydration then occurs to give (31) (loss of remaining tritium). [In these experiments the hyoscyamine (29) isolated showed appropriately no loss of tritium.][44]



(26) (27) (28) (29) (30) (31)

3 Isoquinoline Alkaloids

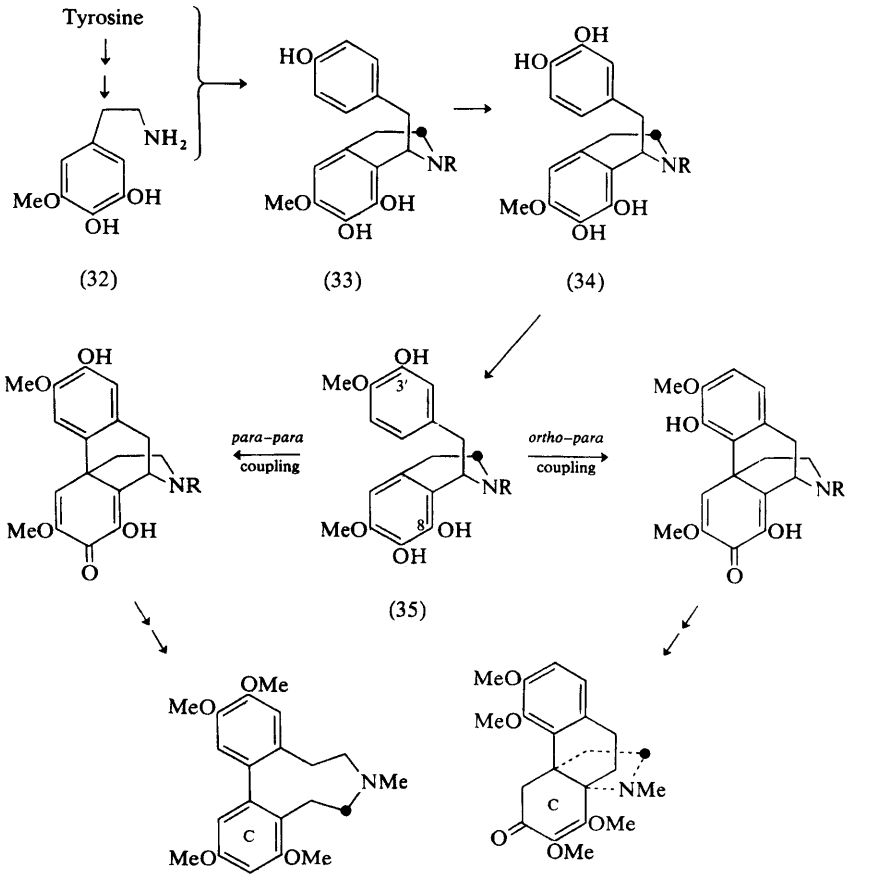
The biosynthesis of isoquinoline alkaloids has been reviewed.[46]

Protostephanine and Hasubanonine.—The unravelling of the biosynthesis of protostephanine (36) and hasubanonine (37), both produced by *Stephania japonica*,

[42] E. Leete, *Phytochemistry*, 1972, **11**, 1713.
[43] A. Romeike, *Flora*, 1956, **143**, 67; *ibid.*, 1959, **148**, 306; A. Romeike and G. Fodor, *Tetrahedron Letters*, 1960, No. 22, p. 1.
[44] E. Leete and D. H. Lucast, *Tetrahedron Letters*, 1976, 3401.
[45] G. Fodor, A. Romeike, G. Janzsó, and I. Koczor, *Tetrahedron Letters*, 1959, No. 7, p. 19.
[46] D. S. Bhakuni, *J. Sci. Ind. Res., India*, 1976, **35**, 461.

has proved to be a long and difficult task. Painstaking experimentation has led to the conclusion that these alkaloids are both constructed from two C_6–C_2 units derived from tyrosine.[47] The unit which is the source of ring C and the attached ethanamine side-chain in (36) and (37) combines as (32) with the other unit.

Sixteen possible benzylisoquinolines synthesized formally from (32) and the acids (38) have been examined[48] as precursors for (36) and (37). Of these, the bases with *O*-methyl groups at C-8 and/or C-3′ [as (35)] were not incorporated, but (35) as well as (33) and (34) were, and specifically so where examined (see Scheme 6 for



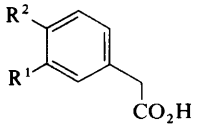
Scheme 6

[47] A. R. Battersby, R. C. F. Jones, R. Kazlauskas, C. Poupat, C. W. Thornber, S. Ruchirawat, and J. Staunton, *J.C.S. Chem. Comm.*, 1974, 773; R. B. Herbert, in ref. 6, p. 26.

[48] A. R. Battersby, A. Minta, A. P. Ottridge, and J. Staunton, *Tetrahedron Letters*, 1977, 1321.

labelling); the results show that the timing of *N*-methylation is not critical. It follows then, and it is an important conclusion, that hasubanonine (37) and protostephanine (36) are members of the large family of modified benzylisoquinolines. The pathway which the results indicate[48] is illustrated in Scheme 6. It is to be noted from the results[47,48] that phenol oxidative coupling must occur on (35) and not an *O*-methylated derivative of it—a so far unique example where two hydroxy-groups must be present on one ring for coupling to occur.

Also examined as precursors in these experiments were four possible bisphenethylamines derived from (32) as well as the acids (38) used to synthesize the benzylisoquinoline precursors. Consistent with biosynthesis of (36) and (37) along the pathway deduced above (Scheme 6) they were not incorporated.[48]



(38) $R^1 = H$, $R^2 = OH$
$R^1 = R^2 = OH$
$R^1 = OMe$, $R^2 = OH$
$R^1 = OH$, $R^2 = OMe$

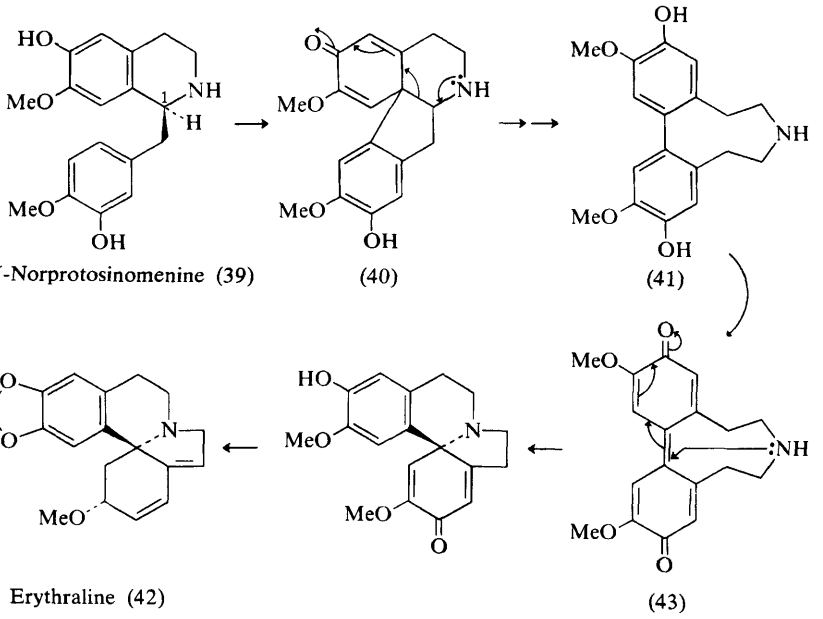
***Erythrina* Alkaloids.**—The biosynthesis of *Erythrina* alkaloids such as erythraline (42) has been proved[49,50] to be from (*S*)-norprotosinomenine (39) by way of the dienone (40) and the dibenzazonine (41) (Scheme 7). The alkaloid isococculidine (46), which lacks a C-16 oxygen function, can be thought of as arising from (44), the reduction product of (40), by rearrangement to (45). Subsequent steps would parallel the route to the alkaloids such as erythraline,[51] although cyclization of (45) could not take a course similar to that proposed for (41) (Scheme 7). Consequently a more acceptable route may be for loss of the oxygen atom in the biosynthesis of (46) to occur at a later stage by cyclization on (47), which is simply a lower-oxidation-level equivalent of (43).

Proof that the biosynthesis of isococculidine (46) parallels the normal *Erythrina* pathway has been obtained by showing that norprotosinomenine [as (39)] is an intact precursor for (46), is enormously more efficiently assimilated into the alkaloid than alternative isoquinoline precursors, nor-reticuline (48) and nororientaline (49), and [by adding carrier (39) during isolation after a tyrosine feeding experiment] is a natural constituent of *Cocculus laurifolius*, the plants used in these experiments.[51] It may be noted that as in the biosynthesis of other *Erythrina* bases (*S*)-norprotosinomenine (39) was much more efficiently utilized than its enantiomer. Further, incorporation of this isoquinoline does not involve loss of tritium label from C-1. Additional results are that norlaudanosoline (50), the undoubted

[49] D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1968, 1529.

[50] D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1970, 1213; D. H. R. Barton, C. J. Potter, and D. A. Widdowson, *J.C.S. Perkin I*, 1974, 346; D. H. R. Barton, R. D. Bracho, C. J. Potter, and D. A. Widdowson, *ibid.*, p. 2278; R. B. Herbert, in ref, 1, p. 22; in ref. 5, p. 24; in ref. 6, p. 25.

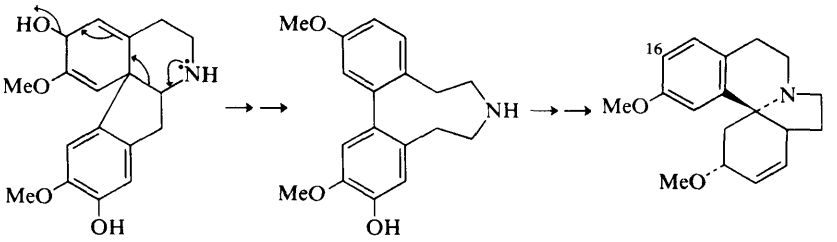
[51] D. S. Bhakuni, A. N. Singh, and R. S. Kapil, *J.C.S. Chem. Comm.*, 1977, 211.



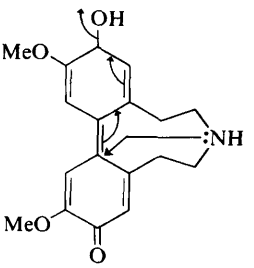
(*S*)-*N*-Norprotosinomenine (39) (40) (41)

Erythraline (42) (43)

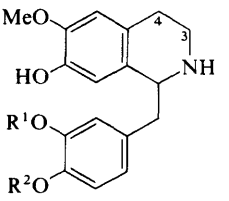
Scheme 7



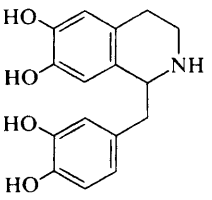
(44) (45) Isococculidine (46)



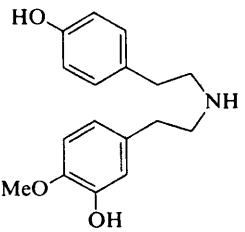
(47)



(48) $R^1 = H$, $R^2 = Me$
(49) $R^1 = Me$, $R^2 = H$



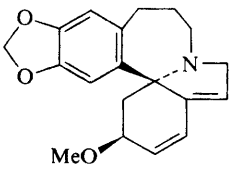
(50)



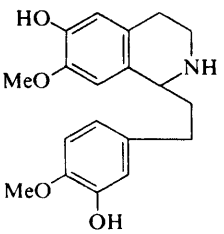
(51)

precursor for (39), was efficiently incorporated into (46), but, as to be expected,[49] (51) was not utilized in biosynthesis.

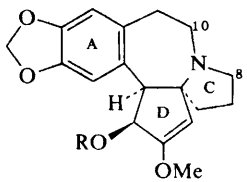
***Cephalotaxus* Alkaloids.**—Preliminary results indicate that the homo-*Erythrina* alkaloid schelhammeridine (52) derives from phenylalanine and tyrosine by way of a phenethylisoquinoline precursor [as (53)].[52] Previous evidence for the biosynthesis of the related alkaloid cephalotaxine (54), obtained with tyrosine labelled in the side-chain, has indicated a different pathway which involves two molecules of this amino-acid.[53] Recently, however, tyrosine labelled in the aromatic ring was examined as a cephalotaxine precursor and was found[54] to label ring A of (54) almost exclusively, *i.e.* only one unit of tyrosine is used for biosynthesis. This is obviously inconsistent with the previous evidence and the early incorporations are



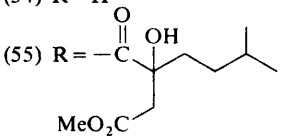
(52)



(53)



Cephalotaxine (54) R = H



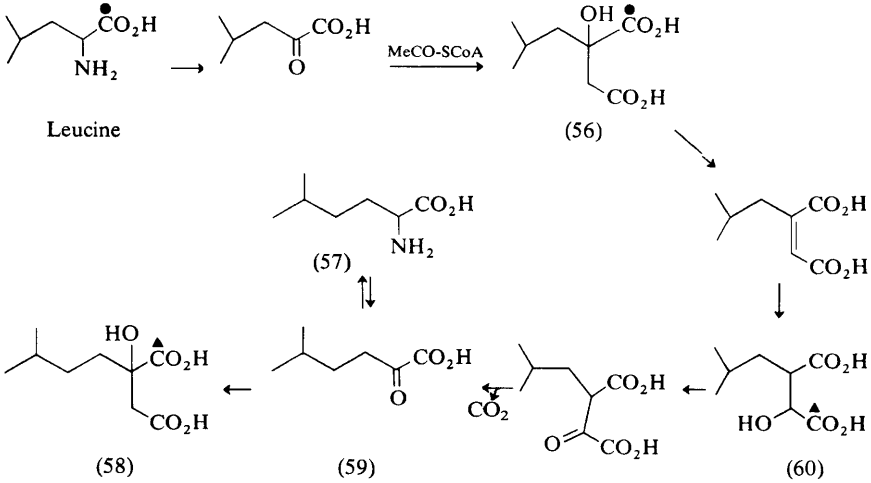
(55) R = —

[52] A. R. Battersby, E. McDonald, J. A. Milner, S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Tetrahedron Letters*, 1975, 3419,; R. B. Herbert, in ref. 7, p. 10.
[53] R. J. Parry and J. M. Schwab, *J. Amer. Chem. Soc.*, 1975, **97**, 2555; R. B. Herbert, in ref. 6, p. 27.
[54] J. M. Schwab, M. N. T. Chang, and R. J. Parry, *J. Amer. Chem. Soc.*, 1977, **99**, 2368.

now attributed in part to tyrosine catabolism in such a way that side-chain label but not ring label enters the pathway to cephalotaxine (54). By shortening the time of the feeding experiments it could be shown that DL-[2-^{14}C]tyrosine primarily labels C-10, consistent with the ring-labelled-tyrosine results; in prolonged experiments label appeared elsewhere.

As expected, if rings C and D do not arise primarily from tyrosine, phenylalanine was incorporated, label from C-1 appearing largely at C-8. This establishes that the amino-acid provides a C_6–C_3 unit for cephalotaxine biosynthesis and is consistent with passage through a phenethylisoquinoline intermediate [as (53)].[52,55,56] Incorporation of phenylalanine would then be expected to be through cinnamic acid,[52,55] but this compound was not incorporated into (54),[54] although phenylalanine was assimilated with loss of one proton from C-3, consistent[57] with passage through an intermediate such as cinnamic acid. The significance of the cinnamic acid incorporation must clearly rest on the results of further experiments.

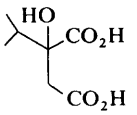
Cephalotaxine (54) may occur naturally as various esters, *e.g.* deoxyharringtonine (55). The acid (58) is analogous to (61), which is an intermediate in the conversion of L-valine into L-leucine.[58] This suggests a related pathway (Scheme 8)



Scheme 8

to (58) beginning with L-leucine.[59] This is supported in a key way by the isolation from *Cephalotaxus harringtonia* of (56) specifically labelled as shown, after feeding [1-^{14}C]leucine, and by the specific incorporation of (60) into (58), labelled as

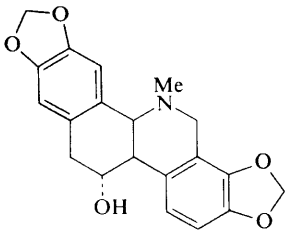
[55] R. B. Herbert, in ref. 4, p. 19, and refs. cited.
[56] R. G. Powell, *Phytochemistry*, 1972, **11**, 1467.
[57] R. H. Wightman, J. Staunton, A. R. Battersby, and K. R. Hanson, *J.C.S. Perkin I.*, 1972, 2355; R. B. Herbert, in ref. 5, p. 18.
[58] C. Jungwirth, P. Margolin, E. Umbarger, and S. R. Gross, *Biochem. Biophys. Res. Comm.*, 1961, **5**, 435; S. R. Gross, C. Jungwirth, and E. Umbarger, *ibid.*, 1962, **7**, 5; S. R. Gross, R. O. Burns, and H. E. Umbarger, *Biochemistry*, 1963, **2**, 1046; J. M. Calvo, M. G. Kalyanpur, and C. M. Stevens, *ibid.*, 1962, **1**, 1157; M. Strassman and L. N. Ceci, *J. Biol. Chem.*, 1963, **238**, 2445.
[59] R. J. Parry, D. D. Sternbach, and M. D. Cabelli, *J. Amer. Chem. Soc.*, 1976, **98**, 6380.



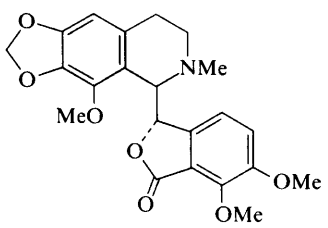
(61)

shown. On the basis of the proposed pathway (59), derivable simply from homoleucine (57), should be an immediate precursor for (58). A highly efficient and specific incorporation of (59) into (58) gives substance to this hypothesis.[59] Attention may be drawn to the biosynthesis of similar esters of pyrrolizidine alkaloids, which also originate from branched-chain amino-acids.[60]

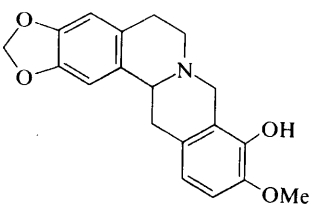
Protoberberine Alkaloids.—In the course of the bioconversion of the protoberberine scoulerine (65) into chelidonine (62) and phthalide-isoquinolines, *e.g.* narcotine (63), C-13 becomes oxidized.[61] Ophiocarpine (68), with a hydroxy-group at C-13, represents an intermediate stage in the modification of the protoberberine skeleton, and results[62] of tracer experiments have shown that scoulerine (65) is also to be included in the biosynthesis of this alkaloid. Tetrahydroprotoberberine (67) is also a precursor, its incorporation indicating that C-13 hydroxylation is a terminal step. As for other protoberberine derivatives,[63] nandinine (64) was not assimilated,[62] and it follows then that (65) is probably converted into (67) by way of isocorypalmine (66).



Chelidonine (62)

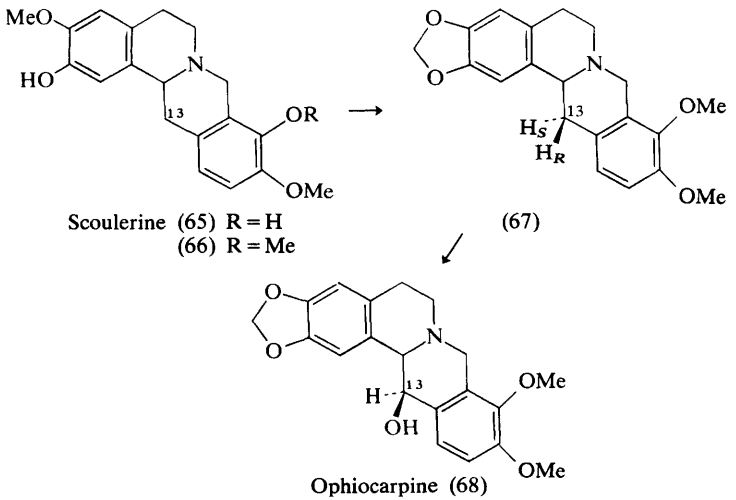


Narcotine (63)



(64)

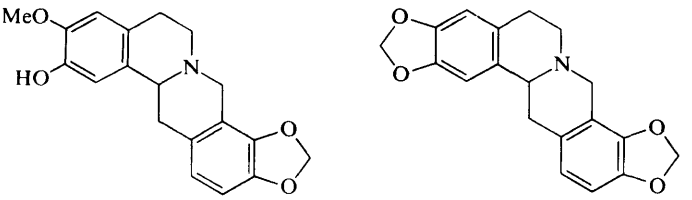
[60] R. B. Herbert, in ref. 6, p. 11; and refs. cited.
[61] A. R. Battersby, J. Staunton, H. R. Wiltshire, B. J. Bircher, and C. Fuganti, *J.C.S. Perkin I*, 1975, 1162; R. B. Herbert, in ref. 7, pp. 12, 16.
[62] P. W. Jeffs and J. D. Scharver, *J. Amer. Chem. Soc.*, 1976, **98**, 4301.
[63] A. R. Battersby, J. Staunton, H. R. Wiltshire, R. J. Francis, and R. Southgate, *J.C.S. Perkin I*, 1975, 1147; R. B. Herbert, in ref. 7, p. 12.



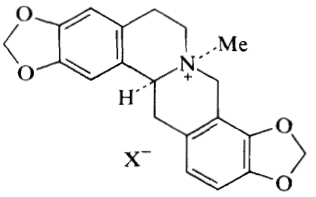
Using chirally tritiated samples of the protoberberine (67) it has been established that hydroxylation of (67) to give (68) occurs with loss of the 13-*pro*-*R* hydrogen atom, *i.e.* normal retention of configuration, and does not involve an enamine intermediate since tritium is not lost from C-14 during the course of this biotransformation.[62] It is to be noted that similar results, associated with C-13, have been observed[61] for narcotine (63) and chelidonine (62) biosynthesis, except that here the 13-*pro*-*S* proton is removed.

The probability[63] that (69) lies along the pathway to protoberberine and derived alkaloids, between scoulerine (65) and stylopine (70), has been supported by the observation that tritiated (69) is a precursor for protopine (73), and also for corynoline (78).[64] Evidence previously obtained for the intermediacy of the metho-salt of stylopine [as (71)] in the biosynthesis of chelidonine (62)[63] and protopine (73)[63,65] has been affirmed, and it is apparently the α-form (71) and not the β-form that is involved. [The authors are mistaken in assuming that (−)-stylopine has the *R*-configuration at C-14; *cf.* ref. 63].

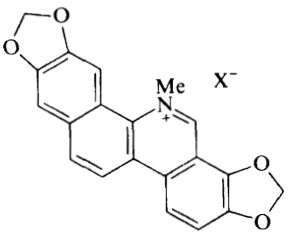
A striking novel result is that [*N*-*methyl*-^{13}C]protopine [as (73)] affords appropriately labelled chelidonine (62) and sanguinarine (72).[64] Previously[63] the formation of chelidonine (62) had been rationalized as involving a pathway through (71)



[64] N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 2859.
[65] C. Tani and K. Tagahara, *Chem. and Pharm. Bull. (Japan)*, 1974, **22**, 2457; R. B. Herbert, in ref. 6, p. 22.

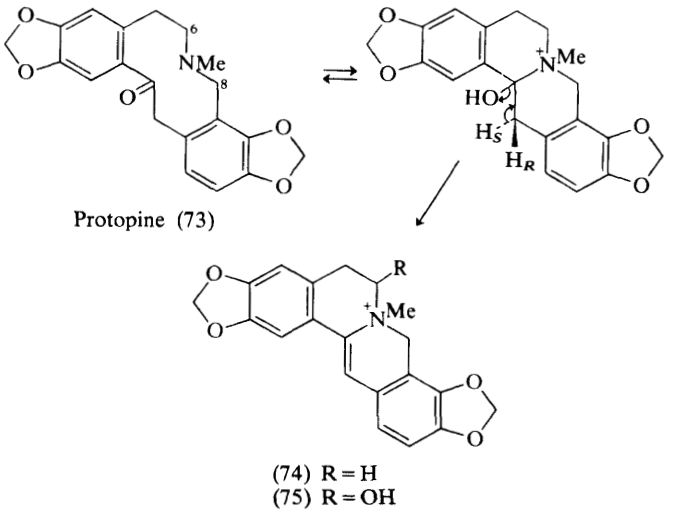


(71)



(72)

which did not include protopine (73). Although protopine is now to be included on the pathway, only minor modification, so far at least, is necessary (Scheme 9; *cf.*



Protopine (73)

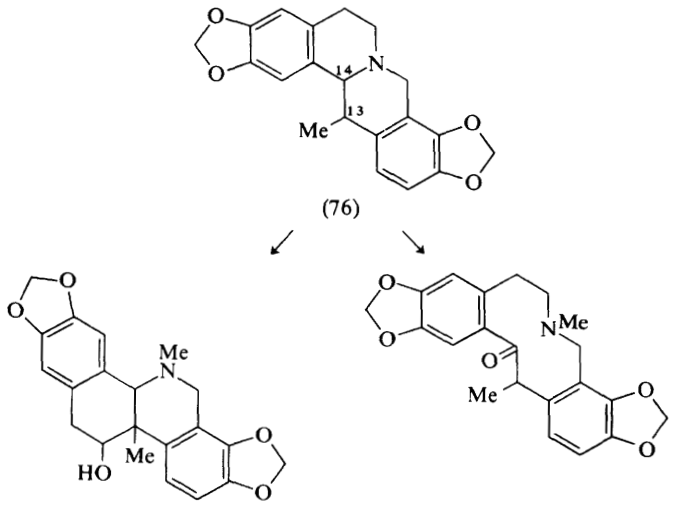
(74) R = H
(75) R = OH

Scheme 9

Scheme 3, p. 15, in ref. 7). As discussed below, protopine (73) and (81) are precursors for rhoeadine (83) and alpinigenine (82), respectively; modified protoberberines in which further C—N bond cleavage must also occur. In this case it is the C-8—N bond [as (73)] which must be broken, whereas in the case of chelidonine (62) it is finally only the C-6—N linkage.

Further detail on the biosynthesis of corynoline (78) and related alkaloids is that (76) is a precursor for corynoline (78) and corycavine (77).[64] In the latter case it was observed that the configurations at C-13 and C-14 in the precursor were unimportant and incorporation occurred *via* the metho-salt. Tetrahydrocorysamine (76) is closely related to corydaline, whose biosynthesis from tyrosine and methionine has been studied.[66] The *C*-methyl group at C-13 was shown to arise from methionine and the mechanism suggested for the methylation involves

[66] H. L. Holland, M. Castillo, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1974, **52**, 2818; R. B. Herbert, in ref. 6, p. 23.

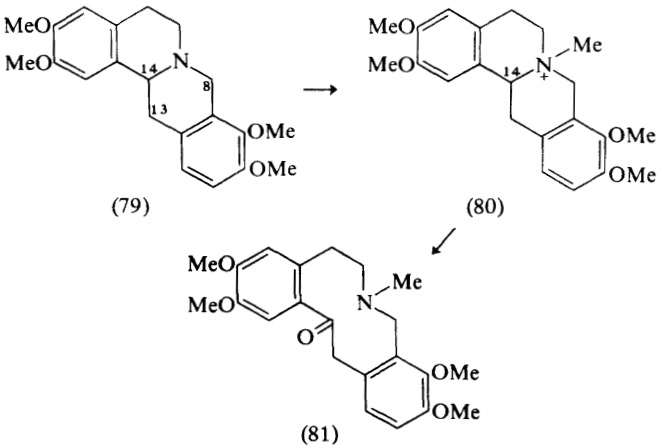


(76)

Corynoline (78) (77)

an enamine [as (74)] similar to the one proposed for chelidonine biosynthesis.[63] Further comparative information on the sequence surrounding this reaction, as on the subsequent ones leading to corynoline (78), will be gleaned by observing which of the C-13 protons is lost; in chelidonine (62) biosynthesis it is the 13-*pro*-*S* proton.

Earlier studies have shown that alpinigenine (82) is derived from two molecules of tyrosine[67] by way of tetrahydropalmatine (79) and possibly its *N*-methyl derivative (80).[68] Recent results[69] further implicate (79) and (80), which were



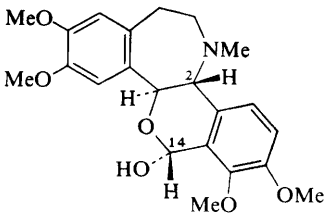
(79) (80)

(81)

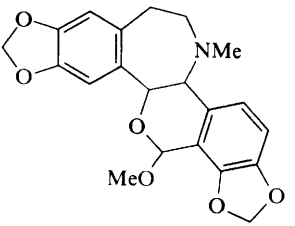
[67] H. Böhm and H. Rönsch, *Z. Naturforsch.*, 1968, **23b**, 1553; H. Rönsch and H. Böhm, in 'Biochemie und Physiologie der Alkaloide', Fourth International Symposium, 1969, ed. K. Mothes, K. Schreiber, and H. R. Schütte, Akademie-Verlag, Berlin, p. 287.

[68] H. Rönsch, *European J. Biochem.*, 1972, **28**, 123; R. B. Herbert, in ref. 4, p. 18.

[69] H. Rönsch, *Phytochemistry*, 1977, **16**, 691.

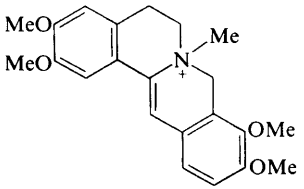


Alpinigenine (82)

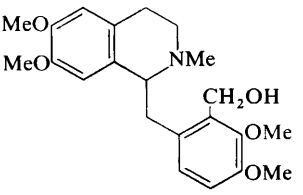


Rhoeadine (83)

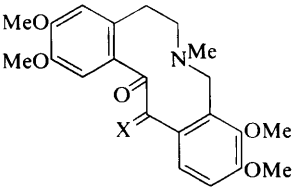
incorporated with loss of tritium label sited at C-8, C-13, and C-14. In the case of the first two sites approximately half of each of the labels was lost [retention at C-14 and C-2 in (82)] and in the case of the C-14 label essentially complete loss was observed. This latter loss is consistent with oxidation of the C-14—N bond in (80), resulting in ring-opening to give (81); the intermediacy in this ring-opening of the enamine (84) [of the type thought to be involved in chelidonine (62) biosynthesis: see above] from precursors such as (79) is excluded by the non-incorporation of (84) into alpinigenine (82). Confirmation of the intermediacy of (81) in alpigenine biosynthesis was obtained by showing that it was an efficient and specific precursor for the alkaloid. Moreover, (79), (80), and (81) were proved by isotope dilution, after feeding radioactive methionine, to be natural constituents of the plant used for the study. Three other compounds, (85), (86), and (87), were shown not to be transformable by the plant into alpinigenine (82).[69]



(84)



(85)

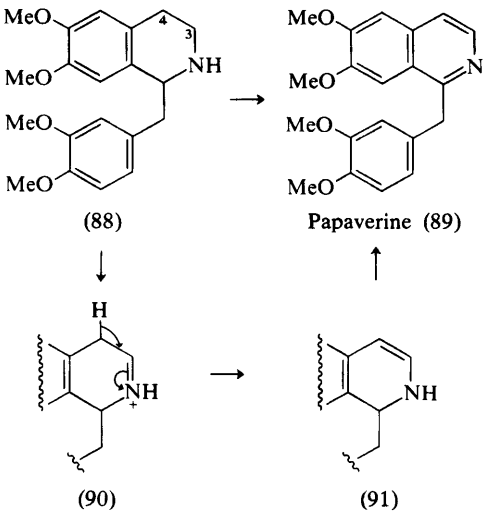


(86) X = H,OH
(87) X = O

Study[70] of the biosynthesis of the closely related alkaloid rhoeadine (83) confirms that the formation of the skeleton common to this alkaloid and (82) involves compounds of the types (80) and (81), in this case (71) and protopine (73) (for interlocking evidence on protopine biosynthesis see above).

[70] C. Tani and K. Tagahara, *J. Pharm. Soc. Japan*, 1977, **97**, 93.

Papaverine.—The biosynthesis of the simple benzylisoquinoline papaverine (89) is known to proceed *via* nor-reticuline (48) and tetrahydropapaverine (88).[71] Dehydrogenation of the latter affords papaverine, and examination of the stereochemistry of the processes involved has led to the conclusion[72] that loss of the proton at C-3 [in nor-reticuline (48)] is stereospecific (loss of the *pro-S* hydrogen atom) but removal of the C-4 proton is essentially non-stereospecific. These observations are perhaps best explained if enzyme-catalysed oxidation of (88) occurs to give (90), subsequent non-stereospecific imine–enamine isomerization occurring without enzyme participation to give (91). A further amine to imine oxidation then occurs to give papaverine (89).[72]



(88) Papaverine (89)

(90) (91)

Aporphine Alkaloids.—A study on the biosynthesis of boldine previously published in preliminary form and reviewed[73] is now available in full[74] without the addition of essentially new information.

4 Amaryllidaceae and Mesembrine Alkaloids

Amaryllidaceae Alkaloids.—Detail has been added to the fairly thoroughly delineated pathways to the Amaryllidaceae alkaloids.[75,76] 11-Hydroxyvittatine (94), previously shown to be a precursor for narciclasine (96),[76] has been proposed as an intermediate in the biosynthesis of haemanthamine (92) and montanine (95) following the observed specific incorporation of vittatine (93) into the two

[71] E. Brochmann-Hanssen, C. Chen, C. R. Chen, H. Chiang, A. Y. Leung, and K. McMurtrey, *J.C.S. Perkin I*, 1975, 1531; H. Uprety, D. S. Bhakuni, and R. S. Kapil, *Phytochemistry*, 1975, **14**, 1535; R. B. Herbert, in ref. 7, p. 12, and refs. cited.

[72] A. R. Battersby, P. W. Sheldrake, J. Staunton, and M. C. Summers, *Bioorg. Chem.*, 1977, **6**, 43.

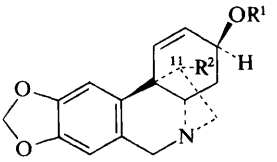
[73] S. Tewari, D. S. Bhakuni, and R. S. Kapil, *J.C.S. Chem. Comm.*, 1974, 940; R. B. Herbert, in ref. 6, p. 20.

[74] D. S. Bhakuni, S. Tewari, and R. S. Kapil, *J.C.S. Perkin I*, 1977, 706.

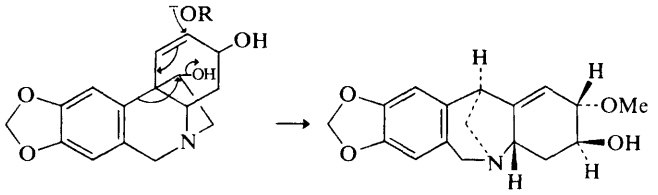
[75] H. R. Schütte, in ref. 16, p. 420; I. D. Spenser, in ref. 17, p. 300; R. B. Herbert, in ref. 5, p. 19; in ref. 4, p. 23; in ref. 3, p. 21; in ref. 1, p. 24; J. Staunton, in ref. 2, p. 16.

[76] C. Fuganti, *Gazzetta*, 1973, **103**, 1255; R. B. Herbert, in ref. 6, p. 39.

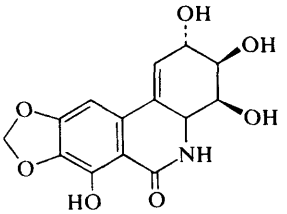
alkaloids.[77] Montanine (95) was previously demonstrated to arise from the haemanthamine (92) precursor *O*-methylnorbelladine (97) but in the course of biosynthesis the 2-*pro*-*S* proton is lost from (97), which is the opposite to proton loss leading to haemanthamine (92).[78] Consequently, if 11-hydroxyvittatine is involved in the biosynthesis of (92) and (95), the alkaloids must be formed from different C-11 epimers of (94).



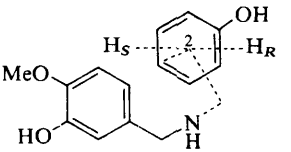
(92) $R^1 = Me$, $R^2 = OH$
(93) $R^1 = R^2 = H$



(94) Montanine (95)

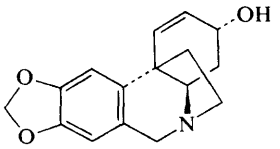


Narciclasine (96)

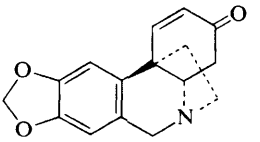


(97)

Results of experiments with labelled (−)-crinine (98), and less conclusively with oxovittatine (99), indicate that the two naturally occurring enantiomeric series represented by (98) and (99) are not interconvertible.[77]



(98)

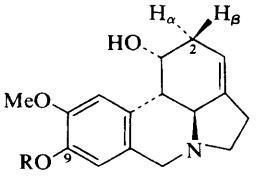


(99)

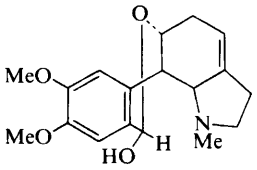
[77] A. I. Feinstein and W. C. Wildman, *J. Org. Chem.*, 1976, **41**, 2447.
[78] C. Fuganti, D. Ghiringhelli, and P. Grasselli, *J.C.S. Chem. Comm.*, 1973, 430.

The observation[79] in an earlier more extensive study that norpluviine (100) is a precursor for lycorenine (102) has been confirmed.[80] Incorporations were also recorded with both norpluviine (100) and pluviine (101) for other alkaloids of related structure to norpluviine, including galanthine (103). Although radio-active narciclasine (96) was also isolated in the experiment with norpluviine, its known derivation[76,81] by way of a different pathway through vittatine (93) indicates that this is not significant.

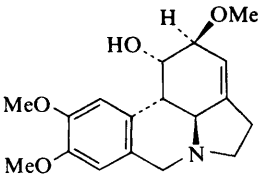
Conflict exists in deciding on the stereochemical course of the hydroxylation at C-2 of, *e.g.*, norpluviine (100), which leads to lycorine (104). One set of results indicates that hydroxylation occurs with normal retention of configuration[82] whereas the other set, obtained in a different plant, indicates that the reaction occurs with unusual inversion of configuration.[83] The conversion of [2β-^{3}H, 9-*OMe*-^{14}C]pluviine [as (101)] into galanthine (103), in 'King Alfred' daffodils, with retention of 79% of the tritium label confirms that the hydroxylation of C-2 may occur with inversion of configuration.[80]



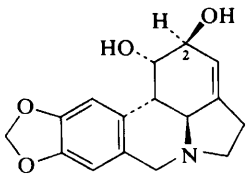
Norpluviine (100) R = H
(101) R = Me



Lycorenine (102)



Galanthine (103)



Lycorine (104)

Mesembrine Alkaloids.—Previous results have indicated that mesembrine (110) and related alkaloids originate from one molecule each of tyrosine and phenylalanine by way of an intermediate which may be formalized as (105).[84] The natural occurrence of sceletenone (106) and other alkaloids which, in contrast to, *e.g.*,

[79] C. Fuganti and M. Mazza, *Chem. Comm.*, 1971, 1196; *J.C.S. Perkin I*, 1973, 954; R. B. Herbert, in ref. 3, p. 23; in ref. 4, p. 23.

[80] R. D. Harken, C. P. Christensen, and W. C. Wildman, *J. Org. Chem.*, 1976, **41**, 2450.

[81] C. Fuganti, J. Staunton, and A. R. Battersby, *Chem. Comm.*, 1971, 1154; C. Fuganti and M. Mazza, *ibid.*, p. 1388; *J.C.S. Chem. Comm.*, 1972, 239; J. Staunton, in ref. 2, p. 16; R. B. Herbert, in ref. 3, p. 21.

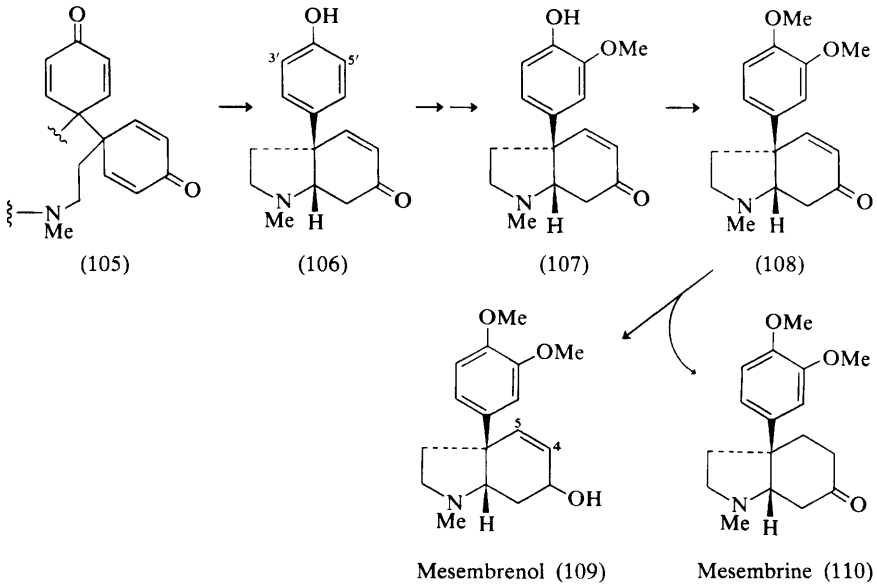
[82] C. Fuganti and M. Mazza, *J.C.S. Chem. Comm.*, 1972, 936; R. B. Herbert, in ref. 4, p. 24.

[83] I. T. Bruce and G. W. Kirby, *Chem. Comm.*, 1968, 207; *Chimia* (*Switz.*), 1968, **22**, 314; W. C. Wildman and N. E. Heimer, *J. Amer. Chem. Soc.*, 1967, **89**, 5265.

[84] P. W. Jeffs, W. C. Archie, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, 1971, **93**, 3752; P. W. Jeffs, H. F. Campbell, D. S. Farrier, G. Ganguli, N. H. Martin, and G. Molina, *Phytochemistry*, 1974, **13**, 933; P. W. Jeffs, D. B. Johnson, N. H. Martin, and B. S. Rauckman, *J.C.S. Chem. Comm.*, 1976, 82; R. B. Herbert, in ref. 3, p. 23; in ref. 5, p. 22; in ref. 7, p. 23.

mesembrine (110), bear mono-oxygenated aromatic muclei, has suggested that the second oxygen atom in *inter alia* mesembrine (110) and mesembrenol (109) arises at a late rather than an early stage of biosynthesis. Accordingly an efficient incorporation of [3′,5′-$^3H_2$]sceletenone (106) into mesembrenol (109) was recorded.[85]

Further detail of biosynthesis is that 4′-*O*-demethylmesembrenone (107) and mesembrenone (108) are efficient precursors for mesembrenol (109) and mesembrine (110); (108) was also recorded as an efficient precursor for mesembranol (109; no 4,5-double bond); (108) was not incorporated into (107), indicating that *O*-demethylation of (108) does not occur to a significant extent.[85] The compounds (107) and (108) lie on the pathway to (109) and (110) most reasonably after sceletenone (106), and the results may be fitted together to give the pathway shown in Scheme 10.

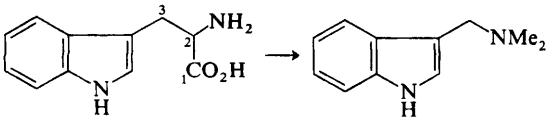


Scheme 10

5 Alkaloids Derived from Tryptophan

Gramine.—The efficient incorporation of [3-^{14}C]tryptophan into gramine (111) in *Phalaris arundinacea* (Graminae), with labelling of the methylene group,[86] indicates that the biosynthesis of this simple indole base takes the same course in this plant as in barley (Graminae)[87] and in *Lupinus hartwegii* (Leguminosae).[88]

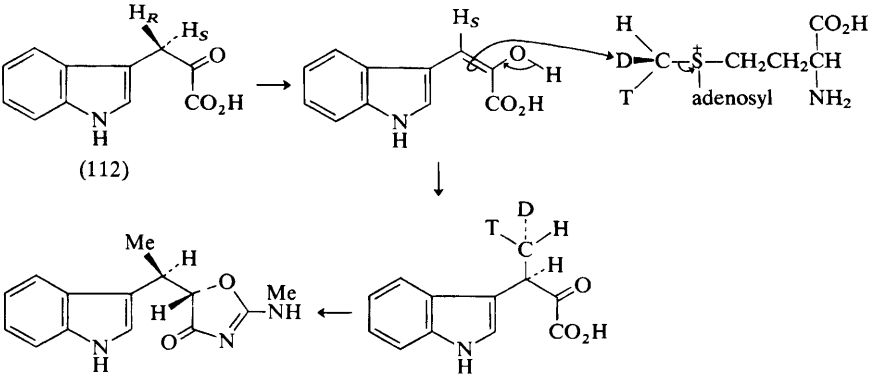
[85] P. W. Jeffs and J. M. Karle, *J.C.S. Chem. Comm.*, 1977, 60.
[86] E. Leete and M. L. Minich, *Phytochemistry*, 1977, **16**, 149.
[87] E. Leete and L. Marion, *Canad. J. Chem.*, 1963, **31**, 1195; K. Bowden and L. Marion, *ibid.*, 1951, **29**, 1037; D. O'Donovan and E. Leete, *J. Amer. Chem. Soc.*, 1963, **85**, 461; D. Gross, H. Lehmann, and H. R. Schütte, *Tetrahedron Letters*, 1971, 4047; R. B. Herbert, in ref. 3, p. 10.
[88] E. Leete, *Phytochemistry*, 1975, **14**, 471.



Tryptophan Gramine (111)

Indolmycin.—The biosynthesis of the *Streptomyces griseus* metabolite indolmycin (113) begins with tryptophan and involves an interesting *C*-methylation reaction on indolepyruvic acid (112).[89,90] Results obtained with (112) stereospecifically tritiated at C-3 indicate that this reaction occurs with retention of configuration at the methylene group, *i.e.* methylation occurs on the same face of the molecule as proton removal.[91] On the other hand, results with methionine chirally labelled, with tritium and deuterium, on the methyl group demonstrate that during methylation this group suffers an inversion of configuration[92] (similar inversion of configuration has been observed in corrin biosynthesis[93]).

It is probable that methyl transferase reactions proceed by nucleophilic attack on *S*-adenosylmethionine[94] and may involve an S_N2-like transition state.[95] Thus, inversion of configuration as observed in indolmycin biosynthesis indicates that an odd number of nucleophilic displacements occurs and suggests that the methyl group is transferred directly from donor to (112), *i.e.* without generation of a methylated-enzyme intermediate.[92] The combined results are summarized in Scheme 11.



(112)

Indolmycin (113)

Scheme 11

[89] U. Hornemann, M. K. Speedie, L. H. Hurley, and H. G. Floss, *J. Amer. Chem. Soc.*, 1971, **93**, 3028; R. B. Herbert, in ref. 3, p. 10.

[90] M. K. Speedie, U. Hornemann, and H. G. Floss, *J. Biol. Chem.*, 1975, **250**, 7819; R. B. Herbert, in ref. 7, p. 16, and refs. cited.

[91] L. Zee, U. Hornemann, and H. G. Floss, *Biochem. Physiol. Pflanzen.*, 1975, **168**, 19.

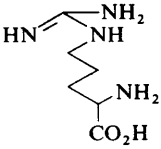
[92] L. Mascaro, jun., R. Hörhammer, S. Eisenstein, L. K. Sellers, K. Mascaro, and H. G. Floss, *J. Amer. Chem. Soc.*, 1977, **99**, 273.

[93] D. Arigoni, paper presented at the International Symposium on Stereochemistry, Kingston, Canada, June 27—July 2, 1976, quoted in ref. 92.

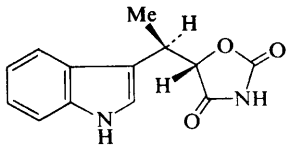
[94] S. H. Mudd and G. L. Cantoni, in 'Comprehensive Biochemistry', ed. M. Florkin and E. H. Stotz, Elsevier, Amsterdam, 1964, Vol. 15, p. 28.

[95] M. F. Hegazi, R. T. Borchardt, and R. L. Schowen, *J. Amer. Chem. Soc.*, 1976, **98**, 3048.

Arginine is a precursor for indolmycin (113)[90] and the incorporation of [*amidino*-^{14}C,^{15}N]arginine [as (114)] without change in isotope ratio and with a ^{15}N labelling pattern consistent with incorporation of both precursor nitrogen atoms indicates that the amidino-group in the precursor is incorporated intact.[91] Further support for this conclusion comes from the very poor incorporation of (115) into indolmycin (113).

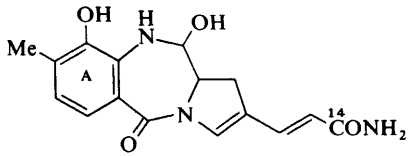


(114)

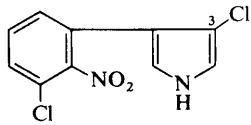


(115)

Anthramycin, Pyrrolnitrin, and Tomaymycin.—An important piece of evidence on the biosynthesis of anthramycin (116) is that methionine provides C-14. In part this evidence comes from a ^{13}C-labelling study,[96] and the conclusion has been supported by the use of ^{13}C–^{1}H long-range coupling in analysing the ^{1}H n.m.r. spectrum of anthramycin (116) derived from [*Me*-^{13}C]methionine.[97] Similar application to the study of pyrrolnitrin (117) biosynthesis has confirmed[97] the mode of tryptophan incorporation[98] [a ^{13}C label at C-3 of the amino-acid appeared at C-3 of (117)].



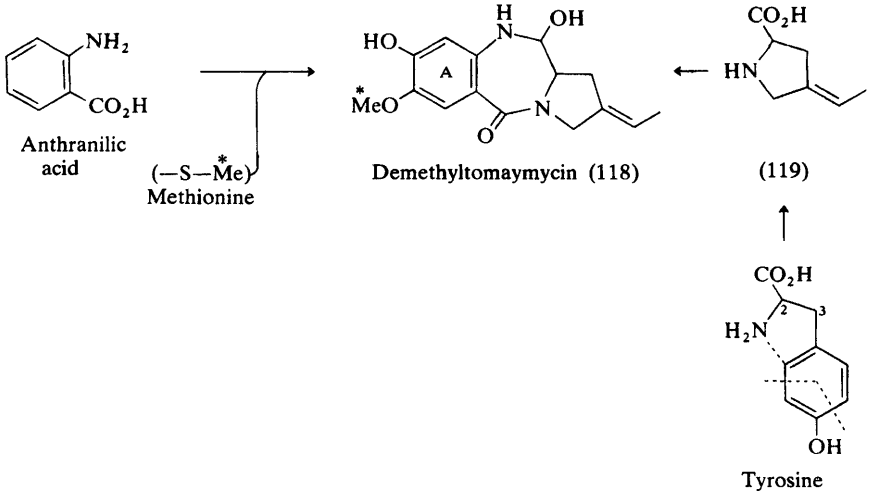
Anthramycin (116)



Pyrrolnitrin (117)

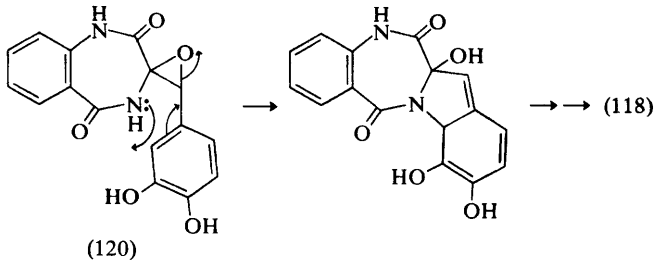
Preliminary results[99] indicated that 11-demethyltomaymycin (118) had a similar genesis to anthramycin (116) from tryptophan and tyrosine, and these results have now been published in full.[100] Tryptophan has been shown to provide ring A, presumably by catabolism through anthranilic acid. The results[99,100] are summarized in Scheme 12. It is to be noted that methionine provides only the aromatic *O*-methyl group [in anthramycin there is an extra carbon present in the unit related to (119) which derives from methionine: see above]. Further evidence from incorporation of labelled tyrosine indicates that the C_7 unit (119) derives from seven tyrosine carbon atoms. The incorporation of L-[1-^{14}C,2,3-$^{3}H_2$]tyrosine (tritium distribution: H-2, 50%; H-3-*pro*-*S*, 41.5%; H-3-*pro*-*R*, 8.5%) with loss of half the tritium label was interpreted reasonably as involving loss only of the C-2

[96] L. H. Hurley, M. Zmijewski, and C. Chang, *J. Amer. Chem. Soc.*, 1975, **97**, 4372; R. B. Herbert, in ref. 7, p. 25.
[97] C. Chang, H. G. Floss, L. H. Hurley, and M. Zmijewski, *J. Org. Chem.*, 1976, **41**, 2932.
[98] L. L. Martin, C. Chang, H. G. Floss, J. A. Mabe, E. W. Hagaman, and E. Wenkert, *J. Amer. Chem. Soc.*, 1972, **94**, 8942; R. B. Herbert in ref. 4, p. 28; in ref. 3, p. 13; and refs. cited.
[99] L. H. Hurley, C. Gairola, and M. J. Zmijewski, jun., *J.C.S. Chem. Comm.*, 1975, 120; R. B. Herbert, in ref. 6, p. 41.
[100] L. H. Hurley, C. Gairola, and N. V. Das, *Biochemistry*, 1976, **17**, 3760.



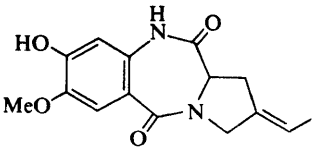
Scheme 12

tritium atom (confirmed by other unpublished results with tyrosine chirally labelled with tritium at C-3). This excludes as intermediates compounds of the type (120) related to cyclopenin (124), which had been considered for a not unlikely role (see Scheme 13) in demethyltomaymycin biosynthesis.



Scheme 13

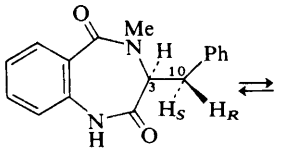
In the above experiments parallel results were obtained for oxotomaymycin (121), and indeed demethyltomaymycin (118) was shown to be a precursor for it.



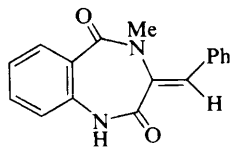
(121)

Results obtained on tritium retention during aromatic hydroxylation of the fragment in (118) derived from tryptophan[101] appear in full,[100] without essentially the addition of new information.

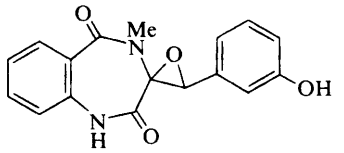
Benzodiazepine Bases.—It is known that phenylalanine is an intact precursor for the benzodiazepine bases cyclopenin (124) and cyclopenol (125), *via* (122) and (123), in *Penicillium cyclopium* cultures.[102] Examination of the stereochemical course of the necessary tritium loss from C-3 of the precursor amino-acid on formation of (124) has given a surprising result: more than half of the tritium was



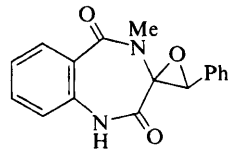
(122)



(123)



Cyclopenol (125)



Cyclopenin (124)

lost from phenylalanine irrespective of the configuration at this centre.[103] This contrasts with the biosynthesis of mycelianamide and cryptoechinulin A, where hydrogen loss from the precursor aromatic amino-acid was measurably stereospecific (see p. 35). The observations with cyclopenin (124) are best explained by non-stereospecific exchange at the phenylalanine stage through interconversion with phenylpyruvic acid, confirmed by showing that protein phenylalanine had also lost tritium extensively from C-3, and almost completely from C-2.[103] Moreover, evidence discussed below indicates that later stereospecific tritium loss does occur. (It may be noted that in the biosynthesis of gliotoxin from phenylalanine stereospecific exchange occurs at C-3 of the amino-acid.[104])

Significant progress has been made in the identification of enzymes from *P. cyclopium* which catalyse the various reactions of cyclopenin (124) and cyclopenol (125) biosynthesis.[105] One of these is cyclopeptine dehydrogenase which catalyses the interconversion of (122) and (123).[105a,106] Further research[107] has shown that

[101] L. Hurley, N. Das, C. Gairola, and M. Zmijewski, *Tetrahedron Letters*, 1976, 1419; R. B. Herbert, in ref. 7, p. 25.

[102] L. Nover and M. Luckner, *European J. Biochem.*, 1969, **10**, 268; J. Framm, L. Nover, A. El Azzouny, H. Richter, K. Winter, S. Werner, and M. Luckner, *ibid.*, 1973, **37**, 78; R. B. Herbert, in ref. 5, p. 39.

[103] G. W. Kirby and S. Narayanaswami, *J.C.S. Perkin I*, 1976, 1564.

[104] N. Johns, G. W. Kirby, J. D. Bu'Lock, and A. P. Ryles, *J.C.S. Perkin I*, 1975, 383; R. B. Herbert, in ref. 6, p. 37.

[105] (*a*) R. B. Herbert, in ref. 7, p. 24; (*b*) and refs. cited.

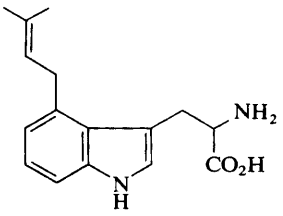
[106] El S. A. Aboutabl and M. Luckner, *Phytochemistry*, 1975, **14**, 2573.

[107] El S. A. Aboutabl, A. El Azzouny, K. Winter, and M. Luckner, *Phytochemistry*, 1976, **15**, 1925.

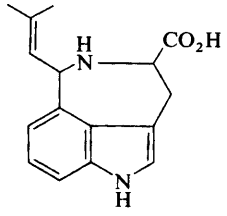
only (122) with the natural 3*S*-stereochemistry is a substrate for the enzyme. Moreover the dehydrogenation reaction involves loss of the 10-*pro*-*S* proton and so the elimination of hydrogen occurs in a *syn*-periplanar sense, as it apparently does in mycelianamide and cryptoechinulin A biosynthesis (see p. 35). Hydride transfer to the coenzyme NAD^+ was to the 4-*pro*-*R* position and tritium in the 4*S*-configuration in NADH was not transferred to (123) in the reverse reaction. Cyclopeptine dehydrogenase thus belongs to the class of A-specific dehydrogenases.[108]

Cyclopiazonic Acid.—Results of further research on the biosynthesis of cyclopiazonic acid, concerned with enzymes involved in diversion of dimethylallyl pyrophosphate from polyisoprenoid biosynthesis to cyclopiazonic acid formation, have been published.[109]

Ergot Alkaloids.—The enzyme which catalyses the first step in ergot alkaloid biosynthesis, namely the conversion of tryptophan into dimethylallyltryptophan (126),[110] has been isolated from a *Claviceps* species and characterized.[111] The biosynthesis of clavicipitic acid (127) may be a major alternative to the synthesis of other ergot metabolites, and further results in a study[112] of an enzyme from *C. purpurea* which catalyses the formation of clavicipitic acid (127) from (126) have been published.[113]



(126)



(127)

Terpenoid Indole Alkaloids.—Experiments in intact plants have in the past given results from which a fairly clear picture of the biosynthesis of terpenoid indole alkaloids has emerged.[114] An important stage in the biosynthesis of these alkaloids is reached when tryptamine (128) condenses with secologanin (129) to give

[108] R. Bentley, 'Molecular Asymmetry in Biology', Academic Press, New York, 1970, Vol. 2, p. 1.

[109] R. M. McGrath, P. N. Nourse, D. C. Neethling, and N. P. Ferreira, *Bioorg. Chem.*, 1977, **6**, 53. For earlier work see R. B. Herbert, in ref. 7, p. 18; in ref. 6, p. 30; and refs. cited.

[110] H. Plieninger, R. Fischer, and V. Liede, *Annalen*, 1964, **672**, 223; H. Plieninger, H. Immel, and H. Völkl, *ibid.*, 1967, **706**, 223; F. Weygand, H. G. Floss, U. Mothes, D. Gröger, and K. Mothes, *Z. Naturforsch.*, 1964, **19b**, 202; S. Agurell, *Acta Pharm. Suecica*, 1966, **3**, 11; J. E. Robbers and H. G. Floss, *Arch. Biochem. Biophys.*, 1968, **126**, 967; S. Agurell and J.-E. Lindgren, *Tetrahedron Letters*, 1968, 5127; R. B. Herbert, in ref. 6, p. 31; in ref. 5, p. 31.

[111] S.-L. Lee, H. G. Floss, and P. Heinstein, *Arch. Biochem. Biophys.*, 1976, **177**, 84 (preliminary communication: P. F. Heinstein, S.-L. Lee, and H. G. Floss, *Biochem. Biophys. Res. Comm.*, 1971, **44**, 1244).

[112] R. S. Bajwa, R.-D. Kohler, M. S. Saini, M. Cheng, and J. A. Anderson, *Phytochemistry*, 1975, **14**, 735; R. B. Herbert, in ref. 6, p. 32.

[113] M. S. Saini, M. Cheng, and J. A. Anderson, *Phytochemistry*, 1976, **15**, 1497.

[114] D. S. Bhakuni, *J. Sci. Ind. Res., India*, 1976, **35**, 449; A. R. Battersby, in ref. 1, p. 31; J. Staunton, in ref. 2, p. 1; R. B. Herbert, in ref. 3, p. 1; in ref. 4, p. 30; in ref. 5, p. 25; in ref. 6, p. 33; in ref. 7, p. 21; A. I. Scott, *Accounts Chem. Res.*, 1970, **3**, 151; G. A. Cordell, *Lloydia*, 1974, **37**, 219.

vincoside (130). In order to understand more precisely the steps which lie beyond vincoside experiments have begun with enzymes isolated from plants producing these bases. Thus a crude cell-free system has been obtained[115] from callus tissue of *Catharanthus roseus* capable of synthesizing ajmalicine (135) and geissoschizine (134) from (128) and (129), and partial purification of the enzymes has been effected.[116] A crude enzyme preparation has also been obtained from a cell suspension culture of *C. roseus* which catalyses the conversion of secologanin (129) and tryptamine (128) into the *Corynanthé*-type alkaloids ajmalicine (135), 19-epi-ajmalicine (136), and tetrahydroalstonine (137); the enzyme preparation had an absolute requirement for reduced pyridine nucleotide (NADPH or NADH).[117] (These observations have been supported by other workers.[116]) A compound was found to accumulate in the absence of reduced pyridine nucleotide,[117] and was identified as 20,21-didehydroajmalicine (132) (given the trivial name cathenamine).[118] Cathenamine (132), which has also been identified from a plant source,[119] was shown to be convertible by the crude enzyme preparation into (135), (136), and (137) in the presence of NADPH.[117,118] An important role for (132) in terpenoid alkaloid biosynthesis in intact plants is thus suggested. In the course of these experiments a compound of unknown structure, more polar than (132), was isolated. It may be a precursor for cathenamine.[118]

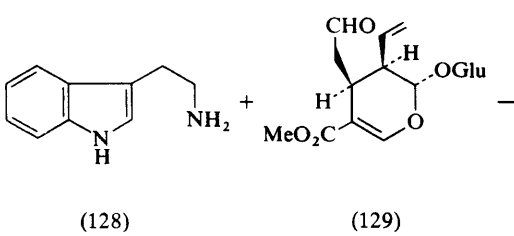
Since ajmalicine (135) is not converted into isomers (136) and (137) by the enzyme mixture, the different C-19 and C-20 configurations are suggested to occur through enzymic equilibration of (132) with (131) and/or (133).[118]

6 Steroidal Alkaloids

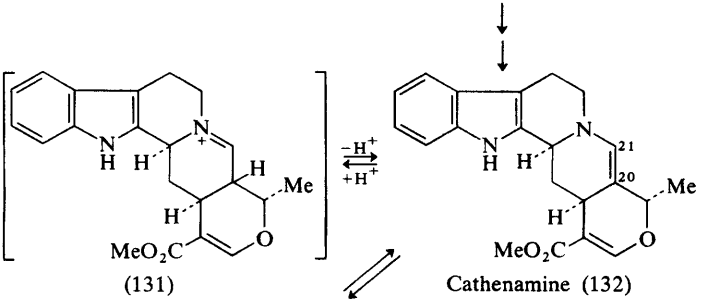
Verazine (138) appears to be an important early intermediate in the biosynthesis of *Veratrum grandiflorum* alkaloids, *e.g.* solanidine (139).[120] Apparent correlation between changes in arginine content and accumulation of verazine (138) in dormant *V. grandiflorum* rhizomes, as well as the observation that L-[^{15}N]arginine is a much more effective source for solanidine biosynthesis than [^{15}N]ammonium chloride, indicates that arginine is a primary source of alkaloidal nitrogen.[121]

It has been concluded that formation of alkaloids such as tomatidine (140) and solasodine (141) occurs by amination of *C*-26-hydroxylated steroids [as (142)], formation of the furan ring being a subsequent step.[122] Incorporation of (25-*RS*)-[25,26-$^{3}H_2$,4-^{14}C]cholesterol (143) into tomatidine (140), soladulcidine (141; no 5,6-double bond), and solasodine (141) without change in isotope ratio is consistent with direct amination of an intermediate *C*-26/27-hydroxylated steroid, *i.e.* no *C*-26/27-oxo-intermediate is formed. Further, since tritium is not lost from C-25, the alkaloids (140) and (141), which are epimeric at this centre, must be formed

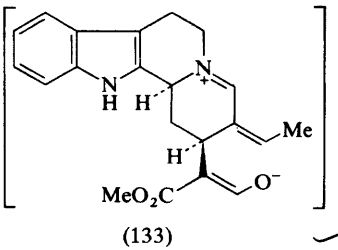
[115] A. I. Scott and S.-L. Lee, *J. Amer. Chem. Soc.*, 1975, **97**, 6906; R. B. Herbert, in ref. 7, p. 22.
[116] A. I. Scott, S.-L. Lee, and W. Wan, *Biochem. Biophys. Res. Comm.*, 1977, **75**, 1004.
[117] J. Stöckigt, J. Treimer, and M. H. Zenk, *F.E.B.S. Letters*, 1976, **70**, 267.
[118] J. Stöckigt, H. P. Husson, C. Kan-Fan, and M. H. Zenk, *J.C.S. Chem. Comm.*, 1977, 164.
[119] H.-P. Husson, C. Kan-Fan, Th. Sévenet, and J.-P. Vidal, *Tetrahedron Letters*, 1977, 1889.
[120] K. Kaneko, H. Seto, C. Motoki, and H. Mitsuhashi, *Phytochemistry*, 1975, **14**, 1295; R. B. Herbert, in ref. 6, p. 52.
[121] K. Kaneko, M. W. Tanaka, and H. Mitsuhashi, *Phytochemistry*, 1976, **15**, 1391.
[122] F. Ronchetti, G. Russo, G. Ferrara, and G. Vecchio, *Phytochemistry*, 1975, **14**, 2423; R. B. Herbert, in ref. 7, p. 32.



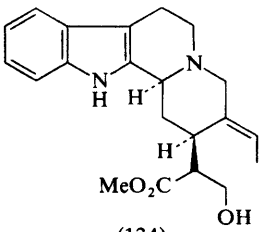
(128) (129) (130)



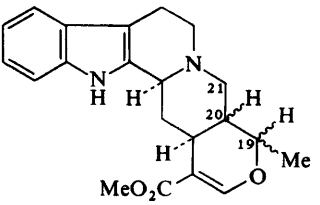
(131) Cathenamine (132)



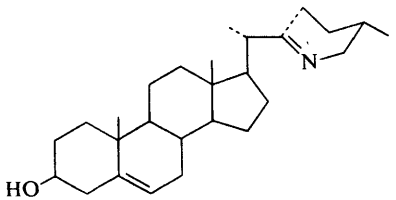
(133)



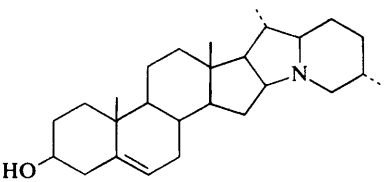
(134)



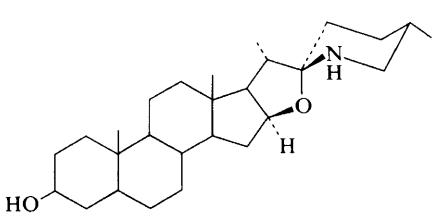
	19-H	20-H
Ajmalicine (135)	β	β
(136)	α	β
(137)	β	α



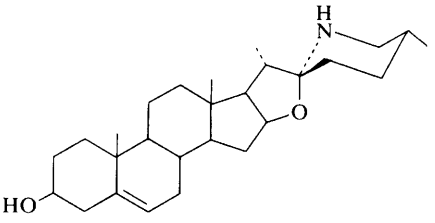
Verazine (138)



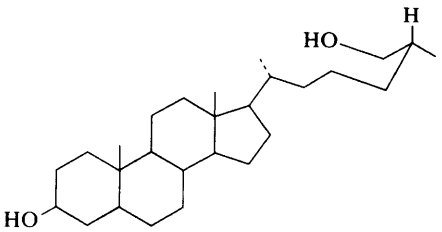
Solanidine (139)



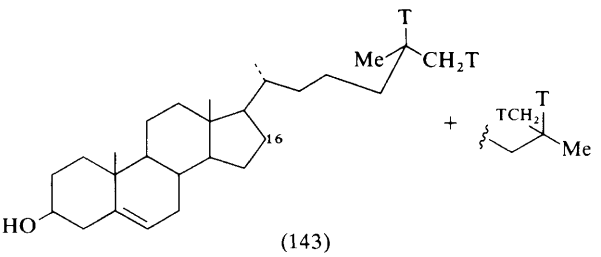
Tomatidine (140)



Solasodine (141)



(142)



(143)

independently by hydroxylation at C-26 or at C-27. This confirms earlier results[123] and is further supported by the observation that (142) is a precursor for (141; no 5,6-double bond) but not (140).[124]

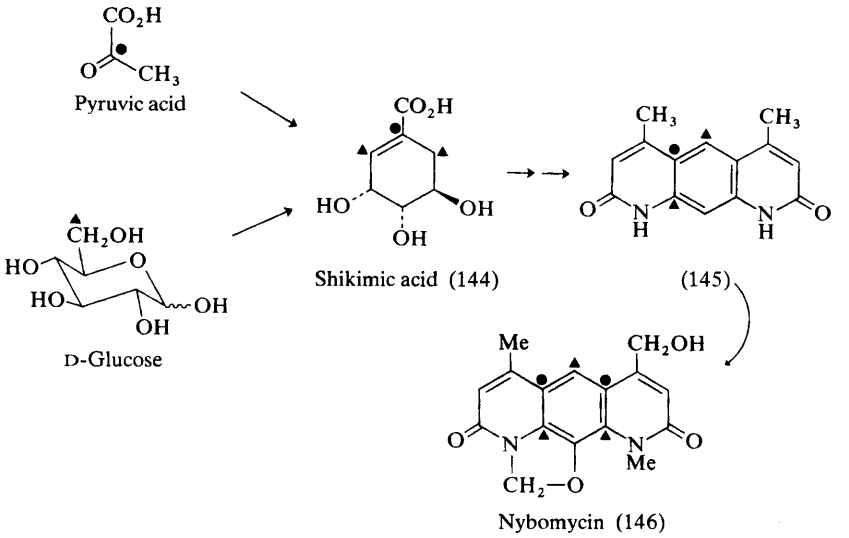
Further exploration[125] of the stereochemistry associated with modification of the steroidal side-chain into that of steroidal alkaloids such as solanidine (139) and tomatidine (140) has revealed that on formation of the furan ring in (140) tritium in the 16β-configuration of cholesterol [as (143)] is retained but appears now in the 16α-configuration. Retention of the tritium excludes a *C*-16-oxo-intermediate, and the fact that an inversion of configuration is observed excludes hydroxylation with normal retention of configuration. Examination of the fate of the cholesterol 16β-proton on incorporation into solanidine (139) revealed that during solanidine biosynthesis this proton is lost.

7 Miscellaneous

Nybomycin and Geldanomycin.—Earlier results have defined the origins of all the carbon atoms of nybomycin (146) except the central ring system.[126] Shikimic acid (144) is a likely source of this fragment and good incorporations of D-[6-^{14}C]-

[123] F. Ronchetti and G. Russo, *J.C.S. Chem. Comm.*, 1974, 785; A. R. Guseva and V. A. Paseshnichenko, *Biochemistry* (*U.S.S.R.*), 1962, **27**, 721; R. B. Herbert, in ref. 6, p. 53.
[124] R. Tschesche, B. Goossens, and A. Töpfer, *Phytochemistry*, 1976, **15**, 1387.
[125] L. Canonica, F. Ronchetti, G. Russo, and G. Sportoletti, *J.C.S. Chem. Comm.*, 1977, 286.
[126] W. M. J. Knöll, R. J. Huxtable, and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1973, **95**, 2703; R. B. Herbert, in ref. 4, p. 44.

glucose, sodium [2-^{14}C]pyruvate, and D-[4-^{14}C]erythrose support this possibility.[127] More significantly, however, ^{13}C n.m.r. analysis of nybomycin derived from D-[6-^{13}C]glucose and [2-^{13}C]pyruvate indicates a specific labelling of the central ring (see Scheme 14) (though with extensive labelling of other carbons also) from which it may be concluded that, if nybomycin biosynthesis proceeds *via* shikimic acid (144), a later symmetrical intermediate, most simply one of type (145), is also involved.[127] Final definition of the origin of the central ring of nybomycin awaits the examination of shikimic acid and close relatives as precursors.

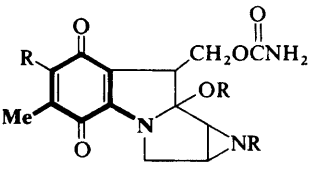


Scheme 14

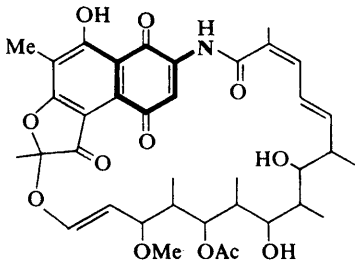
Shikimic acid (144), or a close relative, has been deduced to be the source of a C_7N unit (shown with heavy bonding) common to the antibiotics mitomycin (147)[128,129] and rifamycin S (148);[129–131] a similar unit is also apparent in streptovaricin D (149). Shikimic acid is a proven precursor for bacterial phenazines which are arguably constructed from two related C_7N units[132] (for further research on these metabolites, see below).

Exploration of geldanomycin (150) biosynthesis with D-[6-^{13}C]glucose has revealed that the C_7N unit of this antibiotic has a similar origin (labelling of C-17 and C-21; *cf.* nybomycin above), although shikimic acid (144) itself was a poor precursor.[133] Similar observations were made on shikimic acid incorporation in the

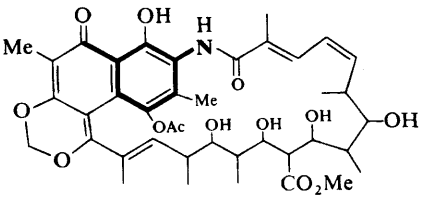
[127] A. M. Nadzan and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1976, **98**, 5012.
[128] U. Hornemann, J. P. Kehrer, and J. H. Eggert, *J.C.S. Chem. Comm.*, 1974, 1045.
[129] R. B. Herbert, in ref. 6, p. 45.
[130] A. Karlsson, G. Sartori, and R. J. White, *European J. Biochem.*, 1974, **47**, 251.
[131] R. J. White and E. Martinelli, *F.E.B.S. Letters*, 1974, **49**, 233.
[132] R. B. Herbert, F. G. Holliman, and J. B. Sheridan, *Tetrahedron Letters*, 1976, 639; R. B. Herbert, in ref. 7, p. 27; in ref. 5, p. 44; and refs. cited.
[133] A. Haber, R. D. Johnson, and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1977, **99**, 3541.



(147)



Rifamycin *S* (148)



Streptovaricin D (149)

study of mitomycin[134] and rifamycin[130,135] biosynthesis, and it seems likely that the C_7N units of these metabolites, including geldanomycin, arise more directly from a compound closely related to shikimic acid than from (144) itself.

Incorporation of acetate, and specific labelling of geldanomycin (150) by [1-^{13}C]propionate, had led to the conclusion that (150) was derived from three propionate and two acetate units.[136] Re-examination of the acetate results with ^{13}C-labelled material has failed to show a useful incorporation.[133] Instead it appears (using [2-^{13}C]malonate, which gave a higher incorporation) that only one C_2 unit (C-3, C-4) arises from this source; the other two C_2 units have an independent genesis from glycerate, probably through glycolate (both compounds labelled with ^{13}C were specifically and appropriately incorporated). The results[133,136] are summarized in (150). They contrast with those obtained on rifamycin and streptovaricin biosynthesis, where the C_2 units were derived exclusively from malonate/acetate.[135,137]

Results of further experiments, with L-[*guanido*-^{14}C]- and L-[*guanido*-$^{15}N_2$,^{13}C]-arginine, have established that the carbamate residue in geldanomycin (150) originates from this amino-acid[133] as does a similar mitomycin residue.[138]

It should be noted, finally, that in the experiment with [6-^{13}C]glucose more extensive labelling of (150) than already mentioned was observed, but the labelling

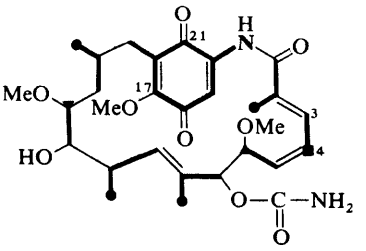
[134] G. S. Bezanson and L. C. Vining, *Canad. J. Biochem.*, 1971, **49**, 911; U. Hornemann and J. C. Cloyd, *Chem. Comm.*, 1971, 301; R. B. Herbert, in ref. 4, p. 40.

[135] R. J. White, E. Martinelli, G. G. Gallo, G. Lancini, and P. Beynon, *Nature*, 1973, **243**, 273; R. B. Herbert, in ref. 5, p. 53.

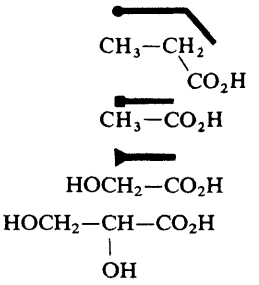
[136] R. D. Johnson, A. Haber, and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1974, **96**, 3316; R. B. Herbert, in ref. 5, p. 52.

[137] B. Milavetz, K. Kakinuma, K. L. Rinehart, jun., T. P. Rolls, and W. J. Haak, *J. Amer. Chem. Soc.*, 1973, **95**, 5793; E. Martinelli, R. J. White, G. G. Gallo, and P. J. Beynon, *Tetrahedron Letters*, 1974, 1367.

[138] U. Hornemann and J. H. Eggert, *J. Antibiotics*, 1975, **28**, 841; R. B. Herbert, in ref. 7, p. 32; and refs. cited.

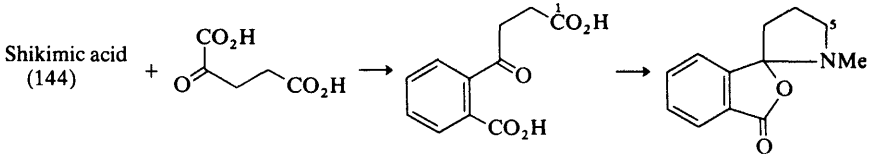


Geldanomycin (150)



pattern was consistent with utilization of this precursor through normal primary metabolism *via* the already deduced precursors.[133]

Shihunine.—Preliminary results[139] indicated that the orchid alkaloid shihunine (153) was derived from (152), an important intermediate in naphthoquinone biosynthesis.[140] Further details are now available in a full paper.[141] The intact incorporation of (152) is affirmed by the observation that (152), labelled with ^{13}C at C-1, was an efficient and specific precursor for (153). [1-^{14}C]Acetate was examined as a shihunine precursor and was found only to label C-5. This is consistent with the expected formation of (152) from shikimic acid (144) and α-ketoglutarate (151),[140] the latter gaining acetate label in its carboxy-groups through the tricarboxylic acid cycle.



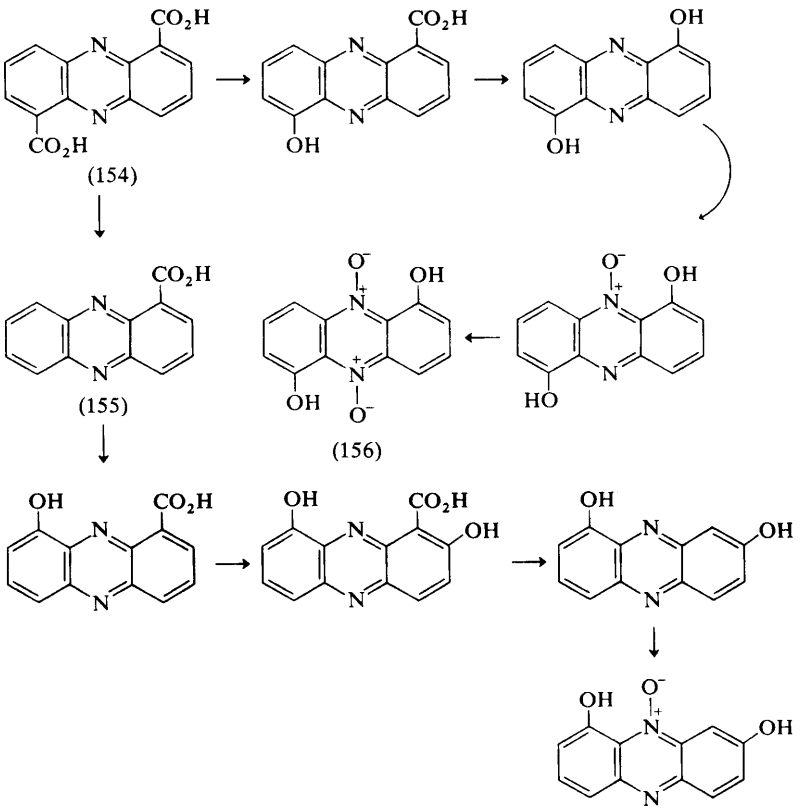
(151) (152) Shihunine (153)

Phenazines.—Although it is known that the bacterial phenazines originate from two molecules of shikimic acid (144),[132] and the later stages in the biosynthesis of most of them have been mapped,[142,143] nothing is known about the stages which lie between shikimic acid and the first phenazines to be formed, apart from the probability that chorismic acid is the last intermediate common to the biosynthesis of phenazines and aromatic amino-acids derived from shikimic acid.[144] The joining together of the two shikimic acid units leads most simply to the naturally occurring phenazine-1,6-dicarboxylic acid (154) as the phenazine from which the others may be derived, but it has failed to act as a phenazine precursor.[145,146] Recently,

[139] E. Leete and G. B. Bodem, *J.C.S. Chem. Comm.*, 1973, 522; R. B. Herbert, in ref. 5, p. 42.
[140] R. Bentley, in 'Biosynthesis', ed. T. A. Geissman, (Specialist Periodical Reports), The Chemical Society, London, 1975, Vol. 3, p. 181; and refs. cited.
[141] E. Leete and G. B. Bodem, *J. Amer. Chem. Soc.*, 1976, **98**, 6321.
[142] R. B. Herbert, in ref. 3, p. 36; and refs. cited.
[143] G. S. Byng and J. M. Turner, *Biochem. J.*, 1977, **164**, 139.
[144] D. H. Calhoun, M. Carson, and J. A. Jensen, *J. Gen. Microbiol.*, 1972, **72**, 581; R. P. Longley, J. E. Halliwell, J. J. R. Campbell, and W. M. Ingledew, *Canad. J. Microbiol.*, 1972, **18**, 1357.
[145] M. E. Flood, R. B. Herbert, and F. G. Holliman, *J.C.S. Perkin I*, 1972, 622.
[146] R. B. Herbert, F. G. Holliman, and P. N. Ibberson, *J.C.S. Chem. Comm.*, 1972, 355.

however, it has been shown that the dimethyl ester of (154), but again not the diacid itself, is an efficient and specific precursor for phenazine-1-carboxylic acid (155) in *Pseudomonas aureofaciens* cultures; it seems likely that the diacid rather than the diester is the true precursor and that the latter is simply more efficiently transported to the site of biosynthesis than the intractable acid.[147] Since phenazine-1-carboxylic acid (155) is a precursor for several phenazines[142] it may be taken that (154) (or the diester) is also a precursor for them.

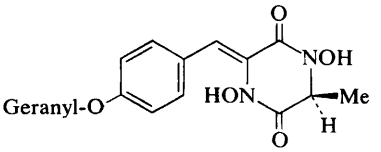
The accumulation of phenazine-1,6-dicarboxylic acid (154) by mutants of *Pseudomonas phenazinium*[148] which normally produce hydroxy-phenazine derivatives supports a role for (154) in phenazine biosynthesis. In further studies[143] with *Ps. phenazinium* the sequence of hydroxylative steps leading to the various phenazines has been deduced[143,148] to be that illustrated in Scheme 15; the biosynthesis deduced for iodinin (156) is in agreement with earlier conclusions about its formation in cultures of another organism (*Brevibacterium iodinum*).[146]



Scheme 15

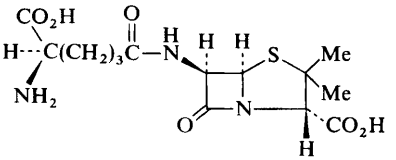
[147] U. Hollstein, G. E. Krisov, and D. L. Mock, *Tetrahedron Letters*, 1976, 3267.
[148] G. S. Byng and J. M. Turner, *J. Gen. Microbiol.*, 1976, **97**, 57.

Mycelianamide.—Full details on the fate of the C-3 protons of tyrosine on incorporation into mycelianamide (157)[149] have been published.[103] In the course of mycelianamide formation the side-chain of tyrosine becomes unsaturated and this reaction involves loss of the 3-*pro*-*S* proton. It is to be noted that in a similar reaction in the conversion of tryptophan into cryptoechinulin A the corresponding 3-*pro*-*S* proton is again lost.[150] If the L-configuration in the amino-acid is assumed then the desaturation reactions occur with formal *cis* stereochemistry, as in the case of benzodiazepine biosynthesis (see above).[107]

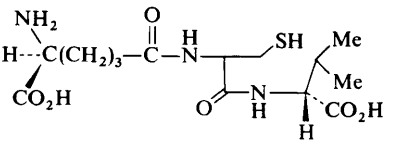


Mycelianamide (157)

β-Lactam Antibiotics.—The tripeptide [as (159)] isolated from *Penicillium chrysogenum*[151] has been accepted as a likely key intermediate in the biosynthesis of penicillins with penicillin N (158), the first of the β-lactams to be formed.[152] It has been shown recently that this tripeptide is formed from radio-active L-α-aminoadipic acid, L-valine, and L-cysteine in *P. chrysogenum* and has the absolute configuration (159).[153] Moreover, it has been shown to be a precursor for penicillin



Penicillin N (158)

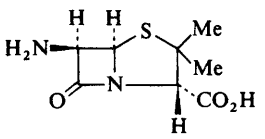


(159)

N, in a cell-free extract of *Cephalosporium acremonium*.[154] Only the naturally occurring tripeptide with the LLD-configuration was utilized for biosynthesis, from which it is clear that L-valine is built into the tripeptide with inversion of configuration and that later formation of penicillin N involves an epimerization in the α-aminoadipyl moiety. Although in these experiments only the valine fragment of the precursor was labelled, intact incorporation is indicated by the failure of L-cysteinyl-D-valine or 6-aminopenicillanic acid (160) to act as penicillin precursors, and by the observation that the formation of labelled valine could not be detected in the feeding experiment with (159).

[149] G. W. Kirby and S. Nayaranaswami, *J.C.S. Chem. Comm.*, 1973, 322; R. B. Herbert, in ref. 4, p. 42.
[150] R. Cardillo, C. Fuganti, D. Ghiringhelli, P. Grasselli, and G. Gatti, *J.C.S. Chem. Comm.* 1975, 778.
[151] H. R. V. Arnstein, N. Artman, D. Morris, and E. J. Toms, *Biochem. J.*, 1960, **76**, 353; H. R. V. Arnstein and D. Morris, *ibid.*, 1960, **76**, 357.
[152] P. A. Lemke and D. R. Brannon, in 'Cephalosporins and Penicillins', ed. E. H. Flynn, Academic Press, New York, 1972, p. 370.
[153] P. Adriaens, B. Meesschaert, W. Wuyts, H. Vanderhaeghe, and H. Eyssen, *Antimicrobiol. Agents Chemotherapy.*, 1975, **8**, 638; J. A. Chan, F.-C. Huang, and C. J. Sih, *Biochemistry*, 1976, **15**, 177.
[154] P. A. Fawcett, J. J. Usher, J. A. Huddleston, R. C. Bleaney, J. J. Nisbet, and E. P. Abraham, *Biochem. J.*, 1976, **157**, 651.

Further studies on cell-free preparations of *C. acremonium* have led to the preparation of an extract which catalyses the conversion of L-valine into penicillin N (158),[155] and one which carries out the transformation of this penicillin into cephalosporins [as (161)].[156]



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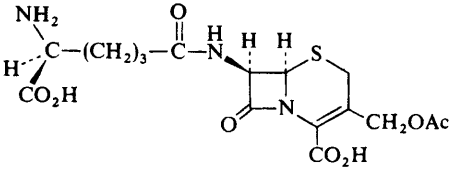
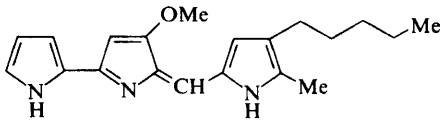


Cephalosporin C (161)

Conclusions[157] drawn about the fates of tritium labels in cysteine and valine on incorporation into the penicillins have been supported by further work: half of the label at C-3 of cysteine and all of the label at C-2 and C-3 of valine was lost (tritium must inevitably be lost from C-3 of valine: these results show that it is not transferred elsewhere in the molecule).[158]

Prodigiosin.—The formation[159] of prodigiosin (162) from intact molecules of L-proline and L-alanine (but with loss of the carboxy-group) has been confirmed[160] by



Prodigiosin (162)

results of a study using wild-type *Serratia marcescens* and mutants deficient in proline, alanine, and histidine catabolism. (Histidine was thereby shown not to be directly involved in the biosynthesis of prodigiosin, although it does affect synthesis of the metabolite.)

[155] P. E. Bost and A. L. Demain, *Biochem. J.*, 1977, **162**, 681.
[156] M. Kohsata and A. L. Demain, *Biochem. Biophys. Res. Comm.*, 1976, **70**, 465.
[157] R. B. Herbert, in ref. 7, p. 30; in ref. 6, p. 49; and refs. cited.
[158] P. Adriaens, H. Vanderhaeghe, B. Meeschaert, and H. Eyssen, *Antimicrobiol. Agents Chemotherapy.*, 1975, **8**, 15.
[159] R. J. Cushley, D. R. Anderson, S. R. Lipsky, R. J. Sykes, and H. H. Wasserman, *J. Amer. Chem. Soc.*, 1971, **93**, 6284; H. H. Wasserman,. R. J. Sykes, P. Pererada, C. K. Shaw, R. J. Cushley, and S. R. Lipsky, *ibid.*, 1973, **95**, 6874; R. B. Herbert, in ref. 5, p. 47.
[160] D. V. Lim, S. M. H. Qadri, C. Nichols, and R. W. Williams, *J. Bacteriol.*, 1977, **129**, 124.

2

Pyrrolidine, Piperidine, and Pyridine Alkaloids

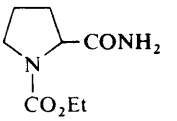
BY A. R. PINDER

A review entitled 'General Methods of Alkaloid Synthesis' includes pyrrolidine, pyridine, and *Sceletium* alkaloids.[1] Another summarizes nitrogen-containing compounds in tobacco and tobacco smoke, and includes some pyrroles, pyrrolidines, pyridines, and alkaloids related to nicotine.[2]

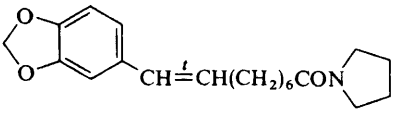
1 Pyrrolidine Alkaloids

The leaves of *Arnica montana* L. contain a new alkaloid, *N*-ethoxycarbonyl-L-prolinamide (1). Its structure has been established by mass, i.r., and n.m.r. spectral analysis, and confirmed by synthesis from L-proline by conversion into the amide followed by reaction with ethyl chloroformate. The synthesis also settles the absolute configuration of the new alkaloid.[3]

Several new alkaloids have been isolated from pepper species. Tricholeine, for example, occurring in the stems of *Piper trichostachyon*, is the pyrrolidine amide (2) of *trans*-9-(3,4-methylenedioxyphenyl)-Δ^8-nonenoic acid, the structure being established by spectroscopic and degradative studies.[4] *Piper guineense* seeds contain okolasine (6-methoxytrichostachine) (3),[5] which is probably identical to the earlier known wisanidine. 4,5-Dihydro-wisanidine (4) is also found in the same



(1)



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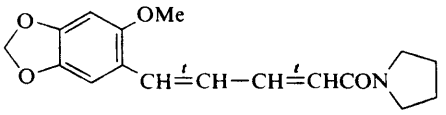

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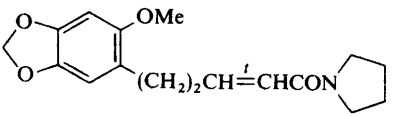


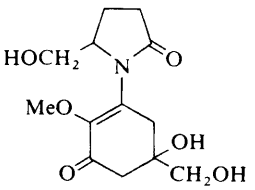
(4)

[1] R. V. Stevens, *Accounts Chem. Res.*, 1977, **10**, 193.
[2] I. Schmeltz and D. Hoffmann, *Chem. Rev.*, 1977, **77**, 295.
[3] M. Holub, J. Poplawski, P. Sedmera, and V. Herout, *Coll. Czech. Chem. Comm.*, 1977, **42**, 151.
[4] J. Singh, D. D. Santani, and K. L. Dhar, *Phytochemistry*, 1976, **15**, 2018.
[5] B. L. Sondengam, S. F. Kimbu, T. Njimi, J. I. Okogun, and D. E. U. Ekong, *Tetrahedron Letters*, 1977, 367.

source; on dehydrogenation it affords wisanidine (3), and on oxidation 2-methoxypiperonal.[6]

The venom of the fire ant, *Solenopsis punctaticeps*, contains several 2,5-dialkyl-pyrrolidines and -pyrrolines; their structures have been settled by combined g.c.–m.s., and confirmed by syntheses employing the Hofmann–Löffler reaction on the corresponding primary amines.[7] A new synthesis of 2,5-dialkyl-pyrrolidines *via* lithiated *N*-nitrosopyrrolidine and two stages of alkylation, followed by removal of the nitroso-group, should be applicable to the synthesis of the venom components. The major products are *trans* in stereochemistry.[8]

Mycosporine-2 is a fungal metabolite of *Botrytis cinerea*, and is formulated as the pyrrolidone (5) on mass and ^{13}C and ^{1}H n.m.r. spectral evidence.[9] The marine sponge *Dysidea herbacea* secretes a chlorine-containing pyrrolinone dysidine, formulated as (6) as a consequence of degradative and spectroscopic studies. Its relative and absolute configurations were settled by *X*-ray diffraction methods.[10] On exposure to strong base the compound is degraded to the pyrrolinone (7), which was synthesized from L-valine methyl ester, and the acid (8), identified by its mass and n.m.r. spectral behaviour.[10]



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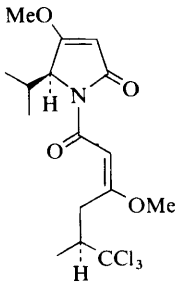

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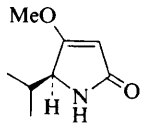

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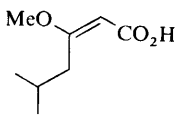
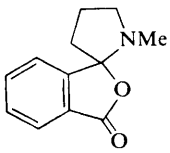


(8)

***Dendrobium* Alkaloids.**—Investigations on the biosynthesis of shihunine (9) have been published in full[11] (see Chapter 1). Full details of the synthesis of 8-epidendrobine, reported briefly earlier, have been published.[12]

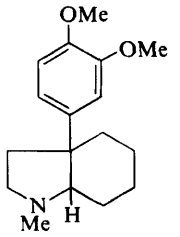


(9)

[6] B. L. Sondengam, S. F. Kimbu, and J. D. Connolly, *Phytochemistry*, 1977, **16**, 1121.
[7] D. J. Pedder, H. M. Fales, T. Jaouni, M. Blum, J. MacConnell, and R. M. Crewe, *Tetrahedron*, 1976, **32**, 2275.
[8] R. R. Fraser and S. Passannanti, *Synthesis*, 1976, 540.
[9] N. Arpin, J. Favre-Bonvin, and S. Thivend, *Tetrahedron Letters*, 1977, 819.
[10] W. Hofheinz and W. E. Oberhänsli, *Helv. Chim. Acta*, 1977, **60**, 660.
[11] E. Leete and G. B. Bodem, *J. Amer. Chem. Soc.*, 1976, **98**, 6321.
[12] R. F. Borch, A. J. Evans, and J. J. Wade, *J. Amer. Chem. Soc.*, 1975, **97**, 6282; 1977, **99**, 1612.

***Sceletium* Alkaloids.**—(−)-Mesembrane has been isolated from *S. namaquense* L. Bolus; *X*-ray diffraction analysis of its hydrochloride monohydrate revealed its relative and absolute configuration (10). (−)-Mesembrine has the absolute configuration (11), in accord with (10), and it is now firmly established that alkaloids of this family belong to a single antipodal series.[13]

Anatoxin-*a* is a toxic alkaloid occurring in the filamentous blue-green alga *Anabaena flos-aquae* and has been responsible for fatalities amongst livestock and wildlife. Mass and n.m.r. spectroscopy, and *X*-ray diffraction analysis of its *N*-acetyl derivative, pointed to structure and absolute stereochemistry (12) for ana-



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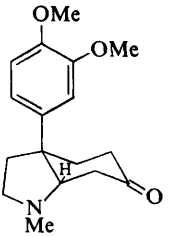

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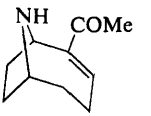
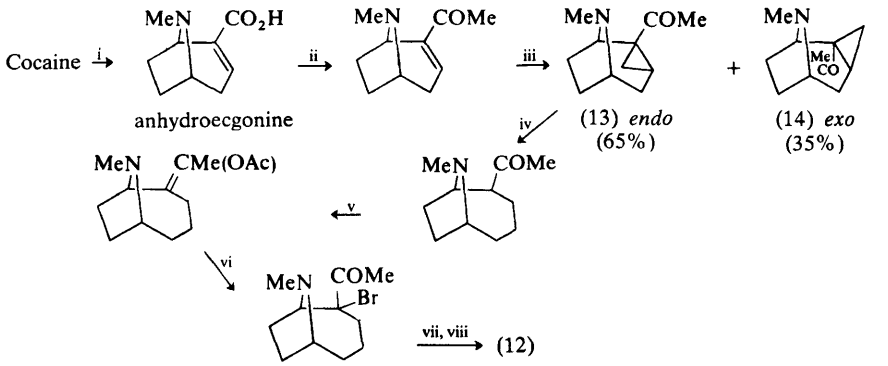


(12)

toxin-*a*.[14] The formulation has been confirmed by synthesis of the alkaloid from cocaine as outlined in Scheme 1. Configurations were assigned to the cyclopropyl ketones (13) and (14) by n.m.r. spectral comparison; the greater proximity of the acetyl and *N*-methyl groups in the *endo*-isomer (13) results in downfield shifts of the protons of the two methyl groups.[15]



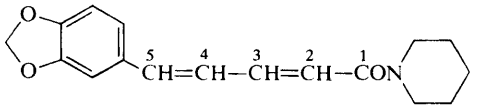
Reagents: i, published procedures; ii, LiMe; iii, $Me_2\overset{+}{S}O\overset{-}{C}H_2$; iv, Li–$NH_3$; v, Ac_2O; vi, Br_2; vii, LiBr–Li_2CO_3; viii, $EtO_2CN{=}NCO_2Et$

Scheme 1

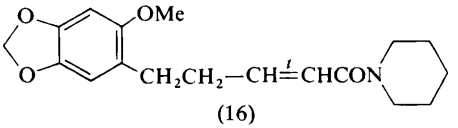
[13] T. M. Capps, K. D. Hargrave, P. W. Jeffs, and A. T. McPhail, *J.C.S. Perkin II*, 1977, 1098.
[14] J. P. Devlin, O. E. Edwards, P. R. Gorham, N. R. Hunter, R. K. Pike, and B. Stavric, *Canad. J. Chem.*, 1977, **55**, 1367.
[15] H. F. Campbell, O. E. Edwards, and R. Kolt, *Canad. J. Chem.*, 1977, **55**, 1372.

2 Piperidine Alkaloids

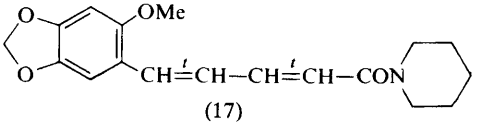
Interest in alkaloids of pepper species continues. The four geometrically isomeric piperines (piperine, isopiperine, chavicine, and isochavicine) have for the first time been isolated in pure condition by h.p.l.c., and their spectra re-examined. The u.v. absorptions are in consonance with a *cis,cis* configuration of structure (15) for chavicine, a *trans,trans* arrangement for piperine, a *cis*,-2,3,*trans*-4,5 combination for isopiperine, and a *trans*-2,3,*cis*-4,5 for isochavicine. The i.r. spectra of all four isomers are closely similar, and their mass spectra are identical. A careful analysis of the splitting patterns of the olefinic protons in their 300 MHz n.m.r. spectra confirms the configurational assignments.[16] The fruit stems and roots of *Piper guineense* contain a new alkaloid 4,5-dihydro-2'-methoxypiperine (16); wisanine (17), 4,5-dihydropiperine,[17] and 2,3-dihydropiperine are also present.[18] The synthesis of wisanine (17) has been described.[19]



(15)

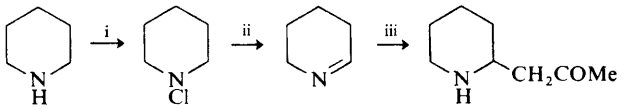


(16)



(17)

A new convenient synthesis of pelletierine (18) has been reported; it is outlined in Scheme 2.[20]



(18)

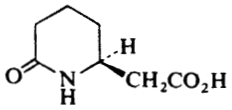
Reagents: i, *N*-chlorosuccinimide in ether; ii, KOH–EtOH; iii, $MeCOCH_2CO_2Na$, then decarboxylation

Scheme 2

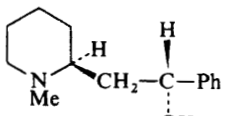
(*S*)-(+)-2-Oxopiperidine-6-acetic acid (19) has been synthesized, starting from glutaric anhydride and (*R*)-(+)-α-phenethylamine; it has been converted into a

[16] R. De Cleyn and M. Verzele, *Bull. Soc., chim. belges*, 1975, **84**, 435.
[17] J. I. Okogun, B. L. Sondengam, and S. F. Kimbu, *Phytochemistry*, 1977, **16**, 1295; B. L. Sondengam and S. F. Kimbu, *Tetrahedron Letters*, 1977, 69.
[18] I. Addae-Mensah, F. G. Torto, I. V. Oppong, I. Baxter, and J. K. M. Sanders, *Phytochemistry*, 1977, **16**, 483.
[19] L. Crombie, G. Pattenden, and G. Stemp, *Phytochemistry*, 1977, **16**, 1437.
[20] J. Quick and R. Oterson, *Synthesis*, 1976, 745.

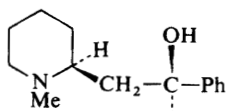
separable mixture of the alkaloids (*S*)-(−)-sedamine (20) and (*S*)-(−)-allosedamine (21).[21] A new synthesis of racemic fire-ant toxin solenopsine-A (22) is



(19)

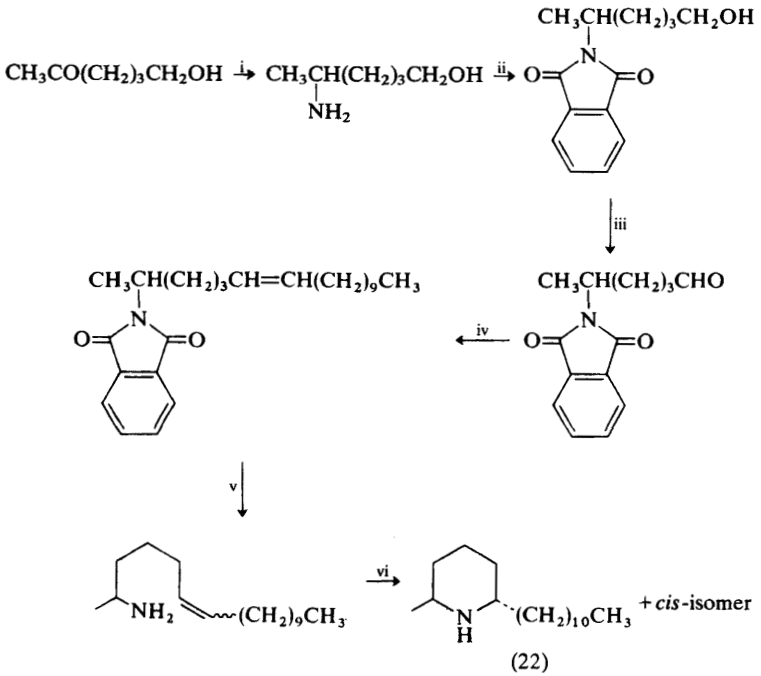


(20)



(21)

summarized in Scheme 3; the geometrically isomeric products were easily separated by column chromatography.[22] The same alkaloid has also been reached



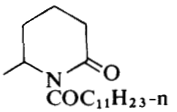
Reagents: i, reductive amination; ii, phthalic anhydride; iii, Collins reagent; iv, Wittig reaction; v, hydrazinolysis; vi, $Hg(OAc)_2$

Scheme 3

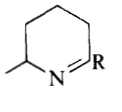
via a Mundy *N*-acyl-lactam rearrangement on *N*-lauryl-6-methyl-2-piperidone (23) to yield imine (24). Borohydride reduction of the latter afforded (22), again accompanied by the *cis*-isomer. A similar sequence, starting with (*S*)-(+)-*N*-n-butyryl-6-methyl-2-piperidone, of known absolute configuration, led to (−)-dihydropinidine hydrochloride (26) *via* imine (25). This proved to be enantiomeric

[21] T. Wakabayashi, K. Watanabe, Y. Kato, and M. Saito, *Chem. Letters*, 1977, 223.
[22] Y. Moriyama, D. Doan-Huynh, C. Monneret, and Q. Khuong-Huu, *Tetrahedron Letters*, 1977, 825.

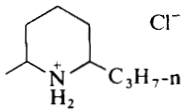
with the hydrochloride of the dihydro-derivative of natural pinidine; the absolute configuration of the natural base (27) is thus confirmed.[23]



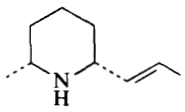
(23)



(24) R = n-$C_{11}H_{23}$
(25) R = n-C_3H_7

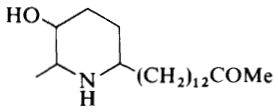


(26)

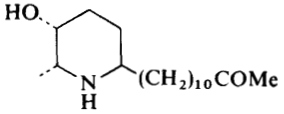


(27)

Two new piperidin-3-ol alkaloids have been encountered in the leaves of *Cassia spectabilis* DC: spectaline, which is (+)-2(*S*)-methyl-6(*R*)-(13′-oxotetradecyl)piperidin-3(*S*)-ol (28), and isocassine, formulated as (−)-2(*R*)-methyl-6(*R*)-(11′-oxodecyl)piperidin-3(*R*)-ol (29), structures having been settled by spectral study. Their absolute configurations were arrived at by application of the Horeau procedure.[24]

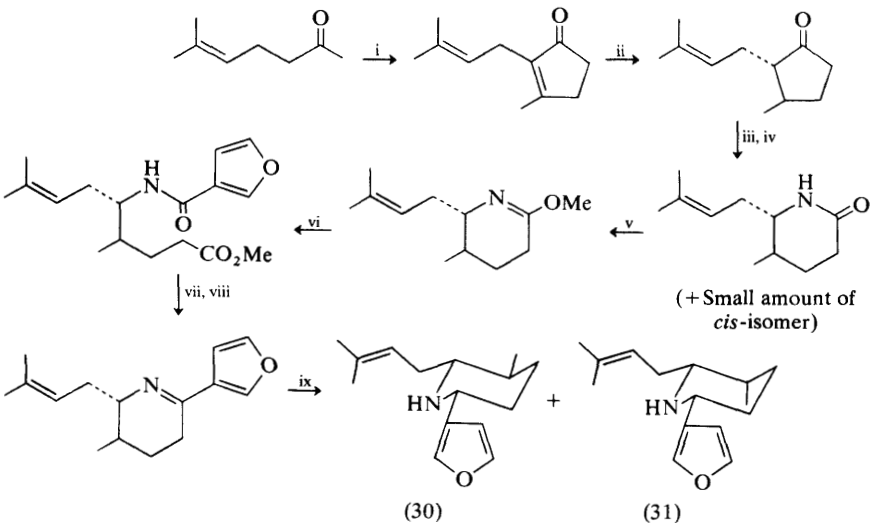


(28)



(29)

A stereocontrolled synthesis of racemic anhydronupharamine (30) has been described (Scheme 4),[25] and its ^1H and ^{13}C n.m.r. spectra have been measured.[25,26]



(30) (31)

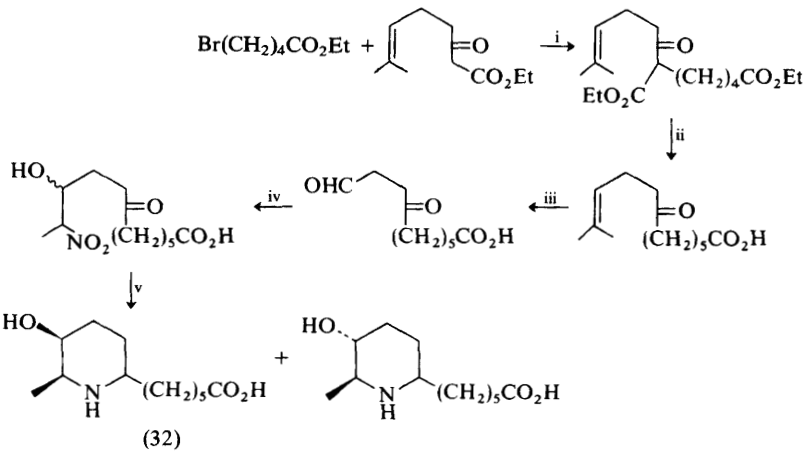
Reagents: i, several published steps; ii, Li–NH_3 (stereospecific); iii, oximation; iv, PCl_5; v, Me_2SO_4–HO^-; vi, LiH–3-furoyl chloride; vii, hydrolysis to acid; viii, CaO, pyrolysis; ix, $NaBH_4$

Scheme 4

[23] R. K. Hill and T. Yuri, *Tetrahedron*, 1977, **33**, 1569.
[24] I. Christofidis, A. Welter, and J. Jadot, *Tetrahedron*, 1977, **33**, 977.
[25] R. T. LaLonde, N. Muhammad, and C. F. Wong, *J. Org. Chem.*, 1977, **42**, 2113.
[26] S. Yasuda, M. Hanaoka, and Y. Arata, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 2521.

The final product was a mixture of piperidines, from which (30) and nuphenine (31) were separated by column chromatography.[25]

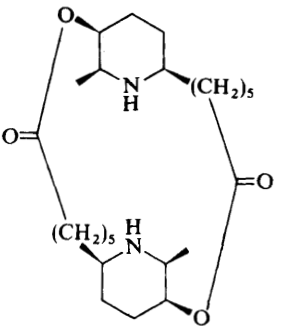
A five-step synthesis of (±)-azimic acid (32), the acidic moiety of the carpaine-like alkaloid azimine (33), has been reported, starting with ethyl 5-bromopentanoate (Scheme 5).[27]



(32)

Reagents: i, NaOEt; ii, $Ba(OH)_2$; iii, O_3; iv, $EtNO_2$; v, H_2–Pd/C, products separated by preparative t.l.c.

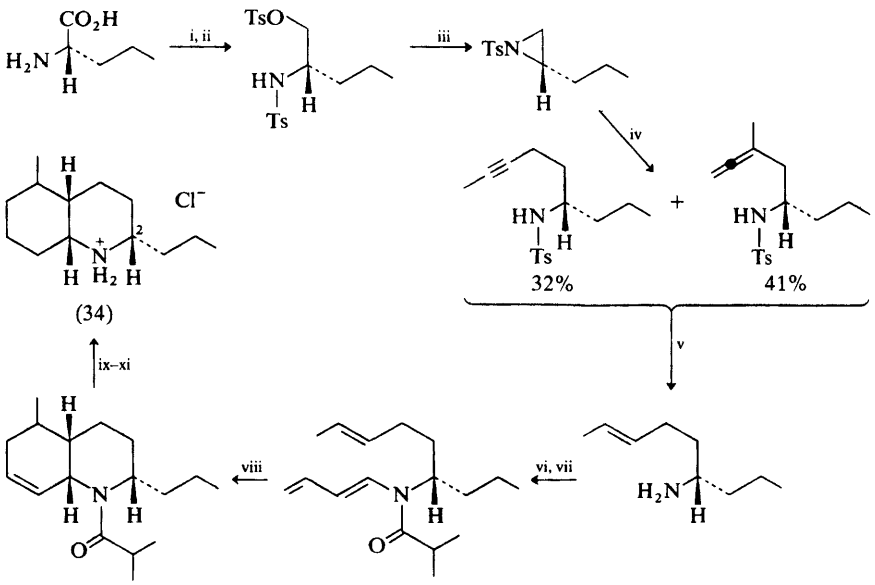
Scheme 5



(33)

Decahydroquinoline Alkaloids.—Full details of an earlier briefly described synthesis of (±)-pumiliotoxin C have been published.[28] Other total syntheses of the same compound have been documented, starting from *trans*-4-hexenal,[29] and from ethyl *trans*-buta-1,3-diene-1-carbamate.[30] An enantioselective synthesis of natural (−)-pumiliotoxin-C hydrochloride (34) has also been described (Scheme 6),

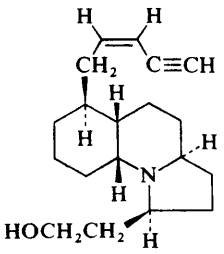
[27] E. Brown and R. Dhal, *J.C.S. Perkin I*, 1976, 2190.
[28] G. Habermehl, H. Andres, K. Miyahara, B. Witkop, and J. W. Daly, *Annalen*, 1976, 1577.
[29] W. Oppolzer, C. Fehr, and J. Warneke, *Helv. Chim. Acta*, 1977, **60**, 48.
[30] L. E. Overman and P. J. Jessup, *Tetrahedron Letters*, 1977, 1253.



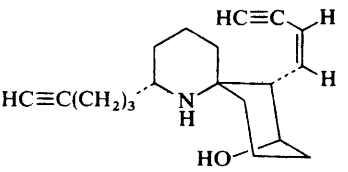
Reagents: i, $LiAlH_4$; ii, TsCl–py; iii, KOH–MeOH; iv, $MeC{\equiv}CCH_2MgBr$; v, $Na–NH_3$; vi, $MeCH{=}CHCHO$; vii, NaH–$Me_2CHCOCl$; viii, thermolysis; ix, H_2–Pd; x, Bu^i_2AlH; xi, HCl

Scheme 6

starting from (*S*)-norvaline. The synthesis proves unequivocally the (2*S*) configuration for the natural base.[31] A new acetylenic alkaloid, gephyrotoxin (35)[32] (see Chapter 4), belongs to this family. It occurs in the skin of the Colombian frog *Dendrobates histrionicus* together with its dihydro-derivative (35; $CH{=}CH_2$ in place of $C{\equiv}CH$), allodihydrohistrionicotoxin (36), and several other related bases of as yet uncertain structure.



(35)



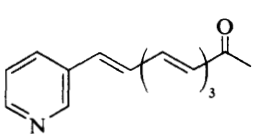
(36)

3 Pyridine Alkaloids

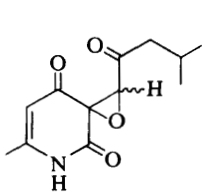
Navenone-A is one of a trio of alarm pheromones produced by the sea slug *Navanax inermis*. Its structure (37) has been deduced from spectral study; in particular, n.m.r. spectroscopy establishes the (*E*) configuration of all the side-

[31] W. Oppolzer and E. Flaskamp, *Helv. Chim. Acta*, 1977, **60**, 204.
[32] J. W. Daly, B. Witkop, T. Tokuyama, T. Nishikawa, and I. L. Karle, *Helv. Chim. Acta*, 1977, **60**, 1128.

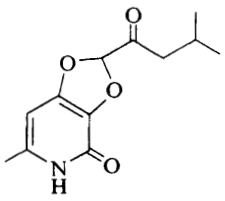
chain double bonds and the position of substitution in the pyridine ring.[33] Flavipucine (38), a metabolite of *Aspergillus flavipes*, has been synthesized as its racemate; it is rearranged to isoflavipucine (39) by heat or base. A mechanism has been proposed for the transformation.[34]



(37)

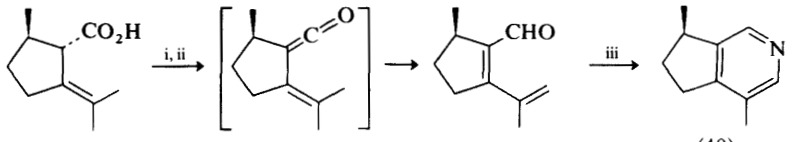


(38)



(39)

The (+)-enantiomer (40) of actinidine, an alkaloid of *Valeriana officinalis* and *Actinidia polygama*, has been synthesized as outlined in Scheme 7, the starting material being obtained from (+)-pulegone.[35]

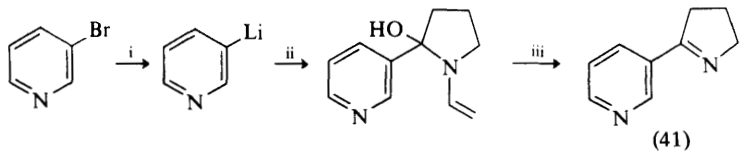


(40)

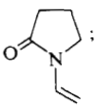
Reagents: i, $(COCl)_2$; ii,  ; iii, NH_2OH, Δ

Scheme 7

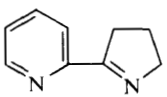
A simple synthesis of alkaloids of the nicotine type is exemplified by that of myosmine (41) and is outlined in Scheme 8. It employs 1-vinyl-2-pyrrolidone as



(41)

Reagents: i, Bu^nLi; ii,  ; iii, H^+

Scheme 8



(42)

[33] H. L. Sleeper and W. Fenical, *J. Amer. Chem. Soc.*, 1977, **99**, 2367.

[34] J. A. Findlay, J. Krepinsky, A. Shum, C. G. Casinovi, and L. Radics, *Canad. J. Chem.*, 1977, **55**, 600; J. A. Findlay, J. W. H. Tam, and J. Krepinsky, *Synth. Comm.*, 1977, **7**, 149; N. N. Girotra, Z. S. Zelawski, and N. L. Wendler, *J.C.S. Chem. Comm.*, 1976, 566.

[35] J. D. Wuest, A. M. Madonik, and D. C. Gordon, *J. Org. Chem.*, 1977, **42**, 2111.

synthon; starting with 2-bromopyridine yields apoferrorosamine (42), a decomposition product of ferrorosamine-A, which may be obtained from *Pseudomonas roseus fluoreszens*. The vinyl group is eliminated as acetaldehyde in the final step.[36]

[36] D. Spitzner, *Synthesis*, 1977, 242.

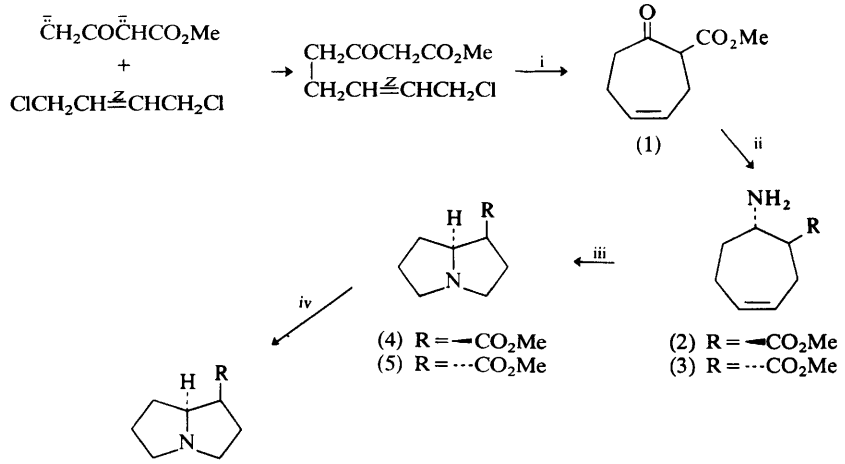
3

Pyrrolizidine Alkaloids

BY D. J. ROBINS

1 Syntheses and Reactions of the Necine Bases

Several syntheses of 1-hydroxymethylpyrrolizidines have been reported. Borch and Ho[1] have utilized a reductive cyclization method for their synthesis of (±)-isoretronecanol (6) and (±)-trachelanthamidine (7). The cycloheptenone ester (1), prepared by a novel route (Scheme 1), was reductively aminated to give a mixture of the diastereoisomeric amino-esters (2) and (3) in 48% yield. These esters could not be separated. Oxidative cleavage of the double bond of the esters, followed by reductive cyclization, gave a 35% yield of the pyrrolizidine esters (4) and (5). Separation of these compounds was achieved by preparative t.l.c., and a final reduction step afforded the racemic alkaloids (6) and (7). The second reductive amination process was stereoselective, because reduction of the unseparated ester mixture (4) and (5) gave a 1:2 ratio (g.l.c.) of the 1-hydroxymethylpyrrolizidines.

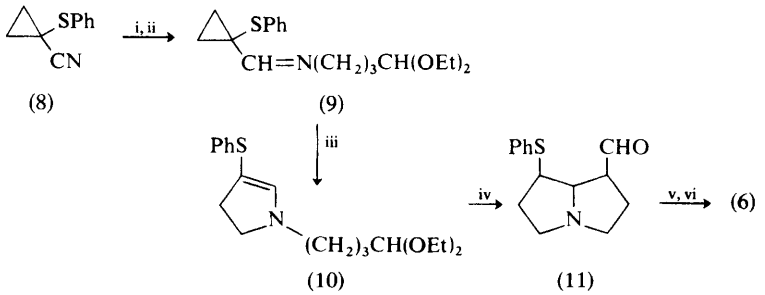


Reagents: i, NaOMe–MeOH; ii, $NaBH_3CN$–NH_4NO_3; iii, OsO_4–$NaIO_4$, $NaBH_3CN$; iv, $LiAlH_4$

Scheme 1

[1] R. F. Borch and B. C. Ho, *J. Org. Chem.*, 1977, **42**, 1255.

Stevens *et al.*[2] have used the acid-catalysed rearrangement of cyclopropylimines to give stabilized endocyclic enamine systems, which can be transformed into bicyclic pyrrolizidine or indolizidine alkaloids. A stereoselective route to (±)-isoretronecanol (6) was developed using this method (Scheme 2), and an overall yield of 35% was obtained for the seven-stage synthesis. The cyclopropane derivative (8) was prepared from phenylthioacetonitrile and 1,2-dichloroethane. Selective reduction to the corresponding aldehyde was followed by formation of a Schiff base to give the imine (9). The key step is the rearrangement of this imine to yield the pyrroline (10). This was accomplished by refluxing in xylene in the presence of suspended ammonium chloride. Cyclization to the pyrrolizidine (11), followed by reduction and desulphurization steps, gave (±)-isoretronecanol (6) with a stereochemical purity >96% (g.l.c. analysis).



Reagents: i, DIBAH; ii, $H_2N(CH_2)_3CH(OEt)_2$; iii, NH_4Cl; iv, MeOH–HCl; v, $LiAlH_4$; vi, Raney Ni

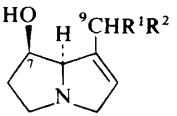
Scheme 2

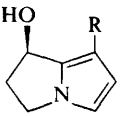
Using established methods, pyrrolizidines with 1- and 2-hydroxy and 1- and 2-hydroxymethyl substituents have been synthesized.[3] The racemates were separated by chromatographic techniques, and resolved by classical methods.

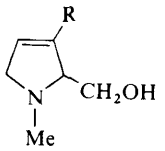
Oxidation of retronecine (12) with manganese dioxide has previously been shown to give the dihydropyrrolizine derivatives (14) and (15).[4] Mattocks[5] has demonstrated that the intermediate pyrroline aldehyde (13) is formed in 30% yield with specially prepared manganese dioxide under carefully controlled conditions. The analogous synthanecine A (16) is also oxidized to the corresponding aldehyde (17) with this reagent.

Hoskins and Crout[6] have carried out the selective esterification of retronecine (12) at C-9 in moderate yield with simple acids using *NN'*-dicyclohexylcarbodiimide. With $\alpha\beta$-unsaturated acids and bulky α-trisubstituted acids, the use of *NN'*-carbonyldi-imidazole, with prior formation of the acyl-imidazole, gave reasonable yields of the C-9 monoesters of (12). The regiospecificity of this

[2] R. V. Stevens, Y. Luh, and J. Sheu, *Tetrahedron Letters*, 1976, 3799; R. V. Stevens, *Accounts Chem. Res.*, 1977, **10**, 193.
[3] J. Schnekenburger and E. Breit, *Arch. Pharm.*, 1977, **310**, 152, 161; J. Schnekenburger and H. Vollhardt, *ibid.*, pp. 177, 186.
[4] C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Austral. J. Chem.*, 1970, **23**, 1869.
[5] A. R. Mattocks, *J. Chem. Research (S)*, 1977, 40.
[6] W. M. Hoskins and D. H. G. Crout, *J.C.S. Perkin I*, 1977, 538.







Retronecine (12) $R^1 = H$, $R^2 = OH$
(13) $R^1R^2 = O$

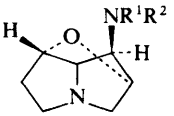
(14) $R = CH_2OH$
(15) $R = CHO$

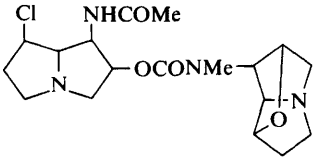
(16) $R = CH_2OH$
(17) $R = CHO$

reaction allows the preparation of unsymmetrical diesters of retronecine by subsequent esterification at the 7-position with a suitable acid chloride. The diesters of (12) are semi-synthetic analogues of the naturally occurring alkaloids.

2 Alkaloids of the Graminae

The simple necine bases loline (18), norloline (19), and lolinine (20) have been identified previously from *Lolium cuneatum* Nevski.[7] Further investigations on the seeds of this plant by Russian workers have established the presence of four new alkaloids. *N*-Formylnorloline (21),[8] *N*-methyl-loline (22), *N*-acetylnorloline (23), and *N*-formyl-loline (24)[9] have been identified. In addition, a novel dimeric pyrrolizidine alkaloid, lolidine, containing chlorine, was isolated in trace amounts (7 mg from 10 kg of seeds). The structure (25) has been suggested for lolidine on the basis of spectral data.[10]





Loline (18) $R^1 = Me$, $R^2 = H$
Norloline (19) $R^1 = R^2 = H$
Lolinine (20) $R^1 = Me$, $R^2 = COMe$
N-Formylnorloline (21) $R^1 = H$, $R^2 = CHO$
N-Methyl-loline (22) $R^1 = R^2 = Me$
N-Acetylnorloline (23) $R^1 = H$, $R^2 = COMe$
N-Formyl-loline (24) $R^1 = Me$, $R^2 = CHO$

Lolidine (25)

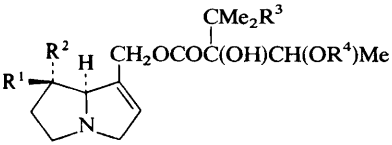
3 Alkaloids of the Boraginaceae

No new alkaloids have been discovered within this family. A phytochemical investigation of plants of the Boraginaceae indigenous to France has been carried out.[11] Pyrrolizidine alkaloids were detected in 23 species from 14 genera, and *N*-oxides were present in 12 species. No definite identifications were made.

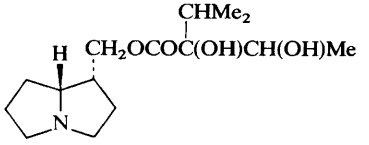
[7] S. T. Akramov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1965, **4**, 262 (*Chem. Abs.*, 1966, **64**, 5152).
[8] E. Kh. Batirov, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 120 (*Chem. Abs.*, 1977, **86**, 13 792).
[9] E. Kh. Batirov, S. A. Khamidkhodzhaev, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 60 (*Chem. Abs.*, 1976, **85**, 59 556).
[10] E. Kh. Batirov, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 63 (*Chem. Abs.*, 1976, **85**, 74 883).
[11] P. Delorme, M. Jay, and S. Ferry, *Plant. Med. Phytother.*, 1977, **11**, 5 (*Chem. Abs.*, 1977, **86**, 185 965).

Previous work on *Heliotropium indicum* L. has demonstrated the presence of indicine (26) and acetylindicine (27).[12] Plants grown in Bangladesh contained indicine as principal alkaloid, together with heliotrine (28), lasiocarpine (29), echinatine (30), supinine (31), and heleurine (32).[13] The *N*-oxide of indicine (26), also isolated from this species, displayed significant antitumour activity.[14] The dried plant material of *H. ramosissimum* contains 0.58% of alkaloids, the majority of which is heliotrine (28).[15]

Echimidine (33) and anadoline (34) have been isolated from *Symphytum tuberosum* of Turkish origin.[16] Extraction of the dried aerial parts of *Lindelofia anchusioides* gave 1.4% of lindelofine (35) by an ion-exchange method.[17]



Indicine (26) $R^1 = OH$, $R^2 = R^3 = R^4 = H$
Acetylindicine (27) $R^1 = OH$, $R^2 = R^3 = H$, $R^4 = COMe$
Heliotrine (28) $R^1 = R^3 = H$, $R^2 = OH$, $R^4 = Me$
Lasiocarpine (29) $R^1 = H$, $R^2 = Z$-OCOCMe=CHMe, $R^3 = OH$, $R^4 = Me$
Echinatine (30) $R^1 = R^3 = R^4 = H$, $R^2 = OH$
Supinine (31) $R^1 = R^2 = R^3 = R^4 = H$
Heleurine (32) $R^1 = R^2 = R^3 = H$, $R^4 = Me$
Echimidine (33) $R^1 = Z$-OCOCMe=CHMe, $R^2 = R^4 = H$, $R^3 = OH$
Anadoline (34) $R^1 = OH$, $R^2 = R^3 = H$, $R^4 = E$-COCMe=CHMe

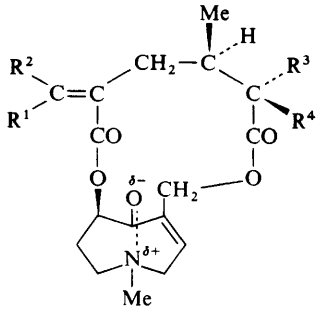


Lindelofine (35)

4 Alkaloids of the Leguminosae

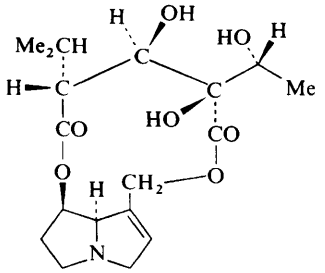
In last year's Report, the identification of crotaverrine (36) and *O*-acetylcrotaverrine (37) from *Crotalaria verrucosa* L. was discussed. The same two alkaloids have been isolated from the seeds of *C. walkeri* Arnott.[18] In an earlier study of this species, the presence of *O*-acetylsenkirkine (39) and isosenkirkine was noted.[19]

[12] A. R. Mattocks, R. Schoental, H. C. Crowley, and C. C. J. Culvenor, *J. Chem. Soc.*, 1961, 5400; A. R. Mattocks, *J. Chem. Soc.* (*C*), 1967, 329.
[13] M. S. Hoque, A. Ghani, and H. Rashid, *Bangladesh Pharm. J.*, 1976, **5**, 13.
[14] M. Kugelman, W.-C. Liu, M. Axelrod, T. J. McBride, and K. V. Rao, *Lloydia*, 1976, **39**, 125.
[15] A.-A. M. Habib, *Bull. Fac. Sci., Riyadh Univ.*, 1975, **7**, 67 (*Chem. Abs.*, 1976, **85**, 119 597).
[16] A. Ulubelen and F. Öcal, *Phytochemistry*, 1977, **16**, 499.
[17] B. Babaev, N. P. Abdullaev, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1976, 116 (*Chem. Abs.*, 1976, **85**, 30 226).
[18] K. A. Suri, R. S. Sawhney, and C. K. Atal, *Indian J. Chem.*, 1976, **14B**, 471.
[19] C. K. Atal and R. S. Sawhney, *Indian J. Pharm.*, 1973, **35**, 1.

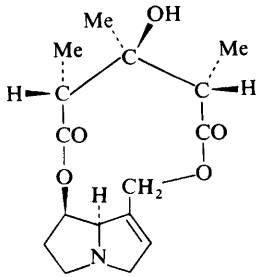


Crotaverrine (36) $R^1 = H, R^2 = R^4 = Me, R^3 = OH$
O-Acetylcrotaverrine (37) $R^1 = H, R^2 = R^4 = Me, R^3 = OCOMe$
Senkirkine (38) $R^1 = R^3 = Me, R^2 = H, R^4 = OH$
O-Acetylsenkirkine (39) $R^1 = R^3 = Me, R^2 = H, R^4 = OCOMe$

Axillarine (40) was isolated from *C. axillaris* Ait. by Crout.[20] The crystal structure of the ethanol solvate of axillarine hydrobromide has been determined by *X*-ray diffraction methods.[21] The absolute configurations of the four chiral centres in the necic acid portion have been established. The overall shape of axillarine is somewhat similar to fulvine (41),[22] which also has an 11-membered macrocyclic



Axillarine (40)



Fulvine (41)

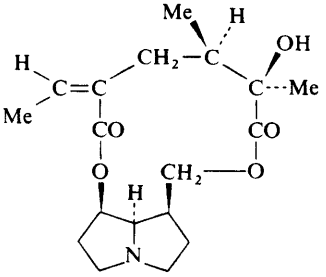
ring. The angle between the five-membered rings of the pyrrolizidine nucleus is 126° (115° in fulvine). The saturated pyrrolidine ring is in the *exo*-puckered form with a puckering angle of 42°. As in fulvine, both carbonyl ester groups of axillarine are directed below the plane of the macro-ring, *i.e.* they are *syn*-parallel. In pyrrolizidine alkaloids with 12-membered rings, the two carbonyl groups are *anti*-parallel.

5 Alkaloids of the Compositae

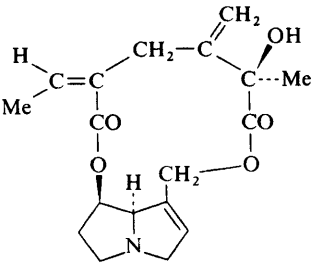
Pyrrolizidine alkaloids are included in a list of alkaloids that have been isolated from the Compositae.[23] All reports this year are concerned with the tribe Senecioneae. Definite identification of pyrrolizidine alkaloids from two new genera,

[20] D. H. G. Crout, *J. Chem. Soc.* (*C*), 1969, 1379.
[21] H. Stoeckli-Evans and D. H. G. Crout, *Helv. Chim. Acta*, 1976, **59**, 2168.
[22] J. L. Sussman and S. J. Wodak, *Acta Cryst.*, 1973, **29B**, 2918.
[23] K. A. Zirvi and M. Ikram, *Pakistan J. Sci. Ind. Res.*, 1975, **18**, 93.

Adenostyles and *Doronicum*, is of chemotaxonomical interest. Pimenov *et al.*[24] have studied the variation in alkaloid content of subspecies of *A. rhombifolia* (Willd.) Pim. All plants contained varying amounts of platyphylline (42), seneciphylline (43), and sarracine. Platyphylline and seneciphylline were also extracted from the roots of *A. alliariae*.[25] The genus *Adenostyles* has been classified by some taxonomists in the tribe Eupatorieae, but its content of macrocyclic pyrrolizidine alkaloids is in accord with its current position in the Senecioneae.

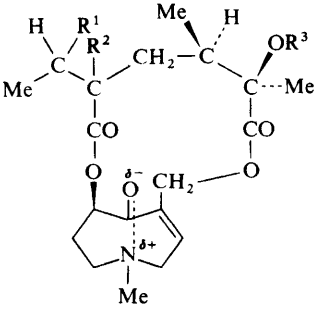


Platyphylline (42)



Seneciphylline (43)

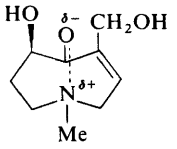
Investigation of *Doronicum macrophyllum* by Russian workers[26] has established the presence of two known[27] alkaloids, otosenine (44) and floridanine (45). In addition, a new alkaloid containing chlorine was isolated. The structure (46) has been suggested for doronine on the basis of spectroscopic studies. Confirmation of this structure was obtained by the conversion of otosenine (44) into doronine (46) with acetyl chloride.[26]



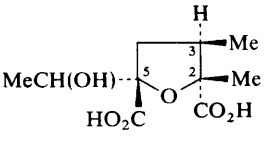
Otosenine (44) R^1, R^2 = α-epoxide, R^3 = H
Floridanine (45) $R^1 = R^2$ = OH, R^3 = COMe
Doronine (46) R^1 = Cl, R^2 = OH, R^3 = COMe
Petasitenine = Fukinotoxin (47) R^1, R^2 = β-epoxide, R^3 = H
Neopetasitenine (48) R^1, R^2 = β-epoxide, R^3 = COMe

[24] M. G. Pimenov, L. D. Yakhontova, D. Pakalne, and L. A. Sapunova, *Rastit. Resur.*, 1975, **11**, 72 (*Chem. Abs.*, 1975, **82**, 152 218).
[25] L. D. Yakhontova, M. G. Pimenov, and L. A. Sapunova, *Khim. prirod. Soedinenii*, 1976, 122 (*Chem. Abs.*, 1976, **85**, 59 575).
[26] Sh. A. Alieva, U. A. Abdullaev, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 194 (*Chem. Abs.*, 1976, **85**, 108 841).
[27] M. P. Cava, K. V. Rao, J. A. Weisbach, R. F. Raffauf, and B. Douglas, *J. Org. Chem.*, 1968, **33**, 3570.

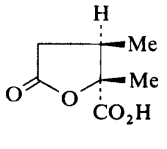
Two groups of Japanese workers have examined the alkaloid content of *Petasites japonicus* Maxim., a plant which has carcinogenic activity. Yamada *et al.*[28] isolated two new alkaloids, petasitenine (47) and neopetasitenine (48), from young flower stalks of *P. japonicus*. Conversion of petasitenine into neopetasitenine was achieved with acetic anhydride under mild basic conditions, confirming their relationship. Hydrolysis of petasitenine (47) gave otonecine (49) and petasitenecic acid (50), which was shown to be diastereoisomeric with jaconecic acid at C-5. Oxidation of this acid (50) gave a γ-lactone (51), identical to that produced by the oxidation of jaconecic acid. This establishes the stereochemistry of three of the chiral centres of the necic acid (50) (C-2, C-3, and C-5). The final stereochemical



Otonecine (49)

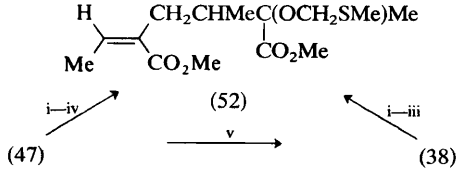


Petasitenecic acid (50)



(51)

detail was settled by correlation of petasitenine (47) with senkirkine (38).[29] Both alkaloids were transformed to the same degradation product (52) (Scheme 3). The



Reagents: i, $ClCH_2SMe$; ii, $Ba(OH)_2$; iii, CH_2N_2; iv, KSeCN; v, WCl_6–Bu^nLi

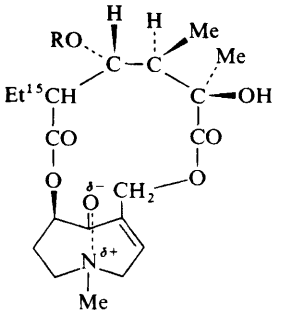
Scheme 3

deoxygenation step, effected by potassium selenocyanate, was stereospecific. Furthermore, petasitenine was also converted directly into senkirkine by deoxygenation (Scheme 3), although 20% of the product was an isomer of senkirkine. Petasitenine is carcinogenic and has high cytotoxic activity.[30] This same alkaloid, named as fukinotoxin (47), was also isolated by Furuya *et al.* from *P. japonicus*.[31] The structure was established by chemical and spectroscopic studies, and the stereochemistry was confirmed by *X*-ray crystallography.

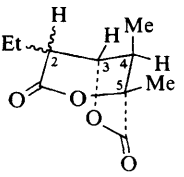
A full paper on the constituents of *Syneilesis palmata* Maxim. has appeared.[32] As well as syneilesine (53), a new alkaloid, *viz.* acetylsyneilesine (54), and senecionine have been extracted from this plant. The structure of this new alkaloid (54) was proved by acetylation of syneilesine with acetic anhydride and sodium acetate. The remaining doubt in the structure of syneilesine (53) is associated with the

[28] K. Yamada, H. Tatematsu, M. Suzuki, Y. Hirata, M. Haga, and I. Hirono, *Chem. Letters*, 1976, 461.
[29] K. Yamada, H. Tatematsu, Y. Hirata, M. Haga, and I. Hirono, *Chem. Letters*, 1976, 1123.
[30] I. Hirono, H. Mori, K. Yamada, Y. Hirata, M. Haga, H. Tatematsu, and S. Kanie, *J. Nat. Cancer Inst.*, 1977, **58**, 1155.
[31] T. Furuya, M. Hikichi, and Y. Iitaka, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 1120.
[32] M. Hikichi and T. Furuya, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 3178.

stereochemistry of the necic acid portion (see these Reports, Vol. 6, Ch. 4). Syneilesinolide C (55) is one of three lactones formed by alkaline hydrolysis of syneilesine. From c.d. spectra of these lactones, C-5 [as in (55)] was shown to have the *R*-configuration. The ready formation of the γ,δ-lactone (55) suggests that the stereochemistry at C-3 is also *R*. The n.m.r. coupling constant, $J = 5.4$ Hz, between the protons on C-3 and C-4 indicates that the dihedral angle between these protons is about 36°, and suggests that the configuration at C-4 is *R*. The stereochemistry at C-2 [*i.e.* C-15 of syneilesine (53)] is not known.

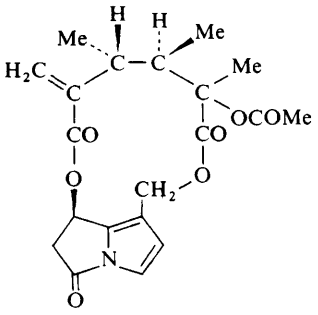


Syneilesine (53) R = H
Acetylsyneilesine (54) R = COMe

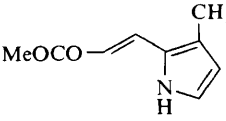


Syneilesinolide C (55)

Much attention is still being received by the very large genus *Senecio*. Bohlmann and co-workers are carrying out extensive investigations into the chemical constituents of *Senecio* species, concentrating mainly on neutral, terpenoid derivatives. In the course of their studies, they have discovered three examples of a most interesting new type of pyrrolizidine alkaloid containing the dihydropyrrolizinone ring system. Pterophorine (56) was extracted from aerial parts of *S. pterophorus* DC.[33] Alkaline hydrolysis did not give the free necine; instead the key feature in the elucidation of the structure was the degradation achieved with sodium methoxide in methanol. The unsaturated pyrrole ester (57) was formed by methanolysis of (56) with simultaneous elimination of the acyl residue to form the conjugated ester. The mode of attachment of the dicarboxylic acid (58), also produced by this



Pterophorine (56)

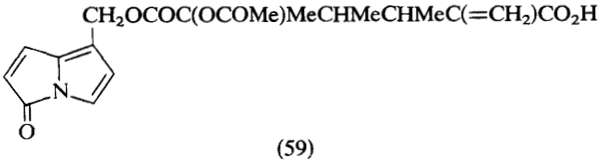


(57)

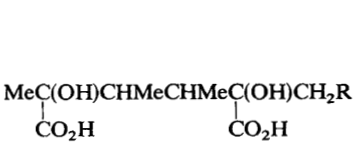
(58)

[33] F. Bohlmann, C. Zdero, and M. Grenz, *Chem. Ber.*, 1977, **110**, 474.

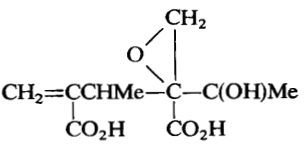
degradation, was established by partial opening of the 12-membered ring with diazabicycloundecane in benzene to give the pyrrolizinone (59). Elimination of the ester group was accompanied by formation of a double bond. The structures of the new compounds (57)—(59) were elucidated mainly by 270 MHz ^1H and ^{13}C n.m.r. spectroscopy. The stereochemistry of the necic acid (58) is unknown. Tentatively, the methyl groups at C-13 and C-14 are assigned as shown in (56), because of the small coupling constant, $J = 4$ Hz, between the protons attached to these carbon atoms. The necic acid (58) is a C_{10} acid of an unusual structural type. Acids with the same carbon skeleton have been found before only in *S. sceleratus* Schweickerdt (60) and *S. swaziensis* Compton (61) (see these Reports, Vol. 6, Ch.



(59)

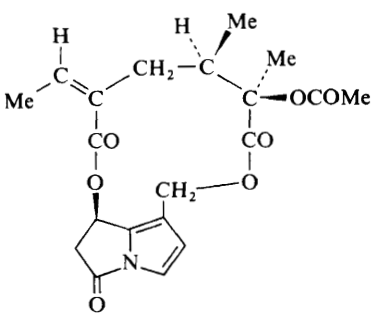


(60) R = OH or Cl

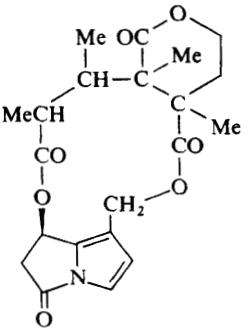


(61)

4). An isomer of pterophorine (56), named senaetnine, was isolated from *S. aetnensis* Jan.[34] On similar treatment with methoxide, senaetnine yielded the same pyrrole derivative (57) as pterophorine. The other degradation product was an acetate, from which senecic acid was obtained, indicating that senaetnine has the structure (62), assuming the usual mode of attachment of the necic acid. The third new pyrrole derivative was extracted from the roots of *S. inaequidens* DC. together with pterophorine (56).[34] The structure (63) has been tentatively suggested for



Senaetnine (62)



Inaequidenine (63)

[34] F. Bohlmann, K.-H. Knoll, C. Zdero, P. K. Mahanta, M. Grenz, A. Suwita, D. Ehlers, N. L. Van, W.-R. Abraham, and A. A. Natu, *Phytochemistry*, 1977, **16**, 965.

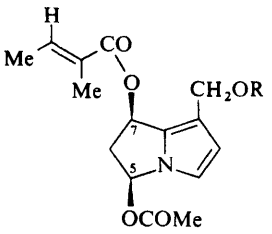
inaequidenine on the basis of ^{1}H n.m.r. spectroscopy. There was insufficient material for degradation. The point of attachment of the δ-lactone to the macrocyclic ring is uncertain. It would obviously be desirable to have confirmation of this acid structure, as it represents a totally new type of necic acid with 13 carbon atoms. No necic acid is known with a skeleton of more than ten carbon atoms, and it is difficult to rationalize the formation of this acid on biogenetic grounds. In each of these three new pyrrole derivatives, (56), (62), and (63), the stereochemistry at C-7 is assumed to be the same as in all other macrocyclic pyrrolizidine alkaloids. The occurrence of these unexpected non-basic pyrrolizidine derivatives in *Senecio* species indicates that further searches are necessary in other plants that produce pyrrolizidine alkaloids to establish their distribution and chemotaxonomic significance. The toxicity of these new compounds is also worthy of investigation. Pyrrole derivatives are known to be the active metabolites of these alkaloids, but it is likely that the reduced nucleophilic character of the lactam nitrogen will render the toxic alkylation process more difficult, and will lessen the toxic effects.

Another new group of pyrrolizidine alkaloids have been discovered by Bohlmann *et al.*[33] in *Senecio cissampelinus* (DC) Sch. Bip. The senampelines were obtained as a mixture of four compounds, which were separated by repeated t.l.c. into two isomeric pairs. Saponification of these isomeric pairs gave a mixture of acids together with the pyrrole derivative (68). Identification was made by ^{1}H n.m.r. spectroscopy. Degradation of the senampelines with methoxide yielded aldehyde esters (69), which proved the position of one of the esterifying acids. The location of the other two ester groups is uncertain, because neither could be selectively removed. On biogenetic grounds, the formulation for senampelines A–D as in (64)—(67) is preferred, since few pyrrolizidine alkaloids are known with an acetoxy residue at C-7. The relative configuration of the two oxygen functions at C-5 and C-7 is *cis* from the n.m.r. coupling constants, but the absolute configuration is not known. Very few *Senecio* species produce alkaloids where the esterifying acids contain five carbon atoms, and this factor may be of use chemotaxonomically. The set of new compounds (56), (62)—(67) contain the first necines to be discovered with oxygen functions at C-5.

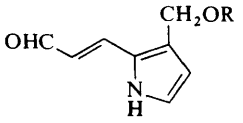
The Bulgarian plant *Senecio nemorensis* L. var. *bulgaricus* (Vel.) Stoj. *et* Stef. was previously shown to contain a novel type of pyrrolizidine alkaloid, nemorensine, which was tentatively formulated as having a 13-membered macrocyclic ring (see these Reports, Vol. 5, Ch. 4). Reinvestigation[35] has confirmed the presence of this alkaloid, but again there was insufficient material for a secure structure determination. Two more new alkaloids were also isolated. Bulgarsenine (70) contained an αβ-unsaturated ester, and gave platynecine and nemorensic acid (71) on alkaline hydrolysis, indicating that a 13-membered ring is again present. The other new alkaloid, retroisosenine, gave retronecine and an isomer of nemorensic acid on alkaline hydrolysis, which suggests the structure (72) for retroisosenine. The stereochemistry of the acid portions of these alkaloids is still uncertain.

Three alkaloids previously isolated[36] from the common *Senecio* species *S. erucifolius* L. (hoary ragwort), *S. jacobaea* L. (ragwort), and *S. vulgaris* L. (groundsel),

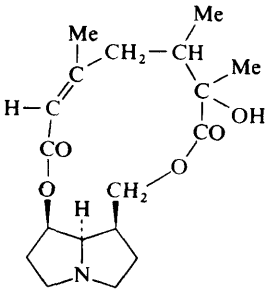
[35] N. T. Nghia, P. Sedmera, A. Klasek, A. Boeva, L. Drjanovska, L. Dolejs, and F. Santavy, *Coll. Czech. Chem. Comm.*, 1976, **41**, 2952.
[36] S. Ferry, *Ann. pharm. franç.*, 1972, **30**, 145.



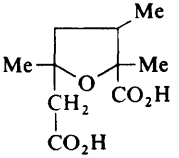
Senampeline A (64) R = COC(*E*-CHMe)$CH_2OCOCH{=}CMe_2$
Senampeline B (65) R = COC(*E*-CHMe)$CH_2OCOCMe$=*E*-CHMe
Senampeline C (66) R = COC(*Z*-CHMe)$CH_2OCOCH{=}CMe_2$
Senampeline D (67) R = COC(*Z*-CHMe)$CH_2OCOCMe$=*E*-CHMe



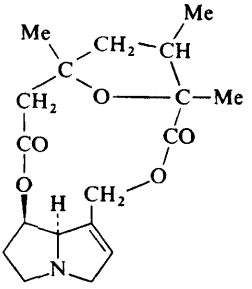
(68) R = Me
(69) R = as in Senampelines A—D



Bulgarsenine (70)



Nemorensic acid (71)



Retroisosenine (72)

have been shown to be senecionine, seneciphylline (43), and retrorsine.[37] Senecionine and seneciphylline have been extracted from *S. scandens.*[38] Senecionine and integerrimine were identified in *S. nebrodensis* L. var. *sicula.*[39] An efficient ion-exchange process has been used to extract sarracine from *S. rhombifolius.*[40]

6 Pyrrolizidine Derivatives in the Lepidoptera

More work has been reported on the nymphalid subfamilies Ithomiinae and Danainae. Dead shoots of *Heliotropium indicum* act as a powerful attractant for male ithomiine and danaine butterflies. The butterflies use alkaloids obtained from these plants for the production of chemicals with pheromone activity. Baiting with alkaloids and their esterifying acids indicated that a volatile product derived from

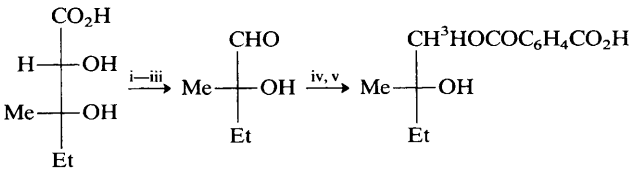
[37] S. Ferry and J. L. Brazier, *Ann. pharm. franç.*, 1976, **34**, 133.
[38] V. Batra and T. R. Rajagopalan, *Current Sci.*, 1977, **46**, 141.
[39] S. Plescia, G. Daidone, and V. Sprio, *Phytochemistry*, 1976, **15**, 2026.
[40] V. E. Dauksha, *Khim. prirod. Soedinenii*, 1976, 831 (*Chem. Abs.*, 1976, **86**, 117 591).

the necic acids attracts males to the plants, where the intact alkaloids then act as phagostimulants.[41] Another reason for the ingestion of pyrrolizidine alkaloids by these butterflies has been advanced.[42] Two species of danaine butterflies, *Danaus plexippus* L. and *D. chrysippus* L., captured in the field were found to contain pyrrolizidine alkaloids present in the food plants at the capture sites. It was noted that *D. plexippus* was able to store alkaloids for several days. However, unlike many other danaines, male butterflies of this species do not secrete alkaloid-derived substances on their hairpencils, nor do the hairpencils figure prominently in courtship.[43] It has therefore been suggested that the alkaloids may contribute to the unpalatability of the butterflies to potential predators.[42]

7 General Studies

The mass spectral fragmentation of pyrrolizidine alkaloids containing otonecine (49) has been studied by Russian workers.[44] Renardine [=senkirkine (38)], otosenine (44), floridanine (45), and floricaline all displayed characteristic *m/e* 168, 151, 150, 122, 110, and 94 for the otonecine nucleus. The detailed fragmentation pattern of each acid portion is also discussed.

The (−)-*erythro*-isomer of 2,3-dihydroxy-3-methylpentanoic acid (73) has been synthesized by Crout and Whitehouse, and shown to be identical with the naturally occurring (−)-acid obtained from strigosine.[45] *trans*-Hydroxylation of *E*-3-methylpent-2-enoic acid with tungstic oxide–hydrogen peroxide gave the (±)-*erythro*-acid, which was resolved as the quinine salts. The absolute configuration of the (−)-*erythro*-acid (73) was determined by degradation (Scheme 4). Methylation,



(73) (74) (75)

Reagents: i, CH_2N_2; ii, $LiAlH_4$; iii, $NaIO_4$; iv, NaB^3H_4; v, phthalic anhydride–C_5H_5N

Scheme 4

reduction, and periodate cleavage of (73) gave the aldehyde (74). Reduction with sodium borotritiide yielded a butanediol, which was converted into its phthaloyl ester (75). Co-crystallization of this ester with authentic 2*R*-phthaloyl ester established that the (−)-isomer of (73) has the 2*R*, 3*R* configuration. This assign-

[41] T. E. Pliske, J. A. Edgar, and C. C. J. Culvenor, *J. Chem. Ecol.*, 1976, **2**, 255.
[42] J. A. Edgar, P. A. Cockrum, and J. L. Frahn, *Experientia*, 1976, **32**, 1535.
[43] T. E. Pliske, *Ann. Entomol. Soc. Amer.*, 1975, **68**, 935.
[44] U. A. Abdullaev, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 66 (*Chem. Abs.*, 1976, **85**, 177 726).
[45] D. H. G. Crout and D. Whitehouse, *J.C.S. Perkin I*, 1977, 544.

ment was confirmed by a corresponding dilution analysis with the brucine salt of the 2*S*-phthaloyl ester.

8 Pharmacological and Biological Studies

A number of human health hazards due to pyrrolizidine alkaloids have been reported. Two recent outbreaks of hepatic veno-occlusive disease have been ascribed to these alkaloids. In Central India, 28 people died and the cause was probably the consumption of cereals mixed with seeds of a *Crotalaria* species.[46] Bread made from wheat contaminated with seeds of *Heliotropium* plants was thought to be to blame for the disease in N.W. Afghanistan.[47] About one quarter of the 7200 inhabitants from affected villages showed evidence of liver damage. An unexpected source of pyrrolizidine alkaloids was in honey produced from the nectar of *Senecio jacobaea* (tansy ragwort).[48] Further possible health hazards of tansy ragwort have been pointed out in two studies which demonstrated that pyrrolizidine alkaloids or their toxic metabolites can be passed through cows' milk. The milk from cows fed dried tansy ragwort at fairly high levels for two weeks was shown to contain pyrrolizidine alkaloids at a concentration of $\sim 100\ \mu g\, l^{-1}$.[49] Hepatic lesions were found in calves which were suckled for several months on cows that had been fed chronic lethal doses of tansy ragwort.[50]

Pyrrolic metabolites of the pyrrolizidine alkaloids, produced by hepatic microsomal enzymes, are believed to be the actual toxic agents. The rates of production of these metabolites by microsomes from eight different animal species were studied.[51] Two-thirds of rats injected with dehydroretronecine (14) developed tumours at the injection site, whereas half of those injected with monocrotaline under the same conditions developed widely dispersed tumours.[52] A possible reason for this dispersal is the need for metabolism of monocrotaline to an active pyrrole metabolite before its carcinogenic potential is realized. Tritiated dehydroretronecine was used to study the distribution of radioactivity in various tissues in young rats.[53] Preferential localization was observed on the gastric mucosa. A similar effect has been noted with tritiated retronecine (see these Reports, Vol. 6, Ch. 4). Application of dehydromonocrotaline to the rat cremaster produced a delayed and prolonged increase in the vascular permeability.[54] The pyrroles produced by hepatic metabolism of pyrrolizidine alkaloids seem to directly inhibit the liver microsomal enzymes involved in their own formation.[55] It has been suggested that prior exposure to these alkaloids could influence their toxicity.

The preparation of tritium-labelled disenecioylretronecine was described in last year's Report. This compound, when injected into rats, produced

[46] B. N. Tandon, R. K. Tandon, H. D. Tandon, M. Narndranathan, and Y. K. Joshi, *Lancet*, 1976, **2**, 271.
[47] O. Mohabbat, R. N. Srivastava, M. S. Younos, G. G. Sediq, A. A. Merzad, and G. N. Aram, *Lancet*, 1976, **2**, 269.
[48] M. L. Deinzer, P. A. Thomson, D. M. Burgett, and D. L. Isaacson, *Science*, 1977, **195**, 497.
[49] J. O. Dickinson, M. P. Cooke, R. R. King, and P. A. Mohamed, *J. Amer. Vet. Med. Assoc.*, 1976, **169**, 1192.
[50] A. E. Johnson, *Amer. J. Vet. Res.*, 1976, **37**, 107.
[51] L. R. Shull, G. W. Buckmaster, and P. R. Cheeke, *J. Anim. Sci.*, 1976, **43**, 1247.
[52] R. C. Schumaker, K. A. Robertson, I. C. Hsu, and J. R. Allen, *J. Nat. Cancer Inst.*, 1976, **56**, 787.
[53] R. C. Schumaker, I. C. Hsu, and J. R. Allen, *J. Pathol.*, 1976, **119**, 21.
[54] J. V. Hurley and M. V. Jago, *Pathology*, 1976, **8**, 7.
[55] L. R. Shull, G. W. Buckmaster, and P. R. Cheeke, *J. Anim. Sci.*, 1976, **43**, 1024.

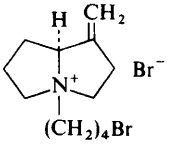
cardiopulmonary[56] and hepatic[57] lesions. The changes observed in rats after injection of seneciphylline (43)[58] and heliotrine (28)[59] have been detailed.

Toxicity has been demonstrated in analogues of pyrrolizidine alkaloids with a pyrrole or dihydropyrrole ring. The vascular changes in the lungs of rats after intravenous injection of pyrrole carbamates have been reported.[60] The distribution of radioactivity in rats given tritium-labelled synthanecine A (16) bis-*N*-ethylcarbamate and bis-hydroxymethyl-1-methylpyrrole has been studied.[61] Biliary excretion is important for the disposal of pyrrolic metabolites from retrorsine and synthanecine A bis-*N*-ethylcarbamate, but not for the parent compounds.[62]

Some pyrrolizidine alkaloids are carcinogens, and Clark[63] has included them in a review of naturally occurring mutagens. A comparative study of the chromosome damage effected by pyrrolizidine alkaloids on cultured leucocyte cells has been made.[64] Some years ago, it was demonstrated that chromosome breakage by lasiocarpine (29) on root tips of onion (*Allium*) bulbs was greatly reduced by addition of cysteine.[65] Now, dietary cysteine has been shown to increase the survival time of rats fed tansy ragwort.[66] Methionine displayed no such protective effect. However, alkaloid metabolism does not result in prolonged sulphydryl depletion.[51] The role of liver glutathione in the acute toxicity of retrorsine to rats has been investigated.[67] Liver lesions developed rapidly in rats treated simultaneously with low doses of lasiocarpine (29) and thioacetamide, which promotes cell division.[68] These compounds produced no lesions on their own, and it has been suggested that cell proliferation accentuates the development of lesions. The effects of administering a mixture of heliotrine (28), thioacetamide, and carbon tetrachloride to rats have been detailed.[69] Preliminary experiments on the effects of heliotrine (28) and nicotinamide on the concentration of plasma insulin and blood glucose in rats have been performed.[70] Rabbits tolerated large amounts of tansy ragwort in their diet, but were extremely susceptible to injected alkaloids, indicating that alkaloid absorption may be low.[71]

Quaternary pyrrolizidines [*e.g.* (76)], prepared by allowing naturally occurring alkaloids to react with dihalogeno-alkanes, possess neuromuscular blocking

[56] R. C. Schumaker, T. J. Raczniak, W. D. Johnson, and J. R. Allen, *Proc. Soc. Exp. Biol. Med.*, 1977, **154**, 57.
[57] R. C. Schumaker, J. L. Seymour, and J. R. Allen, *Res. Comm. Chem. Pathol. Pharmacol.*, 1976, **14**, 53.
[58] K. Ohtsubo, Y. Ito, M. Saito, T. Furuya, and M. Hikichi, *Experientia*, 1977, **33**, 498.
[59] N. Kh. Abdullaev, K. A. Zufarov, and Kh. Ya. Karimov, *Byull. Eksp. Biol. Med.*, 1976, **82**, 1300 (*Chem. Abs.*, 1977, **86**, 26 641).
[60] R. Plestina, H. B. Stoner, G. Jones, W. H. Butler, and A. R. Mattocks, *J. Pathol.*, 1977, **121**, 9.
[61] A. R. Mattocks and I. N. H. White, *Chem.-Biol. Interactions*, 1976, **15**, 173; I. N. H. White and A. R. Mattocks, *Chem.-Biol. Interactions*, 1976, **15**, 185.
[62] I. N. H. White, *Chem.-Biol. Interactions*, 1977, **16**, 169.
[63] A. M. Clark, *Mutation Res.*, 1976, **32**, 361.
[64] Y. A. E. Bick, C. C. J. Culvenor, and M. V. Jago, *Cytobios*, 1975, **14**, 151.
[65] S. Avanzi, *Caryologia*, 1961, **14**, 251 (*Chem. Abs.*, 1962, **56**, 13 268).
[66] G. W. Buckmaster, P. R. Cheeke, and L. R. Shull, *J. Anim. Sci.*, 1976, **43**, 464.
[67] I. N. H. White, *Chem.-Biol. Interactions*, 1976, **13**, 333.
[68] J. K. Reddy, M. S. Rao, and M. V. Jago, *Internat. J. Cancer*, 1976, **17**, 621.
[69] N. Kh. Abdullaev, Kh. Ya. Karimov, and M. K. Irgashev, *Patol. Fiziol. Eksp. Ter.*, 1976, 29 (*Chem. Abs.*, 1977, **87**, 16 772); N. Kh. Abdullaev, Kh. Ya. Karimov, G. R. Sologub, and M. K. Irgashev, *ibid.*, p. 43 (*Chem. Abs.*, 1977, **87**, 16 748).
[70] R. Schoental and K. N. Frayn, *Biochem. Soc. Trans.*, 1976, **4**, 649.
[71] M. L. Pierson, P. R. Cheeke, and E. O. Dickinson, *Res. Comm. Chem. Pathol. Pharmacol.*, 1977, **16**, 561.



(76)

activity, as demonstrated in tests with rats.[72] The syntheses and pharmacological properties of some bisquaternary salts of pyrrolizidines have been published.[73] These compounds have curare-like activity.

Sheep rumen contents are known to detoxify pyrrolizidine alkaloids. A new, obligate anaerobe, *Peptococcus heliotrinreductans*, has been identified from the rumen.[74] It is a Gram-positive coccus, and reduces 1,2-dehydropyrrolizidines, using hydrogen gas or formate as hydrogen donors.

[72] K. A. Suri, R. S. Sawhney, O. P. Gupta, and C. K. Atal, *Indian J. Pharm.*, 1976, **38**, 23; O. P. Gupta, M. M. Ali, B. J. Ghatak, and C. K. Atal, *Indian J. Exp. Biol.*, 1977, **15**, 220.

[73] N. P. Abdullaev, K. M. Shakhidoyatov, and C. S. Kadyrov, *Khim. prirod. Soedinenii*, 1976, 828 (*Chem. Abs.*, 1977, **86**, 106 446); K. M. Shakhidoyatov, N. P. Abdullaev, B. Rustamov, and C. S. Kadyrov, *Khim.-Farm. Zhur.*, 1977, **11**, 44 (*Chem. Abs.*, 1977, **87**, 68 512); K. M. Shakhidoyatov, N. P. Abdullaev, and C. S. Kadyrov, *Khim. prirod. Soedinenii*, 1977, 77 (*Chem. Abs.*, 1978, **88**, 23 214).

[74] G. W. Lanigan, *J. Gen. Microbiol.*, 1976, **94**, 1.

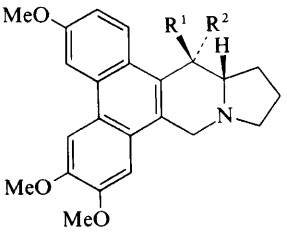
4

Indolizidine Alkaloids

BY J. A. LAMBERTON

1 Alkaloids of *Tylophora* and Related Species

Five phenanthroindolizidine alkaloids, tylophorine, tylophorinidine, pergularinine, desoxypergularinine, and an unidentified base (M^+ 409), have been isolated from roots of *Pergularia pallida*.[1] Pergularinine has a (−) rotation and it is considered to be a new diastereoisomer of (+)-*O*-methyltylophorinidine (1). It has been assigned the structure (2), and the absolute configuration is based on its conversion, by hydrogenolysis of the C-14 hydroxy-group, into (−)-desoxypergularinine, which shows a negative Cotton effect at 270 nm of the same order of magnitude as that observed in the spectrum of tylophorine.



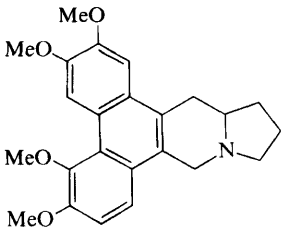
(1) $R^1 = H, R^2 = OH$
(2) $R^1 = OH, R^2 = H$

Details of the previously reported *X*-ray crystallographic study of diacetyltylophorinidine methiodide have now been published.[2]

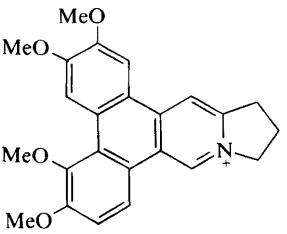
Oxidation of (−)-tylocrebrine (3) and (−)-septicine by *N*-bromosuccinimide leads to aromatization of the six-membered ring of the indolizidine system. Thus (−)-tylocrebrine (3) is converted into the iminium salt (4), which is reduced by sodium borohydride to give (±)-tylocrebrine in high yield.[3]

A full account has now appeared of the stereospecific synthesis of (13a*S*)-(+)-2,3,6-trimethoxy-9,11,12,13,13a,14-hexahydrodibenzo[*f*,*h*]pyrrolo[1,2-*b*]isoquinoline, the optical antipode of (−)-antofine, and of the corresponding 3,4,6-trimethoxy-compound.[4] In this synthesis *S*-2-(pyrrolidon-5-yl)methyl toluene-*p*-sulphonate was used as the source of the chiral centre of the phenanthroindolizidine ring system.

[1] N. B. Mulchandani and S. R. Venkatachalam, *Phytochemistry*, 1976, **15**, 1561.
[2] V. K. Wadhawan and S. K. Sikka, *Acta Cryst.*, 1976, **B32**, 3304.
[3] K. V. Rao and L. S. Kapicak, *J. Heterocyclic Chem.*, 1976, **13**, 1073.
[4] L. Faber and W. Wiegrebe, *Helv. Chim. Acta*, 1976, **59**, 2201.



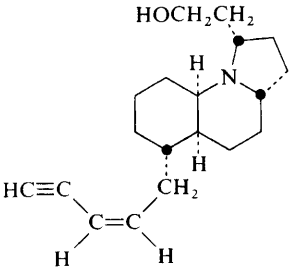
(3)



(4)

2 Gephyrotoxin

An unusual acetylenic alkaloid, gephyrotoxin, has been isolated from skin extracts of the Colombian frog *Dendrobates histrionicus*, and it has been shown to be [1*S*,3a*S*,5a*S*,6*S*(*Z*),9a*R*,10*R*]-dodecahydro-6-(pent-2-en-4-ynyl)pyrrolo[1,2-*a*]quinoline-1-ethanol (5) by *X*-ray crystal structure analysis of gephyrotoxin



(5)

hydrobromide.[5] Gephyrotoxin occurs together with members of the histrionicotoxin and pumiliotoxin C classes of dendrobatid alkaloids, and it bridges these two classes of alkaloid in having the decahydroquinoline system of pumiliotoxin C and the vinylacetylene side-chain of the histrionicotoxins. The carefully reported details of n.m.r. and mass spectral data should prove invaluable in the characterization of further dendrobatid alkaloids which, on present indications, are considered to be very numerous. Dihydrogephyrotoxin, a minor skin constituent, has a 6-(penta-2,4-dienyl) substituent. Gephyrotoxin is a muscarinic antagonist.

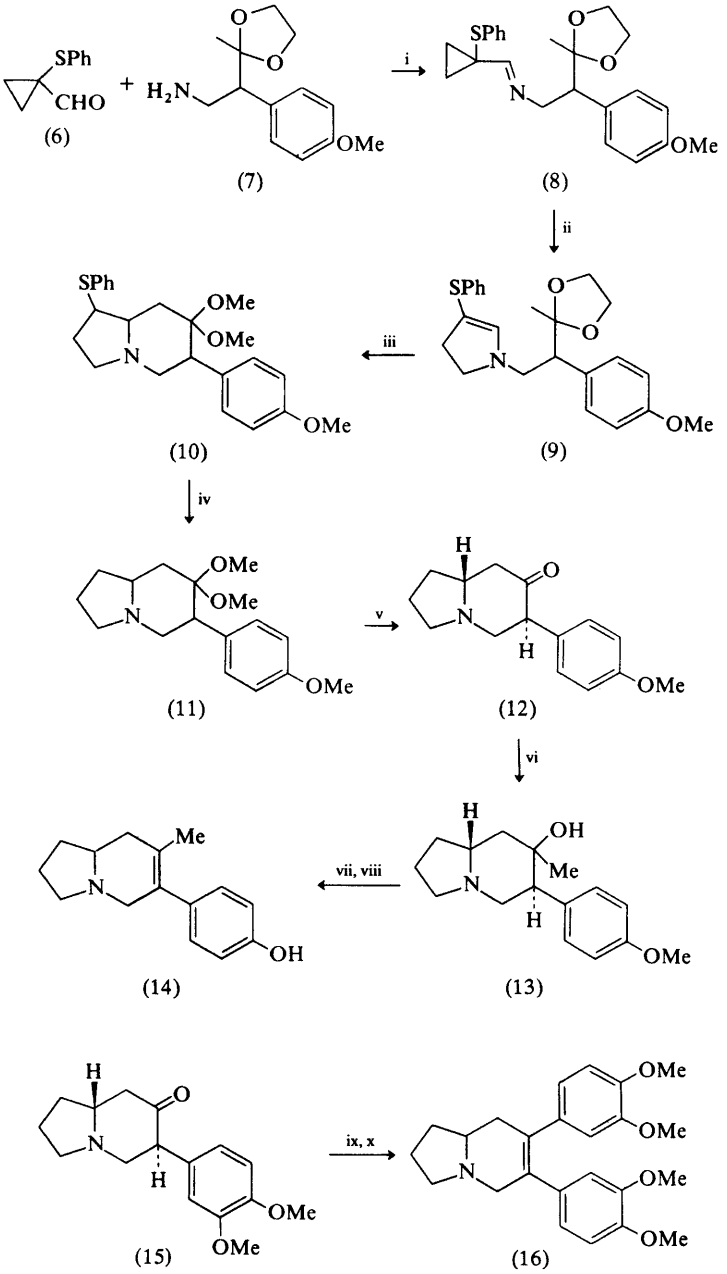
3 *Elaeocarpus* Alkaloids

The known alkaloids (±)-elaeocarpine and (±)-isoelaeocarpine have been isolated from the Indian species *Elaeocarpus ganitrus* Roxb.[6]

4 Trail Pheromone of the Pharaoh's Ant

In a review of current work on the trail pheromone of the Pharaoh's ant, *Monomorium pharaonis*, it is reported that natural monomorine III is the all-*cis*-

[5] J. W. Daley, B. Witkop, T. Tokuyama, T. Nishikawa, and I. L. Karle, *Helv. Chim. Acta*, 1977, **60**, 1128.
[6] A. K. Barua, C. Dasgupta, S. Chakravarti, M. K. Choudhury, and A. Ghosh, *J. Indian Chem. Soc.*, 1976, **53**, 531.



Reagents: i, benzene, reflux; ii, NH_4Cl–xylene, reflux; iii, HCl–MeOH–$(MeO)_3CH$; iv, H_2–Raney Ni, EtOH; v, 1N-HCl–CH_2Cl_2; vi, LiMe; vii, dehydration (H_2SO_4); viii, demethylation; ix, Li 2,4-dimethoxyphenyl; x, dehydration

Scheme

isomer of 5-butyl-3-methyloctahydroindolizidine. The ratio of monomorine III to related pyrrolidine components of the trail pheromone differs markedly in material from workers and queens.[7]

5 General Syntheses of Indolizidines

A new general method has been developed for the synthesis of pyrrolizidines and indolizidines.[8,9] This method, which has been used for the synthesis of the simple unsubstituted indolizidine δ-coniceine,[8] is best exemplified by its application to the synthesis of the more complex alkaloids (±)-ipalbidine and (±)-septicine.[9] As shown (Scheme), the key aldehyde (6) reacts with the appropriately substituted aminoacetal (7), and the resulting imine (8) then undergoes rearrangement to give the corresponding 2-pyrroline (9). Conversion into the indolizidine (10) takes place with the formation of only one of the possible stereoisomers, and after removal of the phenylthio-group to give (11), the ketone (12) is generated by hydrolysis of the acetal group. Ketone (12) is converted into the alcohol (13) and thence into (±)-*O*-methylipalbidine, which undergoes demethylation to give (±)-ipalbidine (14). The ketone (15), prepared like (12), reacts with 2,4-dimethoxyphenyl-lithium to give an alcohol that undergoes dehydration to (±)-septicine (16).

δ-Coniceine has been synthesized by another route that also has potential for the preparation of substituted indolizidines.[10]

[7] F. J. Ritter, I. E. M. Brüggemann-Rotgans, E. Verkuil, and C. J. Persoons, 'Pheromones and Defensive Secretions in Social Insects', Proceedings of the Symposium, University of Dijon, Sept. 1975 (Publ. French Section of International Union for the Study of Social Insects, University of Dijon, 1975), p. 99.

[8] R. V. Stevens, Y. Luh, and J.-T. Sheu, *Tetrahedron Letters*, 1976, 3799.

[9] R. V. Stevens and Y. Luh, *Tetrahedron Letters*, 1977, 979.

[10] M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, 1977, **42**, 909.

5

Quinolizidine Alkaloids

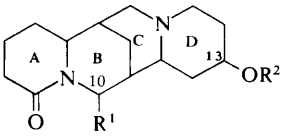
BY M. F. GRUNDON

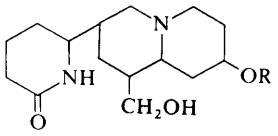
Two English language reviews have appeared this year, one on quinolizidine alkaloids from Leguminoseae species[1] and the other on Lythraceae alkaloids.[2]

1 The Lupinine–Lupanine–Sparteine–Matrine Group and the *Ormosia* Alkaloids

Occurrence.—The isolation of new alkaloids and of alkaloids of established constitution that have been obtained from fresh sources is recorded in the Table.[3—13] Of the new alkaloids, five have been isolated from *Cadia purpurea*.[5]

Lupinine Group.—Previous investigation of *Cadia purpurea* (*cf.* Vol. 7) resulted in the isolation of 13-hydroxylupanine (1) and its derivatives and cadiamine, $C_{15}H_{26}N_2O_3$, containing two hydroxy-groups. Structure (4) for the latter alkaloid has now been proposed.[5] Esters (5) and (6) have also been obtained from the same





13-Hydroxylupanine (1) $R^1 = R^2 = H$
(2) $R^1 = OH$, $R^2 = H$
(3) $R^1 = OH$, $R^2 = 2$-pyrroloyl

Cadiamine (4) $R = H$
(5) $R = 2$-pyrroloyl
(6) $R = COCH_2C_6H_4OH$

species and converted into cadiamine by acid hydrolysis. The presence of a secondary amide group in cadiamine and its esters was apparent from i.r. absorption at 1640—1650 cm^{-1} and from absorption at 3400 cm^{-1} (NH) in the silyl derivative of cadiamine. The n.m.r. spectrum of alkaloid (5) showed that the secondary

[1] E. K. Nowacki and G. R. Waller, *Rev. Latinoamer. Quim.*, 1977, **8**, 49
[2] E. Fujita and K. Fuji, in 'Alkaloids', ed. K. Wiesner, MTP International Review of Science, Organic Chemistry Series Two, Vol. 9, Butterworths, London, 1976, p. 119.
[3] Yu. K. Kushmuradov, Kh. A. Aslanov, and S. Kucharov, *Khim. prirod. Soedinenii*, 1976, 678.
[4] D. Selenge, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 559.
[5] J. L. van Eijk, M. H. Radema, and C. Versluis, *Tetrahedron Letters*, 1976, 2053.
[6] I. Murakoshi, K. Fukuchi, J. Haginiwa, S. Ohmiya, and H. Otomasu, *Phytochemistry*, 1977, **16**, 1460.
[7] B. A. Abdusalamov, O. A. Khoroshkova, and Kh. A. Aslanov, *Khim. prirod. Soedinenii*, 1976, 71.
[8] U. Szmid, *Ann. Acad. Med. Gedanensis*, 1976, **6**, 135 (*Chem. Abs.*, 1977, **86**, 103 051).
[9] J. N. Anderson and R. O. Martin, *J. Org. Chem.*, 1976, **41**, 3441.
[10] V. Batra and T. R. Rajagopalan, *Indian J. Chem.*, 1976, **14B**, 636.
[11] T. Nakano, B. C. De Azcunes, and S. A. Castaldi, *Planta Med.*, 1976, **29**, 241.
[12] P. T. Cheng, S. McLean, R. Misra, and S. C. Nyburg, *Tetrahedron Letters*, 1976, 4245.
[13] G. Faugeras, R. R. Paris, M. N. Alexis, and J. F. Dobremez, *Plant. Med. Phytother.*, 1976, **10**, 85.

Species	*Alkaloid* (*Structure*)	*Ref.*
Ammodendron eichwaldi	Anagyrine	3
	Cytisine	
	Methylcytisine	
	Sparteine	
Ammopiptanthas mongolicus	Lupanine	4
	α-Isosparteine	
	Piptamine (ormosanine)	
	Piptanthine	
	Sparteine	
Cadia purpurea	*Cadiamine (4)	5
	*Cadiamine ester (5)	
	*Cadiamine ester (6)	
	*10,13-Dihydroxylupanine (2)	
	*10,13-Dihydroxylupanine ester (3)	
Echinosophora koreensis	*N-(3-Oxobutyl)cytisine (14)	6
Goebelia pachycarpa	*Sophorbenzamine (17)	7
Laburnum anagyroides	Anagyrine	8
	Cytisine	
	Methylcytisine	
Lupinus hartwegii	Aphylline	9
	10,17-Dioxosparteine	
	Epiaphylline	
	α-Isolupanine	
	Nuttaline	
	4-Oxosparteine	
	Virgiline	
L. hirsutus	Epilupinine	10
	Epilupinine *N*-oxide	
L. verbasciformis	Lindenianine	11
	Virgiline	
Podopetalum ormondii	*Alkaloid (18)	12
Sophora moorcroftiana	α-Matrine	13
	Oxymatrine	
	Sophocarpine	

* New alkaloids

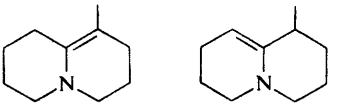
hydroxy-group was esterified, and a fragment ion at $M-C_5H_8NO$ in the mass spectrum indicated that the alkaloid contained a pyridone substituent. Cadiamine can be regarded as a cleavage product of 13-hydroxylupanine, related to pohakuline obtained recently from *Sophora chrysophylla* (*cf.* Vol. 7). Two other new alkaloids of *C. purpurea* are considered to be a 10,13-dihydroxylupanine (2) and its 2-pyrroloyl ester (3) on the basis of spectroscopic data.[5] The mass spectra compared with that of 13-hydroxylupanine suggested that the two compounds possess an additional hydroxy-group in either ring A or ring B; this group was assigned to C-10, since i.r. absorption at 1595 cm^{-1} indicated intramolecular hydrogen-bonding to the amide carbonyl group.

New esters of lupinine have been prepared[14] and the mass spectra of lupinine alkyl and aryl esters have been studied.[15] Pyrolysis of lupinine methiodide yields

[14] A. A. Abduvakhabov, D. N. Dalimov, and Kh. A. Aslanov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1976, 632.

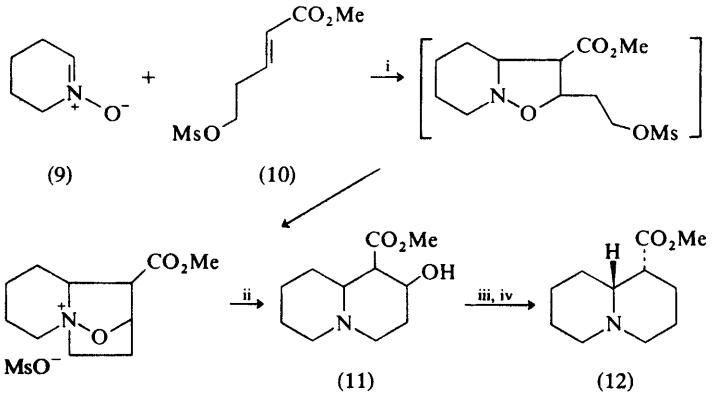
[15] E. Kh. Timbekov, F. Sh. Eshbaev, A. K. Kasimov, and Kh. A. Aslanov, *Uzbek. khim. Zhur.*, 1976, 45 (*Chem. Abs.*, 1976, **85**, 177 725).

lupinine, lupinine methyl ether, and the ether methiodide.[16] A mixture of olefins (7) and (8) is obtained from lupinine in an acid-catalysed elimination reaction.[17]



(7) (8)

Tufariello and Tegeler[18] have described a high-yield synthesis of the quinolizidine (11) by cycloaddition of nitrone (9) and the $\alpha\beta$-unsaturated ester (10) and then reduction (Scheme 1). The ester (10) was prepared conveniently from but-3-en-1-ol by ozonolysis of the tetrahydropyranyl ether followed by a Wittig reaction on the resultant aldehyde. The quinolizidine (11) was converted into lupinine (12) by a conventional procedure.

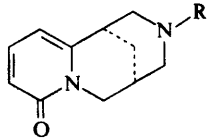


(9) (10) (11) (12)

Reagents: i, PhMe, 0—5 °C; ii, Zn–AcOH; iii, $POCl_3$–pyridine; iv, H_2–Pt

Scheme 1

Lupanine–Sparteine Group.—A new alkaloid isolated from *Echinosophora koreensis* was shown to be *N*-(3-oxobutyl)cytisine (14) by means of spectroscopic studies and by its synthesis from the reaction of cytisine (13) and methyl vinyl



Cytisine (13) R = H
(14) R = CH_2CH_2COMe

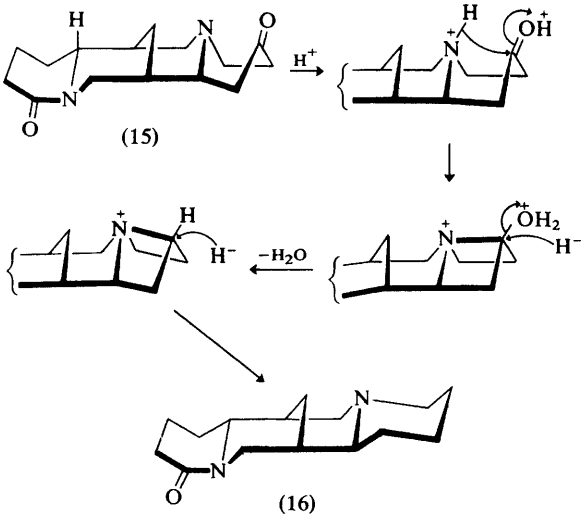
[16] A. I. Begisheva, L. K. Ni, and O. S. Otroshchenko, *Uzbek. khim. Zhur.*, 1976, 52 (*Chem. Abs.*, 1976, **86**, 106 848).

[17] A. I. Begisheva, K. Inoyatova, A. A. Abduvakhabov, Kh. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1976, 495 (*Chem. Abs.*, 1977, **86**, 29 971).

[18] J. J. Tufariello and J. J. Tegeler, *Tetrahedron Letters*, 1976, 4037.

ketone in benzene solution at 60 °C.[6] A series of cytisine derivatives has been prepared.[19]

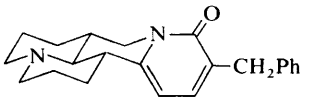
An earlier study of the reduction of 13-oxolupanine (15) indicated that the epimeric 13-hydroxylupanines were formed stereoselectively,[20] but a re-examination of the reactions, using a chromatographic method[21] for the separation of the products, has now produced more precise data.[22] Thus, catalytic hydrogenation with platinum in acetic acid gave the equatorial and axial alcohols in the approximate ratio of 20:75, whereas with sodium borohydride the ratio was 3 : 1. Catalytic reduction of 13-oxolupanine in the presence of hydrochloric acid was also studied. At low molar ratios of HCl:(15), the axial alcohol was the predominant product, but as the ratio increased less axial alcohol was formed, and the hydrogenolysis product, lupanine (16), was also obtained; ratios >2.6:1 gave lupanine only. It was suggested that the presence of unprotonated nitrogen at low acid:base ratios results in adsorption on the catalyst surface, thus favouring addition of hydrogen from the equatorial side of the carbonyl group to give the axial alcohol. The formation of lupanine at high acid:base ratio is thought to occur by intramolecular interaction between the nitrogen atom and the carbonyl group (Scheme 2).



Scheme 2

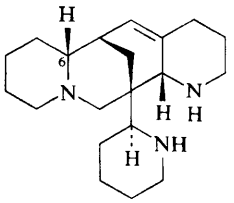
Matrine Group.—A new member of this group, sophorbenzamine, has been isolated from *Goebelia pachycarpa* and shown to be the benzyl derivative (17) on the basis of spectroscopic studies.[7] *Sophora moorcroftiana* contains the known alkaloids α-matrine, oxymatrine, and sophocarpine.[13]

[19] A. B. Mirzaabdullaev, Kh. A. Aslanov, and Yu. K. Kushmuradov, *Uzbek. khim. Zhur.*, 1976, 59 (*Chem. Ab.*, 1976, **85**, 177 730).
[20] W. Wysocka and M. Wiewiorowski, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1974, **22**, 831.
[21] W. Wysocka, *J. Chromatog.*, 1976, **116**, 235.
[22] W. Wysocka, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1976, **24**, 275.



(17)

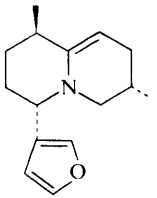
***Ormosia* Group.**—An alkaloid obtained from *Podopetalum ormondii* was shown to have structure (18) by *X*-ray analysis and is thus epimeric with podopetaline at C-6;[12] the same structure was assigned to amazonine, isolated from *Ormosia amazonia*, but it has not yet been possible to establish the identity of the two alkaloids.



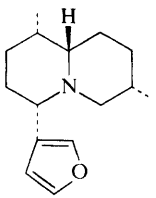
(18)

2 Sesquiterpenoid Alkaloids

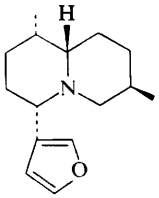
A new unstable base, (+)-nupharopumiline, has been isolated from *Nuphar pumila* and assigned structure (19).[23] Catalytic reduction gave (−)-desoxynupharidine (26), and the position of the double bond was indicated by spectroscopic studies. In the n.m.r. spectrum, for example, resonances at τ5.52 (1H), at 8.97 (3H, d), and at 9.07 (3H, d) indicated the presence of one olefinic proton and two $\geq$CHMe groups.



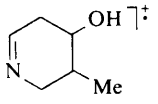
Nupharopumiline (19)



7-Epidesoxynupharidine (20)



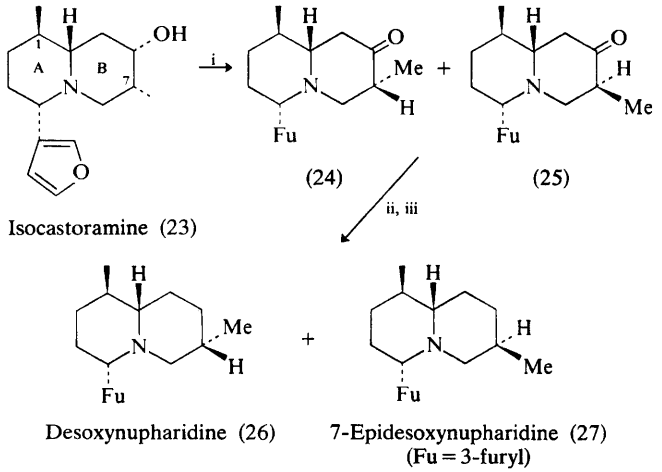
1-Epi-7-epidesoxynupharidine (21)



(22)

[23] P. Peura and M. Lounasmaa, *Phytochemistry*, 1977, **16**, 1122.

The scent gland of the Canadian beaver (*Castor fiber*) was shown previously to contain (−)-castoramine (28). Maurer and Ohloff[24] have now isolated six more sesquiterpenoid quinolizidines in addition to the octahydroindolizine already reported (Vol. 7). Four of the constituents are stereoisomers, (−)-desoxynupharidine (26) and (−)-7-epidesoxynupharidine (27), found in *Nuphar* species, and (−)-1-epidesoxynupharidine (20) and (−)-1-epi-7-epidesoxynupharidine (21), which have been hitherto unknown as natural products. The major alkaloid is (−)-isocastoramine (23), an isomer of castoramine. The i.r. spectrum of the new alkaloid showed absorption at 3640 cm^{-1} (OH) and the presence of Bohlmann bands characteristic of a *trans*-quinolizidine. In the mass spectrum, the fragment ion at *m/e* 114 (22) arises by cleavage of the ring system as observed in *Nuphar* alkaloids and indicates that the hydroxy-group of isocastoramine is in ring B. The positions and configurations of the hydroxy- and methyl groups were apparent from the n.m.r. spectrum. The absolute configuration of isocastoramine was determined by correlation with (−)-desoxynupharidine (26) (Scheme 3). Oxidation gave a



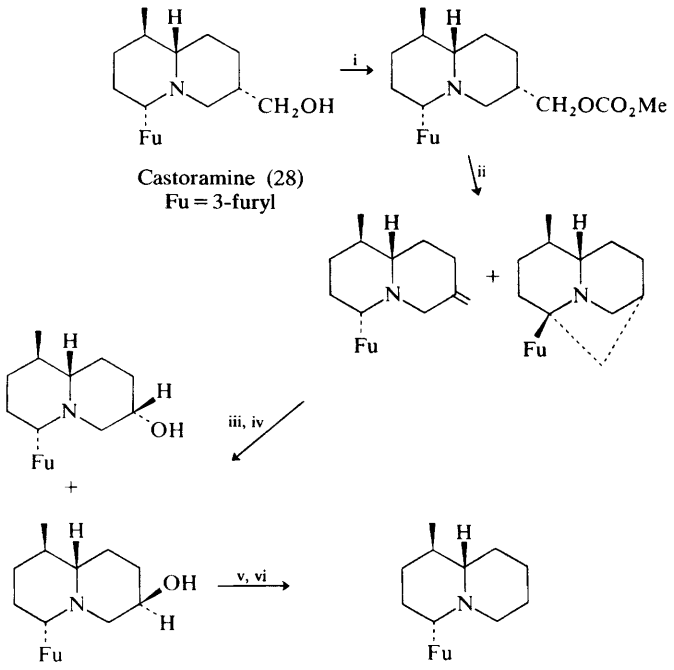
Reagents: i, Ag_2CO_3–Celite–PhMe, reflux; ii, NaOEt; iii, H_2NNH_2–$HO(CH_2)_2OH$–KOH, reflux

Scheme 3

mixture of ketones (24) and (25), shown by equilibration with base to contain the less stable compounds (24) (axial methyl at C-7) as major component. Wolff–Kishner reduction of the equilibrium mixture gave the mixture (26) and (27) (1 : 2), of known configuration. Another constituent of the scent gland (−)-7-demethyldesoxynupharidine (29), apparently is the first C_{14} alkaloid of this type; its structure was established by i.r., n.m.r., and mass spectroscopy and by its synthesis from (−)-castoramine (28) (Scheme 4).

Yasuda, Hanaoka, and Arata[25] have described a new synthesis of (±)-7-epidesoxynupharidine (27) and 1-epi-7-epidesoxynupharidine (21) (Scheme 5). The

[24] B. Maurer and G. Ohloff, *Helv. Chim. Acta*, 1976, **59**, 1169.
[25] S. Yasuda, M. Hanaoka, and Y. Arata, *Heterocycles*, 1977, **6**, 391.

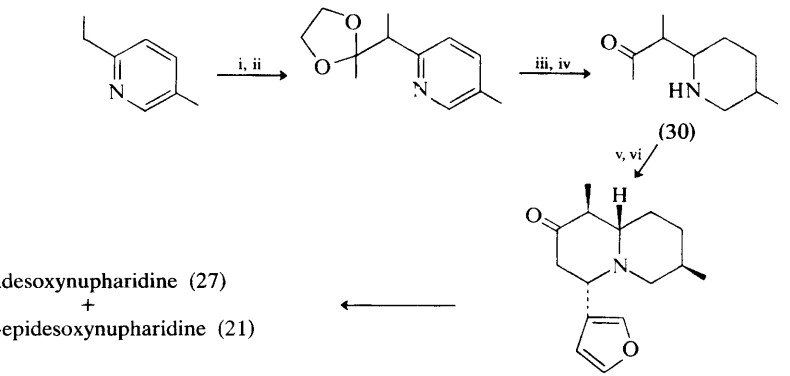


Castoramine (28)
Fu = 3-furyl

7-Demethyldesoxynupharidine (29)

Reagents: i, $ClCO_2Me$–pyridine; ii, 500 °C; iii, OsO_4–$NaIO_4$; iv, $LiAlH_4$; v, $POCl_3$–pyridine; vi, H_2–Pd/C, KOH

Scheme 4



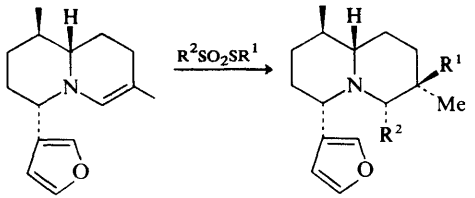
7-Epidesoxynupharidine (27)
+
1-Epi-7-epidesoxynupharidine (21)

Reagents: i, MeCN–PhLi, then H_3O^+; ii, $HOCH_2CH_2OH$; iii, Rh–Al_2O_3–AcOH; iv, aq. H_3O^+; v, 3-$HOCC_4H_3O$; vi, NaOH–MeOH

Scheme 5

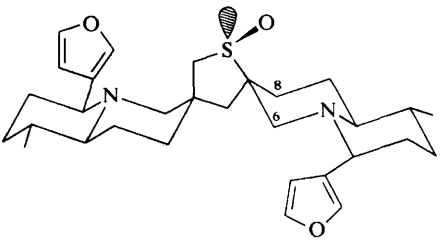
Mannich reaction of the piperidine derivative (30) with 3-formylfuran gave a mixture of the four stereoisomeric quinolizidin-2-ones, *cf.* (31). The major product [as (31), but with a β-furyl group] was isomerized with base to the most stable *trans*-quinolizidinone (31), which on Wolff–Kishner reduction afforded a mixture of alkaloids (27) and (21).

Addition of thiosulphonates to dehydrodesoxynupharidine (32) gives nupharidines (33) showing fungicidal activity.[26]

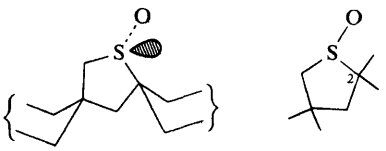


(32) (33)

A neothiobinupharidine sulphoxide, m.pt. 240—242 °C, was isolated some years ago, but the configuration of the sulphoxide group was unknown. The reaction of neothiobinupharidine with hydrogen peroxide gave the natural sulphoxide together with a non-crystalline stereoisomer (10% yield); the latter has now been obtained from neothiobinupharidine in 30% yield by using periodate in aqueous methanol.[27] LaLonde, MacLean, Wrobel, and their co-workers[27] have assigned configurations (34) and (35) to the solid and liquid sulphoxides, respectively, by ^{13}C n.m.r. spectroscopy. Conversion of 2,2,4,4-tetramethylthiolan into its sulphoxide (36) results in deshielding of both methyl groups at C-2 but to differing extents. The sign and magnitude of increments for C-6 and C-8 in neothiobinupharidine on



(34)



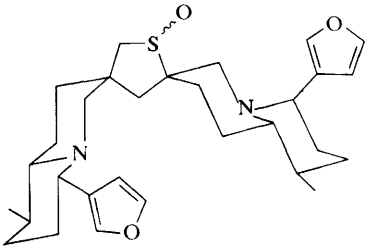
(35) (36)

[26] R. T. LaLonde, A. I.-M. Tsai, C. J. Wang, and C. Wong, Ger. Offen 2 603 140 (*Chem. Abs.*, 1976, **85**, 177 750).

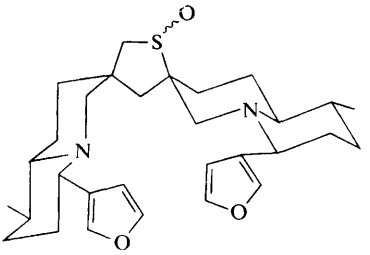
[27] R. T. LaLonde, C. F. Wong, A. I.-M. Tsai, J. T. Wrobel, J. Ruszkowska, K. Kabzinska, T. I. Martin, and D. B. MacLean, *Canad. J. Chem.*, 1976, **54**, 3860.

sulphoxidation, compared with the model thiolan and with penicillin derivatives, indicated a β-configuration for the crystalline sulphoxide (34).

The Polish group[28] have also isolated three new sulphoxides from *Nuphar luteum*. One alkaloid was a thiobinupharidine sulphoxide (37) and was converted into the parent base by reaction with phosphorus trichloride. The other sulphoxides (38), of which only one was isolated in the pure state, were epimeric; reduction



(37)



(38)

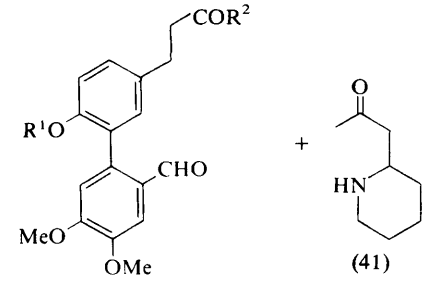
of each with phosphorus trichloride gave thionuphlutine B, and oxidation of the latter compound gave a mixture of the sulphoxide epimers.

3 Lythraceae Alkaloids

The continuing interest in the synthesis of macrocylic alkaloids has been directed this year to the preparation of the *cis*-quinolizidine group. It is apparent from the work of Hanaoka *et al.*[29] that alkaline conditions for the Mannich condensation of isopelletierine (41) with aryl aldehydes, *cf.* (39), favour the formation of *cis*-quinolizidinones. The synthesis of the biphenyl ether alkaloid vertaline (48) was carried out in this way (Vol. 5), and has now been described in full.[30]

cis-Quinolizidine alkaloids of the biphenyl type have also been synthesized (Scheme 6).[31,32] Alkaline condensation of compounds (39) and (41) gave the *cis*-quinolizidinone (43) with less than 10% of its *trans*-isomer. Catalytic reduction in the presence of base then furnished the alcohol (45), which was converted into the alkaloid decamine (46); the methyl ether (47) was obtained similarly. The cinnamoyl derivative (44), formed by acid cleavage of the *cis*-quinolizidinone (43), was cyclized to the *trans*-quinolizidinone (42) in high yield, thus leading to an improved synthesis of decinine, the *trans*-quinolizidine isomer of decamine.[31] The Japanese synthesis of methyldecamine (47) involved conversion of the amide (40) into a *cis*-quinolizidinone, *cf.* (43), which on reduction with borohydride followed by acetylation furnished a mixture of isomeric acetates. Methyldecamine was obtained from the axial acetate, *cf.* (45).[32]

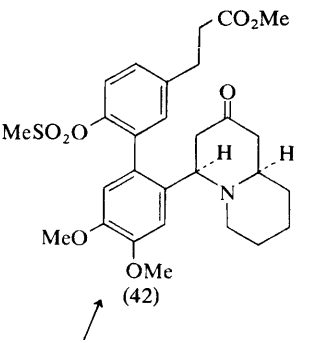
[28] J. Wrobel, A. Iwanow, and K. Wojtasiewicz, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1976, **24**, 99.
[29] M. Hanaoka, N. Ogawa, K. Shimizu, and Y. Arata, *Chem. and Pharm. Bull (Japan)*, 1975, **23**, 1573.
[30] M. Hanaoka, N. Ogawa, and Y. Arata, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 1045.
[31] I. Lantos, C. Razgaitis, H. Van Hoeven, and B. Loev, *J. Org. Chem.*, 1977, **42**, 228.
[32] M. Hanaoka, K. Tanaka, and Y. Arata, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 2272



(39) $R^1 = SO_2Me$, $R^2 = OMe$
(40) $R^1 = Me$, $R^2 = NMe_2$

(41)

(39)+(41), i



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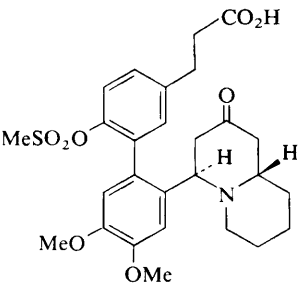

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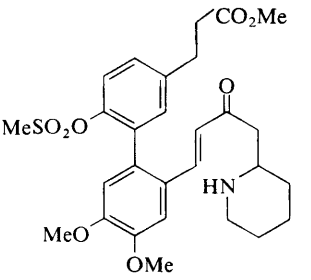
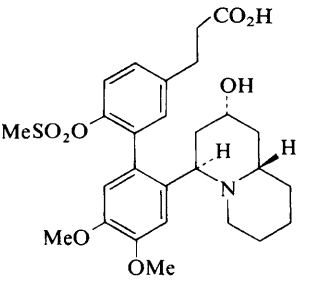


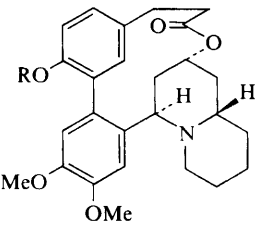
(44)

ii



(45)

iii, iv

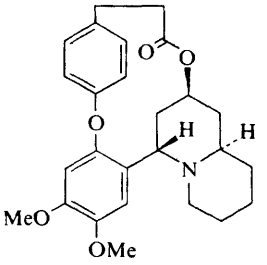


Decamine (46) R = H
Methyldecamine (47) R = Me

Reagents: i, 3 equiv. NaOH, 30% aq. EtOH, 20 °C; ii, H_2–Pt–N-NaOH; iii, TsOH, high dilution; iv, NaOH–aq. MeOH

Scheme 6

The formation of quinolizidinones from pelletierine and benzaldehyde has been studied, and a mechanism involving intramolecular Michael addition, *cf.* (44) → (42), was proposed.[33]



Vertaline (48)

[33] J. Quick and R. Oterson, *Tetrahedron Letters*, 1977, 603.

6

Quinoline, Quinazoline, and Acridone Alkaloids

BY M. F. GRUNDON

Only six new alkaloids of these groups have been obtained this year, but there has been considerable emphasis on synthesis within all three groups. A useful review of the synthesis of quinoline alkaloids has been published.[1]

1 Quinoline Alkaloids

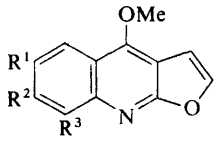
Isolation and Spectroscopic Studies.—The Table (p. 79) records the isolation of new alkaloids and of alkaloids of established constitution obtained from new sources.[2—16] The further investigation of *Haplophyllum perforatum* raises to nineteen the number of quinoline alkaloids found in this species. Another feature of isolation studies this year is the examination of four species of *Myrtopsis*.

From a study of the i.r. spectra of a series of furoquinoline alkaloids containing 4-methoxy-groups, it was concluded that the intensity of ring skeletal vibrations varies with the position of other methoxy-groups and with the nature of the substituents at C-7.[17] The conformational mobility of the dihydropyran ring of

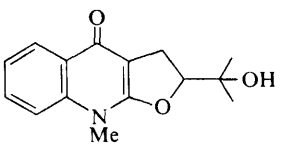
[1] L. A. Mitscher, T. Suzuki, and G. Clark, *Heterocycles*, 1976, **5**, 565.
[2] F. Fish, I. A. Meshal, and P. G. Waterman, *Planta Med.*, 1976, **29**, 310 (*Chem. Abs.*, 1976, **85**, 119 599).
[3] R. Garestier and M. Rideau, *C.R. Congr. Natl. Soc. Savantes, Sect. Sci.*, 1973, **98**, 183 (*Chem. Abs.*, 1976, **85**, 156 534).
[4] E. G. Sharova, S. Yu. Aripova, and A. U. Abdibalimov, *Khim. prirod. Soedinenii*, 1977, 127 (*Chem. Abs.*, 1977, **87**, 50 201).
[5] D. M. Razakova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 682 (*Chem. Abs.*, 1977, **86**, 136 315).
[6] V. I. Akhmedzhanova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 320 (*Chem. Abs.*, 1977, **86**, 43 861).
[7] V. I. Akhmedzhanova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 289 (*Chem. Abs.*, 1977, **87**, 98 863).
[8] M. S. Hifnawy, J. Vaquette, T. Sévenet, J.-L. Pousset, and A. Cavé, *Phytochemistry*, 1977, **16**, 1035.
[9] M. S. Hifnawy, J. Vaquette, T. Sévenet, J.-L. Pousset, and A. Cavé, *Planta Med.*, 1976, **29**, 346.
[10] A. G. Kozlovski, M. U. Arinbasarov, G. I. Yakovlev, A. M. Zyakau, and V. M. Adanin, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1976, 1146 (*Chem. Abs.*, 1977, **86**, 29 964).
[11] X. A. Dominguez, D. Butruille, A. Rudy, and G. S. Sergio, *Rev. Latinoamer. Quim.*, 1977, **8**, 47 (*Chem. Abs.*, 1977, **86**, 117 636).
[12] F. Fish, I. A. Meshal, and P. G. Waterman, *J. Pharm. Pharmacol.*, 1976, **28**, Suppl., p. 72P.
[13] P. T. O. Chang, G. A. Cordell, G. H. Aynilian, H. H. S. Fong, and N. R. Farnsworth, *Lloydia*, 1976, **39**, 134 (*Chem. Abs.*, 1976, **85**, 74 955).
[14] T. Etherington, R. B. Herbert, and F. B. Jackson, *Phytochemistry*, 1977, **16**, 1125.
[15] V. H. Deshpande and R. K. Shastri, *Indian J. Chem.* 1977, **15B**, 95.
[16] H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *Yakugaku Zasshi*, 1976, **96**, 1458 (*Chem. Abs.*, 1977, **86**, 136 297).
[17] E. L. Kristallovich, M. R. Yagudaev, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 233.

(+)-ribalinine (folifine) (3) has been investigated by variable-temperature n.m.r. spectroscopy.[18]

The mass spectra of a number of dihydrofuro- and dihydropyrano-4-quinolones had previously been determined,[19] but now a survey of sixteen alkaloids of this type has been published.[20] Abundant molecular ions are formed from each alkaloid.



(1)



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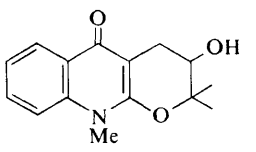

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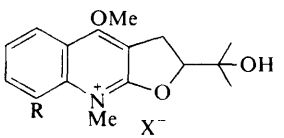

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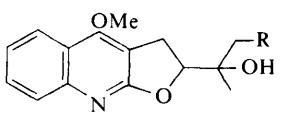

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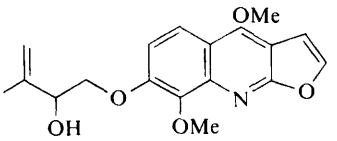

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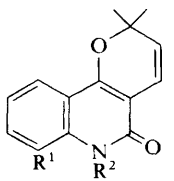

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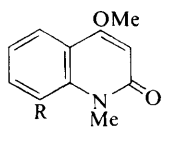

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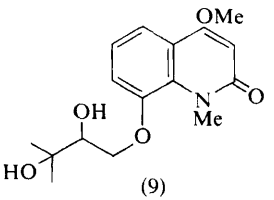

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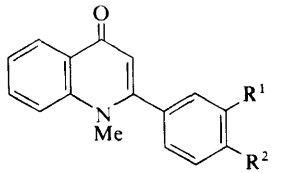

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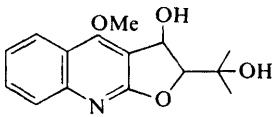
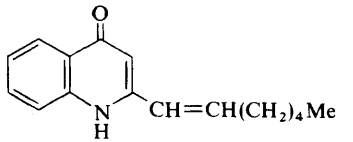


Myrtopsine (11)



(12)

[18] M. R. Yagudaev and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 673.

[19] R. A. Corral and O. O. Orazi, *Tetrahedron*, 1965, **21**, 909; S. K. Talapatra, B. C. Maiti, and B. Talapatra, *Tetrahedron Letters*, 1969, 4789; J. Reisch, K. Szendrei, V. Papay, I. Novak, and E. Minker, *ibid.*, 1970, 3365; Ya. V. Rashkes, Z. S. Faizutdinova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, 107.

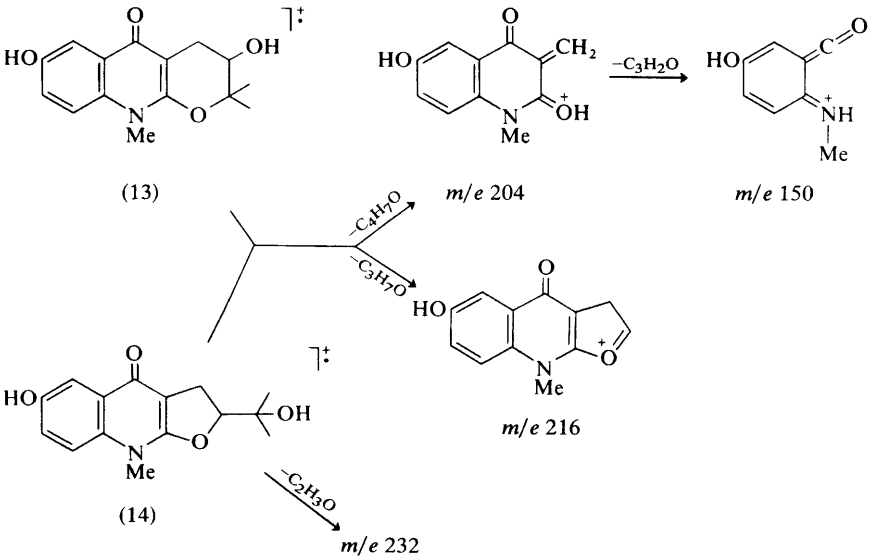
[20] S. Hammerum, A. M. Duffield, R. A. Corral, and O. O. Orazi, *Acta Chem. Scand.* (*B*), 1977, **31**, 31.

Table *Isolation of quinoline alkaloids*

Species	*Alkaloid* (*Structure*)	*Ref.*
Araliopsis tabouensis	Halfordinine (1; $R^1 = R^2 = R^3 = OMe$) (+)-Isoplatydesmine (2) (+)-Ribalinine (3) Skimmianine (1; $R^1 = H$, $R^2 = R^3 = OMe$)	2
Choisya ternata	*N*-Methylplatydesminium salt (4; R = H)	3
Datura stramonium	Skimmianine	4
Haplophyllum perforatum	Dictamnine (1; $R^1 = R^2 = R^3 = H$) Dubinidine (5; R = OH)	5
	Evodine (6)	7
	Flindersine (7; $R^1 = R^2 = H$)	6
	Folimine (8; R = OMe) Foliosidine (9) Graveoline (10; $R^1R^2 = OCH_2O$) *N*-Methyl-2-phenyl-4-quinolone (10; $R^1 = R^2 = H$) Platydesmine (5; R = H)	5
Myrtopsis macrocarpa	Dictamnine *8-Methoxyflindersine (7; $R^1 = OMe$, $R^2 = H$) Skimmianine	8
M. myrtoidea	Dictamnine γ-Fagarine (1; $R^1 = R^2 = H$, $R^3 = OMe$) Skimmianine	8
M. novae-caledoniae	Dictamnine γ-Fagarine *N*-Methylflindersine (7; $R^1 = H$, $R^2 = Me$)	8
	Confusameline (1; $R^1 = R^3 = H$, $R^2 = OH$)	9
M. sellingii	Dictamnine γ-Fagarine 4-Methoxy-1-methyl-2-quinolone (8; R = H) *(−)-Myrtopsine (11) Skimmianine	9
Pseudomonas aeruginosa	*2-(Hept-1-enyl)-4-quinolone (12)	10
Sargentia gregii	Maculine (1; $R^1R^2 = OCH_2O$, $R^3 = H$) Kokusaginine (1; $R^1 = R^2 = OMe$, $R^3 = H$)	11
Teclea verdoorniana	Halfordinine Skimmianine	12
Thamnosma montana	Robustine (1; $R^1 = R^2 = H$, $R^3 = OH$)	13
Tylophora asthmatica	γ-Fagarine Skimmianine	14
Zanthoxylum alatum	Dictamnine γ-Fagarine Robustine	15
Z. cuspidatum Champ.	Dictamnine γ-Fagarine Haplopine (1; $R^1 = H$, $R^2 = OH$, $R^3 = OMe$) 4-Methoxy-1-methyl-2-quinolone Robustine Skimmianine	16
Z. oxyphyllum	γ-Fagarine	15

* New Alkaloids.

The mass spectra of dihydrofuro-4-quinolones not containing a hydroxy-group in the acyclic portion closely resemble those of the dihydropyrano-isomers. When a hydroxy-group is present, for example in ribaline (14) and in ribalinidine (13), the fragmentation patterns are surprisingly similar (Scheme 1), and both compounds show abundant ion peaks at *m/e* 204 and 150. The peak at *m/e* 216 that is formed by loss of a C_3H_7O fragment from the molecular ion is present in the spectra of pyrano- and furo-isomers, but is four times as abundant in those of the latter. A characteristic feature of the hydroxyisopropyldihydrofuro-4-quinolones is the presence of an abundant $[M-C_2H_3O]^+$ fragment.

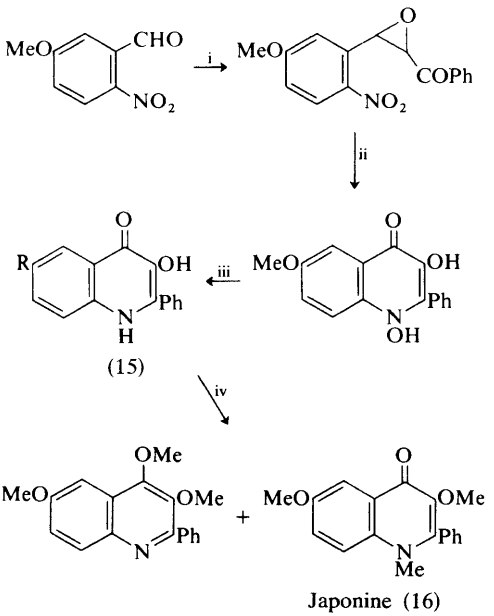


Scheme 1

Non-hemiterpenoid Quinolines.—New sources of the simple quinolines 4-methoxy-1-methyl-2-quinolone and its 8-methoxy-derivative (folimine) have been reported; the former was isolated from *Myrtopsis sellingii*[9] and from *Zanthoxylum cuspidatum*,[16] and folimine was shown to be a constituent of *Haplophyllum perforatum*.[5] The latter species also contains foliosidine (9), previously isolated from *H. foliosum*. The micro-organism *Pseudomonas aeruginosa* has been shown to contain 2-(hept-1-enyl)-4-quinolone (12).[10] The structure of the alkaloid was established by n.m.r. and mass spectroscopy and by its synthesis from aniline and the β-keto-ester $Me(CH_2)_4CH{=}CHCOCH_2CO_2Me$.

Japonine (16), the 3-methoxy-4-quinolone of *Orixa japonica* (see Vol. 2), has beeen synthesized[21] (Scheme 2). The key compound (15; R = OMe) was prepared in good yield by the method used to make the analogous 3-hydroxy-4-quinolone (15; R = H); methylation with methyl iodide and potassium hydroxide in DMF then afforded japonine as the major product.

[21] P. Venturella, A. Bellino, E. Piozzi, and M. L. Marino, *Heterocycles*, 1976, **4**, 1089.



Japonine (16)

Reagents: i, $PhCOCH_2Br$–NaOMe, 12 °C; ii, HCl–hydroquinone–THF; iii, dithionite; iv, MeI–KOH–DMF, 60 °C

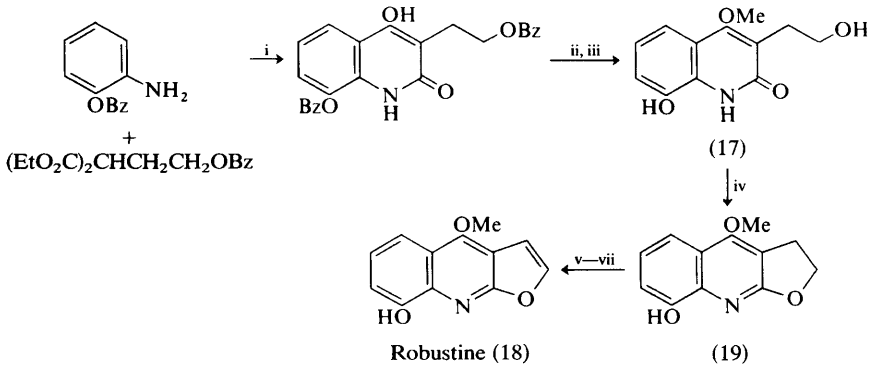
Scheme 2

Furoquinoline Alkaloids.—Well-known furoquinoline alkaloids have been identified for the first time in twelve species of the Rutaceae (see the Table [2,5,8,9,11—13,15,16] on p. 79), and the rare trimethoxydictamnine halfordinine (1; $R^1 = R^2 = R^3 = OMe$) has been obtained from *Araliopsis tabouensis*[2] and from *Teclea verdoorniana*.[12] The isolation of γ-fagarine and skimmianine from *Tylophora asthmatica* (Asclepiadaceae)[14] and skimmianine from *Datura stramonium* (Solanaceae)[4] is of considerable taxonomic interest.

The three phenolic furoquinoline alkaloids robustine (18), haplopine (1; $R^1 = H$, $R^2 = OH$, $R^3 = OMe$), and confusameline (1; $R^1 = R^3 = H$, $R^2 = OH$), which were synthesized some time ago (see Vols. 3 and 5), have now been prepared by a modification of the Grundon–McCorkindale method, as illustrated for robustine (Scheme 3).[22] Polyphosphate ester was found to be more effective than polyphosphoric acid for cyclization of the alcohol (17) to the dihydrofuran (19). Dehydrogenation to a furoquinoline was accomplished by reaction of the benzyl ether of dihydrofuran (19) with DDQ.

3-Prenylquinoline Alkaloids and Related Compounds.—8-Methoxyflindersine (7; $R^1 = OMe$, $R^2 = H$), isolated from *Myrtopsis macrocarpa*,[8] has not been obtained hitherto from natural sources, although it was synthesized some years ago. *N*-Methylflindersine is a constituent of *M. novae-caledoniae*,[8], but its m.pt. (185 °C)

[22] T. Sekiba, *J. Sci. Hiroshima Univ., Ser. A, Phys. Chem.*, 1976, **40**, 143.



Reagents: i, 180 °C at 70 mmHg, then 250 °C; ii, CH_2N_2; iii, H_2–Pd; iv, polyphosphate ester, 120—130 °C; v, $PhCH_2Cl$–NaOEt, reflux in EtOH; vi, DDQ, reflux in PhOMe; vii, HCl–EtOH, reflux

Scheme 3

differs profoundly from that reported (88—85 °C) for the compound obtained from two other species[23] and by methylation of flindersine.[24]

Platydesmine (5; R = H), the biosynthetic precursor of dictamnine and other furoquinoline alkaloids, has been detected for the first time in a *Haplophyllum* species (*H. perforatum*).[5] *Choisya ternata* is known to contain *O*-methylbalfourodinium salt (4; R = OMe), but now *N*-methylplatydesminium salt (4; R = H) has been isolated in equal amount to (4; R = OMe) from the stalks and roots; (4; R = OMe) is the predominant quaternary alkaloid of the leaves.[3]

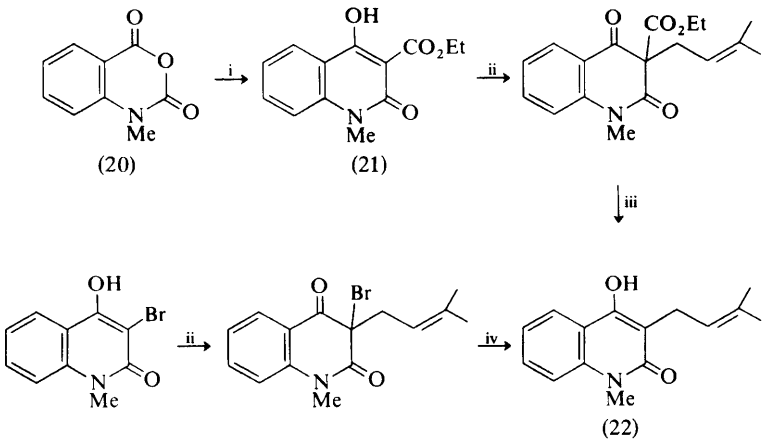
The most interesting new quinoline alkaloid of the year is undoubtedly the hydroxy-platydesmine (11) isolated from *Myrtopsis sellingii* and named myrtopsine.[9] The alkaloid is optically active, and the structure was proposed on the basis of spectroscopic studies and of the formation of a monoacetate and, under more vigorous conditions, a diacetate. In the n.m.r. spectrum of myrtopsine, a resonance centred at 4.26τ appears at *ca.* 3.0τ in the spectrum of the monoacetate, as expected for a compound containing a secondary hydroxy-group. Biosynthetic studies indicated that compound (11) is a possible intermediate in the conversion of platydesmine into dictamnine,[25] and the isolation of myrtopsine from *M. sellingii* in association with the furoquinoline alkaloids dictamnine, γ-fagarine, and skimmianine lends support to this proposal.

The major alkaloid of *Araliopsis tabouensis* is (+)-*N*-methylplatydesminium salt (see Vol. 6), and a study of the minor constituents has now resulted in the isolation of (+)-isoplatydesmine (2) and the pyranoquinolone (+)-ribalinine (folifine) (3).[2]

4-Hydroxy-1-methyl-3-prenyl-2-quinolones, *cf.* (22), are key intermediates in the synthesis of quinoline alkaloids, and usually are prepared in one stage from an *N*-methyl-aniline and diethyl prenylmalonate. Interesting new methods beginning with *N*-methylisatoic anhydrides, *cf.* (20), have been explored and briefly repor-

[23] C. D. Adams, D. R. Taylor, and J. M. Warner, *Phytochemistry*, 1973, **12**, 1359; J. Reisch, J. Körösi, K. Szendrei, I. Novák, and E. Minker, *ibid.*, 1975, **14**, 1678.
[24] R. F. C. Brown, J. J. Hobbs, G. K. Hughes, and E. Ritchie, *Austral. J. Chem.*, 1954, **7**, 348.
[25] M. F. Grundon, D. M. Harrison, and C. G. Spyropoulos, *J.C.S. Perkin I*, 1975, 302,

ted (Scheme 4).[26] A three-step process involving allylation of the initial product (21), followed by decarbethoxylation, affords the prenyl derivative (22) in an overall yield of 27%; although this is no more efficient than the older procedure, orientation problems that could arise in the previous method may now be avoided. In an alternative synthesis of the 3-prenyl-2-quinolone (22),[1,26] diallylation of 4-hydroxy-2-quinolone was blocked by bromination, followed by introduction of a single prenyl group and removal of halogen (Scheme 4); experimental details and yields are not yet available.



Reagants: i, $NaCH(CO_2Et)_2$–glyme, reflux; ii, $BrCH_2CH{=}CMe_2$–K_2CO_3–Me_2CO, reflux; iii, $OP(NMe_2)_3$–$Cu(OAc)_2$, 223 °C; iv, Zn–H_3O^+

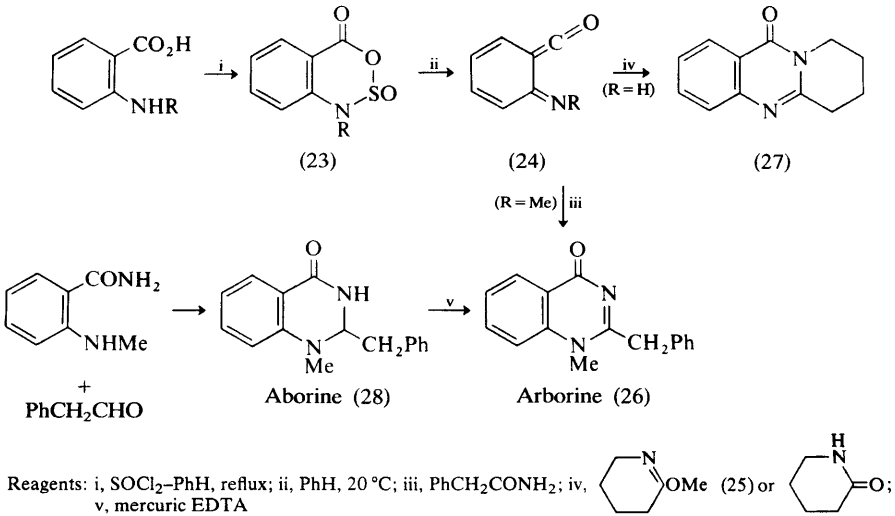
Scheme 4

2 Quinazoline Alkaloids

A convenient synthesis of quinazolines has been reported, and has been applied to the synthesis of representative alkaloids of the quinazoline group (Scheme 5).[27] The procedure depends on the formation of sulphinamide anhydrides (23) from the reaction of anthranilic acids with thionyl chloride and the generation *in situ* of the iminoketens (24). Addition of the latter to the imine (25) or to 2-piperidone, for example, afforded alkaloid (27). Arborine (26) was prepared similarly from *N*-methylanthranilic acid; application of the method to the synthesis of rutecarpine is described in Chapter 11.

Aborine (28) and a large number of other 2-substituted quinazolines have been prepared by intramolecular Mannich reactions of *N*-methylanthranilamide with aldehydes and dehydrogenation of the resultant dihydroquinazolines (Scheme 5).[28]

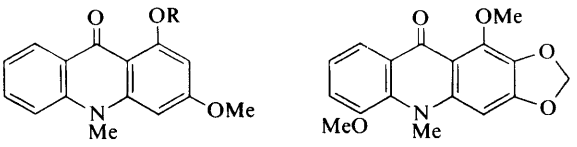
[26] L. A. Mitscher, G. W. Clark, T. Suzuki, and M. S. Bathala, *Heterocycles*, 1975, **3**, 913.
[27] T. Kametani, Chu Van Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *Heterocycles*, 1976, **4**, 1487.
[28] M. Moehrle and C. M. Seidel, *Arch. Pharm.*, 1976, **309**, 503, 572.



Scheme 5

3 Acridone Alkaloids

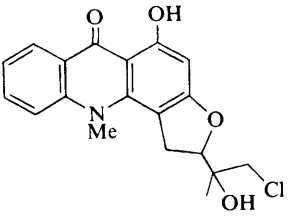
A number of simple acridones have been obtained from new sources. Thus, acridone itself is a constituent of *Thamnosma montana*,[13] and minor components of the root bark of *Teclea verdoorniana* include 1,3-dimethoxy-*N*-methylacridone (29; R = Me) and tecleanthine (30).[12]



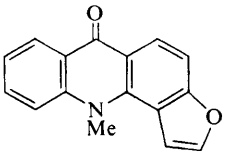
A further study of the root alkaloids of *Ruta graveolens* has resulted in the identification of a new chlorine-containing acridone (31), named isogravacridonchlorine.[29] The same source yielded an inseparable mixture of alkaloids, shown by n.m.r. spectroscopy to consist of the new compound furacridone (32) and the known compound 1-hydroxy-3-methoxy-*N*-methylacridone (29; R = H) in a ratio of 4 : 1.

Rutacridone, previously obtained from *Ruta graveolens*, had been assigned structure (33); the alkaloid has now been isolated from *R. chalepensis* and its structure has been re-examined by n.m.r. spectroscopy.[30] The resonance at -5.2τ indicates the presence of a 5-hydroxy-group intramolecularly hydrogen-bonded to the acridone carbonyl, as in compounds (34) or (35). The linear structure (35) is

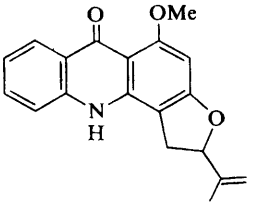
[29] J. Reisch, Z. Rozsa, K. Szendrei, I. Novak, and E. Minker, *Phytochemistry*, 1977, **16**, 151.
[30] G. A. Gonzalez, C. E. Diaz, D. H. Lopez, J. R. Luis, and L. F. Rodriguez, *Anales de Quim.*, 1976, **72**, 94.



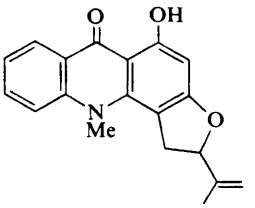
Isogravacridonchlorine (31)



Furacridone (32)



(33)



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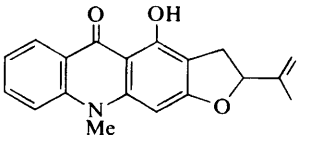


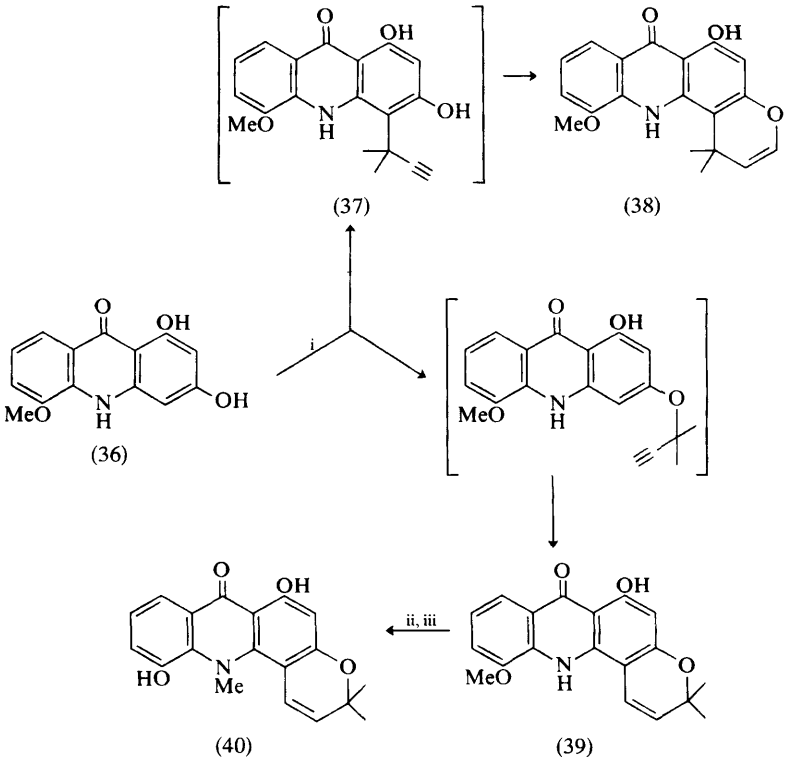
Rutacridone (35)

preferred, since the shift of the signal due to the aromatic proton induced by trifluoroacetic acid accords with the presence of a *para*-hydroxy-group, *cf.* (35), rather than with two adjacent oxygen functions, *cf.* (34).

11-Hydroxynoracronycine (40) is a constituent of *Atalantia ceylonica* and a metabolite of the antitumour compound acronycine; its synthesis has been reported (Scheme 6).[31] The reaction of 1,3-dihydroxy-5-methoxy-9-acridone (36) with 3-chloro-3-methylbut-1-yne and cyclization *in situ* of the products furnished the chromenes (38) and (39); the formation of the intermediate (37) involves *C*-alkylation with the chlorobutyne, a reaction encountered previously during the synthesis of flindersine.[32] Chromene (39) was converted into 11-hydroxy-noracronycine by successive methylation and demethylation.

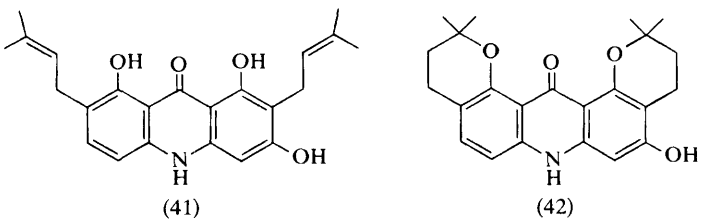
A diprenylacridone (41) obtained from the roots of *Atalantia monophylla*[33] has unfortunately been given the same name, *i.e.* atalaphyllidine, as a different acridone isolated previously from this species (see Vol. 7). The presence of two prenyl groups in the new alkaloid was indicated by the n.m.r. spectrum, by catalytic reduction to a tetrahydro-derivative, and by conversion into compound (42) when treated with formic acid. The reaction of the alkaloid with methyl iodide and potassium carbonate afforded the corresponding *N*-methyltrimethoxyacridone.

[31] J. H. Adams, P. T. Bruce, and J. R. Lewis, *Lloydia*, 1976, **39**, 399.
[32] J. W. Huffman and T. M. Hsu, *Tetrahedron Letters*, 1972, 141.
[33] A. Chatterjee and D. Ganguly, *Phytochemistry*, 1976, **15**, 1303.



Reagents: i, $HC{\equiv}CCClMe_2$–K_2CO_3–NaI–DMF, 70 °C, then reflux in $PhNMe_2$; ii, Me_2SO_4–NaH–THF, 45 °C; iii, BBr_3–CH_2Cl_2, at −70 °C

Scheme 6



Resonances at −1.39 and −2.65τ were attributed to hydrogen-bonded hydroxy-groups at C-1 and at C-9. The third hydroxy-group was placed at C-3 rather than at C-5 on biogenetic grounds and because the OH resonance at 1.09τ in the n.m.r. spectrum of the bicyclo-derivative (42) did not indicate the presence of a neighbouring NH group.

7

β-Phenethylamines and the Isoquinoline Alkaloids

BY K. W. BENTLEY

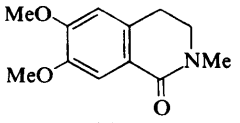
1 β-Phenethylamines

NN-Dimethyl-3,4-dimethoxyphenethylamine and the *N*-methyl analogue have been isolated from the cactus *Echinocereus cinerascens*, and the latter base has also been obtained from another cactus, *Pilosocereus chrysacanthus*.[1] Hordenine hydrochloride has been found in *Coryphantha vivipara* var. *arisonica*,[2] unaccompanied by any other phenethylamine, which is unusual for a *Coryphantha* species.

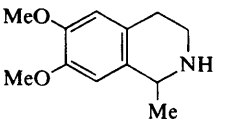
An improved method of preparation of cotarnine and opianic acid by the electrochemical oxidation of narcotine at a graphite anode in the presence of potassium dichromate has been described in a patent.[3] In a study of the pharmacological effects of mescaline, the binding of the alkaloid with rat brain tissue has been examined, using ^{14}C-labelled material.[4] A technique for the separation, identification, and estimation of tyramine, methoxytyramine, and related phenethylamines by g.l.c. of their trimethylsilyl derivatives has been described in detail.[5]

2 Simple Isoquinoline Alkaloids

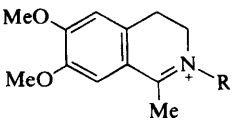
The tetrahydroisoquinolone (1), *N*-methylcorydaldine, has been isolated from *Papaver bracteatum*,[6] and it is apparently a true constituent, not an artefact. The (+)-(*R*)- and (−)-(*S*)-forms of salsolidine (2) have been prepared by the reduction with sodium borohydride of the dihydroisoquinolines [3; R = (+)-(*R*)-PhCHMe, (−)-(*S*)-PhCHMe, (−)-(*S*)-PhCHEt, or (−)-(*S*)-$C_{10}H_7CHMe$] (which were prepared in three steps from 3,4-dimethoxyphenylacetaldehyde and RNH_2) followed by hydrogenolysis over 10% $Pd(OH)_2$ on carbon.[7]



(1)



(2)

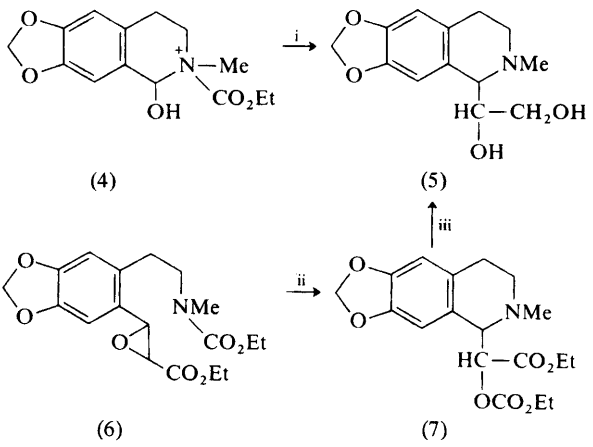


(3)

[1] J. G. Bruhn and H. Sandoz-Mejorada, *Phytochemistry*, 1977, **16**, 622.
[2] R. C. Howe, D. Statz, and J. L. McLoughlin, *Planta Medica*, 1977, **31**, 294.
[3] M. Zh. Zhurinov, M. Ya. Fioshin, and N. A. Prikhod'ko, U.S.S.R. P. 577 593 (*Chem. Abs.*, 1976, **85**, 108 880).
[4] R. K. Datta, W. A. Antopol, and J. J. Ghosh, *Pharmacology*, 1977, **15**, 283.
[5] U. Henke and R. Tschesche, *J. Chromatog.*, 1976, **120**, 477.
[6] H. G. Theuns, J. E. G. van Dam, J. M. Luteijn, and C. A. Salemink, *Phytochemistry*, 1977, **16**, 753.
[7] T. Kametani and T. Okawa, *J.C.S. Perkin I*, 1977, 579.

The hydrastinine derivative (4) has been converted into the diol (5), which has been synthesized from the glycidic ester (6) *via* the diester (7)[8,9] (Scheme 1). The dissociation constants of corypalline and isocorypalline in acetonitrile have been measured.[10]

A new azafluoranthene has been isolated from *Triclisea gilletii*[11] (see Chapter 8).



Reagents: i, $ClCH_2CO_2Et$–HO^-; ii, BF_3,Et_2O; iii, $LiAlH_4$

Scheme 1

3 Benzylisoquinoline Alkaloids

Details of a colour test for papaverine and its tetraethoxy-analogue (ethaverine) have recently become available.[12]

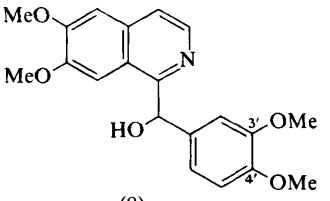
The non-specific tritiation of papaverine has been described,[13] as have methods for the detection of the alkaloid in body fluids.[14,15] The effects of papaverine on the biochemical fate of thymidine phosphate in the thymus,[16] on cyclic AMP and the uptake of calcium in isolated pig auricle,[17] on the monosynaptic reflex,[18] on the L-DOPA-influenced secretion of GH and PRL,[19] on cerebral blood flow,[20] and on longitudinal smooth muscle[21] have been studied, as have the β-receptor-stimulant

[8] M. D. Rozwadowska, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1976, **24**, 101.
[9] M. D. Rozwadowska, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1976, **24**, 685.
[10] J. T. Stock and G. A. Shia, *Analyt. Chim. Acta*, 1976, **84**, 211.
[11] R. Huls, J. Gaspers, and R. Warin, *Bull. Soc. Roy. Sci. Liège*, 1976, **45**, 40.
[12] P. Depovere and M. Piraux, *Bull. Soc. Pharm. Bordeaux*, 1975, **114**, 47.
[13] J. Devillers, M. Winand, and B. Bettens, *J. Labelled Compounds Radiopharm.*, 1976, **12**, 219.
[14] J. De Graeve, P. Kremers, J. van Cantfort, and C. Heusghem, *Drug Interference Drug Meas. Clin. Chim., Proc. Internat. Colloq. Prospective Biol.*, (3rd), 1975, p. 81.
[15] J. De Graeve, J. van Cantfort, and J. E. Gielen, *J. Chromatog.*, 1977, **133**, 15.
[16] H. Sheppard, W.-H. Tsien, and S. Saas, *Biochem. Biophys. Res. Comm.*, 1977, **75**, 457.
[17] S. Holtzmann, T. Meinertz, N. Nawrath, and H. Scholz, *Res. Comm. Chem. Path. Pharmacol.*, 1977, **16**, 457.
[18] J. A. Gonzalez-Vegas, *Acta Cient. Venez.*, 1976, **27**, 148.
[19] D. S. Cooper and L. S. Jacobs, *J. Clin. Endocrinol. Metab.*, 1977, **44**, 585.
[20] D. Cosnier, M. Chende, G. Rispat, and G. Streichenberger, *Therapie*, 1976, **31**, 205.
[21] R. Radomirov and O. Kladec, *Physiol. Bohemoslov.*, 1976, **25**, 349.

properties of tetrahydropapaveroline.[22] Crown ether analogues of papaverine have been prepared from papaverosoline and $ClCH_2CH_2O(CH_2CH_2O)_2CH_2CH_2Cl$.[23]

The stereochemical removal of hydrogen from positions 3 and 4 of the isoquinoline ring during aromatization of papaverine during biosynthesis has been studied by incorporation experiments, using stereospecifically labelled [^{3}H]norreticulines.[24]

Papaverinol (8) has been shown to undergo disproportionation to papaverine and papaveraldine when heated with acetic acid under reflux for 14 hours, whereas with 90% sulphuric acid it is partially demethylated at the 3′-methoxy-group and partially split to the aldehyde (9).[25]



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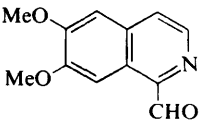


(9)

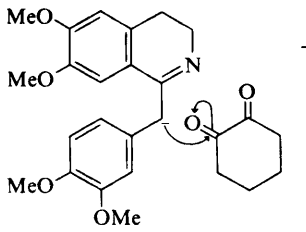
In the study of a model for the possible synthesis of concentrine, 3,4-dihydropapaverine has been condensed with cyclohexane-1,2-dione in the presence of base (preferably Triton B) to give the spiro-ketone (14). The reaction presumably proceeds *via* the carbanion (10) and the intermediates (11), (12), and (13). A similar reaction with benzil affords the diphenyl ketone (15). Catalytic reduction of the ketone (14) yields the corresponding alcohol.[26]

A synthesis of sevanine (16) by Bischler–Napieralski ring-closure of the amide (17) followed by hydrogenolysis and dehydrogenation has been reported.[27] The alkaloid has also been prepared from papaverine by demethylation and methylenation with dichloromethane.[27]

An asymmetric synthesis of (−)-(*R*)-laudanosine has been accomplished, proceeding from L-3,4-dihydroxyphenylalanine *via* the norlaudanosine derivatives (18; $R^1 = H$, $R^2 = CO_2Me$), (18; $R^1 = CH_2Ph$, $R^2 = CONH_2$), and (18; $R^1 = CH_2Ph$, $R^2 = CN$), which was then converted into norlaudanosine (18; $R^1 = R^2 = H$). The nor-base was then *N*-formylated and the *N*-formyl derivative reduced with sodium borohydride. The C-1 epimer of the ester (18; $R^1 = H$, $R^2 = CO_2Me$) was also obtained, and it isomerized to the *trans*-ester when mixed with sodium methoxide in methanol.[28]

Microbiological transformation of laudanosine by the micro-organism *Cunninghamella blakesleeana* is accomplished by selective demethylation, to give *ψ*-codamine (19).[29] Isoquinoline alkaloids that can be selectively halogenated can readily be converted into hydroxy-compounds by lithiation of the bromo-

[22] O. Rohte and P. Ochlich, *Deutsch. Tierarzte Wochr.*, 1976, **83**, 178.
[23] F. Voegtle and K. Frensch, *Angew. Chem.*, 1976, **88**, 722.
[24] A. R. Battersby, P. W. Sheldrake, J. Staunton, and M. C. Summers, *Bio-Org. Chem.*, 1977, **6**, 43.
[25] S. Ruchirawat, N. Tongpenyai, N. Prasitpan, and P. Prempree, *Heterocycles*, 1976, **4**, 1893,
[26] S. Ruchirawat and V. Somchitman, *Tetrahedron Letters*, 1976, 4159.
[27] V. Simanek, V. Preininger, A. Klasek, and J. Jurina, *Heterocycles*, 1976, **4**, 1263.
[28] M. Konda, T. Ohishi, and S. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 69.
[29] P. J. Davis and J. P. Rosazza, *J. Org. Chem.*, 1976, **41**, 2548.



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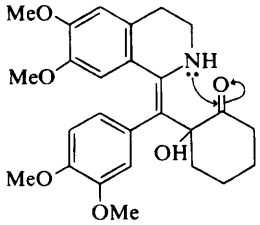

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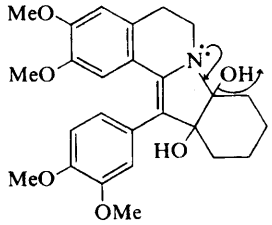

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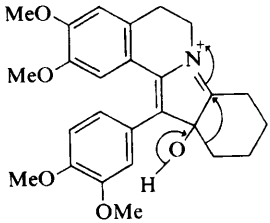

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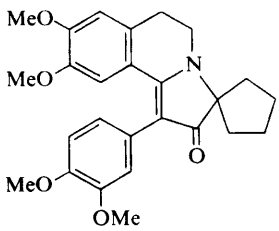

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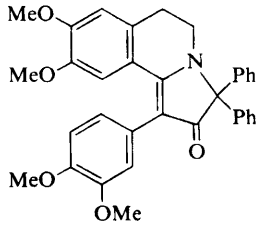

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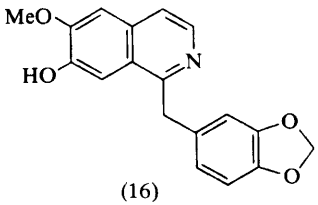

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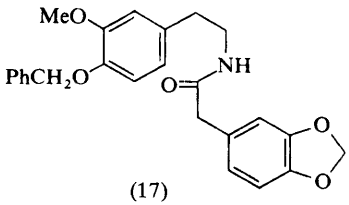

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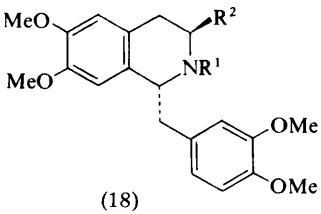

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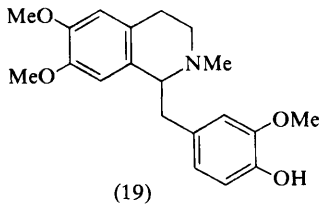
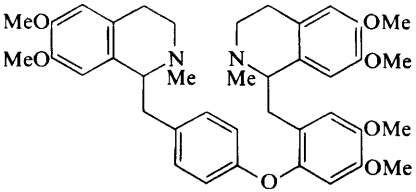


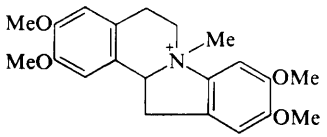
(19)

compound followed by treatment with an excess of nitrobenzene. In this way laudanosine can be converted into 6′-hydroxylaudanosine.[30] 6′-Bromolaudanosine will also react with phenol under improved conditions for the Ullmann reaction, using $(C_6F_5)_4Cu$ as catalyst, in pyridine solution, to give 6′-phenoxylaudanosine. Replacement of phenol by armepavine, nuciferoline, cassythicine, or *N*-methylcassyfiline in this reaction gives rise to analogues of bisbenzylisoquinoline alkaloids differing from the normal forms in the position of the diphenyl ether linkage, *e.g.* (20).[21]



(20)

Bromolaudanosine, on treatment with potassamide or sodamide in liquid ammonia, yields the dibenzo[*b*,*g*]indolizinium salt (21), the reaction presumably proceeding through the aryne, together with aminolaudanosine and the indoline (22) and the indole (23).[32] Photolysis of laudanosine methiodide yields the base (24; R = Me) in methanol and (24; R = H) in water. The latter, on heating with



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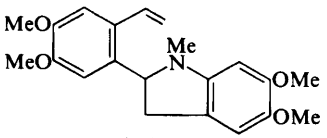

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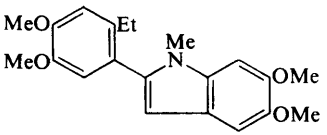

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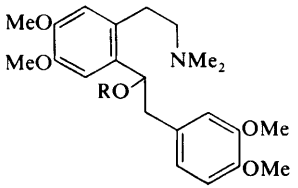


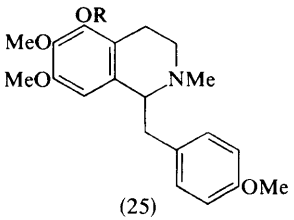
(24)

acetyl chloride, is dehydrated to the stilbene.[33] The photolysis of 6′-bromotetrahydropapaverine has been found to give (±)-norglaucine.[34] Electrochemical oxidation of laudanosine to *O*-methylflavinantine in acetonitrile has been accomplished.[35] Oxidation of reticuline has been further studied, and cleavage to give

[30] P. Wiriyachitra and M. P. Cava, *J. Org. Chem.*, 1977, **42**, 2274.
[31] M. P. Cava and A. Afzali, *J. Org. Chem.*, 1975, **40**, 1553.
[32] I. Ahmad and M. S. Gibson, *Canad. J. Chem.*, 1975, **53**, 3660.
[33] J. B. Bremner and Le Van Thuc, *Chem. and Ind.*, 1976, 453
[34] M. S. Premila and B. S. Pai, *Indian J. Chem.*, 1976, **14B**, 134.
[35] J. Y. Becker, L. L. Miller, and F. R. Stermitz, *J. Electroanalyt. Chem. Interfacial Electrochem.*, 1976, **62**, 181.

7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline has been reported to accompany oxidation with iron(III) chloride in DMF.[36] Oxidation of reticuline perchlorate with oxygen in the absence of copper(I) chloride in pyridine affords pallidine, corytuberine, and isoboldine by radical-coupling reactions, mimicking the biogenesis of these alkaloids.[37]

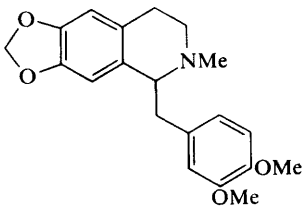
A synthesis of takatonine-like compounds (25; R = H) has been reported, by Bischler–Napieralski cyclization to (25; R = CH_2Ph) followed by routine transformations, and the correlation between chemical shifts in the n.m.r. spectra and the conformation of the isoquinoline system has been examined.[38]



(25)

An improved method for the removal of methylenedioxy-groups in alkaloids of the benzylisoquinoline and tetrahydroberberine series has been derived. Alkaloids such as remneine (26) can be converted into the dihydroxy-bases (27) by treatment with boron trifluoride followed by 5-chloro-5-phenyl-1*H*-tetrazole and subsequent hydrogenolysis of the resulting bis-tetrazolyl ethers. The yields in the process are good.[39]

An examination of *Corydalis ochotensis* has been followed by the isolation of the benzylisoquinoline aobamine (28) and the oxidized base aobamidine (29).[40]



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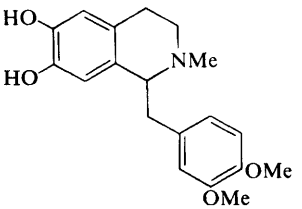

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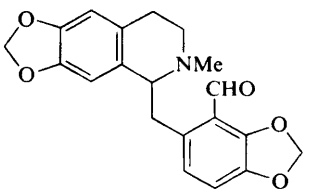

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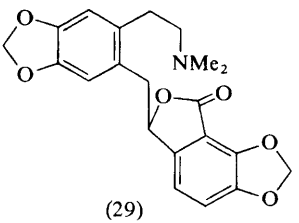

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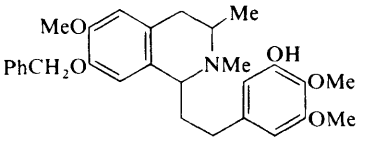
[36] M. Sivakumaran and K. W. Gopinath, *Indian J. Chem.*, 1976, **14B**, 138.
[37] T. Kametani, Y. Satoh, M. Takemura, Y. Ohta, M. Ihara, and K. Fukumoto, *Heterocycles*, 1976, **5**, 175.
[38] T. Tomimatsu, S. Yamada, and R. Yumasa, *Yakugaku Zasshi*, 1977, 217.
[39] S. Teitel and J. P. O'Brien, *Heterocycles*, 1976, **5**, 85.
[40] T. Kametani, M. Takemura, M. Ihara, and K. Fukumoto, *Heterocycles*, 1976, **4**, 723.

4 Phenethylisoquinoline Alkaloids

The structure of autumnaline has been confirmed by an *X*-ray crystallographic study of 3-methyl-7-*O*-benzylautumnaline (30).[41] Autumnaline itself has been isolated from *Colchicum latifolium*.[42]

The oxidation of phenethylisoquinolines in biogenetically modelled syntheses has been studied. Orientaline, when oxidized with oxygen, copper(I) chloride, and pyridine, yields (±)-orientalinone, and the base (31) gives (±)-kreysiginone and its



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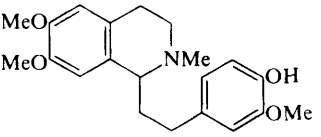
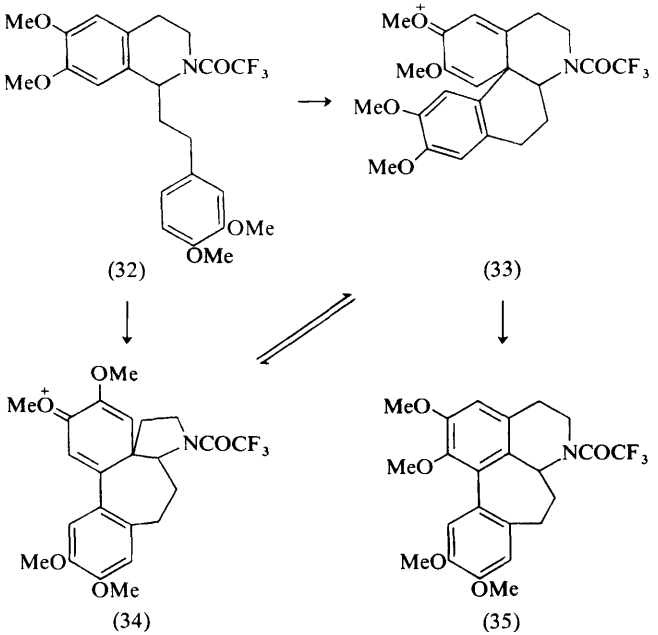


(31)

diastereoisomers.[37] The primary products of oxidative coupling of the non-phenolic trifluoroacetyl derivative (32), when oxidized by vanadium oxyfluoride in trifluoroacetic acid, are oxonium salts of homoproerythradienones (33) and homospirindienones (34), which may be hydrolysed to the corresponding ketones and which further rearrange to homoaporphines (35). An equilibrium is established between the dienones (33) and (34).[43]

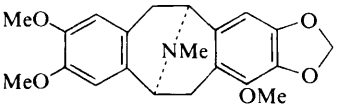


(32) (33) (34) (35)

[41] Z. Shakked and O. Kennard, *Acta Cryst.*, 1977, **B33**, 516.
[42] H. Potesilova, L. Hruban, and F. Santavy, *Coll. Czech. Chem. Comm.*, 1976, **41**, 3166.
[43] S. M. Kupchan, O. P. Dhingra, C.-K. Kim, and V. Kameswaran, *J. Org. Chem.*, 1976, **41**, 4047.

5 Pavines and Isopavines

Eschscholtzidine and argemonine have been isolated from *Thalictrum revolutum*, this being the first isolation of the former from any *Thalictrum* species.[44] The crystal structure and absolute configuration of (−)-argemonine methiodide have been determined.[45] A new base, 2,3,7-trimethoxy-8,9-methylenedioxypavinane (36), has been isolated from *Thalictrum strictum*.[46] Another new base, (±)-caryachine (37), has been isolated from *Cryptocarya chinensis* and its structure confirmed by cyclization of 6,7-methylenedioxy-1-(3-benzyloxy-4-methoxybenzyl)-*N*-methyl-1,2-dihydroisoquinoline, followed by hydrogenolysis.[47] A new isopavine alkaloid, (−)-thalidine (38), has been found in *Thalictrum dioicum*, and has been synthesized in similar manner from 7-benzyloxy-6-methoxy-1-(3-benzyloxy-4-methoxybenzyl)-*N*-methyl-1,2-dihydroisoquinoline.[48] The isomeric base thalicidine (39) has also been isolated from *T. dioicum*.[49] The occurrence of alkaloids in *Thalictrum* species has been the subject of a review.[50]



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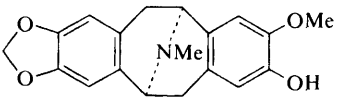

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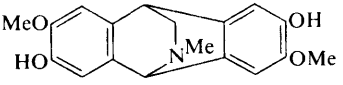


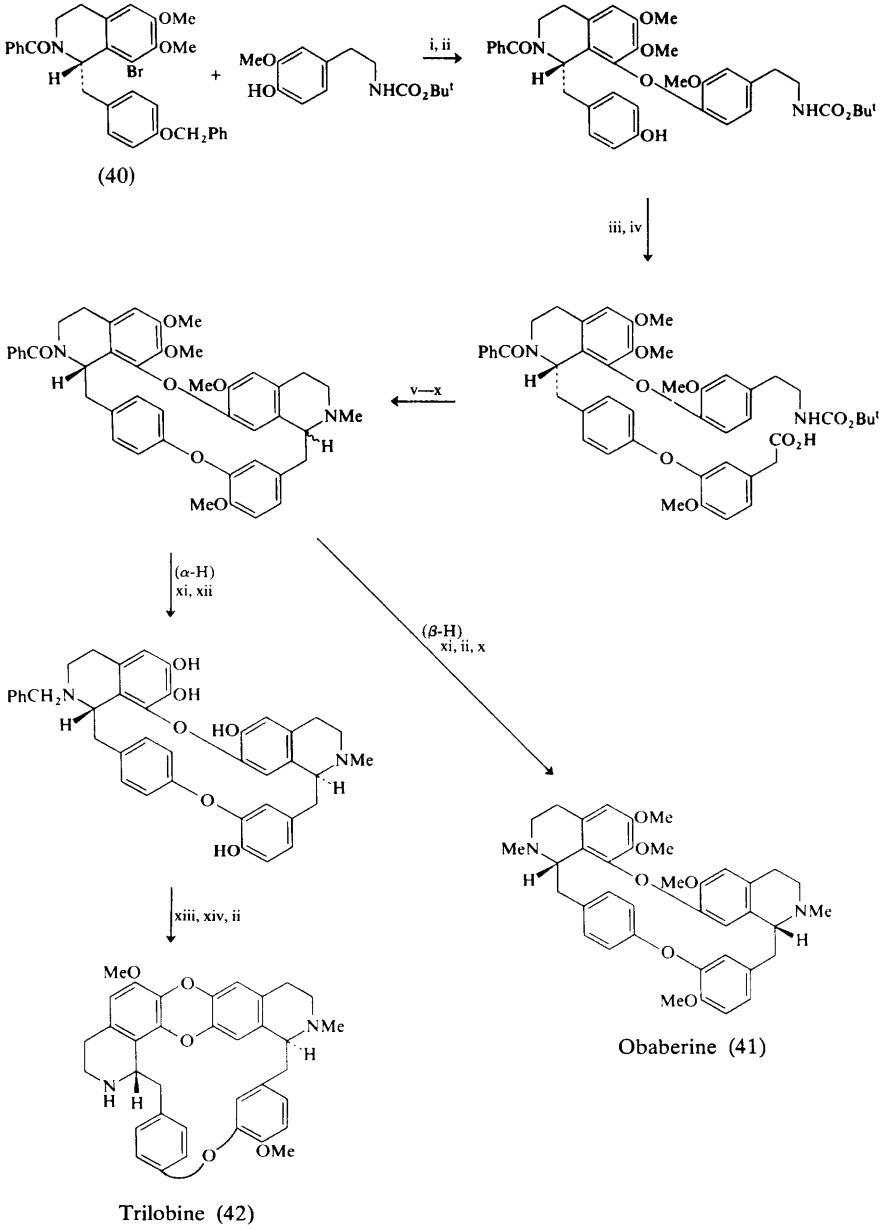
(39)

6 Bisbenzylisoquinoline Alkaloids

Aromoline and thalicberine have been isolated from *Thalictrum lucidum*,[51] and berbamine and oxyacanthine from *Berberis julianeae* Schneid.[52] The biosynthesis of bisbenzylisoquinoline alkaloids has been reviewed.[53] An *X*-ray structure determination of (+)-tubocurarine dibromide methanol solvate has been reported,[54] and neuromuscular sensitivity to tubocurarine[55] and the cardiovascular effects of the alkaloid[56] have been further studied. Highly selective biological *N*-demethylation of tetrandrine to *N*(2′)-nortetrandrine by *Streptomyces griseus* has been described.[29]

Trilobine (42) and obaberine (41) have been synthesized from (*S*)-(+)-*O*-benzyl-8-bromo-*N*-benzoyl-norarmepavine (40)[57] by the route shown (Scheme 2).

[44] J. Wu, J. L. Beal, R. W. Doskotch, and W.-N. Wu, *Lloydia*, 1977, **40**, 224.
[45] T. Kaneda, N. Sakabe, and J. Tanaka, *Bull. Chem. Soc. Japan*, 1976, **49**, 1263.
[46] S. Kh. Maekh and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 116.
[47] J. Wu, C.-H. Chen, N. A. Shaath, and T. O. Soine, *T'ai-Wan Yao Hsueh Tsa Chih*, 1975, **27**, 105.
[48] M. Shamma, A. S. Rothenberg, S. Salger, and G. S. Jayatilake, *Lloydia*, 1976, **39**, 395.
[49] H. Ong and J. Beliveau, *Ann. Pharm. Franç*, 1976, **34**, 223.
[50] T. Tomimatsu, *Shoyakugaku Zasshi*, 1976, **30**, 1.
[51] W.-N. Wu, J. L. Beal, and R. W. Doskotch, *Lloydia*, 1976, **39**, 378.
[52] D. Kostalova, B. Brazdovicova, and J. Tomko, *Chem. Zvesti*, 1976, **30**, 226.
[53] D. S. Bhakuni, *J. Sci. Ind. Res. (India)*, 1976, **35**, 461.
[54] C. D. Reynolds and R. A. Palmer, *Acta Cryst.*, 1976, **B32**, 1431.
[55] C. Lee, A. Barnes, and R. L. Katz, *Brit. J. Anaesth.*, 1976, **48**, 1045.
[56] R. Hughes and D. J. Chapple, *Brit. J. Anaesth.*, 1976, **48**, 847.
[57] Y. Inubushi, Y. Ito, Y. Masaki, and T. Ibuka, *Tetrahedron Letters*, 1976, 2857.

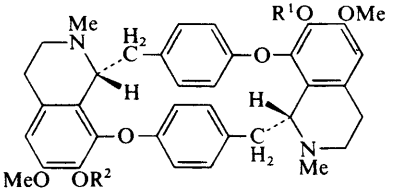


Reagents: i, condensation; ii, H_2–Pd/C; iii, Ullmann condensation (Ar atmosphere); iv, HO^-; v, *p*-$NO_2C_6H_4OH$–DCC; vi, CF_3CO_2H; vii, pyridine–DMF, 70 °C; viii, Bischler–Napieralski cyclization; ix, $NaBH_4$; x, HCHO–$NaBH_4$; xi, $LiAlH_4$–$AlCl_3$; xii, BBr_3–CH_2Cl_2, 0 °C; xiii, aq. HBr, 135—140 °C; xiv, CH_2N_2

Scheme 2

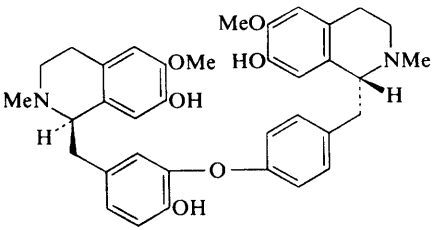
The synthesis of trilobine represents the first synthesis of an alkaloid of this series that has three diphenyl ether linkages.

Cycleanine (43; $R^1 = R^2 = Me$) has been demethylated by hydrobromic acid to a mixture of isochondodendrine (43; $R^1 = R^2 = H$) and 7-nor-cycleanine (43; $R^1 = H$, $R^2 = Me$).[58]

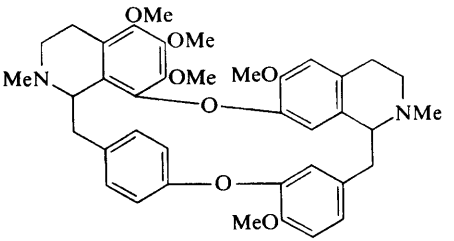


(43)

Lindholdamine, from *Lindera oldhamii* Hemsl., has been shown to have the structure (44) by spectroscopic studies;[59] thalrugosamine, from *Thalictrum rugosum*, is the bis-ether (45).[60]



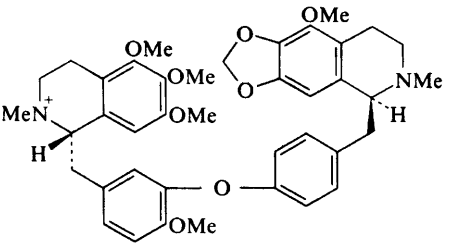
(44)



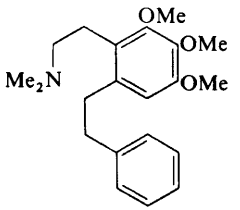
(45)

Thalistyline, a monoquaternary salt from the quaternary fraction of the chloroform-soluble alkaloids of *Thalictrum longistylum* and *T. podocarpum*, has strong hypotensive action at 1.0 mg kg^{-1} in normotensive dogs and rabbits. It has the structure (46), and both the related bis-tertiary base and bis-quaternary salt have been isolated in small quantities from the same plants.[61] The structure of (46) was determined by its fission with sodium in liquid ammonia to form the bases (47) and (48), and by its oxidation to the isoquinolone (49) and the acid (50) when it reacted with potassium permanganate.[61]

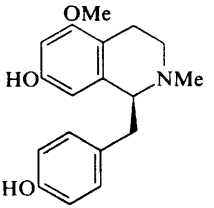
[58] O. Belichenko and O. N. Tolkachev, *Khim. prirod. Soedinenii*, 1976, 125.
[59] S.-T. Lu and I.-S. Chen, *Heterocycles*, 1976, **4**, 1073.
[60] W.-N. Wu, J. L. Beal, G. W. Clark, and L. A. Mitscher, *Lloydia*, 1976, **39**, 65.
[61] W.-N. Wu, J. L. Beal, and R. W. Doskotch, *Tetrahedron Letters*, 1976, 3687.



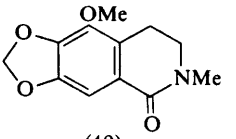
(46)



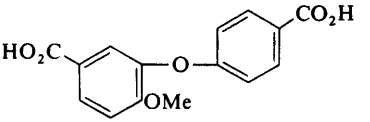
(47)



(48)



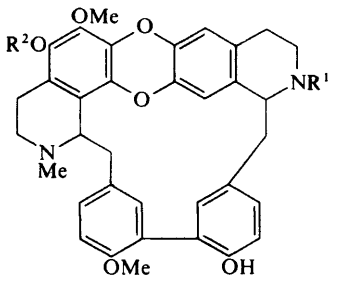
(49)



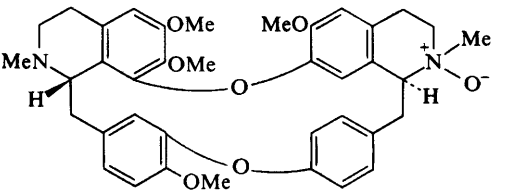
(50)

A new base with a diphenyl linkage and two diphenyl ether links is tiliamosine, from *Tiliacora racemosa*, which has the structure (51; $R^1 = H$, $R^2 = Me$); the *N*-acetyl-nor-compound (51; $R^1 = COMe$, $R^2 = H$) has also been isolated and characterized.[62]

Tetrandrine mono-*N*-2′-oxide (52) has been isolated from Krung Kha Mao, a Thai drug obtained from *Cyclea barbata*, and its structure has been confirmed by partial *N*-oxidation of tetrandrine. Isochondodendrine and chondrocurine have also been isolated from the same source.[63]



(51)

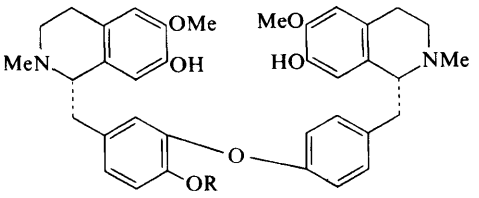


(52)

Two related alkaloids, grisabine (53; R = Me) and grisabutine (53; R = H), have been isolated from *Abuta grisebachii* Triana et Planchon. Their structures were determined by splitting the diphenyl ether linkage with sodium–liquid ammonia;

[62] K. P. Guha, P. C. Das, B. Mukherjee, R. Mukherjee, G. P. Juneau, and N. S. Bhacca, *Tetrahedron Letters*, 1976, 4241.

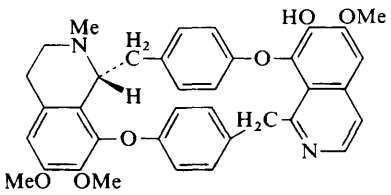
[63] K. Dahmen, P. Pachaly, and F. Zymalkowsky, *Arch. Pharm.*, 1977, **310**, 95.



(53)

grisabine dimethyl ether gave (*R*)-armepavine and (*S*)-armepavine methyl ether; grisabine bis-trideuteriomethyl ether gave (*S*)-7-*O*-trideuteriomethyl-12-*O*-methyl-*N*-methylcoclaurine and (*R*)-7-*O*-trideuteriomethyl-*N*-methylcoclaurine: and grisabutine tristrideuteriomethyl ether gave (*S*)-*OO*-bistrideuteriomethyl-*N*-methylcoclaurine and (*R*)-7-*O*-trideuteriomethyl-*N*-methylcoclaurine.[64]

A novel type of bisbenzylisoquinoline alkaloid containing one fully aromatic isoquinoline system is sciadoline, from *Sciadotenia toxifera* Kruhoff and A. C. Smith (Menispermaceae), which has been shown to have the structure (54) by spectroscopic studies.[65] It is related to cycleanine (43; $R^1 = R^2 = Me$) and 7-norcycleanine (43; $R^1 = H$, $R^2 = Me$).



(54)

A number of bisbenzylisoquinoline alkaloids show antitumour activity, and a study has been made of this property in a group of 23 alkaloids, but no clear structure–activity relationship was uncovered.[66]

The bisbenzylisoquinolines have been classified into 26 different types,[67] and a review has been made of racemization and epimerization within the series.[68]

7 Protoberberines

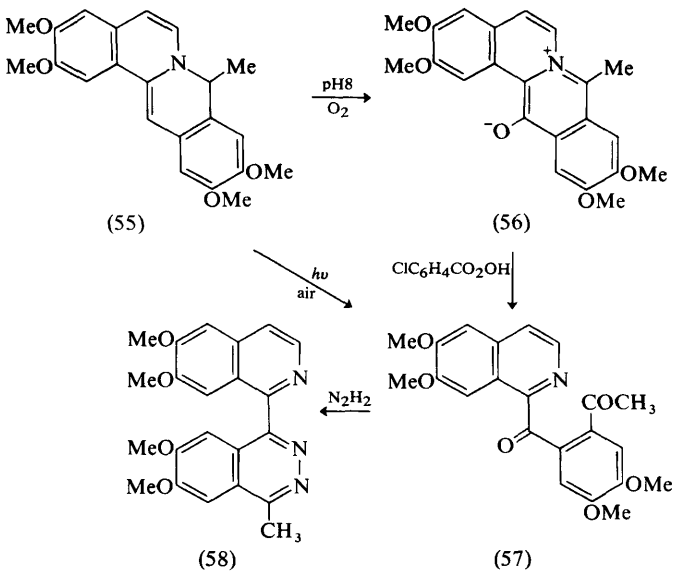
The chemistry of berberine has been reviewed.[69] Several papers on the pharmacological and biochemical action of derivatives of berberine alkaloids have appeared, including studies of the adrenergic neurone-blocking action of dehydrocorydaline,[70,71] the intercalation of coralyne with DNA as a possible mechanism

[64] R. Ahmad and M. P. Cava, *J. Org. Chem.*, 1977, **42**, 2271.
[65] K. Takahashi and M. P. Cava, *Heterocycles*, 1976, **5**, 367.
[66] H. Kuroda, S. Nakazawa, K. Kategiri, O. Shiratori, M. Kozuka, K. Fujitani, and M. Tomita, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 2413.
[67] M. Shamma and J. L. Moniot, *Heterocycles*, 1976, **5**, 1817.
[68] T. Kametani and M. Ihara, *Heterocycles*, 1976, **5**, 649.
[69] L. I. Petlichnaya, *Farm. Zhur. (Kiev)*, 1975, **30**, 22.
[70] K. Kurahashi and M. Fujiwara, *Canad. J. Physiol. Pharmacol.*, 1976, **54**, 287.
[71] M. Tate, Y. Shoji, Y. Matsuno, K. Kawashima, M. Oka, *et al.*, *Yakuri to Chiryo*, 1976, **4**, 877

for antileukaemic action,[72] the inhibition of mammalian virus nucleic acid polymerase by coralyne acetosulphate,[73] the anthelmintic activity of berberine,[74] biochemical effects of tetrandrine and thalicarpine,[75] neuropharmacological studies with (−)-tetrahydrocoptisine,[76] and the anti-inflammatory properties of berberine;[77] a general survey of the relationship between chemical structure and pharmacological activity within the series has also been made.[78]

A study has been made of the relative stabilities of the B/C-*cis*- and -*trans*-isomers of groups of tetrahydroberberines, and the conclusion drawn that the *trans*-form is favoured in alkaloids of 'type I' (*e.g.* tetrahydropalmatine) and the *cis*-form in those of 'type III' (*e.g.* mesocorydaline), and that in bases of 'type II' (*e.g.* capaurine) the stability of the *cis*-isomer increases as the bulk of the substituent at C-1 increases.[79]

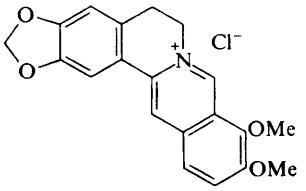
Berberines are reported to be reduced to dihydroberberines rather than the tetrahydro-compounds by sodium bis(2-methoxyethoxy)aluminium hydride.[80] Partial reduction of coralynium salts affords the tertiary dienamine (55), autoxidation of which, at pH 8, yields the betaine (56); this can be oxidized by peracids to 6′-acetylpapaveraldine (57), obtainable directly from the dienamine (55) by photolysis in the presence of air. The diketone reacts with hydrazine to give the 1,2-diazine (58).[81]



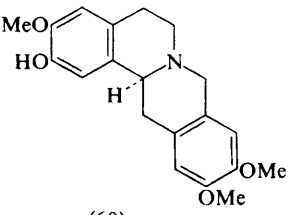
[72] W. D. Wilson, A. N. Gough, J. J. Doyle, and M. W. Davidson, *J. Medicin. Chem.*, 1976, **19**, 1261.
[73] V. S. Sethi, *Cancer Res.*, 1976, **36**, 2390.
[74] K. S. Singhal, *Indian J. Exp. Biol.*, 1976, **14**, 345.
[75] W. A. Creasey, *Biochem. Pharmacol.*, 1976, **25**, 1887.
[76] S. K. Bhattacharya, V. B. Pandey, A. B. Ray, and B. Dasgupta, *Arzneim.-Forsch.*, 1976, **26**, 2187.
[77] M. H. Akhter, M. Sabir, and N. K. Bhide, *Indian J. Med. Res.*, 1977, **65**, 133.
[78] L. P. Naidovich, E. A. Trustneva, O. N. Tolkachev, and V. D. Vasil'eva, *Farmatsiya*, 1976, **25**, 33.
[79] N. Takao and K. Iwasa, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 3185.
[80] H. Nishimura, S. Naruto, and H. Mizuta, Japan. Kokai 77 07 998 (*Chem. Abs.*, 1977, **87**, 23 588).
[81] J. Imai and Y. Kondo, *Heterocycles*, 1976, **5**, 153.

Some positional isomers of coralyne have been synthesized and examined for antileukaemic activity,[82] and the distribution of salts of coralyne after they have been administered to rodents has been studied.[83] Dehydrogenation of canadine to berberrubine (59) can be accomplished in ethylene glycol and hydrochloric acid with palladium or with tris(triphenylphosphinyl)rhodium chloride, the reaction proceeding faster at low temperatures with the latter catalyst.[84] Derivatives of 13-methylberberrubine and its analogues have been synthesized, so that they might be screened to find their potential as antitumour agents.[85]

A new alkaloid of this group, govanine, from *Corydalis govaniana*, has been identified as the phenol (60) by its methylation to xylopinine and by its synthesis.[86]

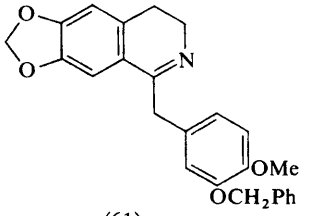


(59)

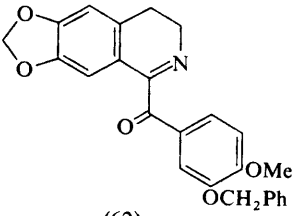


(60)

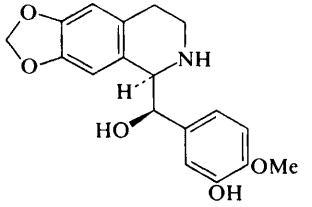
A stereoselective synthesis of (±)-ophiocarpine (64) has been achieved, starting from the benzyldihydroisoquinoline (61) and then proceeding *via* the papaveraldine analogue (62), which can be reduced to the alcohol (63) in stages. Mannich reaction of this phenol with formaldehyde, followed by *O*-methylation, affords ophiocarpine (64).[87]



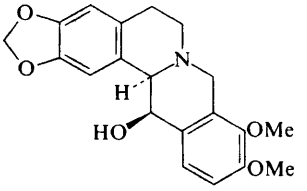
(61)



(62)



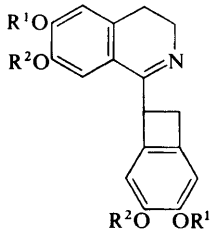
(63)



Ophiocarpine (64)

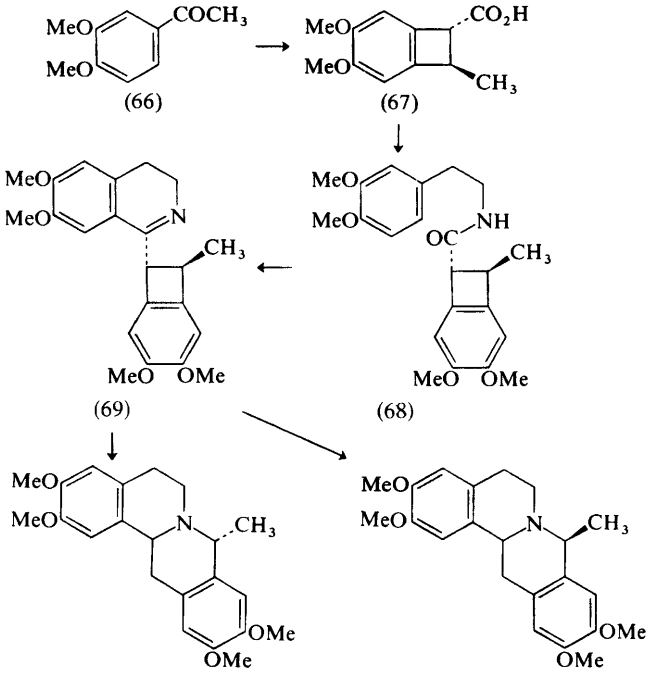
[82] R. K. Y. Zee Cheng and C. C. Cheng, *J. Medicin. Chem.*, 1976, **19**, 882.
[83] J. Plowman, R. L. Cysyk, and R. H. Adamson, *Xenobiotica*, 1976, **6**, 281.
[84] K. K. Kuchkova, A. A. Semenov, and M. O. Broitman, *Khim. prirod. Soedinenii*, 1976, 830.
[85] Y. Sawa, Ger. Offen. 2 527 941 (*Chem. Abs.*, 1977, **86**, 121 600).
[86] K. Mehra, H. S. Garg, D. S. Bhakuni, and N. M. Khanna, *Indian J. Chem.*, 1976, **14B**, 58.
[87] T. Kametani, H. Matsumoto, Y. Satoh, H. Nemoto, and K. Fukumoto, *J.C.S. Perkin I*, 1977, 376.

A patent describes the production of coreximine and its analogues from benzocyclobutenes of type (65) by the action of heat followed by reduction,[88] and in a



(65)

development of this process coralydine (70) and *O*-methylcorytenchirine (71) have been prepared by the thermolysis of the benzocyclobutene (69) followed by reduction with sodium borohydride. The cyclobutene (69) was prepared from acetoveratrone (66) *via* the acid (67) and the amide (68).[89] The crystal structures of these two alkaloids have been determined and the tetra-*O*-demethyl-compounds have been prepared from norlaudanosoline by the cycloaddition of acetaldehyde.[90]



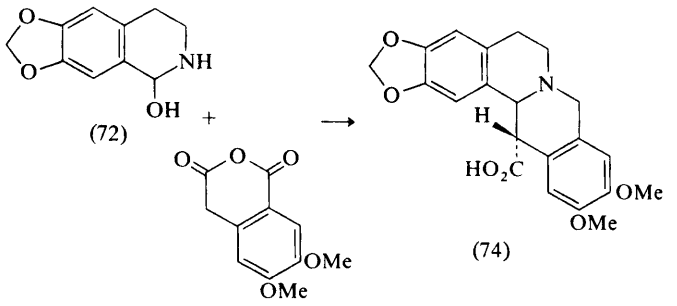
Coralydine (70) *O*-Methylcorytenchirine (71)

[88] T. Kametani, Japan. Kokai 75 129 600 (*Chem. Abs.*, 1976, **85**, 5936).

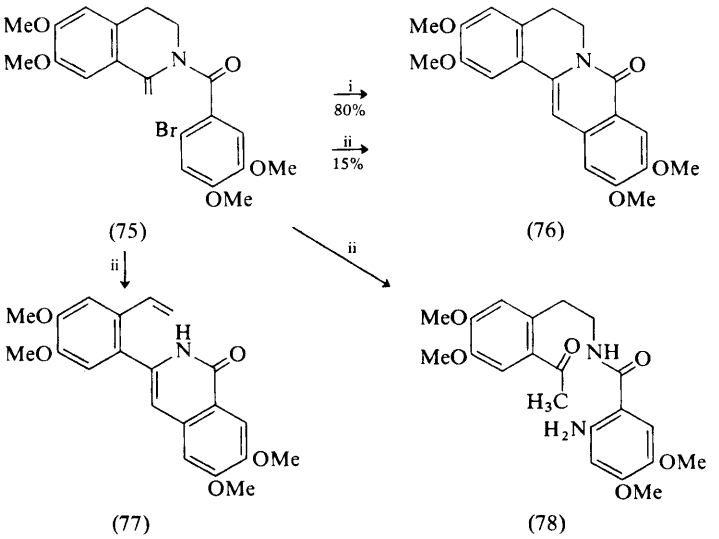
[89] T. Kametani, C. Ohtsuka, H. Nemoto, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 2525.

[90] H. Bruder, J. Metzger, A. Brossi, and J. J. Daly, *Helv. Chem. Acta*, 1976, **59**, 2793.

A route to β-methyl-tetrahydroberberines has been developed from the hydrastinine derivative (72), which can be acylated with the dimethoxyhomophthalic anhydride (73) to give acid (74). Reduction of this with lithium aluminium hydride followed by further reduction of the toluene-*p*-sulphonyl ester of the resulting hydroxymethyl compound yields the 13-methyl compound.[91] An essentially similar synthesis of oxoberberines bearing a carboxy-group at C-13, of general type (74), has been reported by other workers.[92]



9,10-Disubstituted protoberberines have been synthesized in high yield by the photolysis of the related bromo-enamides (Scheme 3). The enamide (75) is converted into the enamide (76) in 80% yield by photolysis, and the cyclized base can



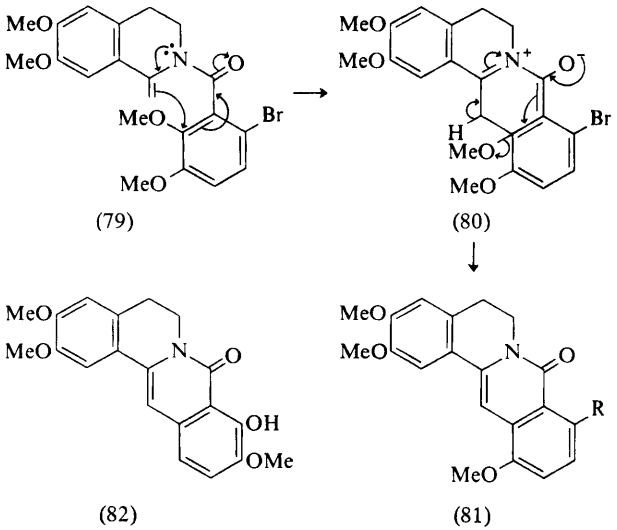
Reagents: i, *hν*; ii, $NaNH_2$–liq. NH_3

Scheme 3

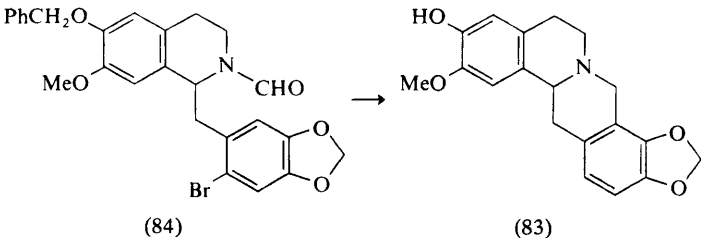
[91] M. Cushman, J. Gentry, and F. W. Dekow, *J. Org. Chem.*, 1977, **42**, 1111.
[92] M. Attaimova, N. M. Mollov, S. C. Ivanova, and A. I. Dimitrova, *Tetrahedron*, 1977, **33**, 331.

be reduced to (±)-xylopinine. The cyclized enamide is also obtained in 15% yield by the action of sodamide and liquid ammonia on the same compound, together with the degradation product (77) and the product of hydrolysis and substitution (78).

The corresponding reaction of the isomeric enamide (79) is more complex. Photolysis of this compound in methanol gives the partially demethylated cyclization product (82), with the expected substitution pattern, in 65% yield, together with the desmethoxy-compound (81; R = H) (20%). In benzene, the main product of photolysis is the desmethoxy-bromo-compound (81; R = Br). The mechanism of the cyclization with loss of a methoxy-group may be represented as in structures (79) and (80). Similar reactions have been accomplished using the 6,7-methylenedioxy-analogue of the bromo-enamides (75) and (79).[93] By the application of this process the alkaloids xylopinine, schefferine, nandinine, corydaline, and thalictricavine have been synthesized.[93]

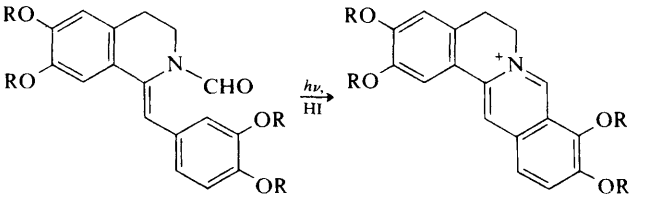


A synthesis of tetrahydrogroenlandicine (83) from the *N*-formyl compound (84) has been achieved by cyclization, reduction, debenzylation, and reductive elimination of the bromine.[94]



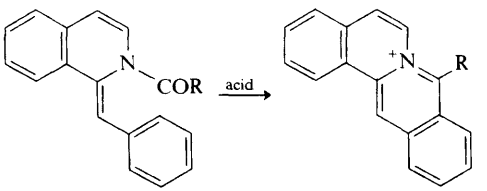
[93] T. Kametani, T. Sugai, Y. Shoji, T.,Honda, F. Satoh, and K. Fukumoto, *J.C.S. Perkin I*, 1977, 1151.
[94] H. Suguna and B. R. Pai, *Coll. Czech. Chem. Comm.*, 1976, **41**, 1219.

A similar photolytic cyclization has been achieved, with concomitant oxidation, of the *N*-formyl-enamine (85) in the presence of hydrogen iodide to produce (86), no evidence being found of non-oxidative cyclization. The enamine with the (*Z*)-configuration is obtained directly from the 3,4-dihydroisoquinoline by the action of formic acid and acetic anhydride.[95]



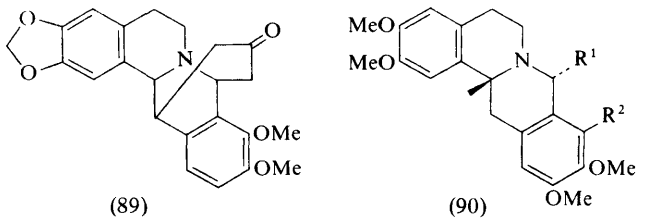
(85) R = H or Me (86)

A general synthesis of *C*-alkyl-dehydroberberines (88) by acid-catalysed cyclization of acyl-dienamines (87) is the subject of a recent patent.[96] The synthesis



(87) (88)

and spectral studies of various 13-alkyl-, 13-alkoxy-9-alkoxy-, and 8-oxo-berberines and related dehydro-compounds has been reported, together with a further preparation of the bridged compound (89).[97] A number of 8-substituted tetrahydroberberines of general structure (90), where R^1 = 4-methoxyphenyl,

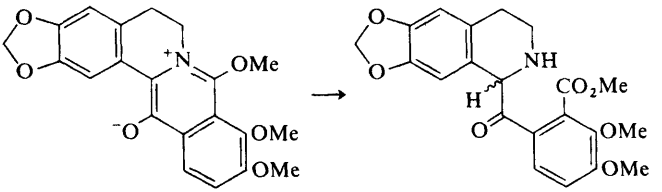


(89) (90)

3,4,5-trimethoxyphenyl, or 3,4,5-trimethoxybenzyl and R^2 = H or OMe, have been prepared, and it has been claimed that they have antiarrhythmic and antifungal properties.[98] Another synthesis of tetrahydroberberines has been reported, but details are not readily accessible.[99]

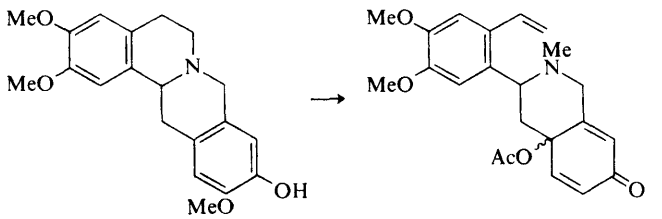
[95] G. R. Lenz, *J. Org. Chem.*, 1977, **42**, 1117.
[96] T. Tayama and Y. Izuka, Japan. Kokai 76 34 200 (*Chem. Abs.*, 1976, **85**, 94 584).
[97] S. Pavelka and J. Kovar, *Coll. Czech. Chem. Comm.*, 1976, **41**, 3654.
[98] G. R. Lenz, U.S. P. 4 013 666 (*Chem. Abs.*, 1977, **87**, 23 587).
[99] H.-C. Chiang and E. Brockmann-Hanssen, *T'ai-wan Yao Hsueh Tsai Chih*, 1975, **27**, 90.

Berberine has been converted into a mixture of α- and β-hydrastines, in the proportions 1:2; oxidation with potassium ferricyanide produced dimeric oxybisberberine, which with methanolic hydrochloric acid yielded the betaine (91). Hydration of this, followed by *N*-methylation, yielded the keto-ester (92), which gave α- and β-hydrastines on reduction with sodium borohydride and subsequent hydrolysis.[100] The photo-oxidation of tetrahydroberberine methiodide to allocryptopine has been reported.[101]

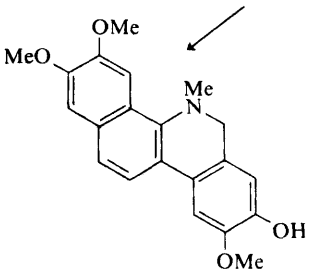


(91) (92)

A conversion of *O*-demethylxylopinine (93) into the sanguinarine analogue (95) *via* the acetoxy-dienone (94) has been reported.[102]



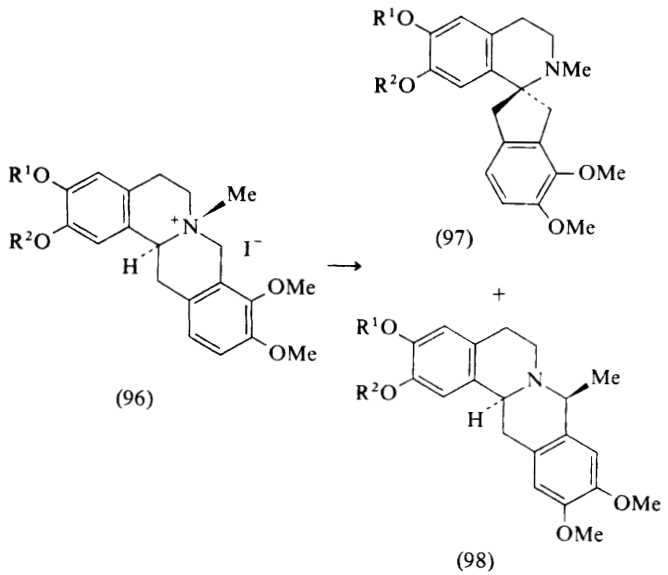
(93) (94)



(95)

Stevens rearrangements of canadine methiodide (96; $R^1R^2 = CH_2$) and of tetrahydropalmatine methiodide (96; $R^1 = R^2 = Me$) occur with sodium di(2-methoxyethoxy)aluminium hydride under reflux in dioxan; each affords a mixture of the corresponding spiro-base (97) and the 8-methyl compound (98) in the proportions of *ca.* 3:2.[103,104]

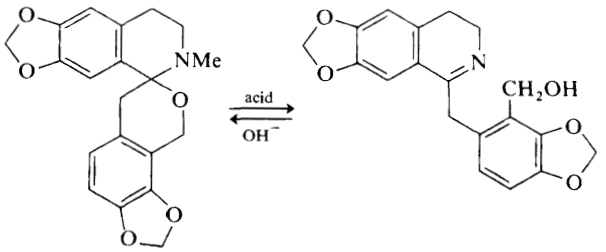
[100] J. L. Moniot and M. Shamma, *J. Amer. Chem. Soc.*, 1976, **98**, 6714.
[101] M. Hanaoka, C. Mukai, and Y. Arata, *Heterocycles.*, 1976, **4**, 1685.
[102] T. Kametani, M. Takemura, M. Ihara, K. Fukumoto, and K. Takahashi, *Heterocycles*, 1977, **6**, 99.
[103] T. Kametani, S.-P. Huang, A. Ujiie, M. Ihara, and K. Fukumoto, *Heterocycles*, 1976, **4**, 1223.
[104] T. Kametani, A. Ujiie, S.-P. Huang, M. Ihara, and K. Fukumoto, *J.C.S. Perkin I*, 1977, 394.



(96) (97) (98)

Bisquaternary salts of berberine, dihydroberberine, and other alkaloids have been prepared by quaternization with dihalides such as 2,2′-dichlorodiethylamine, sarcolysin, and cyclophosphane.[105]

Among modified berberines, hypecorine exhibits cyclo–chain tautomerism, the base (99) being converted into the salt (100), which, on reduction with sodium



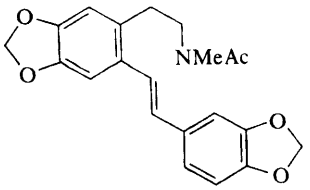
(99) (100)

borohydride and treatment with acetic anhydride, is converted into the amide (101).[106] Macrantaline, a new alkaloid from *Papaver pseudoorientale* (Fedde) Medw., has been assigned the structure (102) on the basis of spectroscopic studies.[107] Berbans of structure (104) have been prepared by cyclization of benzoquinolizidine propionates (103), where R = Me or R R = OCH_2O, followed by

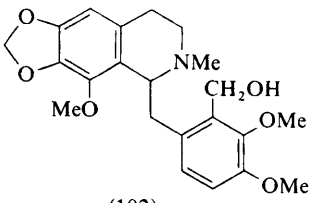
[105] L. I. Petlichnaya, E. L. Besyadetskaya, M. S. Oleiovskaya, O. G. Demchuk, and D. P. Boikiv, *Farm. Zhur. (Kiev)*, 1976, **31**, 34.

[106] L. D. Yakhontova, M. N. Komarova, O. N. Tolkachev, and M. E. Perel'son, *Khim. prirod. Soedinenii*, 1976, 491.

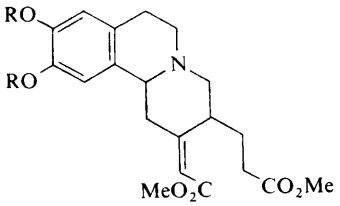
[107] G. Sariyar, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1976, **12**, 171.



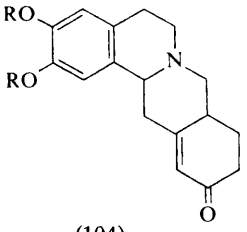
(101)



(102)



(103)



(104)

hydrolysis of the resulting β-keto-esters. They are claimed to be inhibitors of prostaglandin dehydrogenase and of prostaglandin synthetase.[108,109]

8 Protopines

Protopine has been found in *Argemone mexicana*,[110] and allocryptopine in *Thalictrum revolutum*.[44] Allocryptopine has been prepared by photo-oxidation of tetrahydroberberine methiodide.[101]

9 Phthalide-isoquinoline Alkaloids

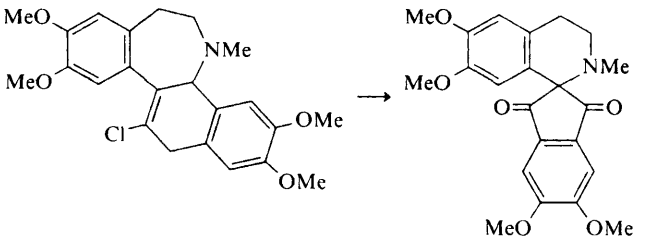
The preparation of cotarnine and opianic acid by the electrolysis of narcotine in the presence of sodium hydrogen sulphate and calcium chloride has been described.[3,111] The separation of narcotine, morphine, and codeine on t.l.c. plates[112] and methods for the detection of metabolites of narcotine and gnoscopine in urine[113] have been reported.

The preparation of α- and β-hydrastines from berberine has been described above.[100] Photoracemization and epimerization of (−)-α-narcotine and of (−)-β-hydrastine to mixtures of (±)-α- and (±)-β-narcotines and of the corresponding hydrastines has been observed.[114]

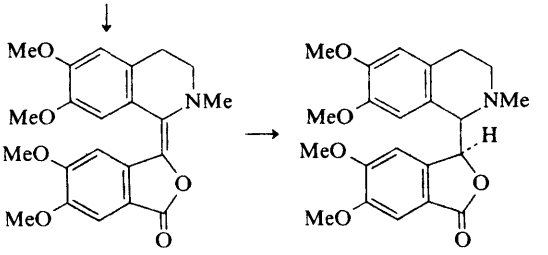
A new synthetic route to the phthalide-isoquinoline and spiro-benzylisoquinoline alkaloids has been developed. The indeno[2,1-*a*]benzazepine (105),

[108] L. Szabo, I. Toth, K. Honty, L. Toke, J. Tamas, and C. Szantay, *Chem. Ber*, 1976, **109**, 1724.
[109] L. Szabo, I. Toth, L. Toke, P. Kolonits, and C. Szantay, *Chem. Ber.*, 1976, **109**, 3390.
[110] W. Doepke, U. Hess, and V. Jimenez, *Z. Chem.*, 1976, **16**, 54.
[111] M. Ya. Fioshin, M. Zh. Zhurinov, and N. A. Prikhod'ko, U.S.S.R. P. 507 561 (*Chem. Abs.*, 1976, **85**, 21 691).
[112] R. L. Munier and A. M. Drapier, *Compt. rend.*, 1976, **283**, *C*, 719.
[113] W. Tsunoda, H. Yoshimura, and H. Kozuka, *Eisei Kagaku*, 1976, **22**, 280.
[114] T. Kametani, H. Inoue, T. Honda, T. Sugahara, and K. Fukumoto, *J.C.S. Perkin I*, 1977, 374.

on oxidation with potassium permanganate in piperidine, is converted into a mixture of the spiro-compound (106) and the enol-lactone (107); reduction of the latter gives a mixture of the *erythro*- and *threo*-isomers of the phthalide-isoquinoline (108).[115]

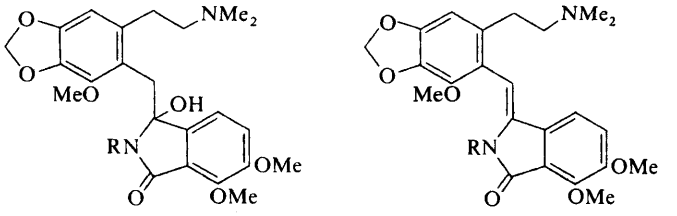


(105) (106)



(107) (108)

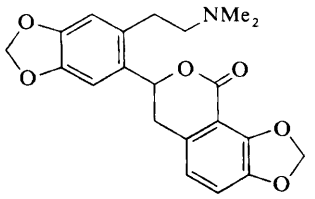
Amides of aponarceine of structure (109) have been prepared by the action of primary amines on aponarceine hydrochloride in warm ethanol, followed by liberation of the base with ammonia. Diamines have been used successfully in the process.[116] Dehydration of the amides yields the corresponding enamides (110).[117]



(109) (110)

The modified alkaloid peshawarine (111) has been isolated from *Hypecoum parviflorum* and the methylenedioxy-dimethoxy-analogue has been prepared from canadaline.[118] Fuller details of work already reported (see Vol. 7) on the isolation and identification of aobamine and aobamidine have been published.[119]

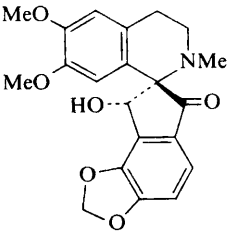
[115] T. Kametani, T. Ohsawa, S. Hirata, M. K. Premila, M. Ihara, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1977, **25**, 321.
[116] Z. Koblicova, J. Kreckova, and J. Trojanek, Czech. P. 165 700 (*Chem. Abs.*, 1977, **86**, 171 702).
[117] Z. Koblicova, J. Kreckova, and J. Trojanek, Czech. P. 165 701 (*Chem. Abs.*, 1977, **86**, 171 703).
[118] M. Shamma, A. S. Rothenberg, G. S. Jayatilake, and S. F. Hussain, *Heterocycles*, 1976, **5**, 41.
[119] T. Kametani, M. Takemura, M. Ihara, and K. Fukumoto, *J.C.S. Perkin I*, 1977, 390.



(111)

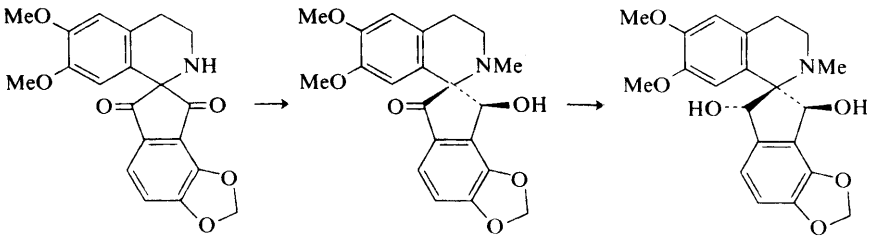
10 Spirobenzylisoquinoline Alkaloids

A new alkaloid, assigned the structure of *O*-methylcarpaine (112), has been isolated from *Corydalis vaginans*.[120] Fuller details of the isolation and inter-



(112)

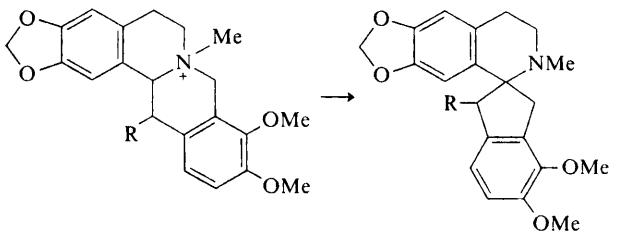
relationships of raddeanamine, raddeanine, and raddeanidine, previously reported (see Vol. 6), have been published.[119] Syntheses of yenhusomine (115) and yenhusomidine (114), by the condensation of homoveratrylamine with methylenedioxytriketohydrindene to give the base (113), followed by *N*-methylation and reduction with sodium borohydride, have been achieved.[121]



(113) (114) (115)

Optically active ochotensanes of structure (117) have been obtained from (+)- and (−)-β-canadine methochloride (116; R = H) and *N*-methylthalictricavine chloride (116; R = Me) by rearrangement with organometallic compounds, other products being the two Hofmann degradation products.[122]

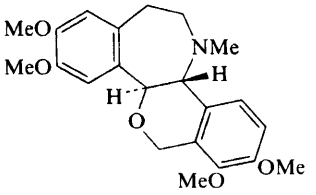
[120] N. N. Margvelashvili, O. E. Lasskaya, A. T. Kir'yanova, and O. N. Tolkachev, *Khim. prirod. Soedinenii*, 1976, 123.
[121] H. Irie, A. Kitagawa, A. Kuno, J. Tanaka, and N. Yokotani, *Heterocycles*, 1976, **4**, 1083.
[122] J. Imai, Y. Kondo, and T. Takemoto, *Tetrahedron*, 1976, **32**, 1973.



(116) (117)

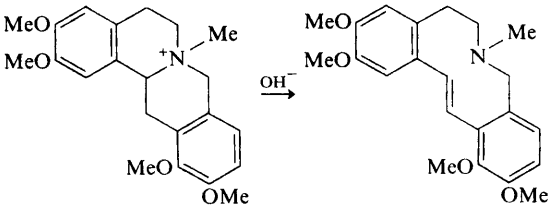
11 Rhoeadine Alkaloids

Alpinigenine (118) has been isolated from *Papaver bracteatum*,[6] and has been shown by feeding experiments to be synthesized in the plant *via* tetrahydro-

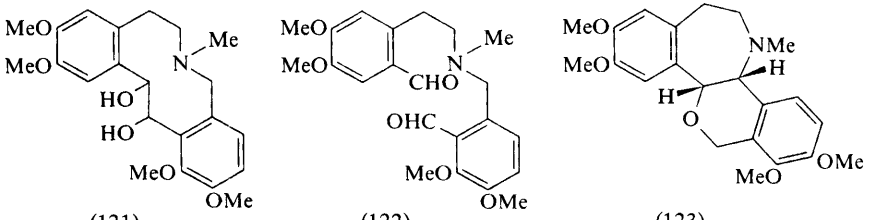


(118)

berberine- and protopine-type intermediates.[123] (±)-*cis*-Alpinigenine (123) has been synthesized by the photolysis of the dialdehyde (122) that is obtained from the unnaturally substituted tetrahydroberberinium salt (119) *via* the methine base (120) and the vicinal diol (121) that results from treatment of (120) with *N*-bromosuccinimide and then hydrolysis of the bromohydrin.[124]



(119) (120)



(121) (122) (123)

[123] H. Roensch, *Phytochemistry*, 1977, **16**, 691.
[124] S. Prabhakar, A. M. Lobo, and I. M. C. Oliveira, *J.C.S. Chem. Comm.*, 1977, 419.

12 Morphine Alkaloids

In the analytical field, methods have been reported for the rapid separation by g.l.c. of picogram quantities of morphine and codeine,[125] for the determination of morphine,[126,127] morphinan,[128] and heroin and its metabolites[129] in urine, for the isolation of hydromorphone (14-hydroxydihydromorphinone) and its metabolites from urine,[130] for the detection of nanogram quantities of codeine in plasma[131] and of hydrocodone (14-hydroxydihydrocodeinone) in serum,[132] for the detection of morphine by t.l.c.,[133,134] and for the assay of the binding of narcotics to brain tissue.[135] Details of methods of radioimmunassay of morphine,[136—138] for the estimation of morphine and codeine in urine[139] and in brain,[140] and reviews of methods of radioimmunassay[141] and of its use in pharmacokinetics[142] have been published.

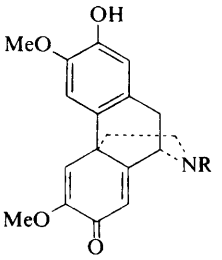
Varieties of *Papaver somniferum* with varying content of morphine alkaloids have been studied, and varieties having a genetically governed low alkaloid content have been identified.[143] The dynamics of the variation of amount of morphine and codeine present in *P. somniferum* with time of harvesting of the capsule have been studied.[144] The thebaine content of *P. bracteatum* in relationship to plant development has been studied, and strains have been isolated from which may be obtained a dried latex that contains >55% thebaine, corresponding theoretically to a yield of 58 kg ha^{-1} or approximately 50 kg ha^{-1} from harvested capsule.[145]

Two isomeric *N*-oxides of morphine, of codeine, and of thebaine have been isolated from *P. somniferum*, and the thebaine *N*-oxides are also present in *P. bracteatum*. The oxides have, in each case, also been prepared by the *N*-oxidation of the free bases. N.m.r. spectroscopic studies suggest that the nitrogen–oxygen bond is axial in the major isomer and equatorial in the minor.[146]

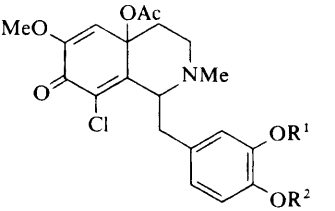
New bases that have been isolated are represented by norpallidine (124; R = H), from *Fumaria vaillantii*, identified by its Eschweiler methylation to pallidine (124; R = Me).[147] Pallidine has been shown to be produced (together with coreximine,

[125] M. J. Cogan and M. A. Chedekel, *J. Pharm. Pharmacol.*, 1976, **28**, 261.
[126] G. J. George, *Clin. Toxicol.*, 1976, **9**, 435.
[127] J. H. Rengerink and I. C. Dijkhuis, *Pharm. Weekblad.*, 1976, **111**, 701.
[128] R. E. Weinfeld, A. Holazo, and S. A. Kaplan, *J. Pharm. Sci.*, 1976, **65**, 1827.
[129] S. Y. Yeh, R. L. McQuinn, and C. W. Gorodetzky, *J. Pharm. Sci.*, 1977, **66**, 201.
[130] E J. Cone, *J. Chromatog.*, 1976, **129**, 355.
[131] P. Haefelfinger, *J. Chromatog.*, 1976, **124**, 351.
[132] J. W. Barnhart and W. I. Caldwell, *J. Chromatog.*, 1977, **130**, 243.
[133] K. K. Kaistha and R. Tadrus, *Clin. Chem.*, (*Winston-Salem N.C.*), 1976, **22**, 1936.
[134] M. Caldini, M. A. Bianchi, and T. Valenza, *Cron. Chim.*, 1976, **48**, 3 and 31.
[135] F. Medzihradsky, *Brain Res.*, 1976, **108**, 212.
[136] G. W. Aherne, E. M. Piall, J. D. Robinson, B. A. Morris, and V. Marks, *Radioimu, Chim. Biochem.*, [Symposium papers], 1975, 81.
[137] K. E. Rubinstein, R. S. Schneider, and E. F. Ullmann, *Mod. Pharmacol. Toxicol.*, 1975, **5**, 367.
[138] A. R. Gintzler, E. Mohacsi, and S. Spector, *European J. Pharmacol.*, 1976, **38**, 149.
[139] N. C. Jain, T. C. Sneath, W. J. Leung, and R. D. Budd, *J. Pharm. Sci.*, 1977, **66**, 66.
[140] D. M. Catlin, J. C. Schaeffer, and M. B. Liewen, *Life Sci.*, 1977, **20**, 123.
[141] S. Spector, *Mod. Pharmacol. Toxicol.*, 1975, **5**, 361.
[142] D. H. Catlin, *J. Pharmacol. Exp. Ther.*, 1977, **200**, 224.
[143] U. Nyman and O. Hall, *Hereditas*, 1976, **84**, 69.
[144] A. I. Dumitrashko, *Issled. Obl. Farm. Khim.*, 1975, 69, 71 (*Chem. Abs.*, 1977, **86**, 52 665, 52 666).
[145] J. W. Fairbairn and K. Helliwell, *J. Pharm. Pharmacol.*, 1977, **29**, 65.
[146] J. D. Phillipson, S. S. Handa, and S. El Dabbas, *J. Pharm. Pharmacol.*, 1976, **28**, suppl., p. 70P
[147] M. Shamma, P. Chinnasamy, S. F. Hussain, and F. Khan, *Phytochemistry*, 1976, **15**, 1802.

scoulerine, and norboldine) from reticuline by enzymes present in rat liver homogenate, the oxidations being stimulated by NAD, NADP, and NADPH. The *N*-methyl group of reticuline is not incorporated into the protoberberines produced in this way.[148] Some analogues of pallidine (126; $R^1R^2 = CH_2$) and (126; $R^1 = R^2 = Me$) have been obtained by the action of trifluoroacetic acid on the acetoxy-dienones (125; $R^1R^2 = CH_2$) and (125; $R^1 = R^2 = Me$), other products of the reactions being the isopavines (127) and aporphines.[149] Similar reactions have been observed with the phenethylisoquinoline analogues of (125).[149]



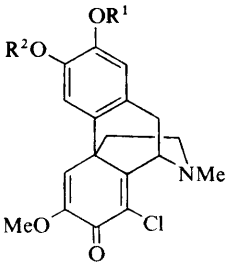
(124)



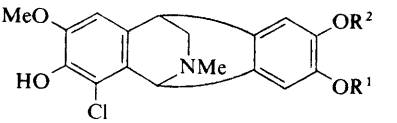
(125)

F_3CCO_2H

F_3CCO_2H



(126)

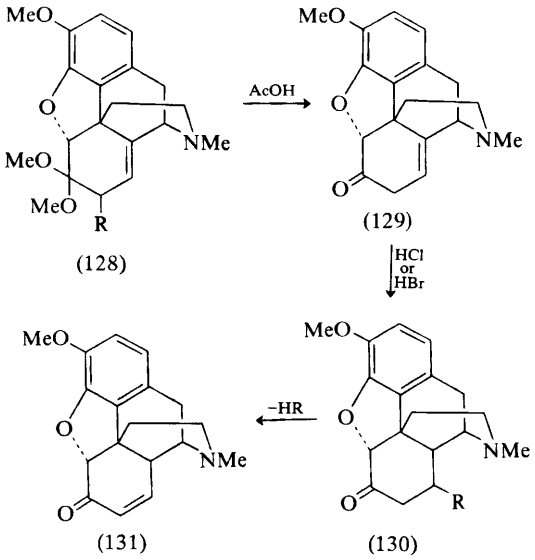


(127)

A new method for the demethylation of codeine to morphine, previously a capricious reaction, has been reported, the product being obtained in good yield. Demethylation by boron tribromide in chloroform gives 90—91%[150] and by potassium t-butoxide in propanethiol gives 80% morphine.[151] A patent describes an improved method for the preparation of codeinone from thebaine, by adding the alkaloid to anhydrous hydrogen bromide in solution in methylene chloride and dibutyl ether at −20 °C, in the presence of small quantities of iodine, followed by hydrolysis with aqueous sodium bicarbonate. The claimed yields of codeinone are 95% crude and 90% after purification.[152] Codeinone is an intermediate in the conversion of thebaine into codeine. An overall yield of 85% of codeine from thebaine, without purification of any of the intermediates, has been claimed for an

[148] T. Kametani, Y. Ohta, M. Takemura, M. Ihasa, and K. Fukumoto, *Heterocycles*, 1977, **6**, 415.
[149] H. Hara, O. Hoshino, and B. Umezawa, *Heterocycles*, 1976, **5**, 1802.
[150] K. C. Rice, *J. Medicin. Chem.*, 1977, **20**, 164.
[151] J. A. Lawson and J. I. DeGraw, *J. Medicin. Chem.*, 1977, **20**, 165.
[152] Fabrica de Productos Quimicos y Farmaceuticos Abello S.A., Belg. P. 839 732 (*Chem. Abs.*, 1977, **87**, 6241).

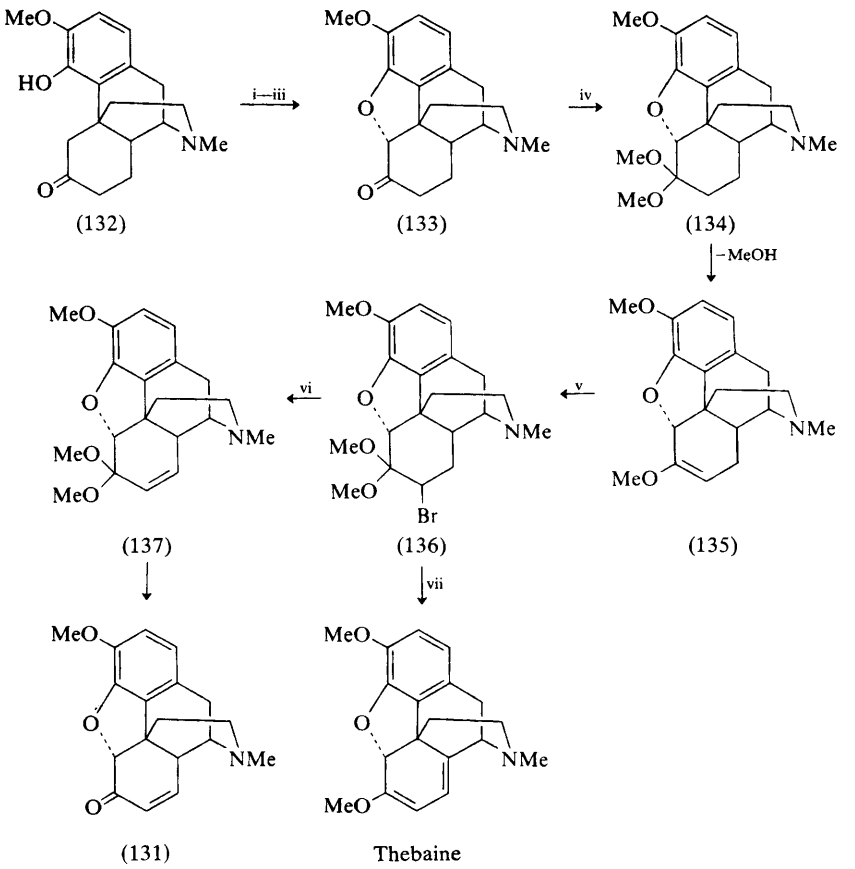
alternative process[153] in which thebaine is converted into 7-acetomercuri-neopinone followed by elimination of hydrogen halide from the resulting 8-chloro- or methanol. This can then be converted into neopinone (129) in 95—100% yield by hydrolysis with 3M-acetic acid, or by reduction with sodium borohydride followed by the hydrolysis of the resulting neopinone ketal (128; R = H). Addition of anyhydrous hydrogen chloride or bromide in ether–methylene chloride to neopinone followed by elimination of hydrogen halide from the resulting 8–chloro- or 8-bromo-dihydrocodeinone (130; R = Cl or Br) yields codeinone (131), reduction of which (by sodium borohydride) gives codeine.



(128) (129) (131) (130)

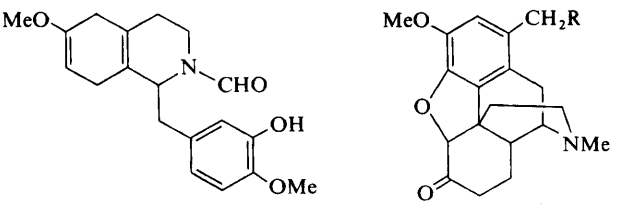
Codeine has also been prepared in 70% overall yield, again without purification of intermediate compounds, from dihydrothebainone (132) by the route (132) → (137) shown in Scheme 4. The initial product of the action of bromine and then alkali on dihydrothebainone is the 1,7-dibromo-derivative of dihydrocodeinone, which can be reduced to dihydrocodeinone (133). This may be converted into 7-bromodihydrocodeinone dimethyl ketal (136), which on treatment with potassium t-butoxide in DMSO at 120 °C is converted exclusively into thebaine, but at 60 °C the product is codeinone dimethyl ketal (137), which can be hydrolysed to codeinone (131).[154] The process has obvious value in the possible synthesis of codeine *via* dihydrothebainone, for which a patent has been filed covering a process that proceeds from the reduced isoquinoline (138);[155] the conversion of *N*-formylnordihydrothebainone into dihydrothebainone by hydrolysis and reductive methylation and by ketalization, reduction, and hydrolysis has been reported.[156]

[153] R. Barber and H. Rappoport, *J. Medicin. Chem.*, 1976, **19**, 1175.
[154] D. D. Weller and H. Rappoport, *J. Medicin. Chem.*, 1975, **19**, 1171.
[155] Akzo N.V., Netherlands Appl. 75 01 214 (*Chem. Abs.*, 1977, **87**, 23 585).
[156] H. C. Beyerman, L. Van Bommel, L. Maat, and C. Olieman, *Rec. Trav. chim.*, 1976, **95**, 312.



Reagents: i, Br_2; ii, OH^-; iii, H_2–Pd; iv, H^+–MeOH; v, MeCONHBr–MeOH; vi, $KOBu^t$–DMSO, 60 °C; vii, $KOBu^t$–DMSO, 120 °C

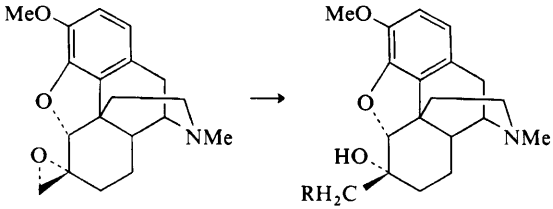
Scheme 4



Chloromethylation of dihydrocodeinone (133) yields the 1-chloromethyl compound (139; R = Cl), reducible (by zinc and acid) to 1-methyldihydrocodeinone (139; R = H), which can be further reduced to 1-methyldihydrocodeine and 1-methyldihydrothebainone.[157] Dihydrocodeinone reacts with dimethylsulphonium

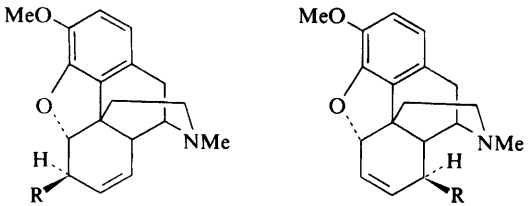
[157] C. Olieman, L. Maat and H. C. Beyerman, *Rec. Trav. chim.*, 1976, **95**, 189.

methylide to give the epoxide (140), which reacts with nucleophiles to give the substituted dihydrocodeines (141; R = H, Cl, N_3, or OH). The isomeric dihydroisocodeines can be obtained in the same way from the isomeric epoxide.[158] Dihydrocodeinone and other 6-ketones of the morphine group can be reduced to dihydrocodeine and analogues by formamidinesulphinic acid in aqueous alkalis.[159]



(140) (141)

Treatment of α-chlorocodide (142; R = Cl) with toluene-*p*-sulphonyl chloride yields ψ-codeine tosylate (143; R = OTs), which is converted by S_N1' reaction with lithium chloride, tetrabutylammonium fluoride, or piperidine into the 6-substituted compounds (142; R = Cl, F, or 1-piperidyl, respectively) and, by S_N1 reaction, with retention of configuration, into the 8-substituted bases (143; R = Br, I, SCN,



(142) (143)

SCOMe, or N_3) on treatment with the appropriate alkali-metal salt.[160] The reaction between 6-*O*-tosylcodeine and lithium chloride has been re-examined. In DMF at 40 °C it gives α-chlorocodide (142; R = Cl) by S_N2 reaction, and at 120 °C it gives β-chlorocodide (143; R = Cl) by S_Ni' rearrangement of the α-compound.[161] The 6-azido-compound (142; R = N_3; 6,7-dihydro) has also been prepared by the action of sodium azide on 6-*O*-toluene-*p*-sulphonyl-dihydrocodeine,[162] and analogous azides have been prepared from the toluene-*p*-sulphonyl esters of dihydromorphine,[163] 3-*O*-morpholinoethyldihydromorphine,[162] and their 14-hydroxy-analogues.[164] The chemical and pharmacological properties of 6-azido-6-deoxydihydroisomorphine have been the subject of a report.[165] The structures of the

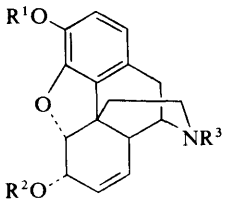
[158] G. Horvath, G. Gaal, P. Kerekes, and R. Bognar, *Magyar Kem. Folyoirat*, 1976, **82**, 418.
[159] N. Chatterjie, J. G. Umans, and C. E. Inturrisi, *J. Org. Chem.*, 1976, **41**, 3624.
[160] S. Makleit, G. Somogyi, and R. Bognar, *Acta Chim. Acad. Sci. Hung.*, 1976, **89**, 173.
[161] S. Makleit, T. Mile, and R. Bognar, *Acta Chim. Acad. Sci. Hung.*, 1976, **89**, 275.
[162] S. Makleit, J. Knoll, R. Bognar, S. Berenyi, G. Somogyi, and G. Kiss, *Magyar Kem. Folyoirat*, 1976, **82**, 432.
[163] S. Makleit, J. Knoll, R. Bognar, S. Berenyi, and G. Kiss, *Magyar Kem. Folyoirat*, 1976, **82**, 430.
[164] S. Makleit, J. Knoll, R. Bognar, S. Berenyi, G. Somogyi, and G. Kiss, *Magyar Kem. Folyoirat*, 1976, **82**, 434.
[165] A. V. Karamanian, H. Nagashima, P. A. Radney, S. Koerner, D. Dimcalf, R. Malovany, and F. F. Foldes, *Drug Alcohol Depend.*, 1976, **1**, 319.

halogeno-morphides have been further examined by n.m.r. spectroscopy, and their interactions with narcotic receptors have been studied.[166]

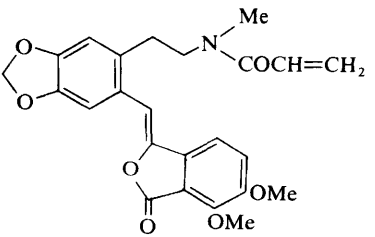
In view of the pharmacological and clinical importance of normophine derivatives and their 14-hydroxy-analogues, improved methods of *N*-demethylation are constantly being sought. Two such processes have recently been reported. *N*-Demethylation of morphine and of codeine by methyl chloroformate, followed by treatment with hydrazine, is reported to give 70—75% yields of the nor-compounds.[167] Using vinyl chloroformate, it has been found possible to capitalize on the disparity between the reactivity of vinylcarbonyl esters and amides towards acid- and base-catalysed hydrolysis, so as to use $CH_2{=}CH{-}CO{-}$ as a protecting group for hydroxy-groups. Morphine (144; $R^1 = R^2 = H$, $R^3 = Me$) reacts with 5 equivalents of vinyl chloroformate and 2 equivalents of 1,8-bisdimethylaminonaphthalene to give 91% of the *N*,3,6-trisubstituted compound (144; $R^1 = R^2 = R^3 = COCH{=}CH_2$), which can be hydrolysed by hydrogen bromide in ether–ethanol to the 3,6-disubstituted secondary base (144; $R^1 = R^2 = COCH{=}CH_2$, $R^3 = H$). Treatment of this with allyl bromide gives the *N*-allyl compound (144; $R^1 = R^2 = COCH{=}CH_2$, $R^3 = CH_2CH{=}CH_2$), which can be hydrolysed by aqueous hydrochloric acid to nalorphine (144; $R^1 = R^2 = H$, $R^3 = CH_2CH{=}CH_2$) in 83% overall yield from morphine.[168] The same general process can be used as an improved method for preparation of naloxone from diacetyl-14-hydroxy-dihydromorphinone.[169]

Like other acid chlorides and cyanogen bromide, vinyl chloroformate brings about fission of benzylic and allylic amines; *e.g.* hydrastine is converted into the enol lactone (145).[169] Normorphine and norcodeine give substituted thioureas (146) with alkyl isothiocyanates.[170]

The role of the gut in the metabolism of buprenorphine (147), etorphine, and dihydromorphine has been studied.[171] Buprenorphine labelled with deuterium at positions 15 and 16 has been prepared by deuteriation of the 15,16-dehydro-compound over 10% palladium on charcoal, without cleavage of the cyclopropane ring,[172] and deuterium-labelled morphine and codeine[173] and tritium-labelled

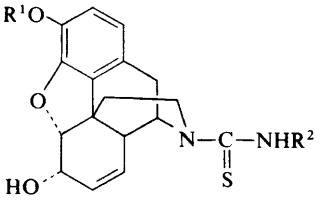


(144)

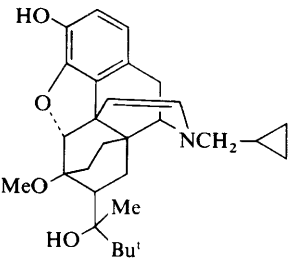


(145)

[166] H. J. C. Yeh, R. S. Wilson, W. A. Klee, and A. E. Jacobson, *J. Pharm. Sci.*, 1976, **65**, 902.
[167] G. A. Brine, K. Boldt, C. K. Hart, and F. I. Carroll, *Org. Prep. Proced. Internat.*, 1976, **8**, 103.
[168] R. A. Olofson and R. C. Schnur, *Tetrahedron Letters*, 1977, 1571.
[169] R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *Tetrahedron Letters*, 1977, 1567.
[170] R. Bognar, G. Gaal, P. Kerekes, G. Horvath, and E. Szikszai, *Acta. Chim. Acad. Sci. Hung.*, 1976, **89**, 55.
[171] M. J. Rance and J. S. Shillingford, *Biochem. Pharmacol.*, 1976, **25**, 735.
[172] M. J. Rance, J. D. Robinson, and K. T. Taylor, *J. Labelled Compounds Radiopharm.*, 1976, **12**, 467.
[173] J. A. Lawson, J. I. DeGraw, and M. Anbar, *J. Heterocyclic Chem.*, 1976, **13**, 593.



(146)

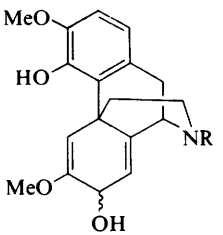


(147)

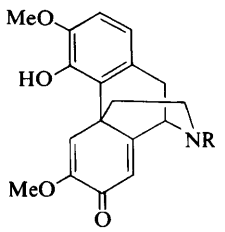
naloxone and naltrexone have been prepared.[174] The binding of labelled naltrexone in human and animal plasma has been studied.[175]

Morphine 6-hemisuccinate has been examined as an analgesic,[176] and novel derivatives of morphine and dihydromorphinone have been prepared by allowing these phenols to react with isocyanates (RNCO), halides ($R^1R^2CHCH_2Cl$), and chlorohydrins [$RCH_2CH(OH)CH_2Cl$].[177] A detailed study has been made of the fluorescence and phosphorescence characteristics of morphine, codeine, neopine, and thebaine, and of some of their derivatives, including representative bases of the 6,14-*endo*-ethenotetrahydrothebaine and oripavine series of highly potent analgesics.[178] Charge-transfer complexes of morphine and codeine with quinonoid acceptors have been prepared and their properties have been studied.[179]

Recent patents cover the conversion of both isomers of salutaridinol (148; R = Me) into thebaine in 80% yield by the action of thionyl chloride, phosphorus pentachloride, or other acid chlorides, followed by decomposition with bases.[180,181] *N*-Acyl-nor-reticulines have been cyclized by thallium tristrifluoroacetate to the *N*-acyl-norsalutaridines [149; R = Ac, F_3CCO, cyclo-C_3H_5CO, EtOCO, or $PhCH_2OCO$), which have been reduced to the corresponding salutaridinols (148); these have been cyclized by sodium hydroxide to the related acyl-northebaines.[182]



(148)

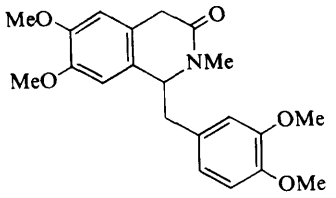


(149)

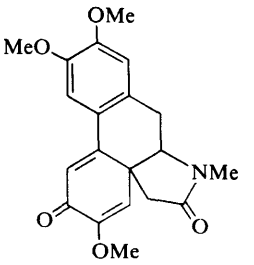
[174] G. A. Brine and J. A. Kepler, *J. Labelled Compounds Radiopharm.*, 1976, **12**, 401.
[175] T. M. Ludden, L. Malspeis, J. D. Baggot, T. D. Sokolski, S. G. Frank, and R. H. Reuning, *J. Pharm. Sci.*, 1976, **65**, 712.
[176] G. F. Gebhart and J. L. Spratt, *Life Sci.*, 1976, **18**, 829.
[177] G. Papaioannou, *European J. Med. Chem.-Chim. Ther.*, 1976, **11**, 287.
[178] A. Bowd and J. H. Turnbull, *J.C.S. Perkin II*, 1977, 121.
[179] A. Lamande, R. Knoesel, and L. Jung, *European J. Med. Chem.-Chim. Ther.*, 1976, **11**, 419.
[180] P. Sohar and E. F. Schoenewalt, Ger. Offen. 2 518 519 (*Chem. Abs.*, 1977, **86**, 55 618).
[181] Merck & Co. Inc., Netherlands Appl. 75 05 109 (*Chem. Abs.*, 1977, **86**, 155 849).
[182] M. A. Schwartz, U.S. P. 4 003 903 (*Chem. Abs.*, 1977, **86**, 155 848).

Reduction of the ethoxycarbonyl compound (149; R = EtOCO) with lithium aluminium hydride yields salutaridinol (148; R = Me).[182]

Morphinandienones have also been synthesized by the oxidation of monophenolic benzylisoquinolines with vanadium oxyfluoride in trifluoroacetic acid, other products of the reaction being proaporphines, and similar oxidations have been accomplished with phenethylisoquinolines.[183] The same reagent will oxidize the lactam (150) to the dienone (151), which is an analogue of dehydrometathebainone, and the same cyclization may be effected by electrochemical oxidation.[184]



(150)

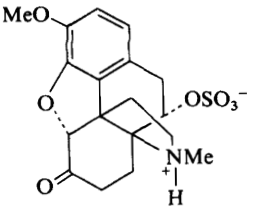


(151)

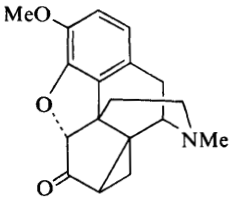
9-Sulpho-oxy-4,5-epoxyhasubananone (152), on treatment with alkalis, has been shown to give 7,14-cyclo-dihydrocodeinone (153) (70%), (14*R*)-14-hydroxy-7,8-dihydrocodeinone (154) (2%), the hasubanan derivatives (155) (3%) and (156) (1.5%), and also the bimolecular compound (157) (3.5%).[185] The key intermediate in most of these transformations is presumably the aziridinium ion (158), which can decompose in alkali by hydrolytic cleavage to the alcohol (154) or, alternatively, through the related carbanion, to the cyclopropane derivative (153). This cyclopropane derivative, when formed, can then be further attacked by the enolate ion derived from (152) in an aldol-type condensation to give an intermediate in which the second cyclopropane ring found in the bimolecular product (157) can subsequently be generated.[185] The two enol ethers may be presumed to arise in this reaction from contaminating enol ethers that are present in small amounts in the starting material (152) and which are generated during its preparation from the corresponding alcohol and dimethyl sulphate, there being no methylating agent present during the reaction with alkali.[186]

Biochemical studies of the effects of morphine and its analogues that have been described include the involvement of the central cholinergic system in the effects of morphine withdrawal;[187] the effects of administration of reserpine and of amphetamine on the development of tolerance to morphine;[188] the possible involvement of vitamin B_6 in dependence on morphine;[189] the loss of calcium from synaptosomes that is caused by morphine, and its reversal by nalorphine;[190] the

[183] S. M. Kupchan, O. P. Dhingra, and C.-K. Kim, *J. Org. Chem.*, 1976, **41**, 4049.
[184] I. W. Elliott, *J. Org. Chem.*, 1977, **42**, 1090.
[185] W. Fleischhacker and A. Klement, *Monatsh.*, 1976, **107**, 1029.
[186] W. Fleischhacker and A. Klement, *Monatsh.*, 1975, **106**, 1513.
[187] E. F. Domino, *Exerpta Med. Int. Congr. Sci.*, 1975, **359**, 287.
[188] I. Bantutova and R. Ovcharov, *Eksp. Med. Morfol.*, 1975, **14**, 196.
[189] P. M. L. Siu, S. West, and A. J. Bogdanova, *J. Neurochem.*, 1976, **26**, 633.
[190] D. H. Ross, S. C. Lynn, and H. L. Cardenas, *Life Sci.*, 1976, **18**, 789.



(152)



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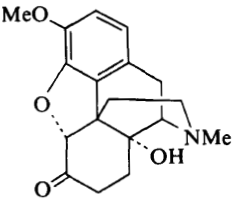

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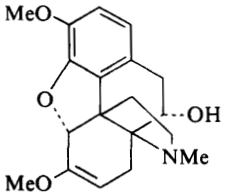
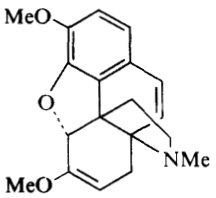
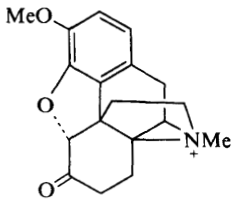


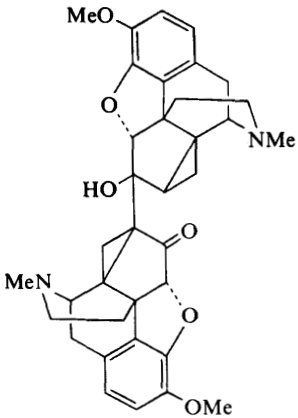
(155)



(156)



(158)



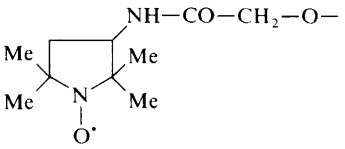
(157)

effects of morphine on calcium levels in brain membranes,[191,192] on brain histamine,[193] and on the retardation of brain growth;[194] morphine antibodies and dependence on morphine;[195] biochemical processes in morphine addicts;[196] studies of the narcotic receptor[197] and of its binding with etorphine[198] and with *N*-

[191] D. M. Ross, S. C. Lynn and D. J. Jones, *Proc. West. Pharmacol. Soc.*, 1976, **19**, 66.
[192] H. A. Yamamoto, R. A. Harris, H. H. Loh, and E. L. Way, *Proc. West. Pharmacol. Soc.*, 1976, **19**, 71.
[193] J. R. Lee and M. R. Fennessy, *Clin. Exp. Pharmacol. & Physiol.*, 1976, **3**, 179.
[194] I. S. Zagon and P. J. McLaughlin, *Pharmacology*, 1977, **15**, 276.
[195] M. Aoki, T. Kusama, N. Kuboyama, M. Makimura, and Y. Murakoshi, *Nippon Daigaku Yakugaku Kenkyu Hokoku*, 1975, **15**, 14.
[196] H. H. Loh, *Neurosci. Res. Program. Bull.*, 1975, **13**, 102, 143.
[197] A. Ward and A. E. Takemori, *J. Pharmacol. Exp. Therap.*, 1976, **199**, 117, 124.
[198] E. J. Simon, *Neurosci. Res. Program. Bull.*, 1975, **13**, 43.

quaternized laevorphanol and its *dextro*-isomer;[199] noradrenalin levels in morphine-tolerant and -dependent subjects;[200—206] morphine-induced changes in the release of acetylcholine;[207] the effect of morphine on testosterone levels and its blockade by nalorphine;[208] inhibition of ovulation by morphine;[209] the distribution and metabolism of naltrexone;[210—212] the chemical binding of morphine in brain;[213] the effects of morphine and of naloxone on the incorporation of thiamin in the central nervous system;[214] and the activating effect of bilirubin on glucuronyl transferase, leading to an increase in the execretion of morphine glucuronide.[215]

An e.s.r. study has been made of the kinetics of stereospecific binding of morphine in an exploration of the opiate receptor of the synaptosome. Morphine that is spin-labelled at C-3 or C-6 with the group (159) was used as the opiate



(159)

ligand, and the broadening of the e.s.r. lines induced by the immobilization of the ligand on the receptor was used to determine the concentration of bound opiate. Stereospecificity was determined by comparing ligand binding in the absence and in the presence of one-thousand-fold excess of dextrorphan and laevorphanol.[216]

The analgesic and antagonist properties of butorphanol (160) have been further studied,[217—219] as have those of the deoxymorphine derivative (161)[220] and the corresponding derivative of 3-hydroxymorphinan.[220] The comparative efficiencies

[199] K. E. Opheim and B. M. Cox, *J. Medicin. Chem.*, 1976, **19**, 857.
[200] M. J. Lewis, J. L. Costa, D. M. Jacobowitz, and D. L. Margules, *Brain Res.*, 1976, **107**, 156.
[201] A. S. Schwartz and P. L. Marchok, *Psychopharmacology*, 1976, **47**, 149.
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[204] L. Shuster, G. W. Webster and G. Yu, *Addict. Dis.*, 1975, **2**, 277.
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[206] J. P. O'Callaghan and S. G. Holtzman, *J. Pharmacol. Exp. Therap.*, 1976, **197**, 533.
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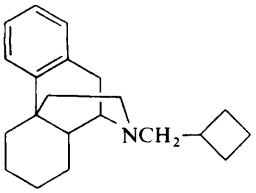
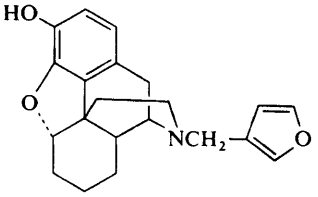
[209] P. M. Packman and J. A. Rothschild, *Endocrinology (Philadelphia)*, 1976, **99**, 7.
[210] A. L. Misra, R. Block, J. Vardy, S. J. Mule, and K. Verebely, *Drug Metab. Dispos.*, 1976, **4**, 276.
[211] L. Malspeis, T. M. Ludden, M. S. Bathala, B. E. Morrison, D. R. Feller, and R. H. Reuning, *Res. Comm. Chem. Pathol. Pharmacol.*, 1976, **14**, 293.
[212] K. Verebely, J. Volavka, S. J. Mule, and R. B. Resnick, *Clin. Pharmacol. Ther.*, 1976, **20**, 315.
[213] H. Yoshimura, R. Natsuki, S. Ida, and K. Oguri, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 906.
[214] A. L. Misra, H. L. Vadlamani and R. B. Pontani, *Experientia*, 1977, **33**, 372.
[215] R. A. Yeary, K. J. Wise, and D. R. Davis, *Res. Comm. Chem. Pathol. Pharmacol.*, 1977, **16**, 463.
[216] E. S. Copeland and L. De Barre, *Biophys. J.*, 1976, **16**, 1245.
[217] A. Pircio, J. A. Gylys, R. L. Cavanagh, J. P. Buyniski, and M. E. Bierwagen, *Arch. Internat. Pharmacodyn. Therap.*, 1976, **220**, 231.
[218] R. L. Cavanagh, J. A. Gylys and M. E. Bierwagen, *Arch. Internat. Pharmacodyn. Therap.*, 1976, **220**, 258.
[219] H. Nagashima, A. V. Karamanian, R. Malovany, P. Radnay, M. Ang., S. Koerner, and F. F. Foldes, *Clin. Pharmacol. Therap.*, 1976, **19**, 738.
[220] F. J. Kuhn and K. Stockhauss, *Arzneim.-Forsch.*, 1976, **26**, 2009.



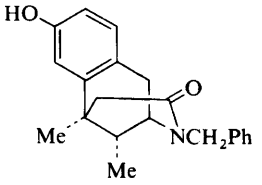
(160)



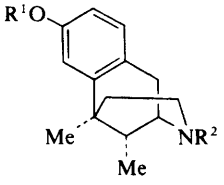
(161)

of nalorphine and naloxone as antagonists to neuroleptanalgesics have been studied.[221]

In the morphinan series, the preparation of 3-alkyl-morphinans[222] and 3-mercapto-morphinans[223] has been described. In the benzomorphan series, a novel cleavage of aryl benzyl ethers and of aryl allyl ethers has been described and used in an improved synthesis of pentazocine. The lactam (162), on hydrogenolysis, gives the benzomorphan (163; $R^1 = R^2 = H$). Treatment of this with dimethylallyl



(162)



(163)

bromide gives the tertiary base (163; $R^1 = R^2 = CH_2CH{=}CMe_2$), which can be subjected to ether cleavage to give pentazocine (163; $R^1 = H$, $R^2 = CH_2CH{=}CMe_2$).[224]

[221] W. D. Smith, *Brit. J. Anaesth.*, 1976, **48**, 1039.
[222] N. Nagano and K. Yoshida, Japan. Kokai 76 04 175 (*Chem. Abs.*, 1976, **85**, 124 220).
[223] M. Hori and H. Fujimura, Japan. Kokai 75 130 767 (*Chem. Abs.*, 1976, **85**, 21 690).
[224] T. Kametani, S.-P. Huang, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, 1976, **41**, 2545.

8

Aporphinoid Alkaloids

BY M. SHAMMA

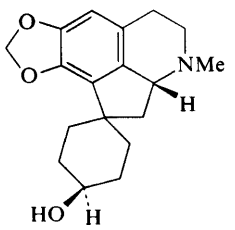
1 Introduction

A record number of new aporphine alkaloids, sixteen, has been isolated and characterized during the year under review. Even better methods for the synthesis of aporphines in high yields have been developed,[1-3] and an interesting relationship between aporphines, morphinandienones, neoproaporphines, and spirinedienones has been pointed out.[1] A novel and unusual alkaloid is eupolauramine (70), which is structurally related to the aristolactams but which incorporates an additional nitrogen atom in ring A.[4]

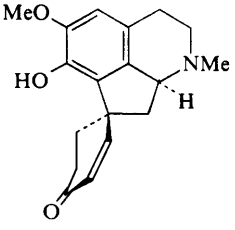
2 Proaporphines

(+)-*N*-Methyl-litsericine (1), a new proaporphine alkaloid, has been isolated from *Neolitsea aurata*.[5]

An *X*-ray study of the relative configuration of (±)-11,12-dihydroglaziovine (2) hydrobromide has been completed, as a result of which new stereochemical assignments for amuronine, amuroline, linearisine, crotsparinine, isocrotsparinine, jacularine, and Base E have been made.[6]



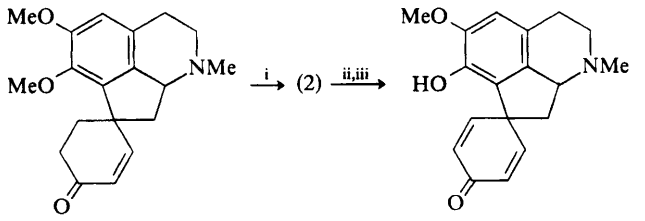
(1)



(2)

A convenient synthesis of glaziovine (4) and *N*-methyloreoline (7) has been described (Scheme 1). Refluxing amuronine (3) in 20% hydrochloric acid resulted in selective *O*-demethylation, to produce 11,12-dihydroglaziovine (2). Acetylation

[1] S. M. Kupchan and C.-K. Kim, *J. Org. Chem.*, 1976, **41**, 3210.
[2] S. M. Kupchan, O. P. Dhingra, and C.-K. Kim, *J. Org. Chem.*, 1976, **41**, 4049.
[3] R. Gottlieb and J. L. Neumeyer, *J. Amer. Chem. Soc.*, 1976, **98**, 7108.
[4] B. F. Bowden, H. C. Freeman, and R. D. G. Jones, *J.C.S. Perkin II*, 1976, 658.
[5] S. T. Lu, T. L. Su, and E. C. Wang, *J. Chinese Chem. Soc. (Formosa)*, 1975, **22**, 349.
[6] A. Colombo, *J.C.S. Perkin II*, 1976, 1218; see also these *Reports*, 1977, Vol. 7, p. 152.

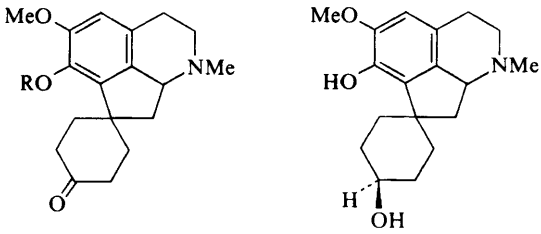


(3) (4)

Reagents: i, 20% HCl; ii, Ac_2O; iii, Br_2–HOAc; removal of HBr

Scheme 1

followed by bromination–dehydrobromination gave glaziovine (4). Similar demethylation of tetrahydropronuciferine (5) led to tetrahydroglaziovine (6). Reduction using triethylborohydride then furnished *N*-methyloreoline (7).[7]



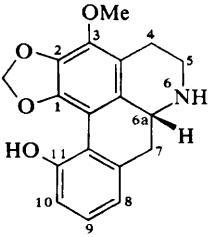
(5) R = Me
(6) R = H

(7)

The phenolic proaporphine alcohols produced by reduction of (2) and of 8,9-dihydroglaziovine with sodium borohydride have shown anxiolytic and antidepressant activity in rabbits.[8]

3 Aporphines

A new aporphine is (−)-elmerrillicine (8), found in the Southeast Asian tree *Elmerillia papuana* (Schltr.) Dandy (Magnoliaceae), and isolated as its *N*-acetyl

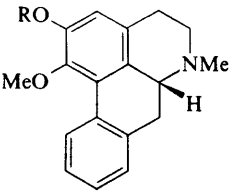


(8)

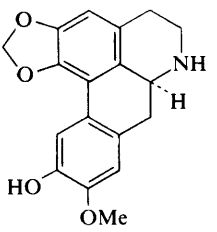
[7] J. S. Bindra and A. Grodski, *J. Org. Chem.*, 1977, **42**, 910; see also SIPHAR S. A., Ger. Offen, 2 534 410 (*Chem. Abs.*, 1976, **85**, 33 245).
[8] SIPHAR S. A., Fr. Demande 2 302 737 (*Chem. Abs.*, 1977, **86**, 190 318).

and *NO*-diacetyl derivatives. The structure of this alkaloid was confirmed by synthesis.[9]

Floripavidine (9) is a glycosidic aporphine found in *Papaver floribundum*. Its hydrolysis gives L-rhamnose and *N*-methylasimilobine.[10] The trunk bark of the northern Indian tree *Litsea sebifera* has yielded the new aporphine litseferine (10) together with the new morphinandienone sebiferine.[11]

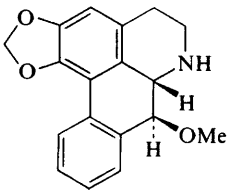


(9) R = L-rhamnose

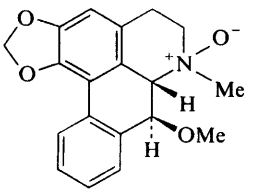


(10)

In an impressive achievement, the French school of Cavé and Leboeuf has reported nine new aporphines, namely (+)-pachypodanthine (11) from the West African trees *Pachypodanthium staudtii* Engl. et Diels (Annonaceae)[12] and from *Polyalthia oliveri* Engl. (Annonaceae);[13] *N*-oxy-*N*-methylpachypondathine (12),



(11)

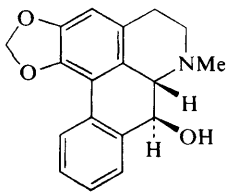


(12)

oliveroline (13), noroliveridine (14), and *N*-oxyoliveroline (15), also present in *P. oliveri*;[13] pachyconfine (16) and *N*-oxyguatterine (17) from *Pachypodanthium confine* Engl. et Diels;[14] and finally *N*-oxyoliverine (18) and *N*-oxyoliveridine (19) from the West African *Enantia pilosa* Exell (Annonaceae).[15]

Two new phenolic aporphines derived from the discolored sapwood of *Liriodendron tulipifera* are (+)-lirioferine (20) and (+)-liriotulipiferine (21).[16] (+)-*N*-Demethylthalphenine (22), previously known synthetically as a racemate, has now been obtained from *Thalictrum revolutum* DC.[17] A new *N*-acetylnoraporphine is (−)-tuliferoline (23), present in *Liriodendron tulipifera*, together

[9] L. Cleaver, S. Nimgirawath, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1976, **29**, 3002.
[10] I. A. Israilov, O. N. Denisenko, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 799 (*Chem. Abs.*, 1977, **86**, 171 679).
[11] M. Sivakumaran and K. W. Gopinath, *Indian J. Chem.*, 1976, **14B**, 150.
[12] F. Bévalot, M. Leboeuf, and A. Cavé, *Compt. rend.*, 1976, **282**, *C*, 865.
[13] M. Hamonnière, M. Leboeuf, and A. Cavé, *Phytochemistry*, 1977, **16**, 1029.
[14] F. Bévalot, M. Leboeuf, A. Bouquet, and A. Cavé, *Ann. Pharm. Franç.*, 1977, **35**, 65.
[15] M. Nieto, A. Cavé, and M. Leboeuf, *Lloydia*, 1976, **39**, 350.
[16] C.-L. Chen, H.-M. Chang, E. B. Cowling, C.-Y. Huang Hsu, and R. P. Gates, *Phytochemistry*, 1976, **15**, 1161.
[17] J. Wu, J. L. Beal, W.-N. Wu, and R. W. Doskotch, *Lloydia*, 1977, **40**, 292.



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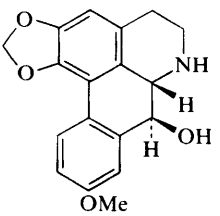

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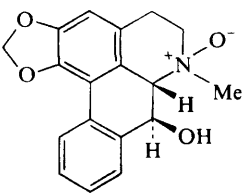
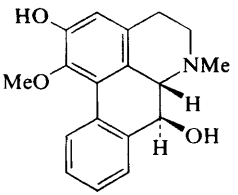
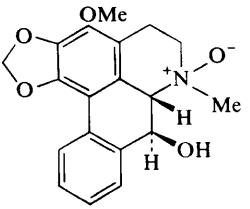


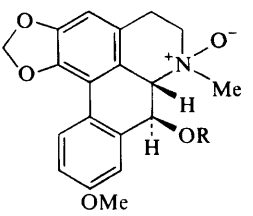
(15)



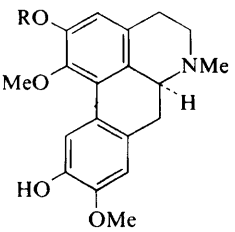
(16)



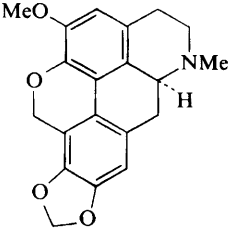
(17)



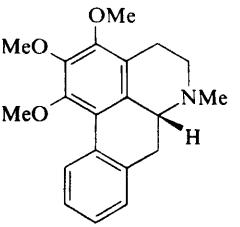
(18) R = Me
(19) R = H



(20) R = Me
(21) R = H



(22)



(23)

with (−)-*N*-acetylanonaine, (−)-*N*-acetylnornuciferine, and (−)-*N*-acetylasimilobine.[18]

Known aporphines that have recently been re-isolated from natural sources include those shown in Table 1.[19–27]

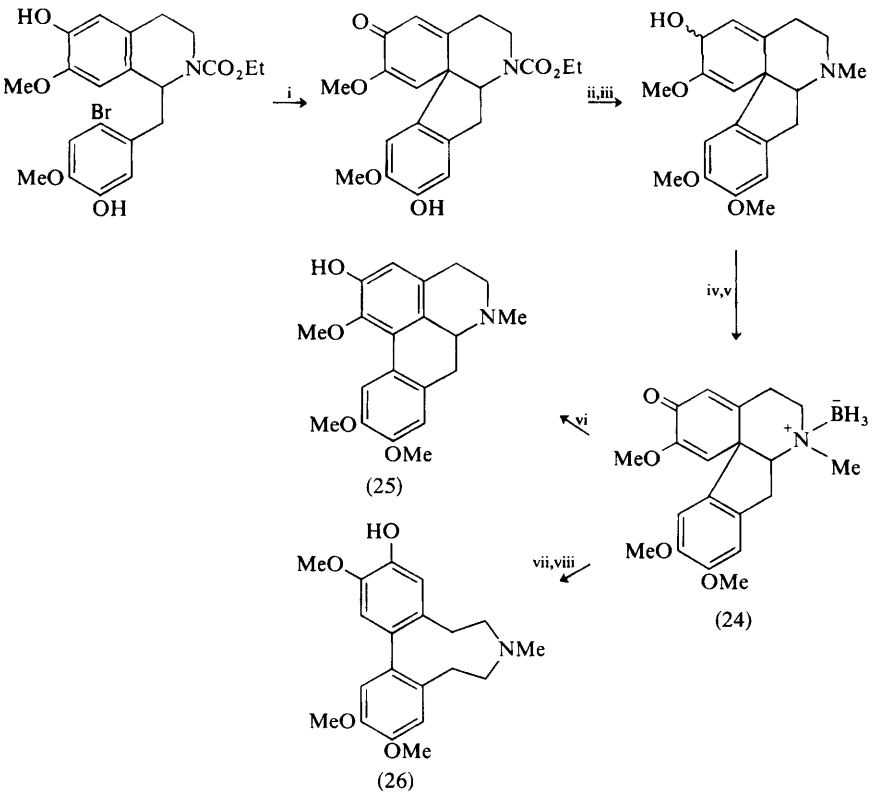
Some of the most interesting endeavours towards the efficient synthesis of aporphines were cut short by Prof. Kupchan's untimely death. The following,

[18] C. D. Hufford, *Phytochemistry*, 1976, **15**, 1169.
[19] A. Shafiee, I. Lalezari, and M. Mahjour, *J. Pharm. Sci.*, 1977, **66**, 593.
[20] A. Urzúa, B. Cassels, E. Sanchez, and J. Comin, *Anales Asoc. Quim. Argentina*, 1975, **63**, 259.
[21] B. K. Chowdhury, M. L. Sethi, H. A. Lloyd, and G. J. Kapadia, *Phytochemistry*, 1976, **15**, 1803.
[22] I. A. Israilov, M. U. Ibragimova, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 612.
[23] W.-N. Wu, J. L. Beal, L. A. Mitscher, K. N. Salman, and P. Patil, *Lloydia*, 1976, **39**, 204.
[24] W.-N. Wu, J. L. Beal, R.-P. Leu, and R. W. Doskotch, *Lloydia*, 1977, **40**, 281.
[25] A. Shafiee, I. Lalezari, F. Assadi, and F. Khalafi, *J. Pharm. Sci.*, 1977, **66**, 1050.
[26] T. Kametani, M. Takemura, and M. Ihara, *Phytochemistry*, 1976, **15**, 2017.
[27] P. G. Gorovoi, A. A. Ibragimov, S. Kh. Maekh, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 533.

Table 1 *Aporphines recently re-isolated from natural sources*

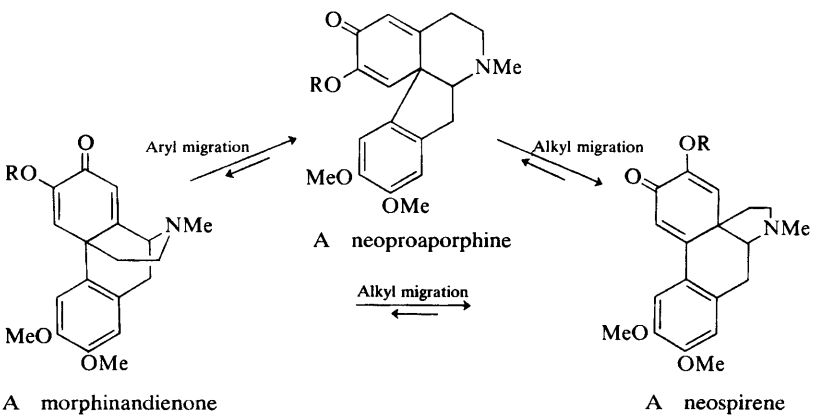
Alkaloid	*Source*	*Ref.*
Glaucine	*Liriodendron tulipifera*	16
	Glaucium oxylobum	19
Norglaucine	*Liriodendron tulipifera*	16
Dehydroglaucine	*Liriodendron tulipifera*	16
Thaliporphine	*Liriodendron tulipifera*	16
Predicentrine	*Liriodendron tulipifera*	16
	Glaucium oxylobum	19
Laurotetanine	*Laurelia sempervirens*, *L. philippiana*	20
N-Methyl-laurotetanine	*Liriodendron tulipifera*	16
Nuciferine	*Liriodendron tulipifera*	16
Nornuciferine	*Liriodendron tulipifera*	16
N-Acetylnornuciferine	*Liriodendron tulipifera*	16
Norushinsunine	*Elmerillia papuana*	9
	Liriodendron tulipifera	16
N-Methylushinsunine	*Elmerillia papuana*	9
Asimilobine	*Liriodendron tulipifera*	16
N-Acetylasimilobine	*Liriodendron tulipifera*	16
Guatterine	*Pachypodanthium confine*	14
Anonaine	*Polyalthia oliveri*	13
N-Methylcorydine	*Polyalthia oliveri*	13
Boldine	*Sassafras albidum*	21
Norboldine	*Sassafras albidum*	21
Isoboldine	*Sassafras albidum*	21
	Corydalis gortschakovii	22
Corydine	*Corydalis gortschakovii*, *C. intermedia*	22
Nantenine	*Laurelia sempervirens*	20
Nornantenine	*Laurelia sempervirens*	20
Magnoflorine	*Thalictrum lucidum*	23
	Thalictrum longistylum	24
Bisnorthalphenine	*Thalictrum revolutum*	17
Isothebaine	*Papaver orientale*	25
Corytuberine	*Corydalis pallida* var. *tenuis*	26
Bracteoline	*Corydalis gortschakovii*	22
Domesticine	*Corydalis gortschakovii*	22
Thalicminine	*Thalictrum strictum*	27
Ocoteine	*Thalictrum strictum*	27
O-Methylcassyfiline	*Thalictrum strictum*	27

however, has been demonstrated (Scheme 2). A neoproaporphine such as (24), obtained as indicated, will efficiently rearrange to the aporphine predicentrine (25) in acid solution, or to a dibenzazonine, *e.g.* (26), in basic medium.[1] At elevated temperatures, and in the presence of ethereal boron trifluoride, an equilibrium exists between a morphinandienone, a neospirene, and a neoproaporphine,[1] as shown in Scheme 3. Thus when *O*-methylflavinantine (27) was treated with ethereal boron trifluoride in refluxing benzene, and the mixture of products was reduced catalytically, thaliporphine (28), predicentrine (25), 2,9,10-trimethoxy-3-hydroxyaporphine (29), and erybidine (26) were obtained in a total overall yield of 80%,[1] as shown in Scheme 4.

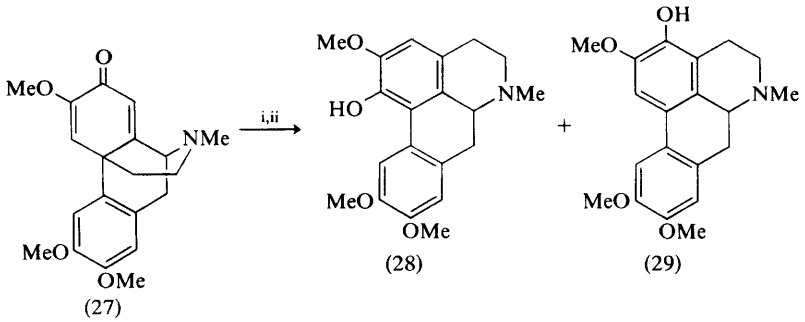


Reagents: i, *hν*, EtOH–NaOH; ii, MeI–K_2CO_3; iii, $LiAlH_4$; iv, BH_3–THF; v, MnO_2; vi, conc. HCl; vii, NaOH; viii, $NaBH_4$

Scheme 2



Scheme 3



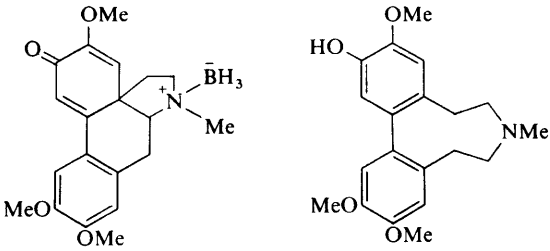
(27) (28) (29)

+(25) + (26)

Reagents: i, BF_3–PhH–ether, Δ; ii, H_2–Pt

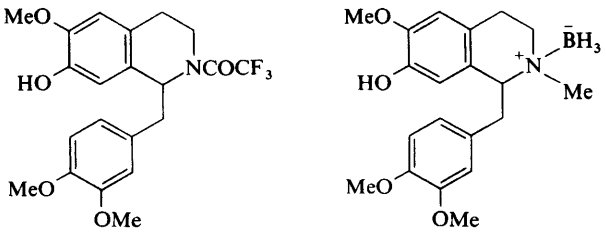
Scheme 4

Similar treatment of the neoproaporphine–borane complex (24) furnished predicentrine (25), erybidine (26), and 2,9,10-trimethoxy-3-hydroxyaporphine (29). Furthermore, the neospirene-borane complex (30), when subjected to the same experimental conditions, supplied thaliporphine (28), the erybidine isomer (31), and 2-hydroxy-3,9,10-trimethoxyaporphine,[1] which does not occur in Nature.



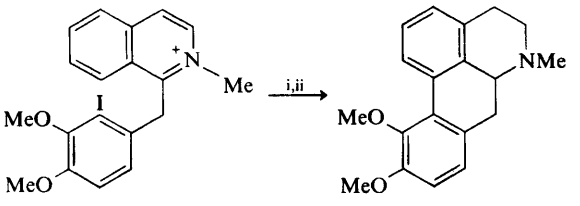
(30) (31)

The oxidation of non-basic and monophenolic tetrahydrobenzylisoquinolines with VOF_3–TFA is a superior method for aporphine preparation. *N*-Trifluoroacetylnorcodamine (32), under these conditions, gives a 70% yield of *N*-trifluoroacetylnorthaliporphine, while the codamine–borane complex (33) provides thaliporphine (28) in 80% yield. The reaction has also been extended to the preparation of homoaporphines.[2]



(32) (33)

Another superior synthesis of aporphines is that devised by Neumeyer and Gottlieb; it proceeds through the cathodic cyclization of a 1-(*o*-iodobenzyl)isoquinoline methiodide (Scheme 5). Electrolysis of (34) followed by reduction gave rise to 10,11-dimethoxyaporphine (35). Aporphine itself has also been prepared, by a parallel route.[3]



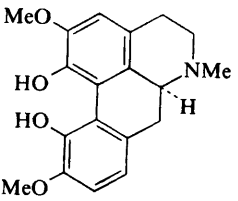
(34) (35)

Reagents: i, electrolysis in MeCN–Et_4NBr, Hg cathode; ii, H_2–Pt

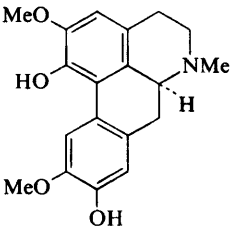
Scheme 5

Oxidation of (+)-reticuline perchlorate with cuprous chloride and oxygen in pyridine produced (+)-corytuberine (36) in 28% yield, and (+)-isoboldine (37) in 8% yield. Oxidation with cuprous chloride, therefore, favours *ortho–ortho* over *ortho–para* coupling.[28]

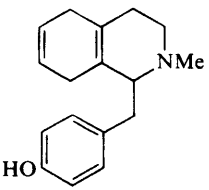
Acid-catalysed Grewe cyclization of the partially reduced benzylisoquinoline (38) resulted in the formation of aporphines (39)—(41).[29]



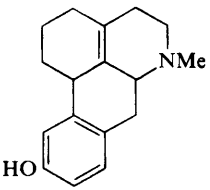
(36)



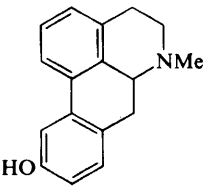
(37)



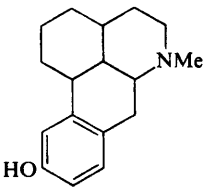
(38)



(39)



(40)



(41)

Full experimental details have appeared on the synthesis of bracteoline, isoboldine, *N*-methyl-laurotetanine, and related aporphines, through oxidation with

[28] T. Kametani, Y. Satoh, M. Takemura, Y. Ohta, M. Ihara, and K. Fukumoto, *Heterocycles*, 1976, **5**, 175.
[29] T. Kametani, T. Uryu, and K. Fukumoto, *J.C.S. Perkin I*, 1977, 383.

lead tetra-acetate and the intermediacy of *p*-quinol acetates.[30] When the initial quinol acetate, derived from oxidation of codamine with lead tetra-acetate, was treated with trifluoroacetic acid, a substantial increase in the yield of thaliporphine (28) was observed, while no *C*-4-oxygenated aporphine could be detected.[31] By appropriate modification of the starting benzylisoquinoline, domesticine as well as 1-hydroxy-2,9,10,11-tetramethoxyaporphine could also be obtained in good yield.[31,32]

Photolytic syntheses of norisoboldine,[33] isoboldine,[34] and norglaucine[34] have appeared.

An improved method for the preparation of apomorphine has been claimed, the details of which were not available to the Reporter.[35] A promising new approach to the aporphines is through the oxidative coupling of two aromatic rings to furnish a biaryl system, using thallium trifluoroacetate.[36]

Reticuline has been biotransformed into the morphinandienone pallidine, the aporphine isoboldine, and the protoberberines coreximine and scoulerine by rat liver enzyme;[37] and the use of isolated enzymes in the formation of natural products, including aporphines, has been reviewed.[38]

Dehydroglaucine and dehydronuciferine readily undergo C-7 to C-7′ coupling, using mercuric acetate or nitrate to form the corresponding aporphine and dehydroaporphine dimers.[39] Nuciferine, which is 1,2-dimethoxyaporphine, can be hydroxylated at C-3 by the sequence (i) bromination in trifluoroacetic acid, (ii) metallation with phenyl-lithium, and (iii) oxidation with excess nitrobenzene.[40]

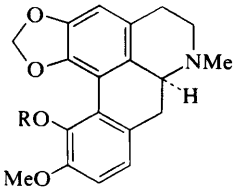
Dehydroaporphines undergo both *N*- and *C*-7-protonation in trifluoroacetic acid, but it is the *C*-7-protonated immonium salt which is formed almost exclusively under equilibration conditions.[41] Some *C*-6a- and *C*-7-deuteriated aporphines can, therefore, be prepared. The reaction of dehydronuciferine with dichlorocarbene yielded dehydronuciferine-7-carboxaldehyde. Reduction of this aldehyde with sodium cyanoborohydride afforded 7-methyldehydronuciferine.[42]

The reaction of (+)-bulbocapnine methyl ether (42) with excess boron trichloride in methylene chloride containing 0.3% ethanol produces the catechol (43) together with the monophenol (44). However, with boron tribromide, it is the diphenol (45) which is produced. Both compounds (44) and (45) can be *O*-methylated with diazomethane to the dimethyl ether (46), and hydrolysis of (46) with dilute hydrochloric acid leads to (+)-corytuberine (47).[43] Alternatively, methylation of (43), using diazomethane, affords (+)-corydine methyl ether (48).

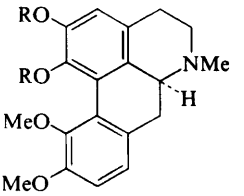
[30] H. Hara, O. Hoshino, and B. Umezawa, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 1921.
[31] H. Hara, O. Hoshino, and B. Umezawa, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 262.
[32] For a less efficient method see H. Hara, O. Hoshino, and B. Umezawa, *Heterocycles*, 1976, **5**, 213.
[33] H. Suguna and B. R. Pai, *Indian J. Chem.*, 1976, **14B**, 841.
[34] M. S. Premila and B. R. Pai, *Indian J. Chem.*, 1976, **14B**, 134.
[35] O. V. Kozlova, *Sb. Tr. Vses. N.-i. Khim.-farmatsevt. In-ta*, 1974, 125 (*Chem. Abs.*, 1976, **85**, 124 210).
[36] A. McKillop, A. G. Tunnell, and E. C. Taylor, *J. Org. Chem.*, 1977, **42**, 764.
[37] T. Kametani, Y. Ohta, M. Takemura, M. Ihara, and K. Fukumoto, *Heterocycles*, 1977, **6**, 415.
[38] K. L. Stuart, *Heterocycles*, 1976, **5**, 701.
[39] L. Castedo, R. Riguera, J. M. Sáa, and R. Suau, *Heterocycles*, 1977, **6**, 677.
[40] P. Wiriyachitra and M. P. Cava, *J. Org. Chem.*, 1966, **42**, 2274.
[41] A. Venkateswarlu and M. P. Cava, *Tetrahedron*, 1976, **32**, 2079.
[42] J. M. Sáa and M. P. Cava, *J. Org. Chem.*, 1977, **42**, 347.
[43] M. Gerecke, R. Borer, and A. Brossi, *Helv. Chim. Acta*, 1976, **59**, 2551.

In ethanol-free methylene chloride, treatment of (42) with boron tribromide supplies a mixture of (45) and the phenanthrene (49).[43]

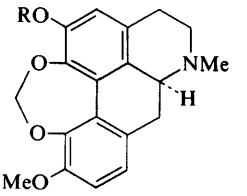
Natural (+)-bulbocapnine (50) can be converted into its enantiomer by oxidation to the dehydro-stage, reduction with zinc and hydrochloric acid, and resolution



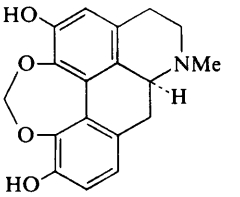
(42) R = Me
(50) R = H



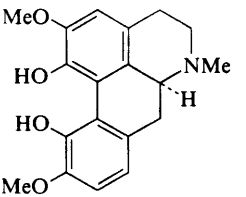
(43) R = H
(48) R = Me



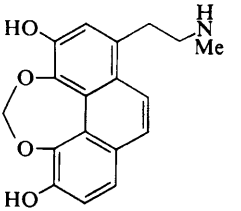
(44) R = H
(46) R = Me



(45)



(47)



(49)

(using L-tartaric acid). Sequential treatment of (−)-bulbocapnine with boron trichloride and then boron tribromide generates (−)-1,2,10,11-tetrahydroxyaporphine.[43] When the diphenol (43) was converted into its bisphenyltetrazolyl ether, and then subjected to hydrogenolysis over palladium, racemic 10,11-dimethoxyaporphine (35), *i.e.* racemic apomorphine dimethyl ether, was obtained.[44]

The *N*-demethylation of apomorphine, using methyl chloroformate followed by cleavage of the crude urethane with hydrazine, has been achieved.[45] Normorphothebaine, obtained by the rearrangement of northebaine, has been converted (in a series of steps) into a nitrogen mustard.[46]

Sodium benzylselenolate in refluxing DMF is a superior reagent for *O*-demethylation at the hindered 1-, 8-, and 11-positions of the aporphine nucleus. Methylenedioxy-functions survive the reaction.[47] The microbial transformation of glaucine produces mainly norglaucine and predicentrine (25).[48]

A review on the pharmacology and biochemistry of apomorphine has appeared.[49] *N*-n-Propylnorapomorphine and *N*-allylnorapomorphine show significant antagonism to morphine in mice and dogs.[50] 8-Hydroxy-*N*-n-propylnoraporphine demonstrates no dopamine agonist activity.[51] The action of

[44] S. Teitel and J. P. O'Brien, *Heterocycles*, 1976, **5**, 85.
[45] J. C. Kim, *Org. Prep. Proced. Internat.*, 1977, **9**, 1 (*Chem. Abs.*, 1977, **87**, 23 574).
[46] F. E. Granchelli, A. H. Soloway, J. L. Neumeyer, and C. N. Filer, *J. Org. Chem.*, 1977, **42**, 2014.
[47] R. Ahmad, J. M. Sáa, and M. P. Cava, *J. Org. Chem.*, 1977, **42**, 1228.
[48] P. J. Davis, D. Wiese, and J. P. Rosazza, *J.C.S. Perkin I*, 1977, 1.
[49] F. C. Colpaert, W. F. M. van Bever, and J. E. Leysen, *Internat. Rev. Neurobiol.*, 1976, **19**, 225.
[50] E. R. Atkinson, S. P. Battista, I. E. Ary, D. G. Richardson, L. S. Harris, and W. L. Dewey, *J. Pharm. Sci.*, 1976, **65**, 1682.
[51] J. L. Neumeyer, W. P. Dafeldecker, B. Costall, and R. J. Naylor, *J. Medicin. Chem.*, 1977, **20**, 190.

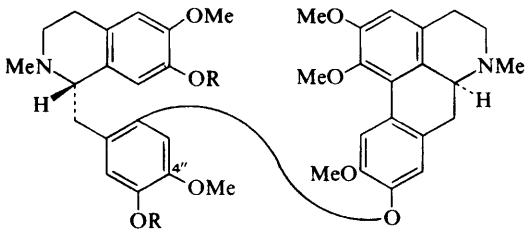
apomorphine on dopamine cyclase is one of stimulation at low concentrations and inhibition at high concentrations. The order of the agonist potency is *N*-allylapomorphine > 2-hydroxyapomorphine = apomorphine > norapomorphine.[52] The dopamine agonist activity of apomorphine has been related to its shape and conformation.[53] A number of diesters of apomorphine have been tested as prodrugs. They elicit prolonged duration of neuropharmacological effects in rats, the duration of action increasing with the size of the ester group.[54]

The new aporphine alkaloid oliveroline (13) exhibits antiparkinsonian activity, while oliveridine (*N*-methyl-14) and oliverine (*N*-deoxy-18) cause a dose-dependent hypotension in normal rats followed by a secondary hypertension. In the isolated rabbit ear, oliveridine has a vasodilating effect comparable to that of papaverine.[55] Cabudine, which corresponds to 1,2-methylenedioxy-3-hydroxymethyl-9-methoxydehydroaporphine, possesses adrenolytic activity.[56]

The H-11 proton of an aporphine incorporating a 1,2-methylenedioxy-group falls relatively upfield in the n.m.r. spectrum, between δ7.47 and δ7.86.[57] The ^{1}H n.m.r. spectra of a number of new aporphines have been tabulated.[16]

4 Aporphine–Benzylisoquinoline Dimers

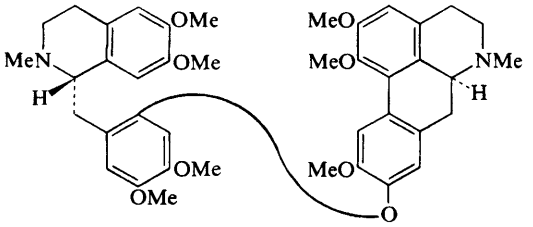
New aporphine–benzylisoquinolines are (+)-thalipine (51), present in *Thalictrum polygamum* Muhl. (Ranunculaceae)[58] and in *R. revolutum* DC,[59] and (+)-revolutopine (53), found in the latter plant.[59]



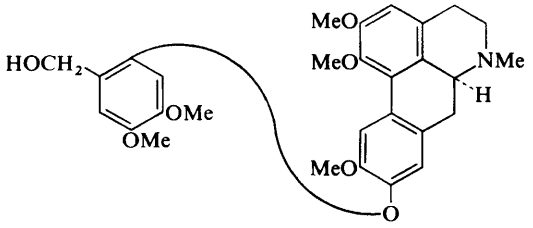
(51) R = H
(52) R = Me

Thalicarpine (52) can be *O*-demethylated at C-1 and at C-4″, using sodium benzylselenolate.[47] This same alkaloid can also be converted into (+)-hernandalinol (54), using the micro-organism *Streptomyces punipalus*.[60] Additionally,

[52] H. Sheppard and C. R. Burghardt, in 'Cyclic Nucleotides in Disease', ed. B. Weiss, University Park Press, Baltimore, 1975, p. 117.
[53] H. Sheppard, C. R. Burghardt, and S. Teitel, *Mol. Pharmacol.*, 1976, **12**, 854.
[54] R. J. Borgman, R. J. Baldessarini, and K. G. Walton, *J. Medicin. Chem.*, 1976, **19**, 717.
[55] A. Quevauviller and M. Hamonnière, *Compt. rend.*, 1977, **284**, *D*, 93.
[56] M. Kurbanov, Kh. Sh. Khusainova, M. Khodzimatov, A. E. Vezen, K. Kh. Khaidarov, and V. K. Burichenko, *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki*, 1972, **54**, 91 (*Chem. Abs.*, 1977, **87**, 33 690).
[57] M. Shamma and J. L. Moniot, *Experientia*, 1976, **32**, 282.
[58] M. Shamma, J. L. Moniot, and P. Chinnasamy, *Heterocycles*, 1977, **6**, 399.
[59] J. Wu, J. L. Beal, W.-N. Wu, and R. W. Doskotch, *Heterocycles*, 1977, **6**, 405.
[60] T. Nabih, P. J. Davis, J. F. Caputo, and J. P. Rosazza, *J. Medicin. Chem.*, 1977, **20**, 914.



(53)

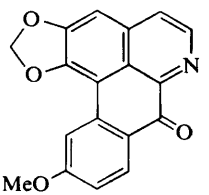


(54)

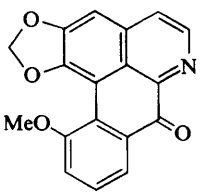
thalicarpine is an antitumour[61] agent which inhibits synthesis of protein, DNA, and RNA.[62]

5 Oxoaporphines

New oxoaporphines are oxolaureline (lauterine) (55), obtained from *Magnolia soulangeana* Soul-Bod (Magnoliaceae),[63] from *Laurelia novae-zelandiae* A. Cunn. (Monimiaceae),[64] and from *Guatteria elata* R. E. Fries (Annonaceae),[65] and oxoputerine (56), which is present, with (55), in *G. elata*.[65]



(55)



(56)

Known oxoaporphines that have been re-isolated from natural sources are shown in Table 2.[66,67]

[61] G. A. Cordell and N. R. Farnsworth, *Lloydia*, 1977, **40**, 1.
[62] W. A. Creasey, *Biochem. Pharmacol.*, 1976, **25**, 1887.
[63] R. Ziyaev, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 528.
[64] A. Urzúa and B. K. Cassels, *Heterocycles*, 1976, **4**, 1881.
[65] C. C. Hsu, R. H. Dobberstein, G. A. Cordell, and N. R. Farnsworth, *Lloydia*, 1977, **40**, 152.
[66] H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *J. Pharm. Soc. Japan*, 1976, **96**, 1458.
[67] R. Braz Filho, S. J. Gabriel, C. M. R. Gomes, O. R. Gottlieb, M. D. G. A. Bichara, and J. G. S. Maia, *Phytochemistry*, 1976, **15**, 1187.

Table 2 *Oxoaporphines recently re-isolated from natural sources*

Alkaloid	*Source*	*Ref.*
Liriodenine	*Xanthoxylum cuspidatum*	66
	Polyalthia oliveri	13
	Laurelia novae-zelandiae	64
	Enantia pilosa	15
	Liriodendron tulipifera	16
	Fusea longifolia	67
	Siparuna guianensis	67
Lanuginosine	*Polyalthia oliveri*	13
	Enantia pilosa	15
Atheroline	*Laurelia sempervirens, L. philippiana*	20
O-Methylatheroline (Oxoglaucine)	*Liriodendron tulipifera*	16
Cassamedine	*Siparuna guianensis*	67
Carunnine	*Liriodendron tulipifera*	16

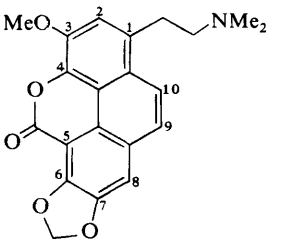
The eosin-sensitized photo-oxidation of glaucine, dehydroglaucine, and norglaucine in ethanol gives *O*-methylatheroline (oxoglaucine) in high yield.[68]

A detailed analysis of the ^{1}H n.m.r. spectra of oxoaporphines has been given. In particular, it has been shown that H-11 does not necessarily appear downfield from H-8.[64]

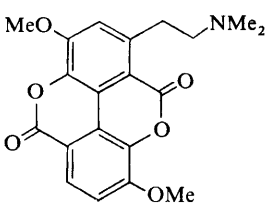
6. Phenanthrenes, Taspine, 4,5-Dioxoaporphines, Aristolochic Acids, and Aristolactams

The previously recorded phenanthrene alkaloid thaliglucinone (57) has now been shown to be present in *Thalictrum lucidum*[23] as well as in *T. longistylum*.[24] The presence of a methylenedioxy-group at C-3,4 in a phenanthrene alkaloid results in an upfield shift of the signal from the proton attached to C-5 to δ8.95—9.00 in the n.m.r. spectrum. Other phenanthrene bases with methoxy- or hydroxy-groups at C-3,4 exhibit the proton at C-5 downfield, between δ9.3 and δ9.9.[57]

The known anti-inflammatory alkaloid taspine (58) is an inhibitor of RNA-directed DNA polymerase, probably as a result of its interaction with the template primer.[69]



(57)



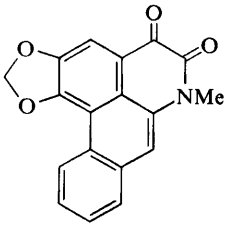
(58)

[68] L. Castedo, R. Suau, and A. Mouriño, *Anales de Quim.*, 1977, **73**, 290.
For a photolytic synthesis of atheroline see T. Kametani, R. Nitadori, H. Terasawa, K. Takahashi, M. Ihara, and K. Fukumoto, *Tetrahedron*, 1977, **33**, 1069.

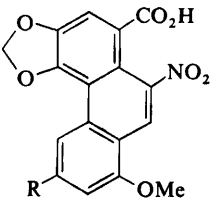
[69] M. L. Sethi, *Canad. J. Pharm. Sci.*, 1977, **12**, 7.

The 4,5-dioxoaporphine cepharadione-A (59) has now been claimed to be present in *Piper sanctum* (Piperaceae).[70]

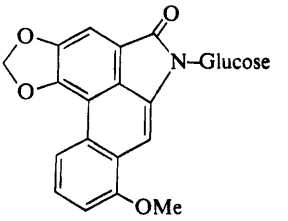
Aristolochic acid (60), aristolochic acid-D (61), and aristolactam-β-D-glucoside (62), reported by earlier workers, have been re-isolated from *Aristolochia indica* (Aristolochiaceae). Of greater interest, five phenanthrene derivatives, (63)—(67), were also found in the plant. Compound (65) was labelled aristolamide, (66) is aristolinic acid methyl ester, and (67) is methyl aristolochate.[71]



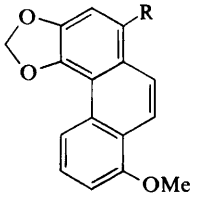
(59)



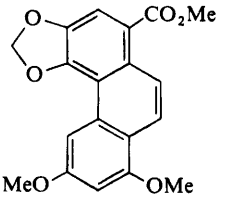
(60) R = H
(61) R = OH



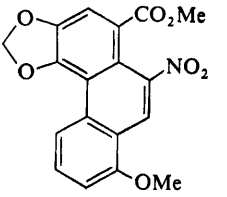
(62)



(63) R = CO_2Me
(64) R = CO_2H
(65) R = $CONH_2$



(66)

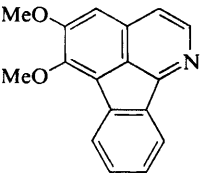


(67)

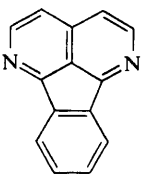
7 Azafluoranthenes and Diazafluoranthenes

The new azafluoranthene (68) has been found in *Triclisia gilletii* (Dewild) Staner.[72]

The 1,6-diazafluoranthene eupolauridine (69) is also found in *Cananga odorata* Hook f. et Thompson (Annonaceae).[73] *Eupomatia laurina* R. Br., which was the



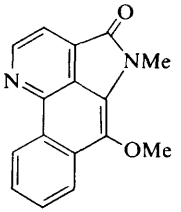
(68)



(69)

[70] R. Hansel and A. Leuschke, *Phytochemistry*, 1976, **15**, 1323.
[71] S. C. Pakrashi, P. Ghosh-Dastidar, S. Basu, and B. Achari, *Phytochemistry*, 1977, **16**, 1103.
[72] R. Huls, J. Gaspers, and R. Warin, *Bull. Soc. Roy. Sci. Liège*, 1976, **45**, 40.
[73] M. Leboeuf and A. Cavé, *Lloydia*, 1976. **39**, 459.

first plant to yield eupolauridine, has also supplied the very unusual aza-aristolactam alkaloid eupolauramine (70), whose structure was elucidated by single-crystal



(70)

X-ray analysis of the free base.[4] The future study of the exact biogenetic pathway for the formation of this alkaloid should prove to be a fascinating endeavour.

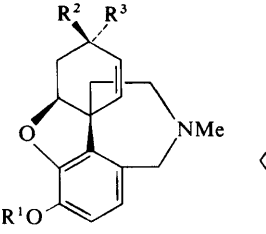
9

Amaryllidaceae and Related Alkaloids

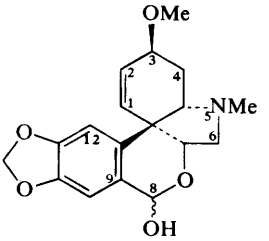
BY J. N. REED AND V. A. SNIECKUS

This group has been included in a review that describes the synthesis of several types of alkaloids by intramolecular radical-coupling reactions.[1] A review of the total synthesis of lycorine and related alkaloids is not easily accessible.[2]

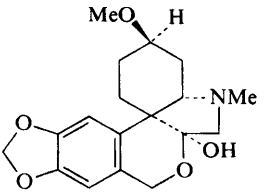
A new phenolic Amaryllidaceae alkaloid, sanguinine (1), and also the known alkaloids lycorine and galanthamine (2) have been isolated from *Lycoris sanguinea*.[3] Sanguinine (1) was shown to be *O*-demethylgalanthamine by comparison of its spectral data with those of galanthamine (2) as well as by its interconversion into the latter alkaloid. Pretazettine (3) has been isolated from *L. radiata* and converted into tazettine (4) under the conditions of the isolation regimen, thus showing that (4) is an artefact formed by rearrangement.[3]



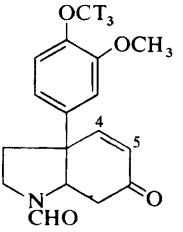
(1) $R^1 = R^3 = H$, $R^2 = OH$
(2) $R^1 = Me$, $R^2 = OH$, $R^3 = H$



(3)



(4)

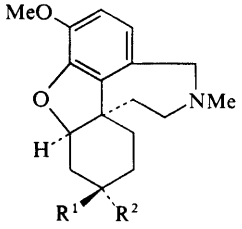


(5)

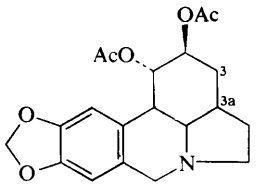
[1] T. Kametani, *Lectures Heterocyclic Chem.*, 1974, **2**, 57.
[2] Y. Tsuda and K. Isobe, *Yuki Gosei Kagaku Kyokai Shi*, 1976, **34**, 625 (*Chem. Abs.*, 1977, **86**, 72 929).
[3] S. Kobayashi, S. Takeda, H. Ishikawa, H. Matsumoto, M. Kihara, T. Shingu, A. Numata, and S. Uyeo, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 1537.

As corrected previously (see Vol. 7 of these Reports), the crystal structure of *N*-demethyl-(±)-galanthamine (norgalanthamine), and not that of (±)-galanthamine, has been determined.[4] The structure of tritiated (±)-*N*-demethyl-*N*-formyl-mesembrenone (5), isolated from *Sceletium strictum* after feeding with [4′-*methoxy*-$^3H_3$]mesembrenone, has been assigned by single-crystal *X*-ray analysis.[5] The orientation of the aromatic ring in (5) differs substantially from that elucidated for analogues which do not have a C(4)–C(5) double bond.

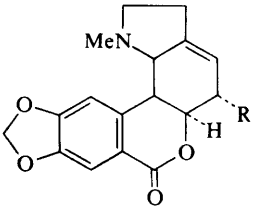
The identification of micro-amounts of a number of Amaryllidaceae alkaloids, obtained from *Crinum bulbispermum* and *Hippeastrum vittatum*, by colour reactions has been described.[6] Solvent-induced changes in the chemical shifts in at least six different solvents have been determined for compounds (6), (7), (8), (9), (10), and (11).[7] It was found that, on changing from CCl_4 to C_6D_6 as the solvent, the methoxy-groups in (6) and (7) undergo a diamagnetic shift of 0.5 p.p.m. Polar solvents were shown to be particularly useful for obtaining chemical shifts and coupling constants in the galanthamine series (6). Conformational changes in (8) as a function of solvent were also studied.



(6) $R^1 = OH, R^2 = H$
(7) $R^1R^2 = O$



(8)
(9) $\Delta^{3,3a}$

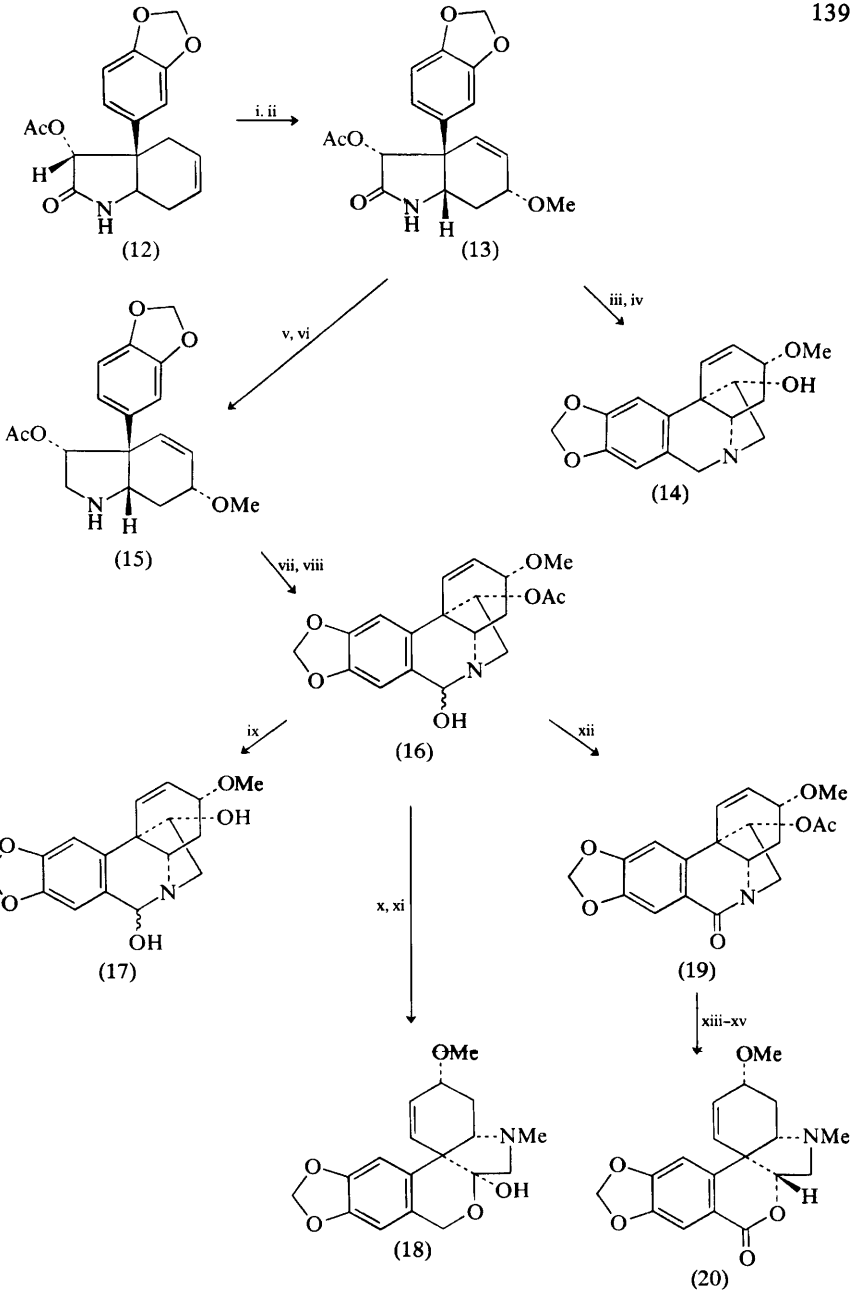


(10) R = OMe
(11) R = OH

The most interesting synthetic achievement involves the preparation of (±)-crinamine (14), (±)-6-hydroxycrinamine (17), (±)-criwelline (18), and (±)-macronine (20) (Scheme 1).[8] The versatile intermediate (12) (see Vol. 3 of these Reports) was converted stereospecifically into the allylic ether (13) in 35% yield by methoxyselenylation and elimination of phenylselenoxide. Reduction with lithium aluminium hydride followed by Pictet–Spengler reaction gave (±)-crinamine (14). On the other hand, treatment of (13) with Meerwein's reagent followed by reduction with sodium borohydride plus a Lewis acid afforded the acetoxy-amine (15). Formylation and Bischler–Napieralski cyclization gave the pivotal intermediate (16), which was converted, in simple steps, into (±)-6-hydroxycrinamine (17), (±)-criwelline (18), and compound (19), as shown. (±)-Macronine (20) was then readily obtained from (19), using known ring-interconversion methodology.

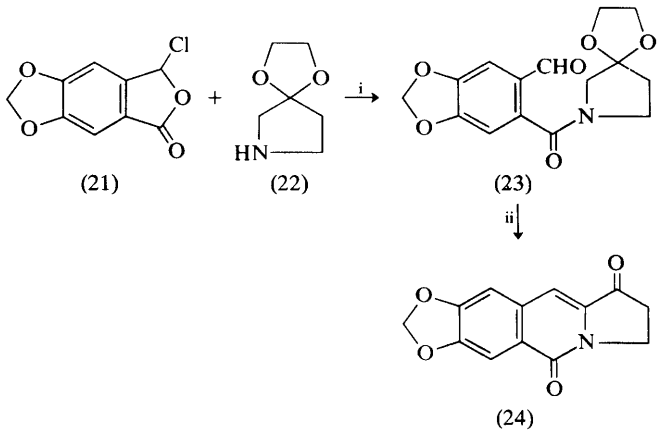
The pyrrolo-isoquinoline (24) has been prepared as part of efforts directed towards the total synthesis of lycorine (Scheme 2).[9] Treatment of the chloro-

[4] R. Roques, J. Lapasset, D. Rogers, and D. J. Williams, *Acta Cryst.*, 1976, **B32**, 3358.
[5] I. M. Karle, *Acta Cryst.*, 1977, **B33**, 185.
[6] A. M. El-Moghazi and A. A. Ali, *Planta Medica*, 1976, **30**, 369.
[7] K. L. Seitanidi and M. R. Yagudaev, *Khim. prirod. Soedinenii*, 1976, 500 (*Chem. Abs.*, 1977, **86**, 140 303).
[8] K. Isobe, J. Taga, and Y. Tsuda, *Tetrahedron Letters*, 1976, 2331.
[9] J. Levisalles and E. Rose, *Bull. Soc. chim. France*, 1976, 1947.



Reagents: i, $(PhSe)_2$–NBA–MeOH, 25 °C; ii, 3% H_2O_2–THF; iii, $LiAlH_4$–THF; iv, 30% HCHO, Δ; v, Et_3O^+ BF_4^-; vi, $NaBH_4$–$SnCl_4$·$2Et_2O$–DME; vii, HCO_2Ac–C_5H_5N; viii, $POCl_3$–PhMe, 120 °C; ix, K_2CO_3–MeOH; x, MeI–MeOH; xi, 5% KOH; xii, MnO_2–CH_2Cl_2; xiii, K_2CO_3; xiv, H_3O^+; xv, HCHO–$NaBH_4$

Scheme 1

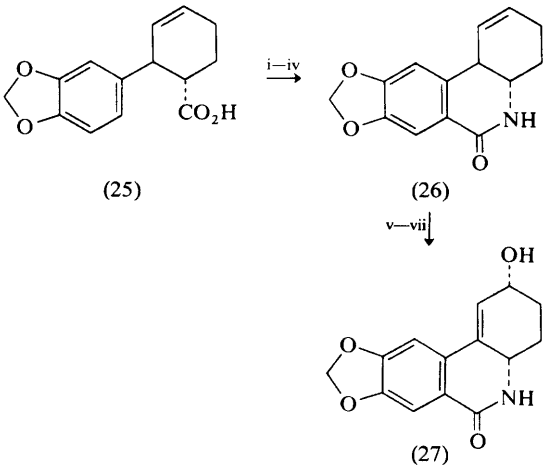


Reagents: i, Me_2CO–K_2CO_3; ii, conc. H_2SO_4, N_2

Scheme 2

phthalide (21) with the pyrrolidine acetal (22) gave amide (23), which upon treatment with acid gave the cyclized product (24) in 46% overall yield. A lengthier, alternative route to the amine corresponding to (24) was also devised, although this compound could not be isolated owing to its inherent instability.

In efforts aimed at delving into structure–activity relationships, the lycoricidine-type compound (27), lacking two hydroxy-groups of the parent alkaloid, has been synthesized (Scheme 3).[10] The known carboxylic acid (25) (see Vol. 7 of these



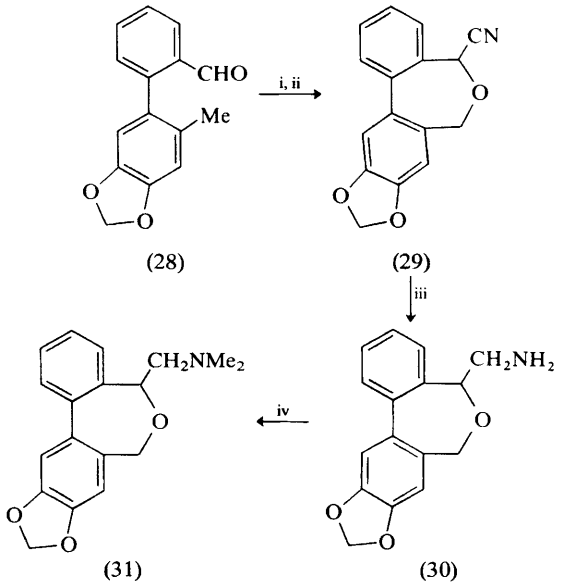
Reagents: i, Me_2CO–H_2O–Et_3N–$ClCO_2Et$; ii, NaN_3; iii, Δ, toluene; iv, BF_3, Et_2O; v, AcOH–NBS; vi, PhH–DBU, Δ; vii, MeOH–NH_3.

Scheme 3

[10] S. Ohta and S. Kimoto, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 2969.

Reports) was converted (by a modified Curtius reaction) into the corresponding isocyanate, which was cyclized in 70—90% yield into the lactam (26), using boron trifluoride etherate. Since these represent new conditions for effecting such a reaction, generalization to a number of substituted phenethyl isocyanates was carried out. Compound (26), upon successive acetoxybromination, dehydrobromination, and hydrolysis, gave the target compound (27), whose quasi-axial α-OH configuration was deduced from n.m.r. data.

(−)-Deoxytazettine neomethide (31), a key degradation product of tazettine, has been prepared (Scheme 4).[11] The biphenyl derivative (28), obtained in low yield by Ullman condensation, was converted into the cyano-oxepin (29) in two steps (34% overall yield). Reduction gave the amine (30), which upon resolution followed by reductive methylation provided a sample of (−)-deoxytazettine neomethide (31) that was identical (including optical rotation) with the degradation product of tazettine.

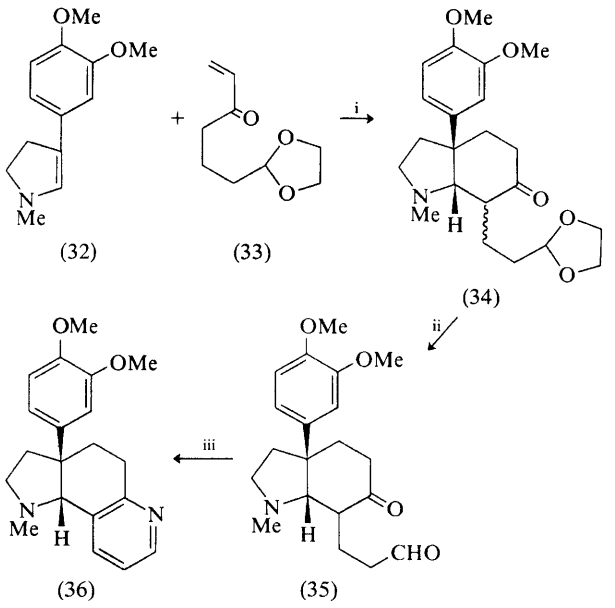


Reagents: i, $(PhCO)_2O_2$–CCl_4–NBS, $h\nu$, N_2; ii, DMF–NaCN–H_2O, 0 °C; iii, $LiAlH_4$–Et_2O; iv, HCO_2H–$(CH_2O)_n$, 100 °C.

Scheme 4

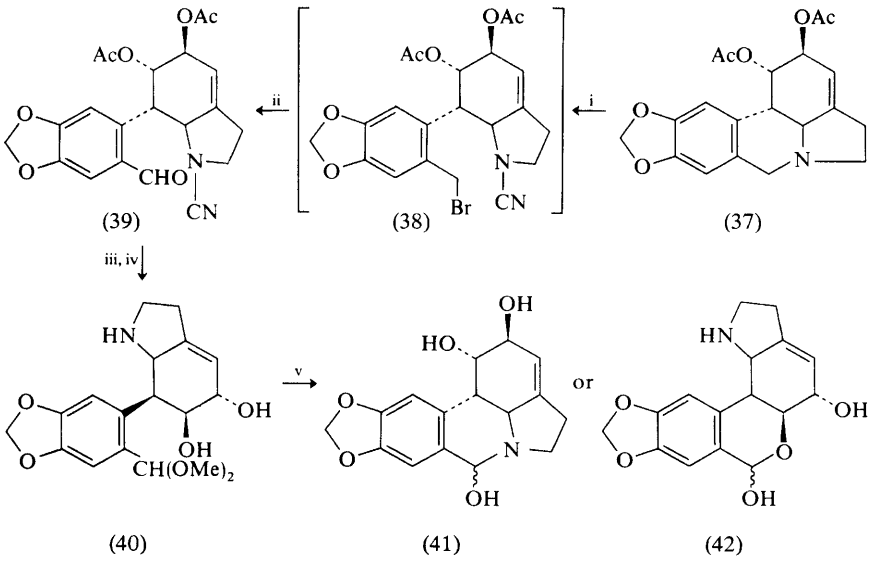
The *Sceletium* alkaloid (±)-A_4 (36) has been synthesized as shown in Scheme 5, using previously developed enamine–vinyl ketone ring annulation methodology (see Vol. 7 of these Reports).[12] Treatment of the hydrochloride of the 2-pyrroline (32) with the acetal enone (33) gave a mixture of epimeric keto-acetals (34) in 85%

[11] S. Kobayashi, M. Kihara, T. Hashimoto, and T. Shingu, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 716.
[12] C. P. Forbes, J. D. Michau, T. van Ree, A. Wiechers, and M. Woudenberg, *Tetrahedron Letters*, 1976, 935.



Reagents: i, MeCN, reflux; ii, *p*-TsOH–dioxan, reflux; iii, reflux, NH_2OH,HCl, abs. EtOH, reflux.

Scheme 5



Reagents: i, CNBr–$CHCl_3$–K_2CO_3; Me_2SO–$NaHCO_3$; iii, HCl–MeOH–$CH(OMe)_3$; iv, THF–$LiAlH_4$, reflux; v, THF–H_2O–6M-HCl.

Scheme 6

yield. Deacetalization gave the keto-aldehyde (35), which upon refluxing with excess hydroxylamine provided alkaloid (±)-A_4 (36).

In connection with biosynthetic studies, compound (41) or (42) has been prepared, starting with *OO*-diacetyl-lycorine (37) (Scheme 6).[13] Treatment of (37) with cyanogen bromide gave the cyanamide (38) in 80% yield; this was not isolated but was directly oxidized to the aldehyde (39). Acetalization followed by reduction with lithium aluminium hydride gave the unstable amine (40), which upon hydrolysis gave a compound which, on the basis of its conversion into lycorine (37; OH in place of OAc) may be formulated as (41). This assignment is in doubt, since spectral evidence favours structure (42).

A number of Amaryllidaceae alkaloids, including haemanthamine, lycorine, narciclasine, and pretazettine, have been shown to inhibit the fundamental step of the formation of a peptide bond in protein synthesis.[14]

[13] R. D. Harken, C. P. Christensen, and W. C. Wildman, *J. Org. Chem.*, 1976, **41**, 2450.
[14] A. Jimenez, A. Santos, G. Alonso, and D. Vazquez, *Biochim. Biophys. Acta*, 1976, **425**, 342.

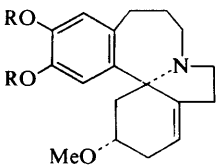
10

Erythrina and Related Alkaloids

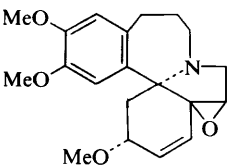
BY S. O. DE SILVA AND V. A. SNIECKUS

A review dealing with the determination of the structure and the synthesis of *Cephalotaxus* alkaloids has appeared.[1] Another review summarizes the isolation, elucidation of structure, synthesis, biogenesis, antitumour activity, and mechanism of physiological action of the *Cephalotaxus* alkaloids.[2] In a review concerning the application of *X*-ray crystallography to the determination of the structure of various classes of alkaloids, limited coverage of the *Erythrina* group is given.[3]

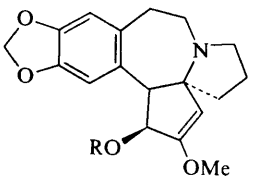
Cephalotaxus wilsoniana, collected in Formosa, has revealed the known alkaloids 3-epi-schelhammericine (1a), 'base VI' (1b), and 3-epi-wilsonine (2) (*Homoerythrina* type) and also cephalotaxine (3a), acetylcephalotaxine (3b), isoharringtonine (3c), and 'alkaloid G' (4) (*Cephalotaxus* type) on examination.[4] Coccolinine, a new lactam isolated from *Cocculus laurifolia*, has been assigned structure (5) on the basis of its spectroscopic and chemical properties.[5] Three new alkaloids, namely cocculidine (8a), isococculidine (6), and coccoline (7), and the known base (8b) were also isolated from the leaves of *C. laurifolia* and characterized by mass spectral and n.m.r. studies.[6] Several species of *Cephalotaxus* have been studied by the g.c.–m.s. technique in order to obtain a quantitative determination of their alkaloid content.[7] This technique has utility in predicting the potential biological activity of new species.



(1) a; RR = CH_2
b; R = Me

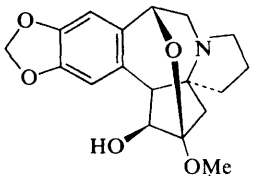


(2)

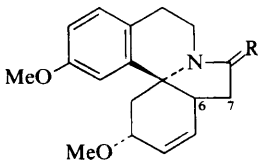


(3) a; R = H
b; R = Ac
c; R = COC(OH)[CH(OH)CO_2Me]·$(CH_2)CHMe_2$

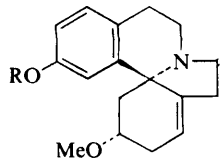
[1] J. A. Findlay, *Internat. Rev. Sci: Org. Chem., Series Two*, 1976, **9**, 23.
[2] C. R. Smith, jun., R. G. Powell, and K. L. Mikolajczak, *Cancer Treat. Rep.*, 1976, **60**, 1157.
[3] A. McL. Mathieson, *Internat. Rev. Sci: Phys. Chem., Series Two*, 1975, **11**, 177.
[4] H. Furukawa, M. Itoigawa, M. Haruna, Y. Jinno, K. Ito, and S.-T. Lu, *Yakugaku Zasshi*, 1976, **96**, 1373 (*Chem. Abs.*, 1977, **86**, 103 043).
[5] H. Pande, N. K. Saxena, and D. S. Bhakuni, *Indian J. Chem.*, 1976, **14B**, 366.
[6] D. S. Bhakuni, H. Uprety, and D. A. Widdowson, *Phytochemistry*, 1976, **15**, 739.
[7] G. F. Spencer, R. D. Plattner, and R. G. Powell, *J. Chromatog.*, 1976, **120**, 335.



(4)



(5) R = O
(6) R = H_2
(7) R = O; $\Delta^{6,7}$



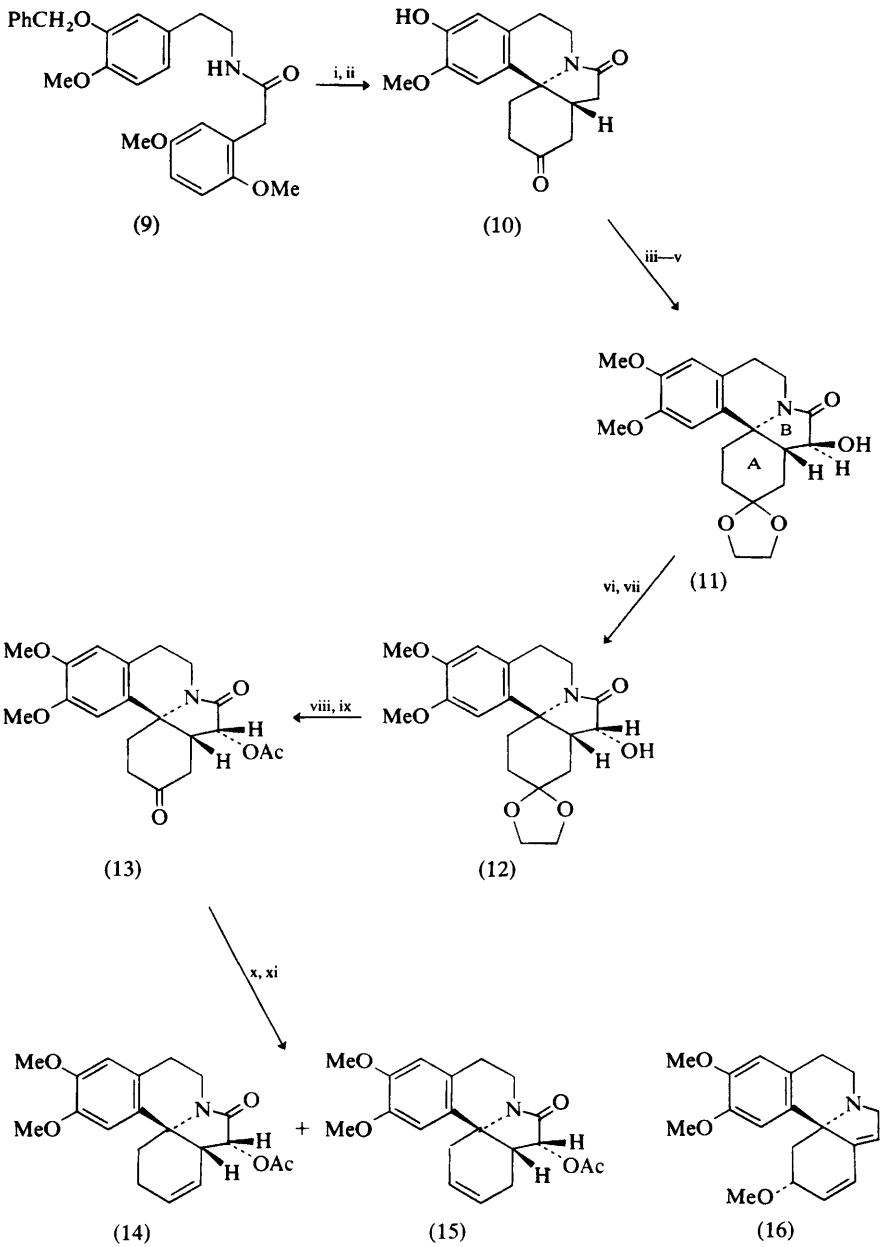
(8) a; R = H
b; R = Me

Synthetic work on *Erythrina* and related alkaloids is continuing at a somewhat slower pace. A previously developed synthetic strategy (see Vol. 7 of these Reports) has been extended to the elaboration of a key intermediate for the synthesis of erysotrine (16) (Scheme 1).[8] The 15-methoxy-16-hydroxy-dioxoerythrinan-2,8-dione (10), which has a *cis* A/B ring fusion, was obtained in 90% overall yield by Birch reduction of the readily accessible amide (9), followed by treatment of the resulting dihydro-compound with sulphuric acid in DMF. Acetalization of (10) with ethylene glycol and boron trifluoride, and then methylation of the phenolic hydroxy-group followed by a key hydroxylation of the lithium enolate of the lactam, afforded the 7-β-hydroxy acetal lactam (11) in 66% overall yield. The 7-β-hydroxy-group was epimerized by successive oxidation and reduction, to give the corresponding α-hydroxy-compound (12), which was readily converted into the 7-α-acetoxy-2-oxo-lactam (13) in good overall yield. Treatment of compound (13) with toluene-α-thiol and boron trifluoride etherate in acetic acid followed by desulphurization with nickel boride gave the required erythrinenone (14) in 35% yield, along with the isomeric by-product (15) in 55% yield. The conversion of erythrinenone (14) into erysotrine (16) has been reported.[9]

A photochemical preparation of a *Cephalotaxus* alkaloid synthon (20) has been reported (Scheme 2).[10] The readily accessible maleimide (17) was iodinated with iodine and silver trifluoroacetate, in 71% yield, and the resulting compound was transformed in two steps (70% overall yield) into the methylene-pyrrolone (18) by the action of methylmagnesium iodide followed by dehydration. Irradiation of (18) afforded (19) (46% yield), which, by successive hydrogenation and reduction with lithium aluminium hydride, gave the dihydro-pyrrolo[2,1-b][3]benzazepine (20). This derivative has served as a key intermediate in the total synthesis of cephalotaxine described previously (see Vol. 7 of these Reports).

Another approach to the erythrinan skeleton has been developed (Scheme 3).[11] The hexahydro-indolone (23), readily available from indoline (21) *via* the imino-enol ether (22), underwent cyclization [in very low yield (4%)] on treatment with phosphorus oxychloride to give the erythrinan derivative (24). Uncyclized compound (25) was identified as a by-product (16%) in this reaction. This latter compound was formed in 47% yield, with no product (24), when the cyclization was attempted in chloroform solution. Extensive variation of reaction conditions failed to give reasonable yields of the required compound (24).

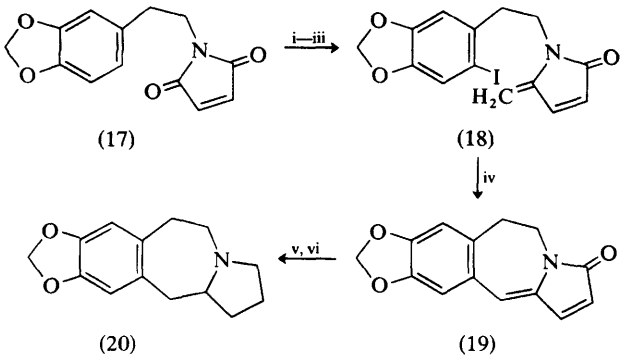
[8] M. Haruna and K. Ito, *J.C.S. Chem. Comm.*, 1976, 345.
[9] A. Mondon and N. J. Nestler, *Angew. Chem.*, 1964, **76**, 651.
[10] I. Tse and V. Snieckus, *J.C.S. Chem. Comm.*, 1976, 505.
[11] H. Iida, S. Aoyagi, K. Kohno, N. Sasaki, and C. Kibayashi, *Heterocycles*, 1976, **4**, 1771.



(9) (10) (11) (12) (13) (14) (15) (16)

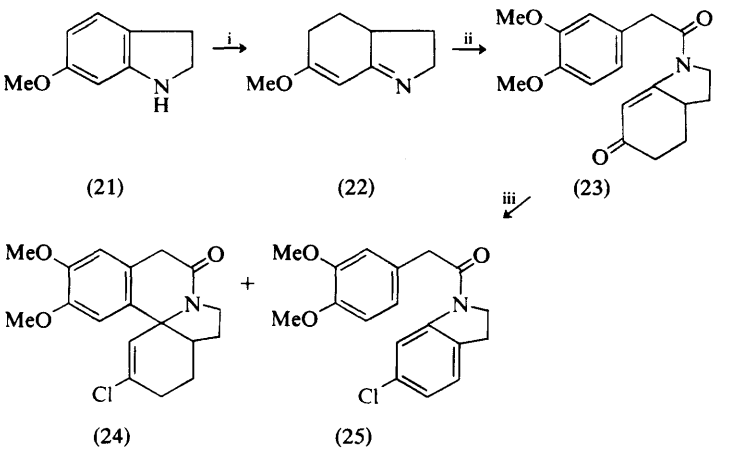
Reagents: i, Na–liq. NH_3–MeOH; ii, 10% H_2SO_4–DMF; iii, BF_3,Et_2O–$(CH_2OH)_2$; iv, MeI–K_2CO_3–DMF; v, $LiNPr^i_2$–THF–O_2; vi, Collins reagent; vii, $NaBH_4$; viii, Ac_2O–pyridine; ix, 2% HCl–Me_2CO; x, toluene-α-thiol–BF_3,Et_2O–AcOH; xi, Ni_2B–EtOH

Scheme 1



Reagents: i, I_2–CF_3CO_2Ag–CH_2Cl_2; ii, MeMgI–Et_2O–PhH; iii, *p*-TsOH–PhH; iv, *hν* (253.7 nm)–PhH–Et_3N; v, H_2–PtO_2–MeOH; vi, $LiAlH_4$

Scheme 2



Reagents: i, Na–liq. NH_3–MeOH; ii, 3,4-dimethoxyphenylacetyl chloride–Et_3N–$CHCl_3$; iii, $POCl_3$–MeCN

Scheme 3

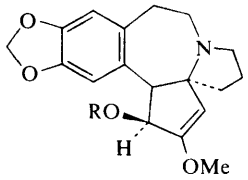
Chinese workers have continued their pharmacological exploration of esters of cephalotaxine (3a) and have reported the transformation of this alkaloid into harringtonine (26a)[12] and *O*-(2-oxo-5-methylhexanoyl)cephalotaxine (26b).[13] The latter compound is an intermediate in the synthesis of the antineoplastic alkaloid deoxyharringtonine (26c). The overall conversion of cephalotaxine into deoxyharringtonine (26c) *via* (26b) has been patented.[14] Of twenty-two esters of (−)-

[12] Institute of Pharmacology, Peoples' Republic of China, *K'o Hsueh T'ung Pao*, 1976, **21**, 512 (*Chem. Abs.*, 1977, **86**, 171 690).

[13] W.-K. Huang, Y.-L. Li, and S.-F. Pan, *K'o H'sueh T'ung Pao*, 1976, **21**, 178 (*Chem. Abs.*, 1976, **85**, 63 208).

[14] K. L. Mikolajczak and C. R. Smith, jun., U.S.P. 3 959 312 (*Chem. Abs.*, 1976, **85**, 108 881).

cephalotaxine tested for anti-tumour activity, only compounds (26d—g) have been shown to have consistent and significant activity against P 388 lymphocytic leukaemia.[15] Interestingly, the (+)-enantiomer of (26d) was shown to be inactive.



(26) a; R = $COC(OH)[CH_2CO_2Me]CH_2CH_2C(OH)Me_2$
b; R = $COCOCH_2CH_2CHMe_2$
c; R = $COC(OH)[CH_2CO_2Me]CH_2CH_2CHMe_2$
d; R = $COC(=CH_2)CH_2CO_2Me$
e; R = $COCH{=}^{t}CHCO_2Me$
f; R = $CO{-}C(H)(OCO_2CH_2CCl_3)(Ph)$
g; R = $CO_2CH_2CCl_3$

Inhibition of protein synthesis in eukaryotic cells by the *Cephalotaxus* alkaloids harringtonine, homoharringtonine, and isoharringtonine has been studied.[16] In model systems, these alkaloids were found not to inhibit any of the initiation steps but to block certain parts of the elongation phase of translation.

Two analogues of *Erythrina* alkaloids that lack the aromatic ring have been synthesized, for use in studies of structure–biological activity relationships.[17]

[15] K. L. Mikolajczak, C. R. Smith, jun., and D. Weisleder, *J. Medicin. Chem.*, 1977, **20**, 328.
[16] M. Fresno, A. Jimenez, and D. Vazquez, *European J. Biochem.*, 1977, **72**, 323.
[17] E. D. Bergman and Y. Migron, *Tetrahedron*, 1976, **32**, 2617, 2621.

11

Indole Alkaloids

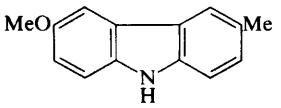
BY J. E. SAXTON

1 Introduction*

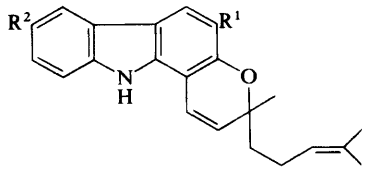
Two new compilations of alkaloid data, published in 1975, have been received during the year under review. The first of these[1a] covers all groups of alkaloids, arranged in alphabetical sequence; the structure, botanical source, and principal physical data are given for each alkaloid, together with a selected bibliography. The second[1b] is an extremely useful collection of data on the indole alkaloids, arranged in order of increasing molecular weight; physical and spectroscopic data are included for each alkaloid of established structure, together with a leading literature reference. A valuable feature of this enterprise is that annual supplements are to be published in the journal *Fitoterapia*; the first of these[1c] has already appeared.

2 Simple Alkaloids

Non-tryptamines.—Glycozoline (1) has been very simply synthesized by the thermal cyclization (350 °C) of 4′-methoxy-4-methyldiphenylamine in the presence of iodine.[2] Details of the syntheses of girinimbine and mahanimbine have now been published,[3] and the method used in the synthesis of the latter has been extended to the synthesis of (±)-isomahanimbine (2); thus, condensation of 2-hydroxy-6-methylcarbazole with citral in pyridine containing a trace of benzoic acid gave



Glycozoline (1)



Isomahanimbine (2) $R^1 = H$, $R^2 = Me$
Mahanimbine (5) $R^1 = Me$, $R^2 = H$

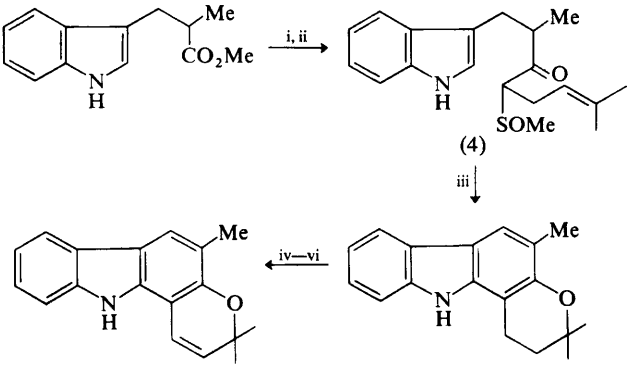
[1] (*a*) J. S. Glasby, 'Encyclopedia of the Alkaloids', Plenum Press, New York, 1975 (2 volumes); (*b*) B. Gabetta and G. Mustich, 'Spectral Data of Indole Alkaloids', Inverni della Beffa, Milan, 1975; (*c*) B. Gabetta, *Fitoterapia*, 1976, **47**, 247.

[2] P. Bhattacharyya, A. R. Mitra, and D. P. Chakraborty, *J. Indian Chem. Soc.*, 1976, **53**, 321.

[3] N. S. Narasimhan, M. V. Paradkar, and A. M. Gokhale, *Indian J. Chem.*, 1976, **14B**, 329.

* The order of discussion in this chapter is the same as in previous volumes in this series, with the exception of the biogenetically related quinoline alkaloids, which are now placed at the end of the chapter.

(±)-isomahanimbine directly. An independent synthesis[4] of girinimbine (3) employs a new method of synthesis of condensed aromatic compounds, the crucial stage in which is the acid-catalysed cyclization, aromatization, and further cyclization of a β-keto-sulphoxide (4) (Scheme 1).

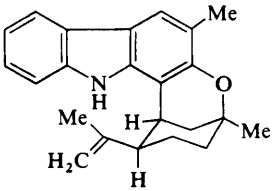


Girinimbine (3)

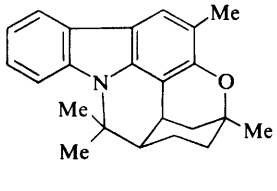
Reagents: i, $MeSOCH_2Na$; ii, $Me_2C{=}CHCH_2Br$–KH; iii, TsOH–MeCN, heat, 3 h; iv, $PhSO_2Cl$–base; v, NBS–azobis-isobutyronitrile–CCl_4; vi, $LiAlH_4$–Et_2O.

Scheme 1

At 150 °C, (+)-mahanimbine (5) undergoes racemization, presumably by opening and re-closure of the dihydropyran ring. At higher temperatures (200 °C), curryanine (cyclomahanimbine) (6) and curryangine (7) are formed;[5] the structure



Curryanine (6)



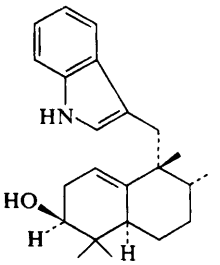
Curryangine (7)

of the former was confirmed from the n.m.r. spectrum, the equatorial configuration of the allyl substituent being indicated by a large (axial–axial) coupling observed in the multiplet owing to the proton attached to the same position in the cyclohexane ring.[5]

The tropical African plant *Polyalthia oliveri* Engl. contains a variety of interesting secondary metabolites. Aporphine alkaloids and a triterpene, polycarpol, have already been isolated, and the plant has now been shown to contain[6] an indole-

[4] Y. Oikawa and O. Yonemitsu, *Heterocycles*, 1976, **5**, 233.
[5] N. S. Narasimhan and S. L. Kelkar, *Indian J. Chem.*, 1976, **14B**, 430.
[6] M. Leboeuf, M. Hamonnière, A. Cavé, H. E. Gottlieb, N. Kunesch, and E. Wenkert, *Tetrahedron Letters*, 1976, 3559.

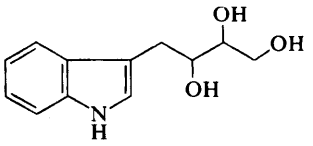
sesquiterpene, polyalthenol, of structure (8). Polyalthenol is presumably obtained by condensation of a sesquiterpene pyrophosphate with tryptophan, followed by extrusion of serine (or its biochemical equivalent) and acid-catalysed rearrangement.



Polyalthenol (8)

Gramine occurs with several quinolizidine alkaloids, of which eight have been identified, in young plants of *Lupinus hartwegii*;[7] although quinolizidine alkaloids are the typical constituents of *Lupinus* species, the occurrence of gramine in this genus is not unknown.

Indolic metabolites continue to be isolated from pathogenic micro-organisms. *Balansia epichloë* Weese is a clavicipitaceous fungus which parasitizes pasture grasses, and which has been implicated in ergot-type syndromes observed in cattle that have grazed on infected grasses. An investigation into the constituents of this fungus has yielded[8] the three indole alcohols (9)—(11), all of which were shown to be toxic to chicken embryos. Compounds (10) and (11) were synthesized by condensation of indole with glyceraldehyde. A contaminant of compound (11), of molecular weight 378, observed in the mass spectrum of (11), is probably the condensation product of (10) with another molecule of glyceraldehyde.



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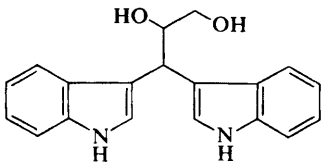

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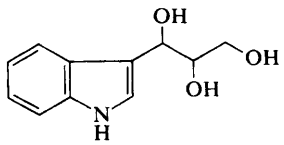
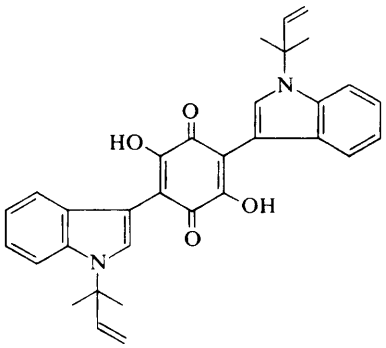


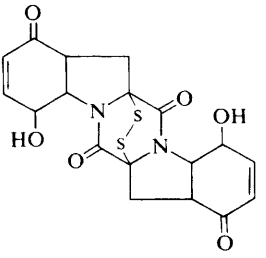
(11)

[7] J. N. Anderson and R. O. Martin, *J. Org. Chem.*, 1976, **41**, 3441.
[8] J. K. Porter, C. W. Bacon, J. D. Robbins, D. S. Himmelsbach, and H. C. Higman, *J. Agric. Food Chem.*, 1977, **25**, 88.

Asterriquinone (12), a metabolite of *Aspergillus terreus* Strain IFO 6123, is simply 2,5-dihydroxybenzoquinone coupled to two isopentenylindole units.[9] Unlike all previously known isopentenylindole mould metabolites, however, the reversed isopentenyl groups are attached, not to carbon atoms, but to the indolic nitrogen atom.



Asterriquinone (12)

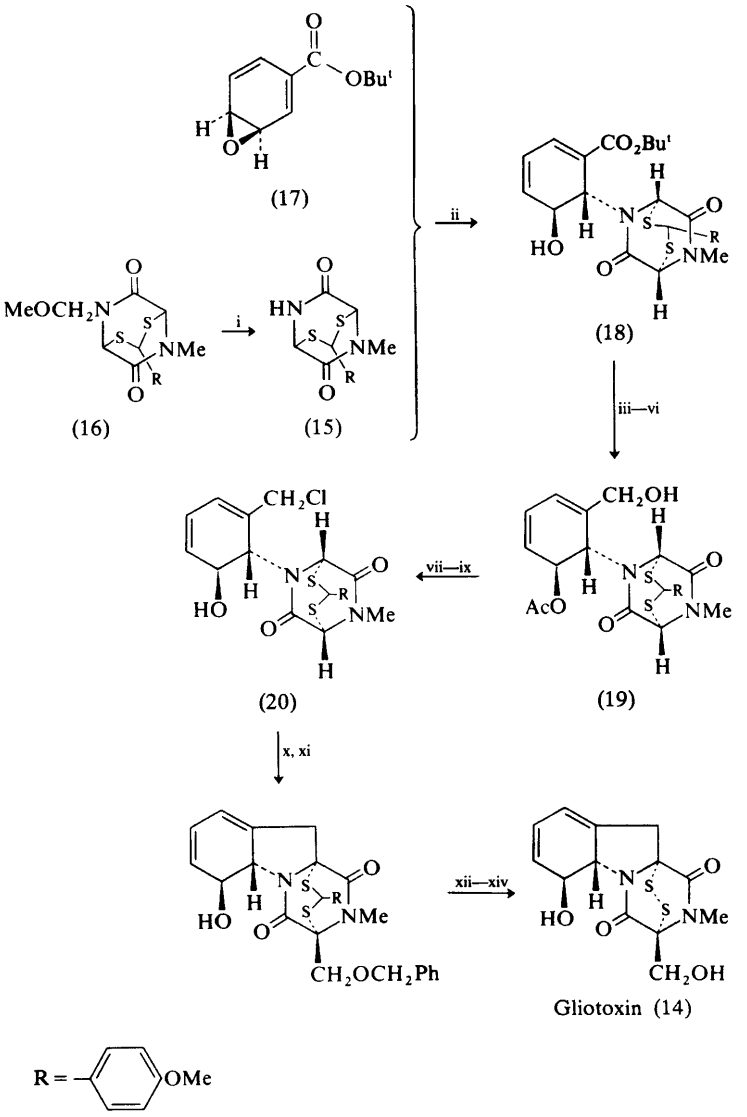


Epicorazine-A (13)

Epicorazine-A (13), a new metabolite from *Epicoccum nigrum* Link, has structural affinities with gliotoxin, since it contains both an epidithiodioxopiperazine unit and a sensitive grouping which is effectively a hydrated dihydroindole ring system;[10] in the symmetrical epicorazine-A molecule, two such groupings are present.

In a characteristically elegant contribution Kishi and his collaborators have reported the first total synthesis of gliotoxin (14) (Scheme 2).[11] The vital stage in the construction of the molecular framework involved the Michael addition of the anion derived from the diketopiperazine derivative (15), prepared from the previously synthesized[12] methoxymethyl compound (16), with the 4-t-butoxycarbonylbenzene oxide (17);[13] discharge of the resulting anion was accompanied by fission of the epoxide function, with formation of the intermediate (18). The product of this reaction proved to be a mixture of (18) and its diasteroisomer in which the thioacetal bridge was *cis* with respect to the hydroxy-group. The latter was the major product when the reaction was conducted in methylene chloride–Triton B, but (18) was favoured in DMSO–Triton B. The ester function in (18) was selectively reduced to the primary alcohol (19) by the mild mixed anhydride–$NaBH_4$ method, and the skeleton was finally completed by an ingenious process in which the dianion derived from the primary chloride (20) was cyclized by nucleophilic displacement of chloride ion and was simultaneously alkylated by reaction with chloromethyl benzyl ether. Conversion of the thioacetal function into the epidithio bridge was then carried out in the same manner as in the earlier synthesis of sporidesmin.[12]

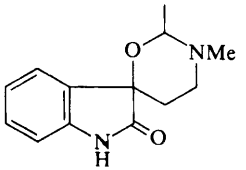
[9] Y. Yamamoto, K. Nishimura, and N. Kiriyama, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 1853.
[10] R. Baute, G. Deffieux, M. A. Baute, M. J. Filleau, and A. Neveu, *Tetrahedron Letters*, 1976, 3943.
[11] T. Fukuyama and Y. Kishi, *J. Amer. Chem. Soc.*, 1976, **98**, 6723.
[12] Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *J. Amer. Chem. Soc.*, 1973, **95**, 6493.
[13] R. M. DeMarinis, C. N. Filer, S. M. Waraszkiewicz, and G. A. Berchtold, *J. Amer. Chem. Soc.*, 1974 **96**, 1193.



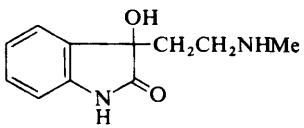
Reagents: i, Conc. HCl–MeOH; ii, Triton B–DMSO, r.t.; iii, Ac_2O–py, r.t.; iv, TFA, r.t.: v, $ClCO_2Et$–NEt_3–CH_2Cl_2, r.t.; vi, $NaBH_4$–MeOH–CH_2Cl_2, 0 °C; vii, MesCl–NEt_3–CH_2Cl_2, r.t.; viii, LiCl–DMF; ix, NaOMe–MeOH–CH_2Cl_2; x, $ClCH_2OCH_2Ph$, −78 °C; xi, PhLi; xii, BCl_3–CH_2Cl_2, 0 °C; xiii, *m*-$ClC_6H_4CO_3H$; xiv, $HClO_4$–CH_2Cl_2, r.t.

Scheme 2

Non-isoprenoid Tryptamines.—The structures (21) and (22) have been deduced for donaxarine and donaxaridine, the alkaloids of *Arundo donax*;[14] the relationship between the two is confirmed by the formation of donaxarine by condensation of



Donaxarine (21)

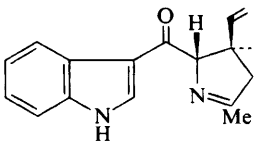


Donaxaridine (22)

donaxaridine with acetaldehyde. *Myrtopsis myrtoidea* (Rutaceae), from New Caledonia, contains *N*-benzoyltryptamine,[15a] and the stem bark of *Acacia simplicifolia* Druce contains N_b-methyltryptamine, N_bN_b-dimethyltryptamine, and 2-methyl-1,2,3,4-tetrahydro-β-carboline;[15b] the leaves contain the same three bases, together with N_b-formyl-N_b-methyltryptamine (not previously isolated from a natural source) and a trace of an unidentified alkaloid. 6-Methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline occurs[16] in association with several alkaloids of the cryptopine–protopine group in various Himalayan *Meconopsis* species; these include *M. napaulensis* (*M. nepalensis* DC.), *M. rudis* Prain, *M. horridula* Hook. f. et Thoms., *M. robusta* Hook. f. et Thoms., and *M. paniculata* (D. Don) Prain. This would appear to be the first substantiated record of the occurrence of an indole alkaloid in the Papaveraceae. All these *Meconopsis* species, together with *M. sinuata* Prain and *M. betonicifolia* Franch, contain an unidentified alkaloid MR1, which also seems highly likely to be a tetrahydro-β-carboline derivative. A second unidentified alkaloid, MR2, was also isolated from *M. rudis*. Three more β-carboline alkaloids have been isolated from *Banisteriopsis caapi*; these are harmic acid amide, acetylnorharmine, and 1-oxo-1,2,3,4-tetrahydro-7-methoxycarboline.[17]

A review[18] of the chemistry of the alkaloids of *Carex brevicollis* is welcome, since the original work (mainly of Russian origin) is relatively inaccessible.

Borreline (23), an alkaloid of an unidentified *Borreria* species from Guyana,[19] is the third alkaloid of a new structural type to be isolated from this genus. The



Borreline (23)

[14] K. A. Ubaidullaev, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 553 (*Chem. Abs.*, 1977, **86**, 121 586).

[15] (*a*) M. S. Hifnawy, J. Vaquette, T. Sévenet, J. L. Pousset, and A. Cavé, *Phytochemistry*, 1977, **16**, 1035; (*b*) C. Poupat, A. Ahond, and T. Sévenet, *ibid.*, 1976, **15**, 2019.

[16] J. Slavik and L. Slavikova, *Coll. Czech. Chem. Comm.*, 1976, **41**, 3343; 1977, **42**, 132.

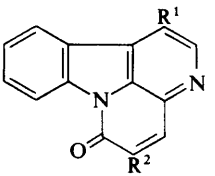
[17] Y. Hashimoto and K. Kawanishi, *Phytochemistry*, 1976, **15**, 1559.

[18] G. Lazurjevski and I. Terentjeva, *Heterocycles*, 1976, **4**, 1783.

[19] A. Jössang, H. Jacquemin, J. L. Pousset, A. Cáve, M. Damak, and C. Riche, *Tetrahedron Letters*, 1977, 1219.

biosynthesis of borreline is clearly 'non-classical', and presents an interesting problem for future investigation.

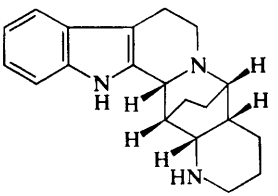
Ailanthus altissima Swingle (fam. Simaroubaceae), the Japanese 'Tree of Heaven', has been widely investigated in the past, the first investigation dating back to 1891, and a number of non-nitrogenous constituents have been isolated. A new extraction[20a] has revealed the presence in this species of three alkaloids, *i.e.* canthin-6-one, canthin-6-one 3-oxide (not previously found in Nature), and a new base, 1-methoxycanthin-6-one (24a). The structure of (24a) was deduced by its oxidation to 4-methoxy-1-methoxycarbonyl-β-carboline, the position of the methoxy-group in which was established by n.m.r. spectral comparison with model compounds. Another member of the same family, *Simarouba amara* Aubl., contains[20b] 5-hydroxycanthin-6-one (24b).



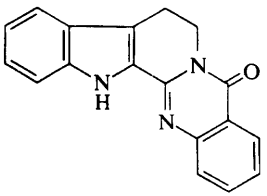
(24a) $R^1 = OMe$, $R^2 = H$
(24b) $R^1 = H$, $R^2 = OH$

Details of the *X*-ray crystal structure analysis of nitrarine (25) are now available.[21]

Details of Kametani's synthesis of evodiamine and rutaecarpine by the 'retro mass-spectral' approach[22a] have also been published.[23a] An extension of this method afforded a new synthesis[23b] of rutaecarpine (26); thus, condensation of the



(25)



(26)

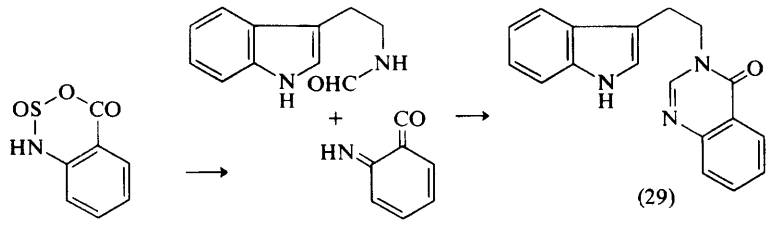
iminoketen (27), which was prepared *in situ* by decomposition of the sulphinamide anhydride (28), with N_b-formyltryptamine gave the tetracyclic intermediate (29), which on acid-catalysed cyclization and concomitant dehydrogenation afforded

[20] (*a*) T. Ohmoto, R. Tanaka, and T. Nikaido, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 1532; (*b*) E. V. Lassak, J. Polonsky, and H. Jacquemin, *Phytochemistry*, 1977, **16**, 1126.

[21] S. M. Nasirov, A. A. Ibragimov, V. G. Andrianov, S. K. Maekh, Yu. T. Struchkov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 334 (*Chem. Abs.*, 1977, **86**, 121 593).

[22] J. E. Saxton, in 'The Alkaloids', ed. M. F. Grundon (Specialist Periodical Reports), The Chemical Society, London, 1977, Vol. 7; (*a*) p. 188; (*b*) p. 198; (*c*) p. 210; (*d*) p. 210; (*e*) p. 210; (*f*) p. 199; (*g*) p. 218; (*h*) p. 227; (*i*) p. 227; (*j*) p. 232; (*k*) p. 233; (*l*) p. 239; (*m*) p. 244; (*n*) p. 235.

[23] (*a*) T. Kametani, T. Higa, C. Van Loc, M. Ihara, M. Koizumi, and K. Fukumoto, *J. Amer. Chem. Soc.*, 1976, **98**, 6186; (*b*) T. Kametani, C. Van Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *Heterocycles*, 1976, **4**, 1487; *J. Amer. Chem. Soc.*, 1977, **99**, 2306.



(28) (27) (29)

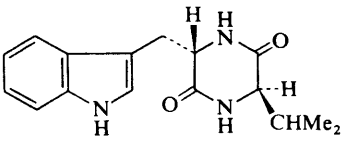
rutaecarpine (26). The mass spectra of evodiamine and rutaecarpine have been discussed, apparently for the first time.[24]

Some ^{13}C n.m.r. data for sporidesmin and sporidesmin-D have been published,[25] and evidence has been presented for there being a certain amount of strain in the sporidesmin molecule, imposed by the epidithio bridge.

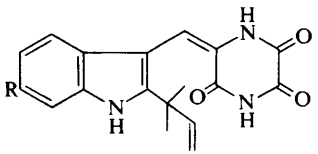
3 Isoprenoid Tryptamine and Tryptophan Alkaloids.

Mould Metabolites.—The presence of 'pre-echinulin' [L-alanyl-2-(1,1-dimethylallyl)-L-tryptophan anhydride] in *Aspergillus chevalieri* has been confirmed,[26] and two new metabolites, L-alanyl-L-tryptophan anhydride[27a] and D-valyl-L-tryptophan anhydride (30),[27b] have been isolated; it is interesting to note that (30), unlike the other metabolites of this micro-organism, contains an amino-acid of the D series.

Details of the structure elucidation of neoechinulins A—D have been published,[28] and a related, new didehydro-peptide, *i.e.* neoechinulin E (31), has been isolated. The n.m.r. spectrum of neoechinulin E is very similar to that of neoechinulin (32) apart from the absence in the spectrum of (31) of signals owing



(30)



Neoechinulin E (31) R = H
Neoechinulin (32) R = $Me_2C{=}CHCH_2$

to the isopentenyl group at position 6. The absence of this grouping was confirmed by the isolation of 2-(1,1-dimethylallyl)indole and the derived 3-carboxaldehyde following alkaline hydrolysis of neoechinulin E.

The structures previously proposed for bromohexahydroechinulin and nitrohexahydroechinulin are invalid, as they were based on an erroneous structure for echinulin. A recent ^{13}C n.m.r. study of several model alkyl-indoles and these two

[24] J. Tamás, G. Bujtás, K. Horváth-Dóra, and O. Clauder, *Acta Chim. Acad. Sci. Hung.*, 1976, **89**, 85.
[25] J. W. Ronaldson, *Austral. J. Chem.*, 1976, **29**, 2307.
[26] R. D. Stipanovic and H. W. Schroeder, *Trans. Brit. Mycological Soc.*, 1976, **66**, 178.
[27] (*a*) T. Hamasaki, K. Nagayama, and Y. Hatsuda, *Agric. and Biol. Chem. (Japan)*, 1976, **40**, 2487; (*b*) R. D. Stipanovic, H. W. Schroeder, and H. Hein, *Lloydia*, 1976, **39**, 158.
[28] R. Marchelli, A. Dossena, A. Pochini, and E. Dradi, *J.C.S. Perkin I*, 1977, 713.

hexahydroechinulin derivatives has shown[29] that they are 4-bromohexahydroechinulin and 6-nitrohexahydroechinulin.

A further common source of fumitremorgin B and verruculogen has been found in *Penicillium piscarium*, isolated from ryegrass.[30]

Interest in the mycotoxins of *Aspergillus* species continues, and the structures of several metabolites have been elucidated. Fumitremorgins A and B (FTA and FTB) are accompanied in *A. fumigatus* by six related indole-containing metabolites (FTC to FTH) which, however, appear to have no detectable tremorgenic properties. The first of these, FTC, exhibits very similar functionality and spectroscopic properties to tryptoquivaline, although the two compounds are not identical. However, FTC acetate and tryptoquivaline acetate (33) are identical; hence FTC (34) differs from tryptoquivaline (35) solely in the position of the acetate group.[31]

FTD exhibits similar spectral properties to FTC and tryptoquivaline except that in the n.m.r. spectrum the two singlets arising from the methyl groups attached to ring D of (34) and (35) are replaced by a three-proton doublet owing to a $CH_3\overset{\diagup}{C}H\overset{\diagdown}{}$ group at position 15. That the difference between FTC (34) and FTD (36) is solely due to the substitution in ring D is confirmed by the fact that oxidation (CrO_3–90% AcOH) of both compounds results in fission of ring D, with the formation of the same product, formulated as (37).

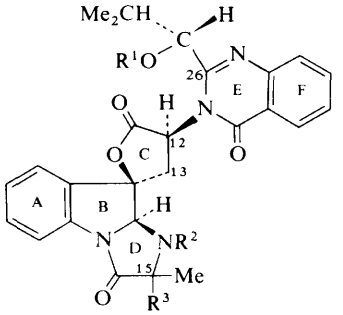
The remaining metabolites, FTE to FTH, are very closely related to each other, and to tryptoquivaline, except that they appear to lack the substituent at position 26. A detailed examination of their spectra, particularly their n.m.r. spectra, led to the formulation of FTE—FTH as (38)—(41).[31] FTE and FTH would appear to be epimers, although no detailed stereochemical proposals have been made. However, it may be noted that the n.m.r. pattern owing to the three-proton system at positions 12 and 13 in FTH resembles that of 12-epitryptoquivaline acetate [the C-12 epimer of (33)], as do the comparable n.m.r. signals in the spectra of FTE and tryptoquivaline acetate. Hence FTH may be a C-12 epimer of FTE and may be an artefact, since it is known that tryptoquivaline can be readily isomerized by base, and presumably so can FTE.[31]

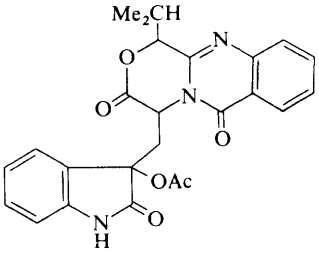
Six toxic metabolites have also been isolated from a strain of *A. clavatus* (strain MIT-M-18), which was one of several collected from mould-infested rice in a Thai household in which a child had died of an unidentified toxicosis.[32] Two of these metabolites, tryptoquivaline (35) and nortryptoquivalone, had been isolated earlier from a different strain of *A. clavatus*, but the remainder were new. One of them behaves in very similar manner to norisotryptoquivaline (FTD) (36), but is not identical with it, and hence is formulated as nortryptoquivaline (42). A second metabolite contains one oxygen atom fewer than tryptoquivaline and gives a negative triphenyltetrazolium test for hydroxylamines; since it can be oxidized (*m*-$ClC_6H_4CO_3H$) to tryptoquivaline, it has been formulated as deoxytryptoquivaline (43). The third of these mycotoxins is deoxynortryptoquivalone (44), since it can be oxidized to nortryptoquivalone (45). Similarly, the last metabolite

[29] R. R. Fraser, S. Passannanti, and F. Piozzi, *Canad. J. Chem.*, 1976, **54**, 2915.
[30] R. T. Gallagher and G. C. M. Latch, *Applied and Environmental Microbiology*, 1977, **33**, 730.
[31] M. Yamazaki, H. Fujimoto, and E. Okuyama, *Tetrahedron Letters*, 1976, 2861.
[32] G. Büchi, K. C. Luk, B. Kobbe, and J. M. Townsend, *J. Org. Chem.*, 1977, **42**, 244.

proves to be deoxynortryptoquivaline (46), since it can be oxidized, also by peracid, to nortryptoquivaline (42).[32]

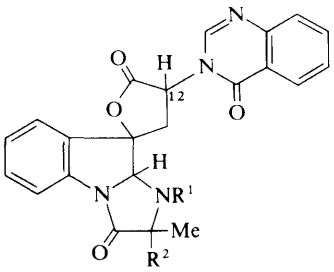
Details of the elucidation of the structure of oxaline, a metabolite of the microfungus *Penicillium oxalicum*,[33a] have now been published.[34]

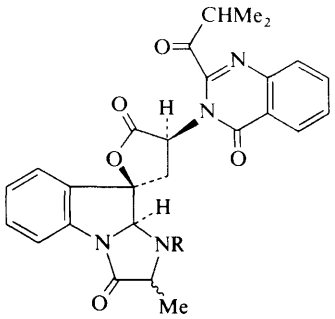




(37)

		R^1	R^2	R^3
Tryptoquivaline acetate	(33)	Ac	OAc	Me
FTC (Isotryptoquivaline)	(34)	H	OAc	Me
Tryptoquivaline	(35)	Ac	OH	Me
FTD (Norisotryptoquivaline)	(36)	H	OAc	H
Nortryptoquivaline	(42)	Ac	OH	H
Deoxytryptoquivaline	(43)	Ac	H	Me
Deoxynortryptoquivaline	(46)	Ac	H	H





		R^1	R^2
FTE	(38)	OH	H
FTF	(39)	H	H
FTG	(40)	OH	Me
FTH	(41)	OH	H

Deoxynortryptoquivalone (44) R = H
Nortryptoquivalone (45) R = OH

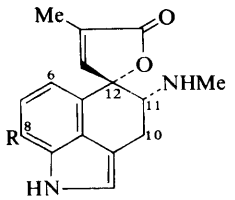
Ergot Alkaloids.—The two toxic, chlorine-containing metabolites earlier obtained from *Penicillium islandicum* found growing on freshly dug green peanuts are accompanied by two non-chlorinated analogues, identified[35] as rugulovasines A

[33] J. E. Saxton, in 'The Alkaloids', ed. M. F. Grundon (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6; (*a*) p. 199; (*b*) p. 203; (*c*) p. 208; (*d*) p. 209; (*e*) p. 211; (*f*) p. 214; (*g*) p. 219; (*h*) p. 206; (*i*) p. 233; (*j*) p. 237.

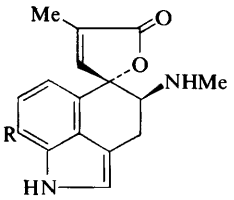
[34] D. W. Nagel, K. G. R. Pachler, P. S. Steyn, R. Vleggaar, and P. L. Wessels, *Tetrahedron*, 1976, **32**, 2625.

[35] R. J. Cole, J. W. Kirksey, J. Clardy, N. Eickman, S. M. Weinreb, P. Singh, and D. Kim, *Tetrahedron Letters*, 1976, 3849.

and B, first isolated[36] from *P. concavo-rugulosum*. The gross structures proposed[37] for these last two compounds have now been confirmed, and stereochemical detail has been added, by the *X*-ray crystal structure analysis of rugulovasine A (47). The facile interconversion of rugulovasines A and B (for example, on warming their solutions in polar solvents), is readily explained by invoking a reverse Mannich fission of the 11,12-bond in the vinylogous β-amino-lactone system, to give an achiral intermediate which can re-cyclize to either rugulovasine A (47) or to rugulovasine B (48). The products of this equilibration must necessarily be racemic; hence it is of interest to note that both the natural products are racemic. It is conceivable, therefore, that only one of the stereoisomers is the true natural product, the remainder being artefacts. The two chlorine-containing derivatives are formulated as the 8-chloro-analogues (49) and (50) on the basis of their n.m.r. spectra, alone and in the presence of lanthanide shift reagents. As with the parent bases, the chlorinated derivatives (49) and (50) are readily interconverted, and both appear to be racemic.[35] They also appear to be the first naturally occurring halogenated ergot alkaloids.



Rugulovasine A (47) R = H
(49) R = Cl



Rugulovasine B (48) R = H
(50) R = Cl

Several indole alkaloids occur in *P. concavo-rugulosum* in addition to rugulovasines A and B, and chanoclavine I; one of them has been identified[38] as racemic chanoclavine II.

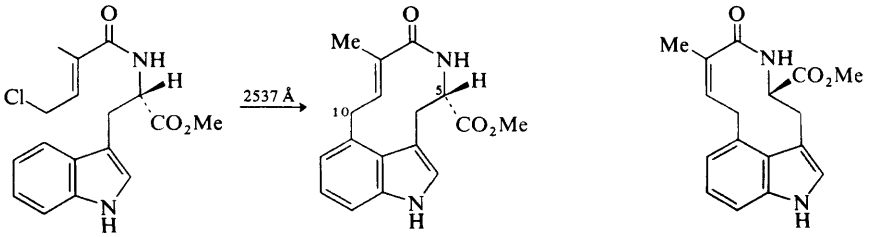
The neurotoxin roquefortine appears to occur generally in blue cheeses, and has been detected[39] in all sixteen varieties of cheese studied, in amounts up to 6.8 p.p.m.; in most varieties isofumigaclavine A was also present, in amounts up to 4.7 p.p.m. In order to study more closely the toxicological properties of these compounds, four strains of *P. roquefortii* from blue cheeses have been grown in liquid media, with a view to optimizing neurotoxin production; in one experiment, as much as 100 mg l^{-1} of roquefortine were produced after incubation for 16 days in a sucrose–yeast extract.[40]

The occurrence of *N*-[*N*-*d*-lysergyl-L-valyl]-L-phenylalanyl-D-proline lactam in an ergot sample which produces mainly ergocristine has again been noted.[41] An

[36] M. Abe, S. Ohmomo, T. Ohashi, and T. Tabuchi, *Agric. and Biol. Chem. (Japan)*, 1969, **33**, 469.
[37] S. Yamatodani, Y. Asahi, A. Matsukura, S. Ohmomo, and M. Abe, *Agric. and Biol. Chem. (Japan)*, 1970, **34**, 485.
[38] S. Ohmomo and M. Abe, *Nippon Nogei Kagaku Kaishi*, 1976, **50**, 331 (*Chem. Abs.*, 1976, **85**, 188 802).
[39] P. M. Scott and B. P. C. Kennedy, *J. Agric. Food Chem.*, 1976, **24**, 865.
[40] P. M. Scott, B. P. C. Kennedy, J. Harwig, and B. J. Blanchfield, *Applied and Environmental Microbiology*, 1977, **33**, 249.
[41] A. Černý, A. Krajicek, J. Spacil, M. Beran, B. Kakac, and M. Semonský, *Coll. Czech. Chem. Comm.*, 1976, **41**, 3415.

Argentinian strain of *Claviceps purpurea* contains a much higher proportion of ergotoxine–ergotoxinine than European ergot, and much less of the ergotamine group; it would therefore appear to be an economic source of alkaloids of the ergotoxine group.[42]

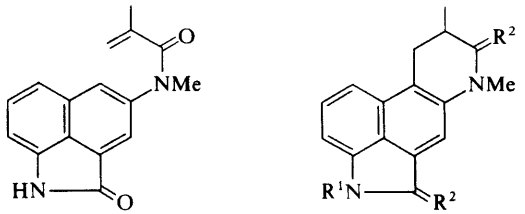
Hitherto, all attempts to simulate the biochemical process in which the dimethylallyl fragment is introduced onto the 4-position of a tryptophan molecule during the biosynthesis of the ergot alkaloids have been uniformly unsuccessful. A new approach[43] to the problem of introducing a five-carbon unit involves a photochemical cyclization of the γ-chlorotigloyl amide of L-tryptophan methyl ester (51), which afforded a mixture of the cyclized tigloyl amide (52) (33%) and its angeloyl isomer (53) (19%). This could prove an attractive approach to the ergoline skeleton if an efficient method of forming the 5,10-bond in (52) could be developed.



(51) (52) (53)

The synthesis of (±)-chanoclavine I by Plieninger *et al.*[33b] has now been described in detail.[44]

Irradiation of the amide (54) gives the photocyclized product (55) which, on reduction and acetylation, affords[45] the product (56) containing the clavine ring



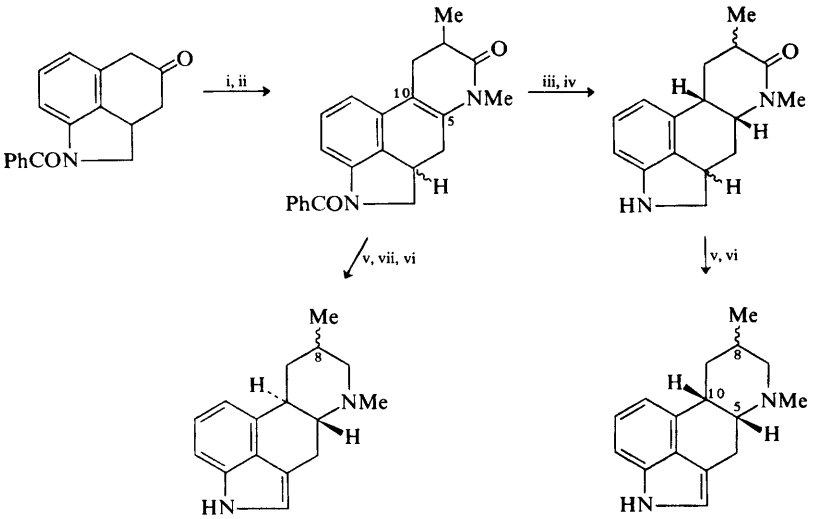
(54)

(55) $R^1 = H, R^2 = O$
(56) $R^1 = Ac, R^2 = H_2$

system; however, this new approach to clavines has not yet resulted in the synthesis of an alkaloid. Another contribution from the same laboratory provides a new synthesis[46] of costaclavine (57) (Scheme 3), together with its C-8 epimer, *i.e.* epicostaclavine (58), and festuclavine (59). Comparison of the n.m.r. spectra of

[42] G. E. Ferraro, S. L. Debenedetti, and J. D. Coussio, *J. Pharm. Pharmacol.*, 1976, **28**, 729.
[43] N. G. Anderson and R. G. Lawton, *Tetrahedron Letters*, 1977, 1843.
[44] H. Plieninger and D. Schmalz, *Chem. Ber.*, 1976, **109**, 2140.
[45] I. Ninomiya, T. Kiguchi, and T. Naito, *Heterocycles*, 1976, **4**, 973.
[46] I. Ninomiya and T. Kiguchi, *J.C.S. Chem. Comm.*, 1976, 624.

(57)—(60) confirmed the equatorial configuration of the methyl group at C-8 in festuclavine and the axial configuration of the same group in pyroclavine (60). Costaclavine (57) exists in a conformation in which the indole ring (bond to C-10) is axial and the methyl group at C-8 is equatorial. Epicostaclavine (58), hitherto unknown, therefore has an axial methyl group.



Festuclavine (59) β-Me at C-8
Pyroclavine (60) α-Me at C-8

Costaclavine (57) β-Me at C-8
Epicostaclavine (58) α-Me at C-8

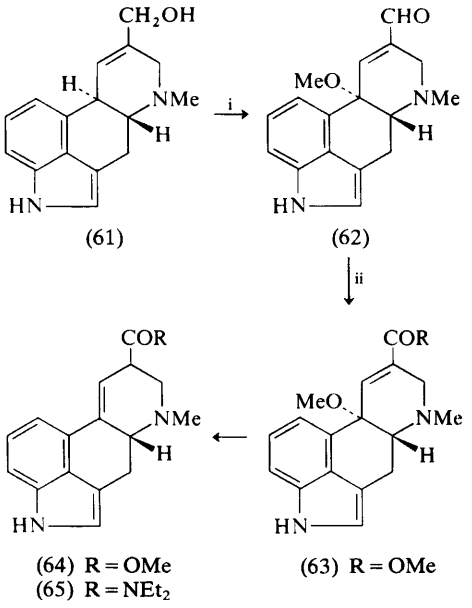
Reagents: i, $MeNH_2$; ii, $CH_2{=}CMeCOCl$; iii, H_2–PtO_2; iv, HCl; v, $LiAlH_4$; vi, MnO_2; vii, Na–NH_3

Scheme 3

Two new, formal syntheses of lysergic acid have recently been reported.[47,48] The first of these (Scheme 4) involves the first efficient conversion of a clavine alkaloid into lysergic acid. Oxidation of elymoclavine (61) by means of manganese dioxide in methanol gives the methoxy-aldehyde (62) which, on oxidation by the Corey method, gives the methyl ester (63), reduction of which gives a high yield of methyl lysergate (64). By substituting the appropriate amine for methanol in the Corey oxidation step, a neat conversion into lysergic acid diethylamide (65) is achieved.[47]

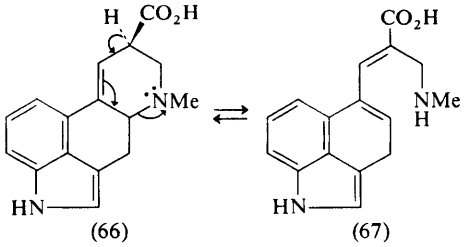
The second synthesis was inspired by Woodward's suggestion that epimerization/racemization of lysergic acid (66) or isolysergic acid proceeds *via* the achiral intermediate (67). The synthetic strategy (Scheme 5) therefore involved the construction of a related amine (68), which, as in the original Woodward synthesis of lysergic acid, was destined to lead to 2,3-dihydrolysergic acid, to avoid the possibility of undesired aromatization to a naphthalene derivative during the intermediate stages. It was expected that methylation of the basic nitrogen in (68) would facilitate cyclization; in fact, none of the related tertiary amine was obtained

[47] T. C. Choong and H. R. Shough, *Tetrahedron Letters*, 1977, 1627.
[48] V. W. Armstrong, S. Coulton, and R. Ramage, *Tetrahedron Letters*, 1976, 4311.



Reagents: i, MnO_2–MeOH; ii, MnO_2–MeOH–CN^-

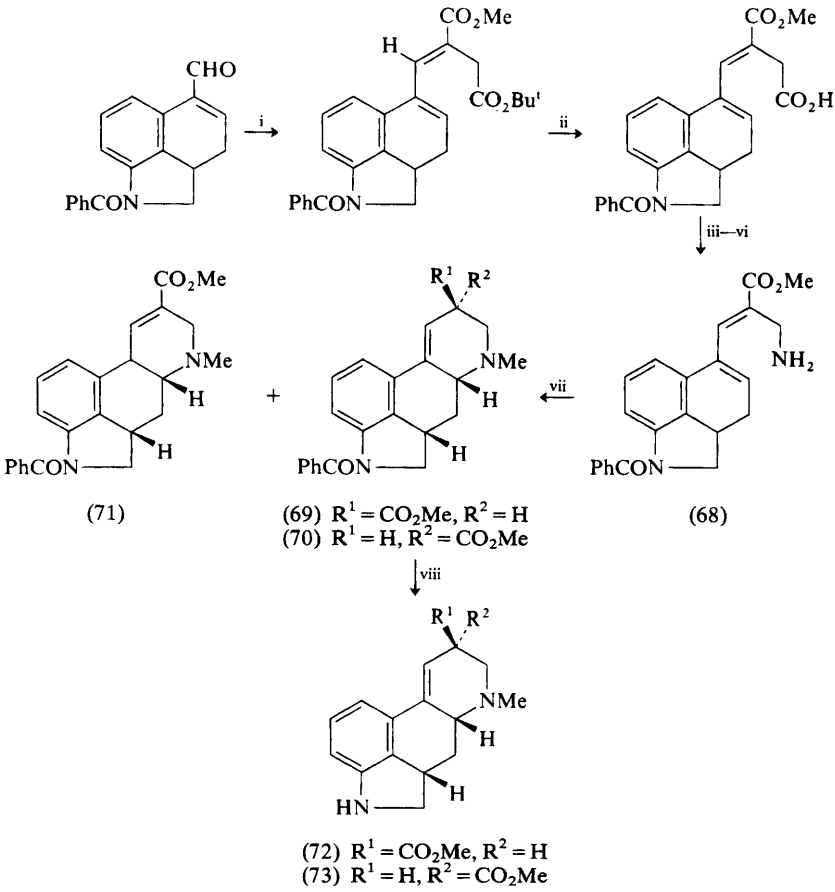
Scheme 4



on methylation, the product being a mixture of the epimers (69) (major product), (70), and the conjugated ester (71). Fractional crystallization followed by chromatography afforded mainly (69) contaminated with some (70), which was methanolysed to a mixture of 2,3-dihydrolysergic acids (72) and (73), identical with the penultimate product of the original synthesis of (±)-lysergic acid by Woodward *et al.* This elegant new route to lysergic acid thus substantiates Woodward's proposal for the mechanism of epimerization of lysergic acid, and also incidentally reveals that Woodward's synthetic dihydrolysergic acid is actually a mixture of epimers (72) and (73), by the use of analytical techniques not available in 1953.

The reaction of the 9-hydroxy-ergoline derivative (74), prepared by reduction with diborane and anti-Markovnikov hydration of lysergic acid, with phosphorus oxychloride–pyridine results[49] in expansion of ring C by displacement of the equa-

[49] L. Bernardi, C. Elli, and A. Temperilli, *J.C.S. Chem. Comm.*, 1976, 570.



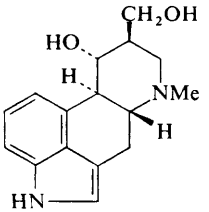
(71) (69) $R^1 = CO_2Me$, $R^2 = H$ (68)
(70) $R^1 = H$, $R^2 = CO_2Me$

(72) $R^1 = CO_2Me$, $R^2 = H$
(73) $R^1 = H$, $R^2 = CO_2Me$

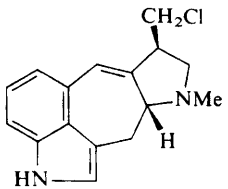
Reagents: i, $Ph_3P{=}C(CO_2Me)CO_2Bu^t$–PhH–$Bu^tOH$, heat, 4 days; ii, 90% TFA, 25 °C, 2 h; iii, Ph_2POCl–*N*-methylmorpholine–CH_2Cl_2, −20 °C; iv, tetramethylguanidinium azide–MeCN, 0 °C; v, PhH, reflux; vi, TsOH,H_2O–Et_2O–PhH; vii, CH_2O–HCO_2H, 100 °C; viii, MeOH–HCl, reflux

Scheme 5

torial hydroxy-group at C-9 by the appropriately placed *anti*-periplanar 5,10-bond; the product is thus the primary chloride of structure (75).



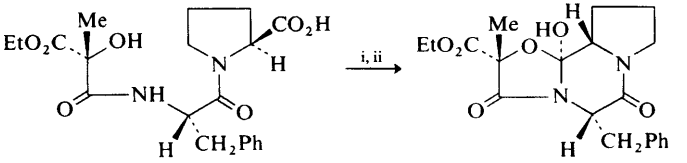
(74)



(75)

Numerous ergoline derivatives have been prepared for pharmacological evaluation; these include 6-alkyl derivatives of 6-norfestuclavine and 8-cyanomethylergoline,[50a] amides[50b] (including unsaturated amides[50d]) and esters[50c] of 6-methyl-8-ergolin-1-ylacetic acid, esters of 2-halogeno-6-methyl-8-ergolin-1-ylacetic acid,[50c] some unsaturated amides of dihydrolysergic-I acid,[50d] and various ureas of 8-aminomethyl-6-methylergoline and its 2-chloro-derivative.[50e]

Attention has also been given to the development of improved cyclol ester syntheses; thus, acylated dipeptides such as (76) can be converted efficiently into the related cyclol esters [*e.g.* (77)] by the reaction of their *p*-nitrophenyl esters with base in polar aprotic solvents (Scheme 6).[51]



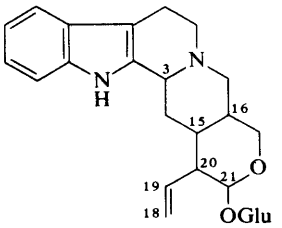
(76) (77)

Reagents: i, EtOAc–*p*-$HOC_6H_4NO_2$–DCC; ii, NaH–DMF, or $EtNPr^i_2$–DMF

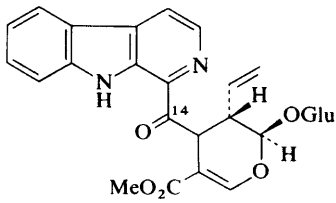
Scheme 6

Monoterpenoid Alkaloids.—*Corynantheine–Heteroyohimbine–Yohimbine Group, and Related Oxindoles.* The leaves of *Strychnos decussata* (Pappe) Gil. contain a new glycosidic alkaloid for which the gross structure (78) has been proposed;[52] so far, nothing is known about its stereochemistry. Nevertheless it seems distinctly possible that this alkaloid is a close biosynthetic relative of vallesiachotamine.

The isolation of lyaloside from the root bark of *Pauridiantha lyalli* was recorded earlier;[33c] recently, a second glucosidic alkaloid, pauridianthoside (79), has been



(78)



Pauridianthoside (79)

found in association with lyaloside in the leaves.[53] Since pauridianthoside is simply 14-oxo-lyaloside, the possibility that it is an artefact cannot be ruled out; however,

[50] (*a*) J. Křepelka, A. Černý, R. Kotva, and M. Semonský, *Coll. Czech. Chem. Comm.*, 1977, **42**, 1209; (*b*) M. Beran, J. Křepelka, and M. Semonský, *ibid.*, p. 1216; (*c*) M. Beran, J. Křepelka, K. Řežábek, M. Šeda, and M. Semonský, *ibid.*, p. 1407; (*d*) J. Křepelka, M. Šeda, K. Řežábek, and M. Semonský, *ibid.*, p. 1412; (*e*) M. Beran, J. Křepelka, V. Zikán, K. Řežábek, M. Šeda, and M. Semonský, *ibid.*, p. 1417.

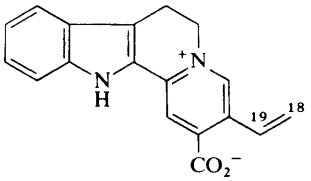
[51] P. Stütz and P. A. Stadler, *Monatsh.*, 1976, **107**, 763.

[52] A. Petitjean, P. Rasoanaivo, and J. M. Razafintsalama, *Phytochemistry*, 1977, **16**, 154.

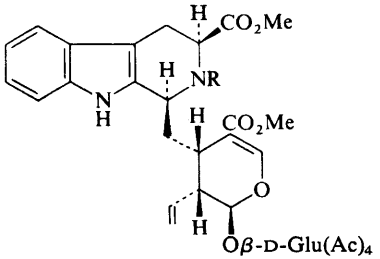
[53] J. Levesque, J. L. Pousset, and A. Cavé, *Fitoterapia*, 1977, **48**, 5.

lyaloside appears not to be oxidized spontaneously under the extraction conditions adopted.

Another biosynthetic variant in the corynantheine series has been encountered with vincarpine (80) and dihydrovincarpine (81), two new, zwitterionic alkaloids of *Vinca major* L. var. *elegantissima* Hort.[54a] These alkaloids presumably arise from a late intermediate in the corynantheine biosynthesis by oxidation of C-16 and dehydrogenation of ring D. The first glycosidic base has also been isolated from this species;[54b] methylation of the total glycosidic bases followed by acetylation gave 5β-methoxycarbonyl-strictosidine penta-acetate (82) and its N_b-methyl-N_b-deacetyl derivative (83). This method of isolation does not allow the degree of methylation of the naturally occurring strictosidine derivative to be determined, so the identity of the actual plant constituent is still unknown.



Vincarpine (80)
Dihydrovincarpine (81) 18,19-dihydro



(82) R = Ac
(83) R = Me

The occurrence of geissoschizine in the leaves of *Rhazya stricta* has been confirmed,[55a] and it has also been isolated from *Bonafousia tetrastachya*.[55b]

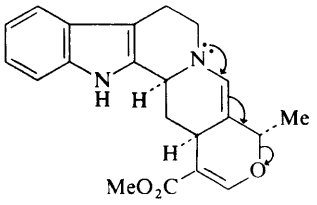
The isolation of cathenamine (20,21-dehydroajmalicine) (84) from the leaves of *Guettarda eximia* (Rubiaceae)[56] and from the incubation of tryptamine and secologanin with a cell-free enzyme extract of *Catharanthus roseus*[57] fills an important gap in the biosynthetic sequence between vincoside and the heteroyohimbine alkaloids. The importance of (84) as a late precursor is emphasized by the fact that in the absence of NADPH or NADH it accumulates in the incubation medium, but in their presence it is converted[57] into ajmalicine (85a), 19-epiajmalicine (85b), and tetrahydroalstonine (85c). The complete stereochemistry for cathenamine becomes clear from its reduction ($NaBH_4$) to tetrahydroalstonine;[56,57] hence its conversion into 19-epiajmalicine must depend on the possibility of its equilibration with transient forms in which ring E is opened [*cf.* arrows in (84)]. This is supported by the isolation of an unstable artefact (86) when the extracts of *G. eximia* are basified with ammonia instead of with sodium carbonate during work-up.[56]

[54] E. Ali, V. S. Giri, and S. C. Pakrashi, (*a*) *Tetrahedron Letters*, 1976, 4887; (*b*) *Indian J. Chem.*, 1976, **14B**, 306.

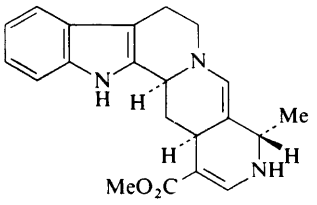
[55] (*a*) A. Chatterjee, A. Banerji, P. Majumder, and R. Majumder, *Bull. Chem. Soc. Japan*, 1976, **49**, 2000; (*b*) M. Damak, A. Ahond, P. Potier, and M. M. Janot, *Tetrahedron Letters*, 1976, 4731.

[56] H. P. Husson, C. Kan-Fan, T. Sévenet, and J. P. Vidal, *Tetrahedron Letters*, 1977, 1889.

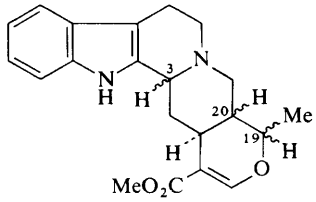
[57] (*a*) J. Stöckigt, J. Treimer, and M. H. Zenk, *F.E.B.S. Letters*, 1976, **70**, 267; (*b*) J. Stöckigt, H. P. Husson, C. Kan-Fan, and M. H. Zenk, *J.C.S. Chem. Comm.*, 1977, 164.



Cathenamine (84)

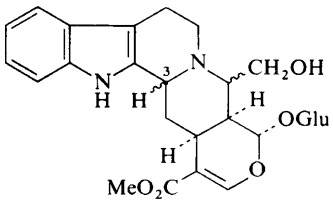


(86)

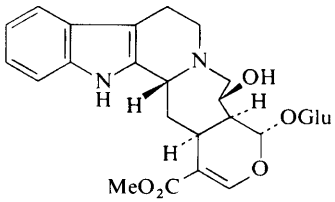


		3-H	19-H	20-H
Ajmalicine	(85a)	α	β	β
19-Epiajmalicine	(85b)	α	α	β
Tetrahydroalstonine	(85c)	α	β	α
3-Isorauniticine	(85d)	β	α	α
Rauniticine	(85e)	α	α	α
3-Iso-19-epiajmalicine	(85f)	β	α	β
Akuammigine	(85g)	β	β	α
3-Isoajmalicine	(85h)	β	β	β

The alkaloids cadamine and isocadamine[22b] contain β-hydrogen at C-3, and may well be formed from the previously unknown 3β-analogues of iso-dihydrocadambine (87a), which occurs in the same plant (*Anthocephalus cadamba*). Support for this view comes from the recent extraction[58] from this plant of the presumed precursor, 3β-isodihydrocadambine (87b), together with a second glycosidic alkaloid, 3β-dihydrocadambine (88).



(87a) 3α-H
(87b) 3β-H



(88)

New extractions of alkaloids in this group include hunterburnine α-methochloride, huntabrine and yohimbol methochlorides, and pleiocarpamine from Ghanaian *Hunteria elliottii* (Stapf) Pichon,[59a] tetrahydroalstonine from the flowers of *Alstonia scholaris*,[59b] and aricine, reserpine, reserpiline, and isoreserpiline (major alkaloid) from the roots of *Rauwolfia cambodiana*.[60] The presence of alstonine in *R. obscura* has been confirmed,[61] and methyl reserpate, α-yohimbine, rescinnamine, and tetrahydroalstonine have also been isolated. Details of the extraction of geissoschizol, among other alkaloids, from *Peschiera laeta* Mart. have

[58] R. T. Brown and C. L. Chapple, *Tetrahedron Letters*, 1976, 2723.
[59] (*a*) I. Søndergaard and F. Nartey, *Phytochemistry*, 1976, **15**, 1322; (*b*) S. C. Dutta, S. K. Bhattacharya, and A. B. Ray, *Planta Med.*, 1976, **30**, 86 (*Chem. Abs.*, 1976, **85**, 119 611).
[60] W. Boonchuay and W. E. Court, *Planta Med.*, 1976, **29**, 201 (*Chem. Abs.*, 1976, **85**, 43 703).
[61] P. Timmins and W. E. Court, *Planta Med.*, 1976, **29**, 283 (*Chem. Abs.*, 1976, **85**, 43 705).

been published;[62] this base, and also α-yohimbine, have been found in the leaves of *R. vomitoria*.[63a]

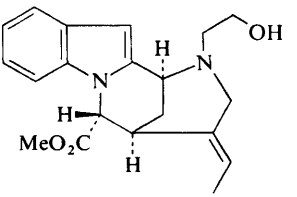
A re-examination of the constituents of *Pseudocinchona mayumbensis* (*Corynanthe mayumbensis*) has resulted in the isolation of several alkaloids, among which are the six stereoisomers (85b)—(85g) of ajmalicine (85a).[63b] The original alkaloid, mayumbine, isolated from this source was subsequently formulated as (85d), *i.e.* 3-isorauniticine, but it has now been shown to be identical with 19-epiajmalicine (85b). The authentic 3-isorauniticine is nevertheless a constituent of this plant, and was identified by comparison with material prepared by dehydrogenation [$Hg(OAc)_2$] of rauniticine, followed by reduction (Zn–acid). Since 3-isoajmalicine (85h) is also a known alkaloid, all eight stereoisomers (85a)—(85h) are now known to occur naturally.

In a chemotaxonomic survey of seven of the eight species of the genus *Hazunta*, which is endemic to the Malagasy Republic, twenty-four alkaloids have been encountered, of which ten are new.[64a] Reserpiline and 3-isoreserpiline were the only alkaloids of this group to be isolated, and these were found in only one of the seven species, *H. membranacea* (DC.) Pichon forma *pilifera* Mgf.

11-Methoxy-yohimbine and 11-methoxypseudoyohimbine, which were previously unknown, have been isolated from the bark of a specimen of *Rauwolfia capuroni* Mgf. collected in the Malagasy Republic.[64b]

The structural data from which the structure of vinoxine (89) was deduced have been described in greater detail.[65] The configuration at C-16 is based on the closer resemblance of the ^1H n.m.r. spectrum of vinoxine to that of 16-epipleiocarpamine rather than that of pleiocarpamine. In reference 65, for some unspecified reason, the configuration given for the double bond is different from that illustrated in (89) and postulated in the earlier communication;[33d] however, the similarity of the chemical shifts of the protons of the ethylidene group with the corresponding ones in the pleiocarpamine series makes it extremely probable that the configuration about the double bond [*i.e.* (*E*)] is the same in all these alkaloids.

In the oxindole series, the corynoxeine isomers have been found in old specimens of *Mitragyna stipulosa*, but the related tetrahydrocarboline derivative hirsuteine appears to be absent;[66] however, young plants of the same species contain hirsutine (dihydrohirsuteine).

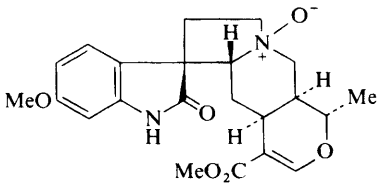


Vinoxine (89)

[62] Z. Votický, L. Jahodář, and M. P. Cava, *Coll. Czech. Chem. Comm.*, 1977, **42**, 1403.
[63] (*a*) J. L. Pousset, M. Debray, and J. Poisson, *Phytochemistry*, 1977, **16**, 153; (*b*) J. Melchio, A. Bouquet, M. Païs, and R. Goutarel, *Tetrahedron Letters*, 1977, 315.
[64] (*a*) A. M. Bui, M. M. Debray, P. Boiteau, and P. Potier, *Phytochemistry*, 1977, **16**, 703; (*b*) C. Miet, G. Croquelois, and J. Poisson, *ibid.*, p. 803.
[65] Z. Votický, E. Grossmann, and P. Potier, *Coll. Czech. Chem. Comm.*, 1977, **42**, 548.
[66] P. J. Houghton, P. K. Lala, E. J. Shellard, and K. Sarpong, *J. Pharm. Pharmacol.*, 1976, **28**, 664.

The root bark of an uncharacterized *Uncaria* species from Peru contains[67] pteropodine, isopteropodine, speciophylline, uncarine F, and isomitraphylline.

Majdinine and a new alkaloid, vinerine N_b-oxide (90), are two of the recently isolated constituents of *Vinca erecta*.[68a] Reduction (Zn–HCl) of vinerine N_b-oxide



Vinerine N_b-oxide (90)

gives vinerine, which is now stated to give, on equilibration in acetic acid, a mixture of vinerine, vineridine, caboxine, and isovineridine; the last base is described as the C-3 epimer of vineridine. In view of these results, and the comments made earlier,[33e] it seems likely that isovineridine is the *allo*-A-isomer, caboxine A, and that the caboxine obtained in the above equilibration is the corresponding *allo*-B-isomer. Although the structures are not illustrated in reference 68*a*, this agrees with the Russian authors' statement that vinerine and vineridine have β-hydrogen at C-3, whereas caboxine (caboxine B?) and isovineridine have α-hydrogen at this position. In this oxindole alkaloid series the *allo*- and *epiallo*-isomers can be distinguished by means of their n.m.r. spectra, and the relevant data have been tabulated for several of these bases.[68b]

A brief, selective review of epimerizations in the isoquinoline and indole alkaloid series inevitably gives prominence to epimerizations at C-3 of tetrahydro-β-carboline derivatives, in particular of reserpine and reserpic acid lactone; the epimerizations involved in Brown's synthesis[33f] of N_a-methyl-tetrahydroalstonine and 3β-H,20β-H-N_a-methyldihydrogeissoschizine, from N_b-benzyl-N_a-methylvincoside, are also discussed.[69]

Considerable effort continues to be expended on the synthesis of alkaloids of this group and on studying further their interconversion. However, an efficient synthesis of dihydroantirhine, uncontaminated by epimers, still eludes investigators. In the most recent synthetic study it was shown that hydrogenation of the acetate of the tetracyclic base (91a), prepared earlier,[70a] followed by deacetylation, affords a mixture of the C-20 epimeric 3-epidihydroantirhines (91b).[70b]

Following a close examination of the spectra of geissoschizine and its derivatives,[55b,71a] together with those of several synthetic relatives in which the double bond has the geometrically isomeric (*Z*) configuration,[71b] it has been concluded

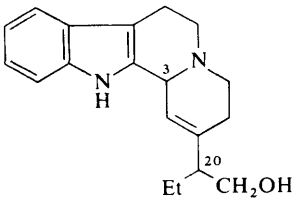
[67] S. Montenegro de Matta, F. Delle Monache, F. Ferrari, and G. B. Marini-Bettòlo, *Farmaco, Ed. Sci.*, 1976, **31**, 527 (*Chem. Abs.*, 1976, **85**, 59 691).

[68] (*a*) M. R. Sharipov, M. M. Khalmirzaev, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 401 (*Chem. Abs.*, 1977, **86**, 29 972); (*b*) M. R. Yagudaev and S. Yu. Yunusov, *ibid.*, p. 345 (*Chem. Abs.*, 1977, **86**, 43 877).

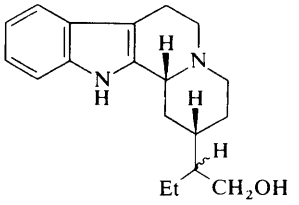
[69] T. Kametani and M. Ihara, *Heterocycles*, 1976, **5**, 649.

[70] (*a*) H. P. Husson, L. Chevolot, Y. Langlois, C. Thal, and P. Potier, *J.C.S. Chem. Comm.*, 1972, 930; (*b*) L. Chevolot, A. Husson, C. Kan-Fan, H. P. Husson, and P. Potier, *Bull. Soc. chim. France*, 1976, 1222.

[71] (*a*) G. Rackur and E. Winterfeldt, *Chem. Ber.*, 1976, **109**, 3837; (*b*) G. Rackur, M. Stahl, and M. Walkowiak, *ibid.*, p. 3817; (*c*) B. Hachmeister, D. Thielke, and E. Winterfeldt., *ibid.*, p. 3825.

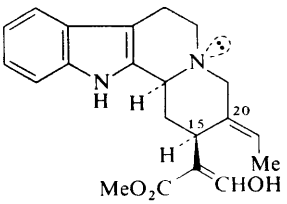


(91a)

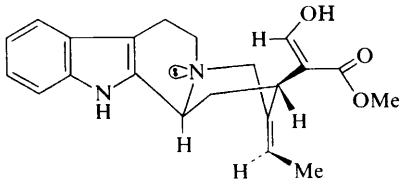


(91b)

that geissoschizine (92) has a 3α-hydrogen atom in a *cis*-C/D quinolizidine ring system. However, the coupling constants for the hydrogen at C-3 (11 and 2 Hz) are not those expected of an equatorial proton to ring D, and the ^{13}C chemical shifts of C-6 and C-15 are also anomalous. The available data are best explained by a flexible boat conformation for ring D in geissoschizine, as shown in (92a); this



Geissoschizine (92)



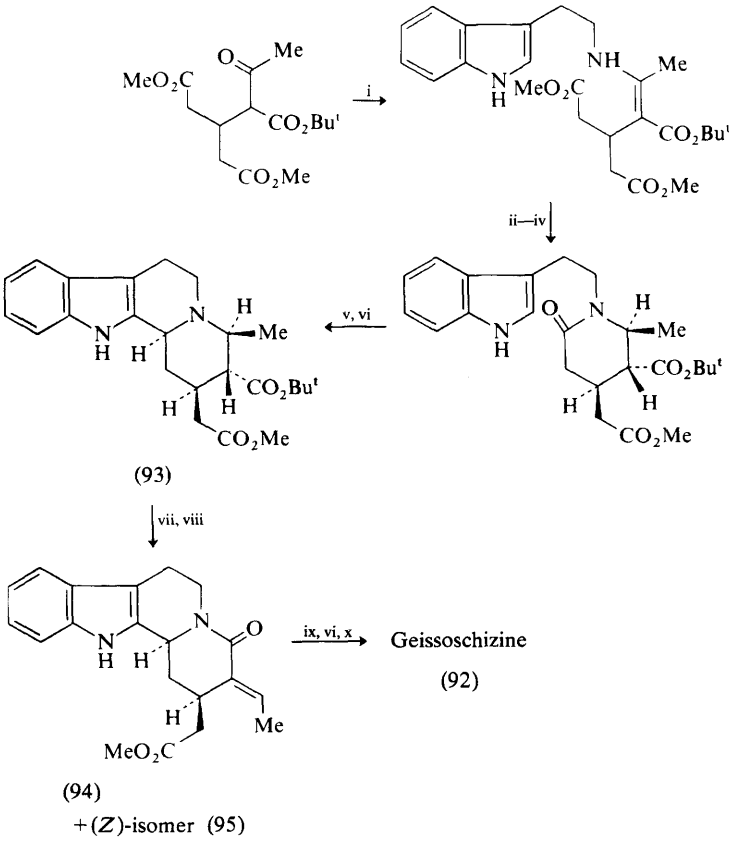
(92a)

avoids serious non-bonded interactions between the substituents at C-15 and C-20 in the *trans*-C/D isomer and in one of the conformations of the *cis*-C/D isomer, and between the indole ring and the substituent at C-15 in the alternative *cis*-C/D conformation, in all of which ring D is chair-shaped.

Two total syntheses of (±)-geissoschizine have been reported by Winterfeldt and his collaborators.[71c] The first of these (Scheme 7) involved as the critical stage the methylene-lactam rearrangement of the sterically homogeneous racemate (93), which gave a mixture of the lactam (94) and its geometrical (*Z*)-isomer (95). Subsequently it was shown that (94) is the thermodynamically preferred isomer, and it can be obtained as the major isomer either by equilibration of (95) or by rearrangement of the mixture of stereoisomers having the gross structure (93). Removal of the lactam carbonyl group in (94), followed by formylation, completed the synthesis.

The second synthesis (Scheme 8) uses a less stereoselective, but nevertheless ingenious, route for the construction of a tetracyclic lactam (96), and takes advantage of the greater stability of the (*E*)-isomer having the stereochemistry shown in (96). Confirmation of the stereochemistry of (96) was provided by its correlation with (94). A selective two-stage reduction of the dimethyl ester corresponding to (96) with dialkyl-aluminium hydride then gave (±)-geissoschizine (92), the reduction presumably being halted at the appropriate stage by the formation of a complex with aluminium.[71c]

In earlier experiments the stereochemistry at positions 3, 5, and 15 in adirubine (97) had been established, but the configuration at C-20 and C-16 remained

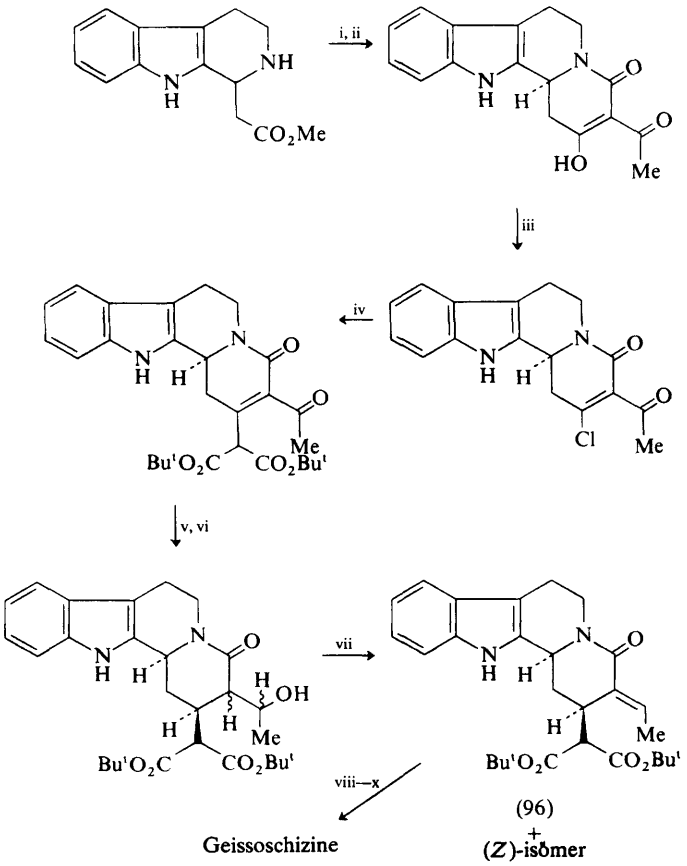


Reagents: i, Tryptamine–dioxan, r.t., 2 days; ii, $NaBH_4$–AcOH; iii, AcOH–2-pyridone; iv, separate all-*trans*-isomer by crystallization; v, $POCl_3$–pyridine; vi, $NaBH_4$; vii, TFA; viii, Ac_2O; ix, $Et_3O^+ BF_4^-$–CH_2Cl_2; x, HCO_2Et–NaH

Scheme 7

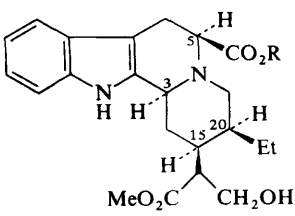
unknown. However, adirubine triacetate (98a), on equilibration in refluxing acetic acid, is largely converted into the 3β-epimer (98b), a behaviour which is characteristic of an *allo–epiallo* system rather than a *normal–pseudo* pair of isomers.[72] Hence adirubine (97) probably belongs to the *allo*-series, a conclusion which was confirmed by the synthesis of 3-epiadirubine triacetate (98b), the initial stage in which involved the condensation of methyl L-tryptophanate with dihydrosecologanin. As in the analogous reaction with tryptamine the product, 5-methoxycarbonyldihydromancunine (99), was predominantly the 20α-H isomer. Reduction ($NaBH_4$) of (99), followed by separation of the products, gave a methoxycarbonyldihydrositsirikine (98c) which, on reduction ($LiAlH_4$) and acetylation, gave 3-epiadirubine triacetate (98b).[72]

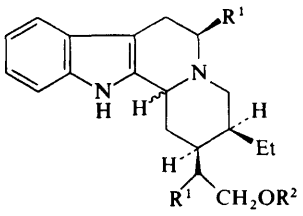
[72] R. T. Brown and D. M. Duckworth, *J.C.S. Chem. Comm.*, 1976, 530.

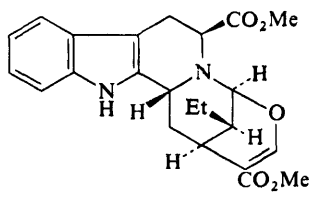


Reagents: i, Diketen; ii, $KOBu^t$–Bu^tOH–dioxan; iii, $POCl_3$–DMF–CH_2Cl_2; iv, $CH_2(CO_2Bu^t)_2$–NaH; v, $Ca(BH_4)_2$; vi, $NaBH_4$; vii, $POCl_3$–pyridine; viii, MeOH–H_2SO_4; ix, Bu^i_2AlH–PhMe–$(MeOCH_2)_2$, −70 °C; x, $AlEt_2H$–THF, −70 °C

Scheme 8



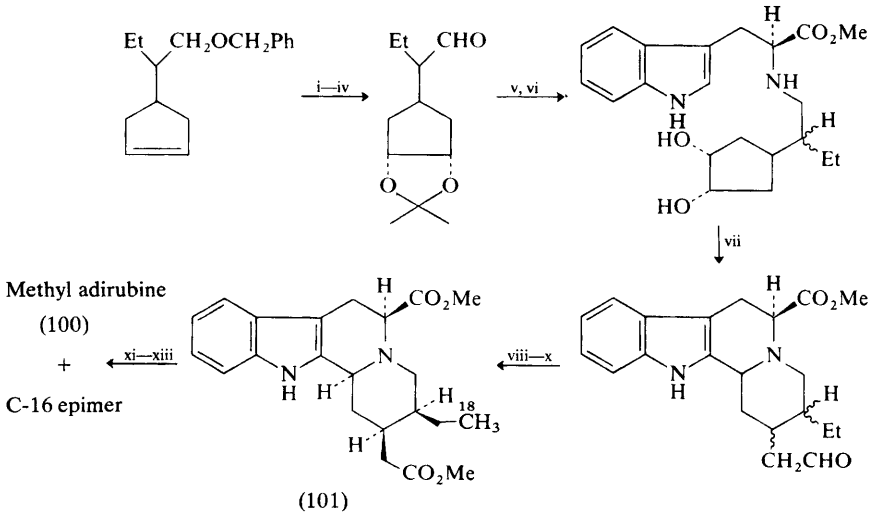




		3-H	R^1	R^2
Adirubine (97) R = H	(98a)	α	CH_2OAc	Ac
Methyl adirubine (100) R = Me	(98b)	β	CH_2OAc	Ac
	(98c)	β	CO_2Me	H

(99)

The same conclusion concerning the stereochemistry of adirubine emerged from an independent, non-stereospecific synthesis of methyl adirubine (100) (Scheme 9).[73] The tetracyclic diester was obtained as a mixture of at least six stereoisomers,



Reagents: i, $KMnO_4$–OH^-; ii, $Me_2C(OMe)_2$–Me_2CO–TsOH; iii, H_2–Pd/C; iv, CrO_3,2py; v, methyl L-tryptophanate–$NaBH_3CN$–MeCN; vi, HCl–MeOH–H_2O, r.t.; vii, HIO_4–THF–H_2O–AcOH–AcONa; viii, Ag_2O–OH^-; ix, MeOH–$Me_2C(OMe)_2$–HCl; x, separation of isomers; xi, $LiN(C_6H_{11})_2$–HCO_2Me–THF–HMPA; xii, $NaBH_4$–MeOH; xiii, separation of C-16 epimers

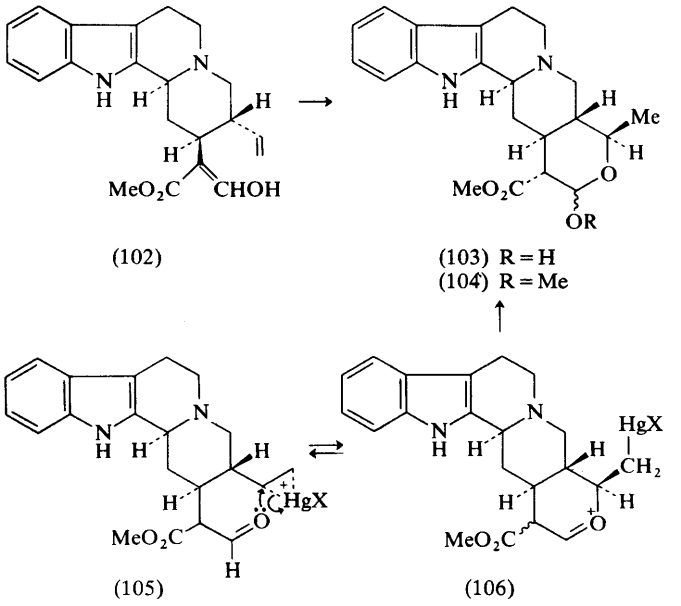
Scheme 9

of which five were isolated in amounts sufficient to allow of their analysis by n.m.r. spectroscopy. One of these esters (101) gave spectra remarkably similar to those of methyl adirubine, and therefore presumably possessed the same stereochemistry; this was subsequently confirmed by conversion of this ester into methyl adirubine and its C-16 epimer. The configuration at C-20 was elucidated by an examination of the degree of resolution of the triplet signal in the n.m.r. spectrum of (101) owing to the C-18 methyl group. In *allo*-compounds of the corynantheidine series this triplet is much better resolved than the corresponding signal in the spectra of the *normal* isomers, *e.g.* dihydrocorynantheine. Unfortunately, this criterion is not generally applicable, and depends to some extent on the nature of the substituent at C-15. It has been shown to be diagnostically useful in the corynantheidine–dihydrocorynantheine series,[74] but it appears not to be applicable in the case of methyl adirubine (100). However, it was shown to be valid in model esters related to (101) but lacking the 5-methoxycarbonyl group, and was then applied to (101) itself. The well-defined triplet arising from the C-18 methyl group in the n.m.r. spectrum of (101) was consistent with the *allo* configuration, which is therefore also the configuration of methyl adirubine (100).[73]

[73] E. E. van Tamelen and C. Dorschel, *J.C.S. Chem. Comm.*, 1976, 529; *Bioorganic Chemistry*, 1976, **5**, 203.

[74] W. F. Trager, C. M. Lee, and A. H. Beckett, *Tetrahedron*, 1967, **23**, 365, 375.

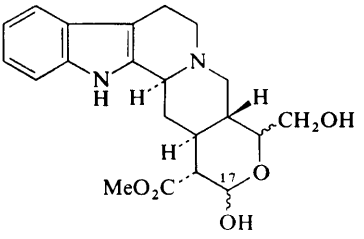
The oxymercuration of demethylcorynantheine in hot acetic acid, followed by reduction ($NaBH_4$), was earlier shown[22c] to give a mixture of ajmalicine, 19-epiajmalicine, and a product in which ring E had contracted, presumably by non-stereospecific Markovnikov attack of the enol oxygen on an 18,19-mercurinium ion, together with anti-Markovnikov attack by the nucleophilic C-16 on the same ion. Confirmation of this mechanism has now been obtained[75] by a study of the behaviour of the N_b-benzyl quaternary derivative of demethylcorynantheine in the same reaction, followed by reduction with $NaBD_4$, then debenzylation. Since the ring-contracted product is the major one in this reaction, it clearly does not afford a viable route to the heteroyohimbine alkaloids. However, the reaction of demethylcorynantheine (102) with mercury(II) trifluoroacetate in THF–water, followed by demercuration ($NaBH_4$), proceeds differently, and the products are the epimeric hemiacetals (103). In methanol solution the products are the acetals (104). Both hemiacetals (103) and acetals (104) are converted by polyphosphoric acid into 19-epiajmalicine; hence the configuration at C-19 is not in doubt. The configuration at C-16 follows from the n.m.r. spectrum. The preferential formation of 19-epiajmalicine in this reaction is explained by postulating the *reversible* formation of an oxonium ion (106) by intramolecular attack on the mercurinium ion by the the C-17 carbonyl oxygen atom in (105). The predominant product would be expected to be that containing



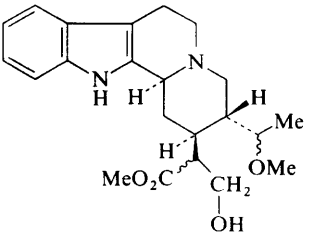
an equatorial methyl group at C-19. The by-products in these reactions depend on the solvent employed. In aqueous THF, a mixture of C-17 epimeric hemiacetals (107; configuration at C-19 unknown) is obtained, presumably by aerial oxidation of the mercurinium ion. In methanol solution the primary alcohol (108) is

[75] J. Boivin, M. Païs, and R. Goutarel, *Tetrahedron*, 1977, **33**, 305.

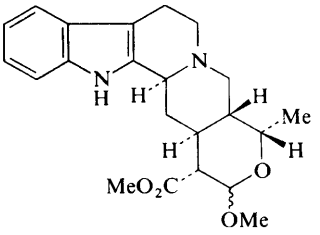
obtained, together with a small amount of the acetal (109), which has the ajmalicine stereochemistry; this acetal can also be obtained by the addition of methanol to ajmalicine in the presence of hydrogen chloride.



(107)



(108)



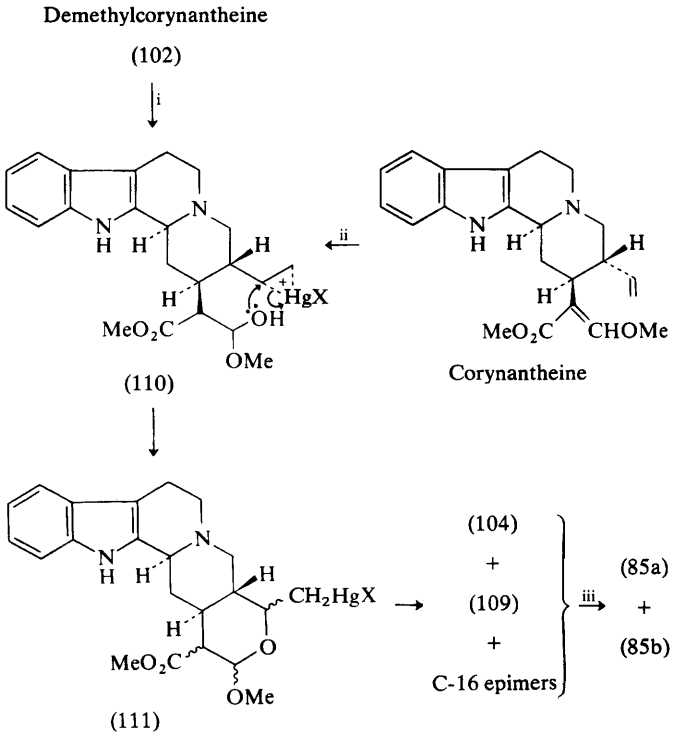
(109)

An alternative mechanism (shown in Scheme 10) for the formation of (109) from demethylcorynantheine (102) postulates the prior formation of a hemiacetal (110) followed by an *irreversible* attack on the mercurinium ion by the hydroxy-group to give an intermediate of structure (111). The inherent plausibility of such a mechanism led Goutarel *et al.*[75] to study the mercuration–demercuration of corynantheine which, in an aqueous medium, can in principle give rise to the same hemiacetal (110), and thence the acetal (111). In fact this reaction gave a mixture of the acetals (104), (109), and their C-16 epimers which, on treatment with polyphosphoric acid, gave a mixture of ajmalicine (85a) and 19-epiajmalicine (85b) in a ratio of *ca.* 45:55.

Further details have been given concerning the reaction that occurs when either corynantheine or corynantheal is heated with dilute hydrochloric acid for long periods.[76] Contrary to the previous report,[22d] the two starting materials give essentially the same amounts of the two diols (112) and (113); in addition, corynantheine gives some 19β-chloro-β-yohimbine (114). The stereochemistry of (112) follows from its n.m.r. spectrum (both hydrogens at C-17 and C-19 are axial), and the stereochemistry of (113) (one axial hydrogen, one equatorial hydrogen at positions 17 and 19, not necessarily respectively) was deduced by correlation with the known unsaturated ketone (115), prepared from (113) *via* the monotosylate (116) (preferential tosylation of the equatorial hydroxy-group).

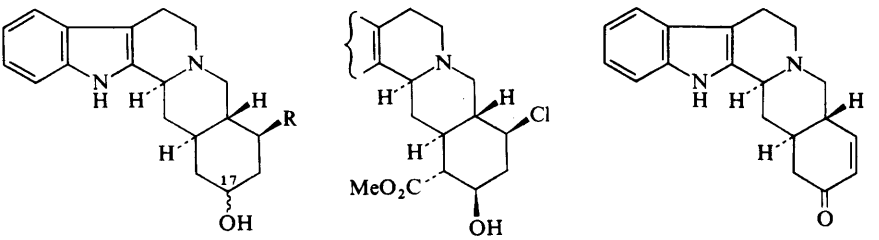
The formation of 19β-chloro-β-yohimbine (114) involves the closure of the carbocyclic ring E by the formation of the 17,18-bond in a reaction which is the

[76] M. Païs, L. A. Djakouré, F. X. Jarreau, and R. Goutarel, *Tetrahedron*, 1977, **33**, 1449.



Reagents: i, $Hg(OCOCF_3)_2$–MeOH; ii, $Hg(OCOCF_3)_2$–H_2O–THF; iii, polyphosphoric acid

Scheme 10



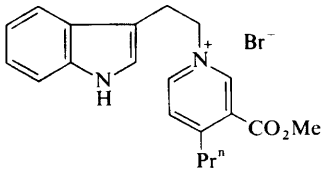
	17-OH	R
(112)	β	OH
(113)	α	OH
(116)	α	OTs

(114) (115)

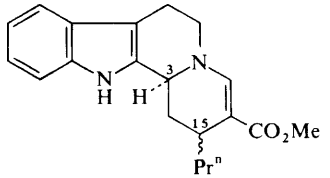
closest analogy yet observed *in vitro* for the biosynthesis of the yohimbine ring system, in which the double bond between positions 18 and 19 in the precursor is presumably present in an enamine function. Details of the genesis of the yohimbine isomers are still obscure, however; the above process, starting from corynantheine, appears to be stereospecific at positions 16 and 17, whereas yohimbine

isomers differing in the configuration at one or both of these centres are known, as well as those differing at position 3 and/or 20.

The reduction of *N*-(β-indolylethyl)-pyridinium salts [*e.g.* (117)] by means of sodium dithionite is accompanied by cyclization in the acidic reaction medium of the 1,4-dihydropyridine so generated, with the formation of tetracyclic bases [*e.g.* (118)] that are useful as models for the synthesis of vallesiachotamine. If, however, the reaction medium is buffered, the intermediate 1,4-dihydropyridine can be isolated; subsequent acid-induced cyclization of this gives the thermodynamically more stable tetracyclic base (119), containing an equatorial substituent at C-15; a high degree of stereoselectivity at positions 3 and 15 is therefore possible in this synthetic approach.[77a]

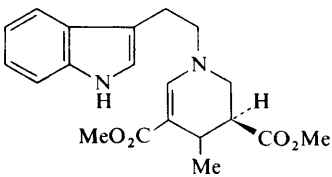


(117)

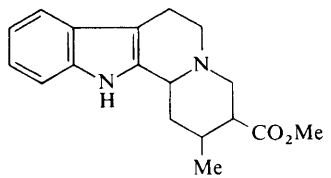


(118) 15β-H
(119) 15α-H

Another route to this tetracyclic system involves the decarboxylative cyclization of indolylethyl-tetrahydropyridine derivatives. As an example, heating the diester (120) with aqueous alkali results in hydrolysis, decarboxylation, and cyclization, with the formation (after re-esterification) of one diastereoisomer of the tetracyclic monoester (121).[77b] However, the stereochemistry of this product has not yet been clarified.



(120)



(121)

Cyclization of an indolylethyl-tetrahydropyridine derivative is also a key stage in an extremely brief and elegant synthesis of the yohimbine ring system and a number of ajmalicinoid bases by Wenkert and his collaborators.[78] Thus, internal nucleophilic attack by enolate anion at the γ-position to the nitrogen atom in (122) gave a tetrahydropyridine derivative which readily cyclized to the pentacyclic enamine (123), reduction of which gave (±)-pseudoyohimbone (124) (Scheme 11).

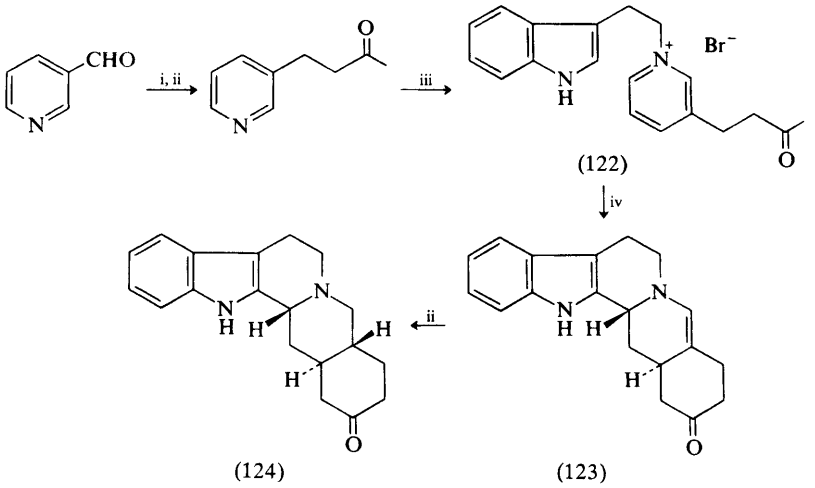
In a development of this approach malonate anion was added to the salt (125) with the formation, after cyclization, of the tetracyclic keto-ester (126) (Scheme 12). Hydrogenation of (126) gave the saturated keto-esters (127) and (128); the

[77] (*a*) M. Lounasmaa and C. J. Johansson, *Tetrahedron*, 1977, **33**, 113; (*b*) M. Lounasmaa, C. J. Johansson, and J. Svensson, *Acta Chem. Scand.* (*B*), 1976, **30**, 251.

former had already been converted into (±)-ajmalicine (85a) and (±)-3-iso-ajmalicine (85h) by Winterfeldt and his collaborators. Alternatively, mild reduction ($NaBH_4$) of (128) gave a pentacyclic lactone ester (129) which, after more vigorous reduction by the same reagent and then acid-catalysed dehydration, gave (±)-akuammigine (85g). This represents the shortest synthesis of this alkaloid achieved to date. Epimerization of (85g) at C-3 by familiar methods gave tetrahydroalstonine (85c), also obtainable by the synthetic sequence summarized in Scheme 12 from the C-3 epimer of (129), which is a minor product of the hydrogenation of (126). This notable paper also contains a comprehensive summary, with appropriate assignments, of the ^{13}C n.m.r. spectra of numerous yohimbinoid and ajmalicinoid bases.[78]

A partial synthesis of burnamicine (131) from geissoschizine methyl ether (130) takes advantage of the C/D ring cleavage of tetrahydro-β-carbolines by means of ethyl chloroformate (Scheme 13),[79] which simultaneously introduces a function into position 3, thereby facilitating the formation of the 3-oxo-substituent. An exactly analogous route was used for the synthesis of 19,20-dihydroburnamicine (133) from hirsutine (132).

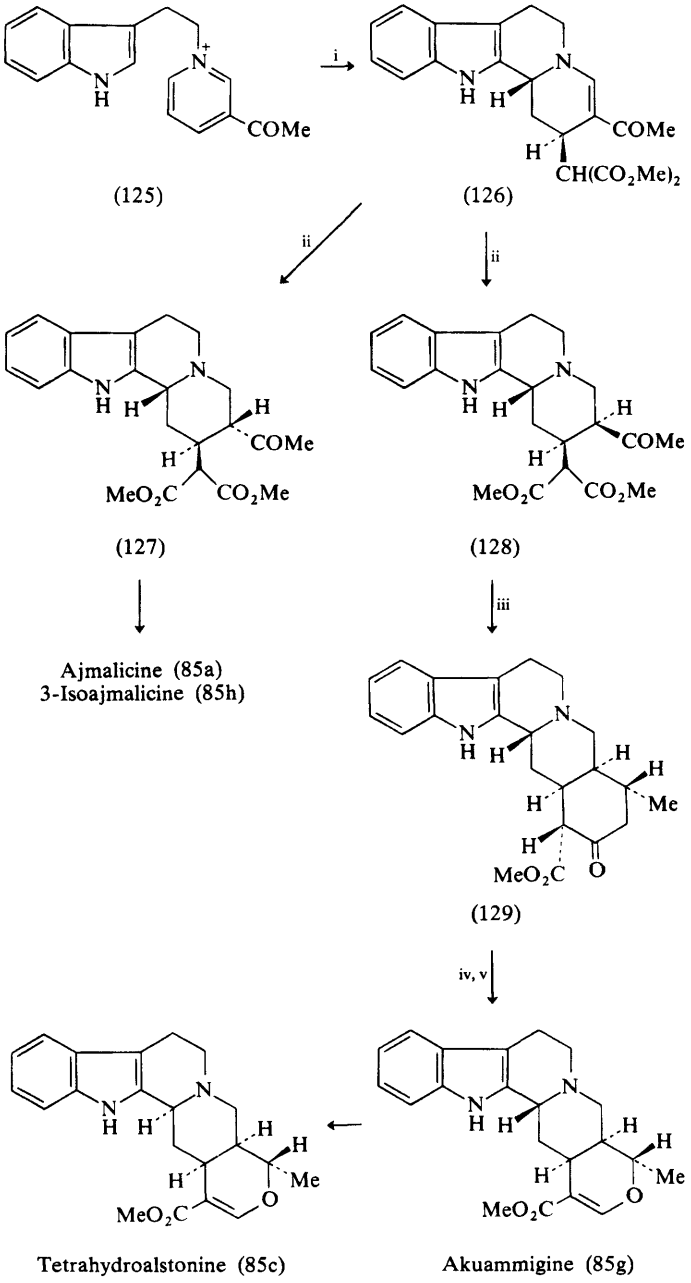
The route used earlier[33g] in the partial synthesis of dihydro-epipleiocarpamine from dihydrocorynantheine has now been adapted to the synthesis of 16-epipleiocarpamine (134) from geissoschizine.[80] The major modification required was the protection of the enolic hydroxy-group at C-17 in geissoschizine (92) by the formation of a carbonate ester with ethyl chloroformate; following fission of the



Reagents: i, Me_2CO–20%KOH–H_2O; ii, H_2–Pd/C–EtOH: iii, β-indolylethyl bromide–MeOH, r.t., 60 h; iv, KOH–H_2O–Et_2O–N_2

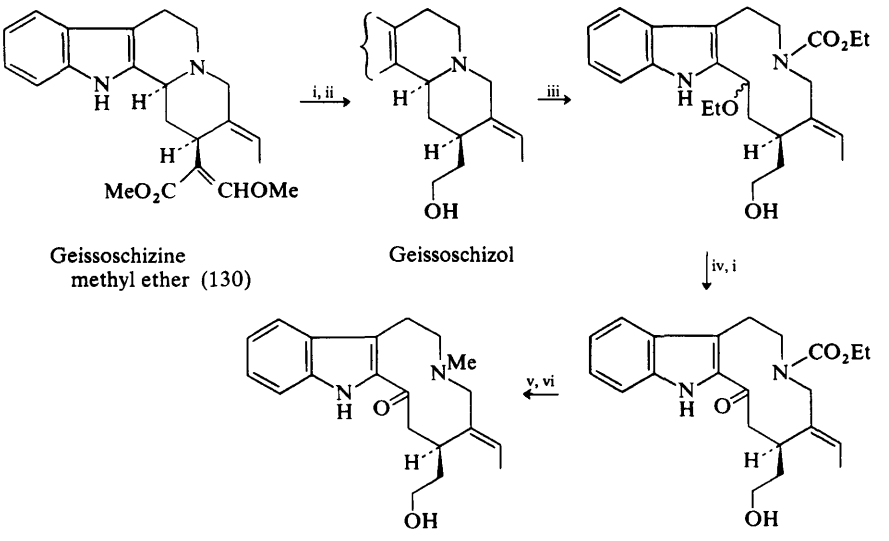
Scheme 11

[78] E. Wenkert, C. J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Amer. Chem. Soc.*, 1976, **98**, 3645.
[79] S. Sakai, E. Yamanaka, and L. J. Dolby, *Heterocycles*, 1976, **4**, 981; *Yakugaku Zasshi*, 1977, **97**, 309.
[80] S. Sakai and N. Shinma, *Heterocycles*, 1976, **4**, 985.



Reagents: i, $NaCH(CO_2Me)_2$–DME–N_2, then PhH–HCl, 60 °C; ii, H_2–Pt–AcOH; iii, $NaBH_4$–MeOH–THF, −30 °C, 90 min; iv, $NaBH_4$–MeOH–THF, −30 °C, 8 h; v, polyphosphoric acid–DME

Scheme 12



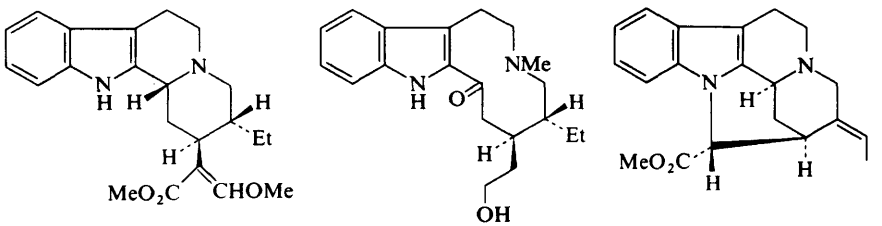
Geissoschizine methyl ether (130)

Geissoschizol

Burnamicine (131)

Reagents: i, H_3O^+; ii, $NaBH_4$; iii, $ClCO_2Et$–EtOH–$CHCl_3$–Na_2CO_3; iv, Bu^tOCl; v, $LiAlH_4$; vi, MnO_2

Scheme 13



Hirsutine (132) Dihydroburnamicine (133) (134)

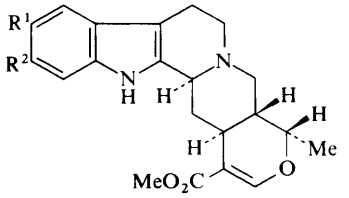
bond between N_b and C-3 by von Braun's method, the carbonate group was removed by hydrolysis. Otherwise the stages in the synthesis were unchanged.

A detailed description of Kametani's second synthesis of yohimbine, described in last year's Report,[22e] has now been published.[81]

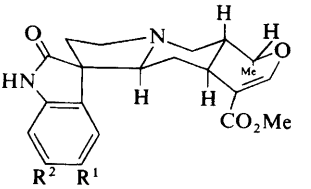
Cabucine (10-methoxyajmalicine) (135) and tetraphylline (11-methoxyajmalicine) (136) have been converted into the corresponding oxindole A and B analogues (137–140) *via* the corresponding 7-chloro-indolenine derivatives.[82]

The reaction of yohimbine hydrochloride with *m*-chloroperbenzoic acid also results in the formation of a 7-chloro-indolenine derivative; hence the product, following normal N_b-oxidation, is the N_b-oxide (141). In contrast to the 7-chloro-indolenine derivatives, no conversion into the corresponding oxindole analogue

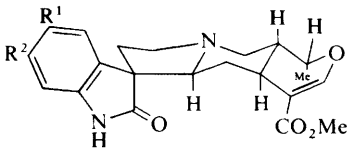
[81] T. Kametani, Y. Hirai, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 2500.
[82] F. Titeux, L. Le Men-Olivier, and J. Le Men, *Bull. Soc. chim. France*, 1976, 1473.



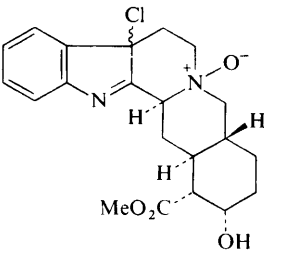
	R^1	R^2
Cabucine (135)	MeO	H
Tetraphylline (136)	H	MeO



	R^1	R^2
(137)	MeO	H
(138)	H	MeO

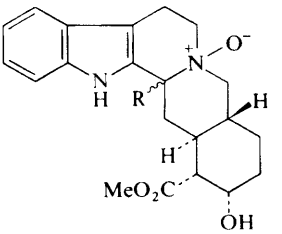


	R^1	R^2
(139)	MeO	H
(140)	H	MeO



(141)

could be achieved; however, the reaction with a variety of nucleophiles gave the 3-substituted yohimbine *N*-oxides (142)—(145).[83]

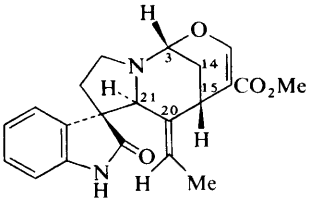


	R
(142)	OH
(143)	OMe
(144)	CN
(145)	$CH(CO_2Me)_2$

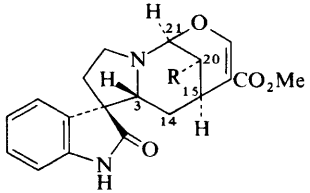
Although not an alkaloid, condoxine (146) is a compound of considerable interest, and it is relevant to include it here. In contrast to dihydrosecologanin aglycone, which condenses with 2-oxotryptamine with the formation of the oxindole analogue (147) of dihydromancunine, secologanin aglycone reacts with 2-oxotryptamine to produce an oxindole base, condoxine, of structure (146).[84] Condoxine is thus obtained by cyclization of N_b and the prospective C-7 in

[83] N. Aimi, Y. Asada, S. Tsuge, T. Kohmoto, K. Mogi, and S. Sakai, *Heterocycles*, 1976, **5**, 267.
[84] R. T. Brown and R. Platt, *Tetrahedron Letters*, 1976, 2721.

2-oxotryptamine with the masked aldehyde function at C-21 rather than with the one at C-3; however, there is no obvious reason why the reaction should take this course rather than the alternative one, which would give rise to (148).



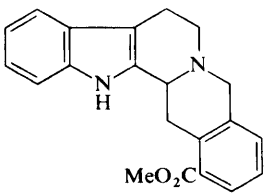
Condoxine (146)



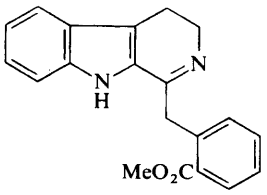
(147) R = Et
(148) R = CH=CH$_2$

Dihydrogambirtannine (149) has been synthesized[85] from the dihydro-β-carboline (150) (itself prepared by the obvious Bischler–Napieralski route) by reduction, formylation, and cyclization; unfortunately, details of this work are not readily available.

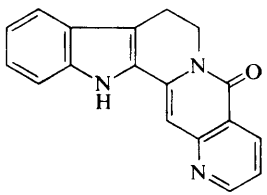
Details of the synthesis[33h] of demethoxycarbonyl-dihydrogambirtannine, angustidine, naucletine, and angustoline by the photochemical cyclization route have now been published.[86] Other work which has been described in detail includes the synthesis[22f] of angustine and nauclefine by Kametani *et al.*,[87] and the synthesis of nauclefine by Sainsbury and his collaborators.[88] Contrary to the previous report,[22f] the photocyclization stage in this last synthesis is not completely regiospecific, and some 10% of isonauclefine (151) was obtained. The same workers have effected[89]



(149)



(150)

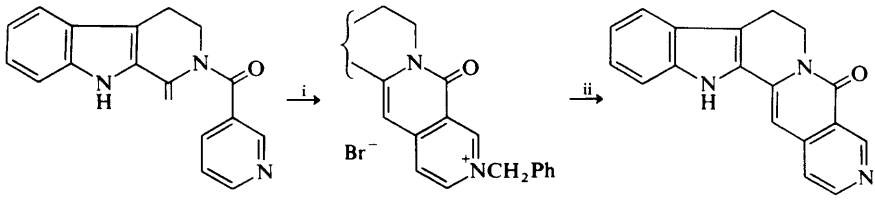


(151)

a new synthesis of nauclefine (152) (Scheme 14) which avoids isomer formation, and which affords an overall yield of (152) of 55% from the enamide (153), prepared as before from harmalan and nicotinoyl chloride.

Finally, in this group, McLean's work on the alkaloids of *Nauclea diderrichii* has been published in full.[90] The structure earlier given to naucledérine (154) receives support from its synthesis (Scheme 15), although it is admitted that this does not amount to an unequivocal proof of structure, owing to uncertainty concerning the

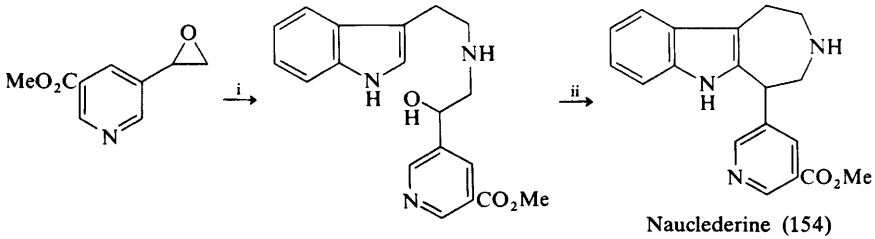
[85] E. A. Markaryan, L. P. Solomina, T. O. Astryan, and A. S. Tsatinyan, *Armyan. khim. Zhur.*, 1976, **29**, 326 (*Chem. Abs.*, 1977, **86**, 140 317).
[86] I. Ninomiya, T. Naito, and H. Takasugi, *J.C.S. Perkin I*, 1976, 1865.
[87] T. Kametani, M. Takeshita, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, 1976, **41**, 2542.
[88] M. Sainsbury and N. L. Uttley, *J.C.S. Perkin I*, 1976, 2416.
[89] M. Sainsbury and N. L. Uttley, *J.C.S. Chem. Comm.*, 1977, 319.
[90] S. McLean, G. I. Dmitrienko, and A. Szakolcai, *Canad. J. Chem.*, 1976, **54**, 1262.



(153) Nauclefine (152)

Reagents: i, $PhCH_2Br$; ii, PhMe–AcOH–AcONa, heat

Scheme 14



Naucledérine (154)

Reagents: i, Tryptamine–MeOH–N_2; ii, polyphosphoric acid–N_2, 95 °C

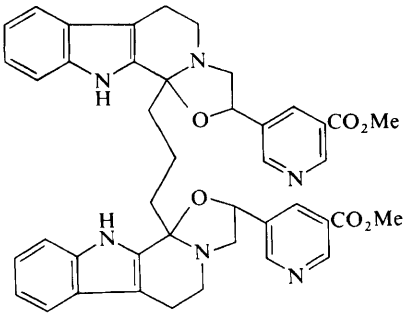
Scheme 15

exact mechanism of the final, acid-catalysed cyclization stage, which has so far only been accomplished in very low yield.

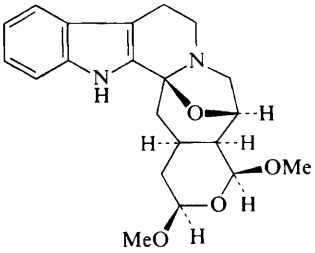
A minor alkaloid (ND-363B) from this same source, not referred to in the earlier communications, gives mass and n.m.r. spectra very similar to those of naucleonidine, and it was therefore initially concluded that it was an impure specimen of naucleonidine. The presence of mass spectral peaks at *m/e* 741 and 739, however, and the 'doubling' of the signals in the n.m.r. spectrum of this alkaloid, compared with that of naucleonidine, coupled with the absence of peaks at δ 1.78 p.p.m. (methyl group), lend support for the view that this alkaloid may well be a dimeric species formed from the Mannich condensation of two molecules of naucleonidine (hydroxy-enamine tautomer) with one of formaldehyde; the structure (155a) has thus been tentatively suggested.

The structures of two further alkaloids have been clarified since the preliminary communications were published. One of these is identical with Brown's 3α-dihydrocadambine and the other is a tetrahydrocarboline base in which N_b is also part of an oxazolidine unit (*cf.* naucleonidine). Following the elucidation of the structure of naucleonidine, a re-assessment of the available spectroscopic data led to the conclusion[90] that this alkaloid, designated ND-370, has the structure (155b) (*cf.* cadambine).

Sarpagine–Ajmaline–Picraline Group. Ajmaline and pelirine are among the constituents of the roots of *Rauwolfia cambodiana*,[60] and ajmaline, 12-methoxy-ajmaline, vomalidine, norajmaline, rauvomitine, tetraphyllicine, and ajmaline 17-*O*-trimethoxybenzoate occur in the roots of *R. obscura*.[61] Vincamajine has been



ND-363B (155a)

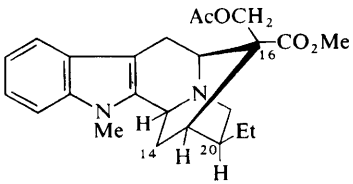


ND-370 (155b)

isolated from herbaceous periwinkle (*Vinca herbacea*), apparently for the first time.[91a] The leaves and twigs of *Peschiera laeta* contain several indole alkaloids, among which are affinine, akuammidine, tombozine, and vobasine;[62] this first full report on the constituents of this plant supports its classification in the genus *Tabernaemontana*, with which *Peschiera* is probably synonymous.

Burnamine and akuammidine have been shown to occur in the Ghanaian plant *Hunteria elliottii*.[59a]

17-*O*-Acetyl-19,20-dihydrovoachalotine (156) is a new alkaloid, isolated from the root bark of *Voacanga chalotiana*;[91b] the orientation at C-20 was deduced



(156)

from the ^{13}C n.m.r. spectrum, which showed that the C-16 signal had moved upfield compared with the corresponding signal in the ^{13}C n.m.r. spectra of voachalotine and its derivatives. An α-orientation of the substituent at C-20 would have similarly affected the signal from C-14, as has been observed in the ajmaline–isoajmaline series.

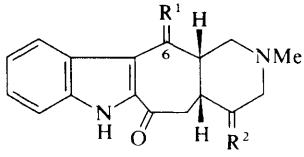
The chemotaxonomic survey of *Hazunta* species that was referred to earlier has revealed the widespread occurrence in this genus of several alkaloids of this group.[64a] All the species examined, *i.e. H. coffeoides* (Bojer) Pichon, *H. costata* Mgf., *H. membranacea* (A. DC.) Pichon, *H. membranacea* (DC.) Pichon forma *pilifera* Mgf., *H. modesta* var. *methuenii* Stapf et M. L. Green, *H. modesta* var. *methuenii* subvar. *methuenii*, *H. modesta* var. *modesta*, *H. modesta* var. *modesta* subvar. *modesta*, and *H. silicicola* Pichon, contain silicine (157) and methuenine (158), and all except *H. membranacea* forma *pilifera* contain tabernaemontanine and dregamine. In addition, *H. membranacea* forma *pilifera* contains tetraphyll-

[91] (*a*) A. M. Aliev and N. A. Babaev, *Farmatsiya* (*Moscow*), 1976, **25**, 30 (*Chem. Abs.*, 1976, **85**, 106 639); (*b*) E. Bombardelli, A. Bonati, B. Gabetta, E. Martinelli, G. Mustich, and B. Danieli, *Phytochemistry*, 1976, **15**, 2021; (*c*) C. Riche and C. Pascard-Billy, *Acta Cryst.*, 1977, **B33**, 133.

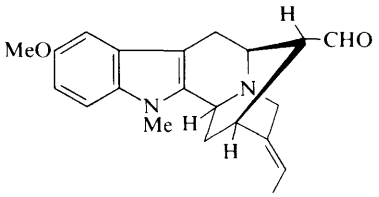
icine and its mono-, di-, and tri-methoxybenzoates, *H. modesta* var. *methuenii* and *H. modesta* var. *modesta* contain normacusine B, *H. modesta* var. *methuenii* subvar. *methuenii* contains 6-oxomethuenine (159) and 20-episilicine (160), and *H. silicicola* contains 6-oxosilicine (161).

Of these alkaloids, 6-oxosilicine (161) was discussed in last year's Report,[22g] because details of the elucidation of its structure and of its synthesis became available before the accounts of its isolation. Other new alkaloids are methuenine (158), 20-episilicine (160), and 6-oxomethuenine (159). Silicine (157) is stated to be identical with demethoxycarbonyl-dihydrovobasine. Methuenine (158), as expected from its constitution, gives a mixture of silicine and 20-episilicine on hydrogenation, while benzylic oxidation of silicine (157) and methuenine (158) gives 6-oxosilicine (161) and 6-oxomethuenine (159) respectively.[64a] Details of the *X*-ray crystal structure determination of 20-episilicine (16-demethoxycarbonyl-20-epiervatamine), mentioned in last year's Report, have now been published.[91c]

Majvinine, a minor alkaloid of the aerial parts of *Vinca major*, is a new alkaloid, which proves to be 10-methoxy-N_a-methylvellosimine (162).[92]

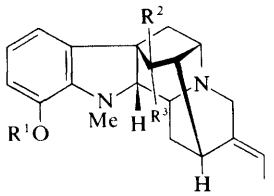


	R^1	R^2
Silicine (157)	H_2	H,β-Et
Methuenine (158)	H_2	=CHMe
6-Oxomethuenine (159)	=O	=CHMe
20-Episilicine (160)	H_2	H,α-Et
6-Oxosilicine (161)	=O	H,β-Et



Majvinine (162)

Two further alkaloids have been obtained from the leaves of *Rauwolfia reflexa* Teijsm. et Binn.[93] One of these was identified as purpeline (163), a structure which was confirmed by its demethylation to mitoridine (164). The second base, reflexine, $C_{21}H_{26}N_2O_2$, m.pt. 260 °C, $[\alpha]_D + 126°$, exhibits the spectra of a dihydropurpeline, and can in fact be prepared by the reduction ($NaBH_4$) of purpeline. Reflexine (165) is thus the C-17 epimer of seredamine (166) and has not previously



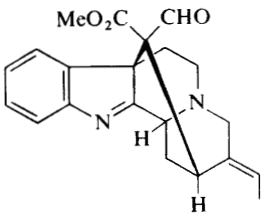
	R^1	R^2	R^3
Purpeline (163)	Me	=O	
Mitoridine (164)	H	=O	
Reflexine (165)	Me	H	OH
Seredamine (166)	Me	OH	H

[92] A. Banerji and M. Chakrabarty, *Phytochemistry*, 1977, **16**, 1124.
[93] A. Chatterjee, A. K. Ghosh, and M. Chakrabarty, *Experientia*, 1976, **32**, 1236.

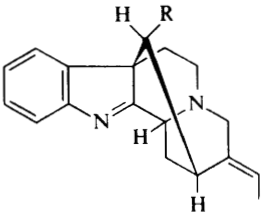
been obtained from natural sources, although it has been prepared[94] but not thoroughly characterized.

Rhazinaline, one of the minor alkaloids of *Rhazya stricta*, has been formulated[55a] as (167), *i.e.* 16-formyl-16-epistrictamine, and may well be identical with the alkaloid of this structure isolated earlier from the same source by Smith and his collaborators.[95] However, it has not yet proved possible to compare the two specimens directly.

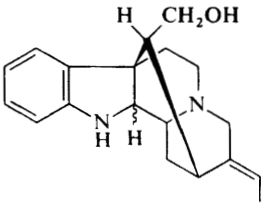
Other alkaloids isolated from *Rhazya stricta* include[96] strictamine (168) and strictalamine (169). The structure and relative configuration of strictamine were confirmed by *X*-ray crystal structure analysis; strictalamine is then (169), since reduction of (168) and (169) affords the same primary alcohol (170), with retention of stereochemical integrity at C-17. Conversely, Oppenauer oxidation of (170)



Rhazinaline (167)



Strictamine (168) R = CO_2Me
Strictalamine (169) R = CHO



(170)

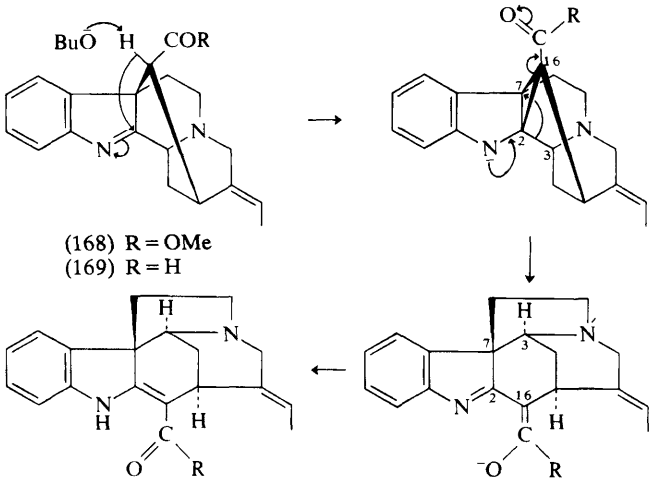
gives strictalamine (169), together with some (−)-nor-C-fluorocurarine (171); the formation of this last compound presumably involved the rearrangement of strictalamine in the presence of strong base (Scheme 16), analogous to the formation of (−)-akuammicine (172) by treatment of strictamine (168) with potassium t-butoxide. The isolation of (−)-nor-C-fluorocurarine establishes the absolute configuration of strictamine and strictalamine, and, by extrapolation, the absolute configuration of all the *Picralima* alkaloids.

In connection with the rearrangement of strictalamine to (−)-nor-C-fluorocurarine (171), it is of interest to note that this latter compound has also been found[96] to occur in *Rhazya stricta*; a rearrangement of the type (169)→(171) may therefore provide a possible alternative mode of biosynthesis of (171) and akuammicine derivatives.

In spite of some discrepancies between the reported physical constants, it seems more than likely that deacetyldeformylakuammiline (Base A), isolated from *Rauwolfia vomitoria*,[97] is identical with strictamine (168), in view of its reported chemical properties.

In a re-investigation[98] of the constituents of the leaves of *Alstonia scholaris*, akuammidine, picralinal, picrinine, and pseudoakuammigine have been isolated,

[94] J. Poisson, P. R. Ulshafer, L. E. Paszek, and W I. Taylor, *Bull. Soc. chim. France*, 1964, 2683.
[95] Z. Dabrowski, D. A. Evans, G. N. Smith, and G. F. Smith, in 'Abstracts of the 5th IUPAC Symposium on Natural Products, London, 1968', p. 425.
[96] Y. Ahmad, K. Fatima, Atta-ur-Rahman, J. L. Occolowitz, B. A. Solheim, J. Clardy, R. L. Garnick, and P. W. Le Quesne, *J. Amer. Chem. Soc.*, 1977, **99**, 1943
[97] J. L. Pousset, J. Poisson, L. Olivier, J. Le Men, and M. M. Janot, *Compt. rend.*, 1965, **261**, 5538.
[98] Y. Morita, M. Hesse, H. Schmid, A. Banerji, J. Banerji, A. Chatterjee, and W. E. Oberhänsli, *Helv. Chim. Acta*, 1977, **60**, 1419.



(168) R = OMe
(169) R = H

Nor-C-fluorocurarine (171) R = H
Akuammicine (172) R = OMe

Scheme 16

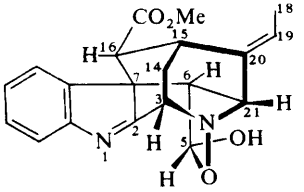
together with a new alkaloid, nareline (173), whose structure and absolute configuration were determined by single-crystal *X*-ray diffraction. Nareline possesses a ring system not previously encountered, in which C-5 is exocyclic and N_b is part of a hydroxylamine function. Biogenetically, nareline could be formed from picraline (174) by oxidation at C-21, followed by fragmentation, further oxidation, closure of the 6,21-bond, deacetylation, and deformylation.[98] More succinctly, it could also be formed by essentially the same route from strictamine *via* picrinine.

In general, the chemical properties of nareline are those expected of a compound containing the complex functionality of (173), including the unusual hemiacetal unit formed from an aldehyde and a hydroxylamine derivative. However, the oxidation by chromic acid in acetic acid takes a course that would have been difficult to predict, and affords a product, oxonareline (175), which is presumably formed from (173) by oxidative fission of the 2, 3, N_b system to give an oxindole function (176), followed by internal acetal formation between oxygen attached to C-5 and a carbinolamine equivalent at C-3.[98]

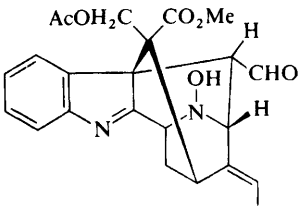
Other workers have re-examined the flowers[59b] and stems[99] of *Alstonia scholaris*. The flowers contain picrinine and strictamine, while the stems[99] contain picrinine, in addition to several bases of the *Strychnos* group.

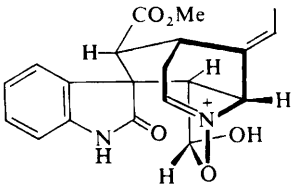
Vomifoline has been isolated[63a] from the leaves of *Rauwolfia vomitoria* collected from the Ivory Coast, and a re-examination of its chemical behaviour and its physical properties has shown that it is identical with peraksine (177); previously the alternative hemiacetal structure had been accepted as the structure of vomifoline.

[99] W. Boonchuay and W. E. Court, *Planta Med.*, 1976, **29**, 380 (*Chem. Abs.*, 1976, **85**, 119 603).

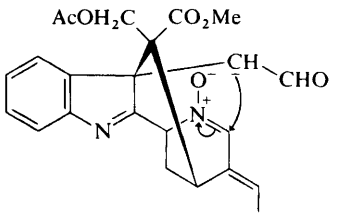


Nareline (173)

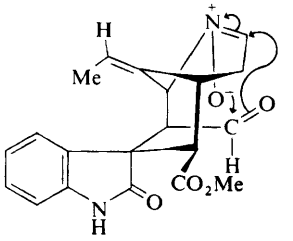


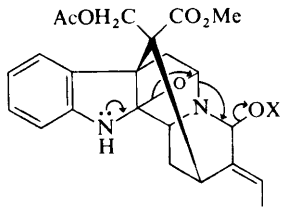


(176)

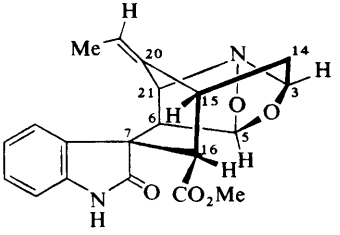


[O]

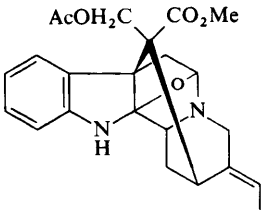




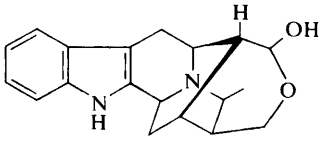
[O]



Oxonareline (175)



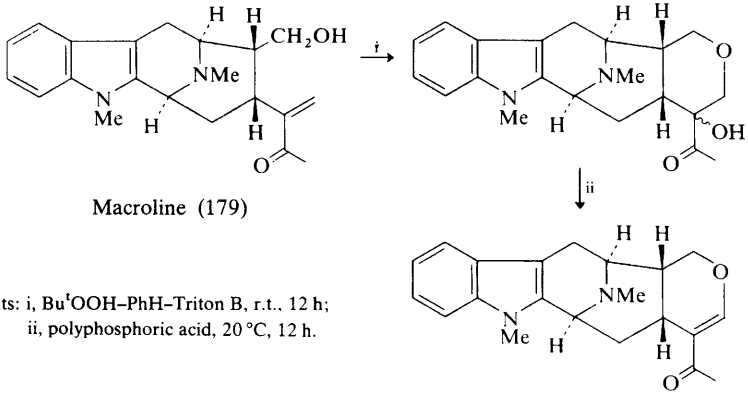
Picraline (174)



Peraksine ≡ Vomifoline (177)

Details of the synthesis of ajmaline by van Tamelen and co-workers have now been published.[100]

A partial synthesis[101] of alstonerine (178) from macroline (179) (shown in Scheme 17) is of considerable interest, in view of the strategic position occupied by macroline as a possible precursor of both the monomeric *Alstonia* alkaloids (*e.g.* alstonerine) and the dimeric alkaloids (*e.g.* villalstonine and macralstonine).



Macroline (179)

Reagents: i, Bu^{t}OOH–PhH–Triton B, r.t., 12 h; ii, polyphosphoric acid, 20 °C, 12 h.

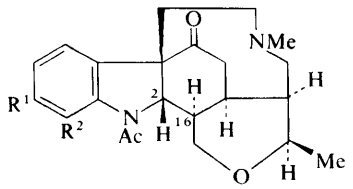
Scheme 17

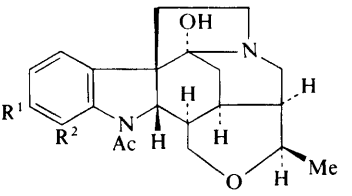
Alstonerine (178)

Strychnine–Akuammicine–Condylocarpine–Ellipticine–Uleine Group. Akuammicine, akuammicine N_b-oxide, akuammicine N_b-metho-salt (as its iodide), pseudoakuammicine, N_b-demethyl-echitamine, tubotaiwine, echitamine (principal alkaloid), and some unspecified echitamidine isomers have been isolated from the roots of *Alstonia scholaris*.[99] 18-Deoxy-Wieland–Gumlich aldehyde occurs in association with several bis-strychninoid alkaloids in the stem bark of *Strychnos dolichothyrsa* Gilg. ex Onochie et Hepper.[102] As mentioned above, (−)-nor-C-fluorocurarine has been found in the leaves of *Rhazya stricta*.[96] Among the alkaloids encountered in the survey of *Hazunta* species[64a] are vincanidine, which accounts for 90% of the alkaloids of the leaves of *H. membranacea* and *H. membranacea* forma *pilifera*, and 1,2-dihydroellipticine, which occurs in the stem bark of this latter species, and also in the root bark of *H. silicicola*.

Of the seven alkaloids so far isolated from the stem bark of *Strychnos fendleri* Sprague et Sandwith, the structures of four new ones have been elucidated.[103] These prove to be strychnofendlerine (180), 12-hydroxy-11-methoxystrychnofendlerine (181), N_a-acetylstrychnosplendine (182), and 12-hydroxy-11-methoxy-N_a-acetylstrychnosplendine (183). Strychnofendlerine gives a mass spectrum almost identical with that of isosplendine, and the two alkaloids are clearly

[100] E. E. van Tamelen and L. K. Oliver, *Bio-Organic Chemistry*, 1976, **5**, 309.
[101] R. L. Garnick and P. W. Le Quesne, *Tetrahedron Letters*, 1976, 3249.
[102] R. Verpoorte and A. B. Svendsen, *Lloydia*, 1976, **39**, 357.
[103] C. Galeffi, A. Lupi, and G. B. Marini-Bettòlo, *Gazzetta*, 1976, **106**, 773.





	R^1	R^2
Strychnofendlerine (180)	H	H
12-Hydroxy-11-methoxy-strychnofendlerine (181)	OMe	OH

	R^1	R^2
N_a-Acetylstrychnosplendine (182)	H	H
12-Hydroxy-11-methoxy-N_a-acetylstrychnosplendine (183)	OMe	OH

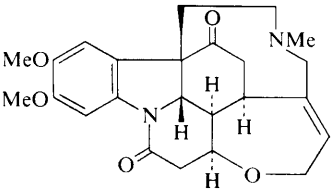
stereoisomers. The n.m.r. spectrum of strychnofendlerine indicates a *trans*-diaxial disposition of hydrogen atoms at positions 2 and 16 and an axial hydrogen at C-19; hence strychnofendlerine has the relative stereochemistry shown in (180). The absolute configuration follows from its o.r.d. spectrum. Hence strychnofendlerine is the C-19 epimer of isosplendine. The other *ar.*-unsubstituted alkaloid was identified as N_a-acetylstrychnosplendine (182), and the structure of (180) was then further confirmed by its preparation by methylation of (182). The remaining two alkaloids form an analogous pair of 12-hydroxy-11-methoxy derivatives, the relationship being emphasized by the methylation of (183), which yielded (181).[103]

In a most extensive contribution, Bisset and Phillipson[104] have reported the screening of 234 samples from 36 of the 44 known Asian species of *Strychnos* for the presence of alkaloids. Some of the alkaloids were identified, but the presence of numerous minor, unidentified bases was also recorded. Some of these constituents have already been investigated by other workers, but at the same time this screening programme affords a wide-ranging preliminary survey of the genus *Strychnos* which will doubtless provide many pointers for further research in this field. The literature on the alkaloids and the pharmacology of Asian species of *Strychnos* is also reviewed.[104]

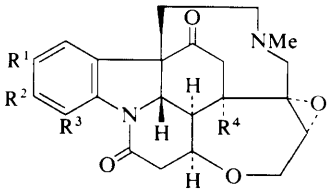
The root bark of *S. variabilis* De Wild., from Zaire, contains two alkaloids, identified as (−)-2β,16β-dihydro-akuammicinol and (+)-N_a-acetyl-2β,16α-dihydro-akuammicinal; a third alkaloid, probably dimeric, was also isolated, but in too small an amount to allow elucidation of its structure.[105]

New extractions of the leaves of *S. icaja*, also from Zaire, have resulted in the isolation of seven known alkaloids, together with novacine (184), also known, but not hitherto reported to occur in this species.[106] A ninth alkaloid is new, and appears to be 19,20-α-epoxy-12,15-dihydro-11-methoxy-N_b-methyl *sec.*-pseudostrychnine (185). The leaves of a specimen of this same plant from Cameroun contained four known alkaloids, plus a new one, 19,20-α-epoxy-11,12-dimethoxy-N_b-methyl *sec.*-pseudostrychnine (186). The fruits of a Gabonese sample, which had reputedly been exhibited at the Paris Colonial Exhibition of 1889, contained eight alkaloids, namely icajine, vomicine, 19,20-α-epoxynovacine, 19,20-α-epoxy-12,15-dihydroxy-N_b-methyl *sec.*-pseudostrychnine (187), and the related bases (185) and (188)—(190), of which (190) was the major constituent.[106]

[104] N. G. Bisset and J. D. Phillipson, *Lloydia*, 1976, **39**, 263.
[105] C. Richard, C. Delaude, L. Le Men-Olivier, J. Lévy, and J. Le Men, *Phytochemistry*, 1976, **15**, 1805.
[106] N. G. Bisset and A. A. Khalil, *Phytochemistry*, 1976, **15**, 1973.



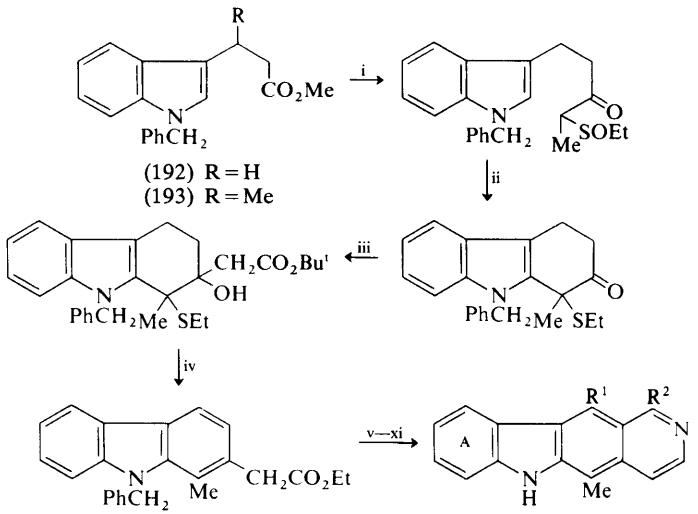
Novacine (184)



	R^1	R^2	R^3	R^4
(185)	H	OMe	OH	OH
(186)	H	OMe	OMe	H
(187)	H	H	OH	OH
(188)	OMe	OMe	H	OH
(189)	H	H	OMe	H
(190)	H	H	OMe	OH

The ^{13}C n.m.r. spectra of strychnine, brucine, and brucine N_b-methiodide have again been discussed, and complete assignments made.[107]

The only synthetic work in this area reported during the year provides yet more syntheses of the ellipticine ring system. Oikawa and Yonemitsu have applied their carbazole synthesis to a very efficient, if lengthy, preparation of olivacine (191) (Scheme 18);[108] the overall yield of olivacine from the starting indole ester (192) is



(192) R = H
(193) R = Me

	R^1	R^2
Olivacine (191)	H	Me
Ellipticine (194)	Me	H

Reagents: i, Et_2SO–$LiNPr^i_2$; ii, TFA–PhH; iii, $LiCH_2CO_2Bu^t$–PhH; iv, $C_6H_4Me_2$–EtOH–TsOH, heat, 16 h; v, MeOH–MeONa–NH_3; vi, TsCl–py; vii, Ni–H_2; viii, Ac_2O; ix, Na–NH_3–THF; x, $POCl_3$; xi, Pd/C, heat

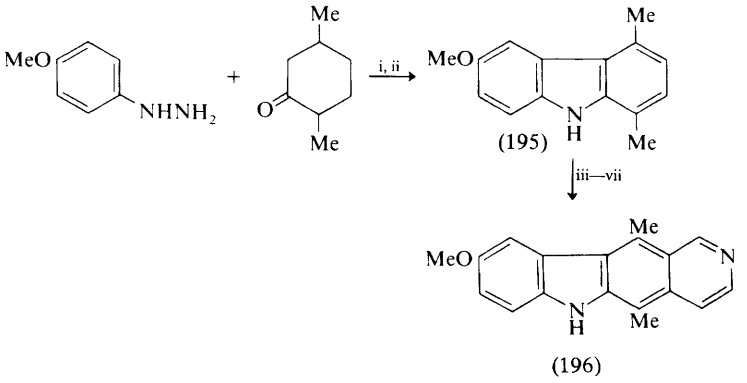
Scheme 18

[107] (*a*) P. R. Srinivasan and R. L. Lichter, *Org. Magn. Resonance*, 1976, **8**, 198; (*b*) R. Verpoorte and A. B. Svendsen, *Pharm. Weekblad*, 1976, **111**, 745 (*Chem. Abs.*, 1976, **85**, 177 739).

[108] Y. Oikawa and O. Yonemitsu, *J.C.S. Perkin I*, 1976, 1479.

reported to be 28%. Appropriate modification of the synthesis, utilizing the ester (193), affords a new synthesis of ellipticine (194), in 23% overall yield.

An improved approach[109] which allows the direct synthesis of ring-A-substituted pyrido-carbazoles [*e.g.* 9-methoxyellipticine (196)] applies the Borsche method for the preparation of the intermediate carbazole (195) (Scheme 19); the synthesis is then completed by application of the modified[110] Cranwell–Saxton route.



(196)

Reagents: i, EtOH–HCl, 70 °C; ii, chloranil–THF, heat; iii, $POCl_3$–PhNMeCHO; iv, $H_2NCH_2CH(OEt)_2$–PhMe, azeotropic distillation; v, $NaBH_4$–MeOH; vi, TsCl–THF–H_2O–Na_2CO_3; vii, 6M-HCl–dioxan

Scheme 19

Aspidospermine–Aspidofractine–Eburnamine Group. The structural and biosynthetic relationships between the various alkaloids in this group, which are referred to by the authors as the plumerane alkaloids, since they occur exclusively in plants of the subfamily Plumerioidae of the Apocynaceae, have been discussed in some detail.[111a]

Pleiocarpine and eburnamine are among the alkaloids of *Hunteria elliotti*; the former occurs in the seeds and the latter in the stem-bark and leaves.[59a] A base, described as 14,15-didehydro-3-oxokopsinine *N*-oxide, has been isolated[68a] from *Vinca erecta*, but the evidence on which this structure is based is lacking.

Voaphylline has been found in the seeds of *Pagiantha macrocarpa*, a species which has not previously been investigated.[111b]

Details of the method used for the extraction of craspidospermine from *Craspidospermum verticillatum* are now available,[112] and its partial synthesis from Δ^{14}-vincine, mentioned in a previous Report,[33i] has been described;[70b] details of the ^{13}C n.m.r. spectrum of this base are included in the first of these communications.[112]

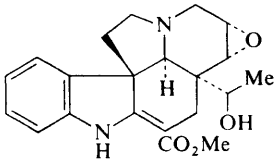
[109] D. Rousselle, J. Gilbert, and C. Viel, *Compt. rend.*, 1977, **284**, *C*, 377.

[110] R. W. Guthrie, A. Brossi, F. A. Mennona, J. G. Mullin, R. W. Kierstead, and E. Grunberg, *J. Medicin. Chem.*, 1975, **18**, 755.

[111] (*a*) D. Ganzinger and M. Hesse, *Lloydia*, 1976, **39**, 326; (*b*) C. Miet and J. Poisson, *Phytochemistry*, 1977, **16**, 153.

[112] C. Kan-Fan, H. P. Husson, and P. Potier, *Bull. Soc. chim. France*, 1976, 1227.

The only new alkaloid belonging to this group that has been reported during the year is cathovalinine, from *Catharanthus ovalis*, for which the structure (197) has been established by *X*-ray crystal structure analysis.[113] In common with all the anilino-acrylate bases, cathovalinine, $[\alpha]_D$ −492°, exhibits a very high rotatory power; the sign of rotation indicates that it belongs to the (−)-tabersonine series, in which case (197) also represents the absolute configuration. Cathovaline is a

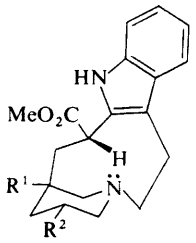


Cathovalinine (197)

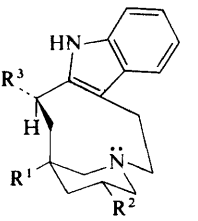
stereoisomer of hörhammericine at positions 14/15 and/or position 19, and is one of the first epoxide bases in this series for which the complete stereochemistry has been elucidated; the complete stereochemistry of hörhammericine is as yet unknown.

The *X*-ray crystal structure determination of quebrachamine reveals that the conformation adopted by the molecule is one in which the lone electrons on N_b are sterically shielded by other atoms; if this conformation is preferred in solution, the reluctance of quebrachamine to form quaternary salts is explained.[114] This conclusion agrees with that derived from ^{13}C n.m.r. spectroscopy,[115] which in turn is consistent with deductions made earlier on the basis of ^1H n.m.r. spectroscopy.

(+)-Epivincadine (198) adopts a conformation in which the lone electrons on N_b and the substituent at C-17 are axially disposed to ring D. Owing to steric crowding, its C-16 epimer, *i.e.* (+)-vincadine, cannot adopt this conformation, and instead adopts an alternative conformation (199) of the nine-membered ring, in which the lone electrons on N_b and the substituent at C-17 are still axial to ring D. Quebrachamine (200) appears to adopt this same conformation, in which approach



		R^1	R^2
(+)-Epivincadine	(198)	Et	H
	(229)	H	Et



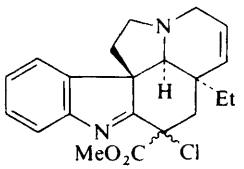
		R^1	R^2	R^3
(+)-Vincadine	(199)	Et	H	CO_2Me
Quebrachamine	(200)	Et	H	H
	(230)	H	Et	CO_2Me

[113] A. Chiaroni, C. Riche, L. Diatta, R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron*, 1976, **32**, 1899.
[114] C. Puglisi, R. F. Baggio, and S. Baggio, *Acta Cryst.*, 1976, **B32**, 1900.
[115] E. Wenkert, E. W. Hagaman, N. Kunesch, N. Wang, and B. Zsadon, *Helv. Chim. Acta*, 1976, **59**, 2711.

to the lone electrons on N_b is severely hindered by the indole ring, and particularly by C-2. This paper also includes a discussion of the ^{13}C n.m.r. spectra and conformations of the 14,15-dehydro-derivatives of these alkaloids.[115]

Details of the *X*-ray crystal structure determination of vindolinine hemihydrochloride hemiperchlorate have now been published.[116]

Oxidation of tabersonine hydrochloride with *m*-chloroperbenzoic acid does not give a 16-hydroxy-derivative, as expected, but a 16-chloro-indolenine derivative (201), presumably *via* the generation of Cl^+ from chloride ion and the oxidant; in the presence of an excess of oxidant, the N_b-oxide of (201) is formed.[83]



(201)

Several simple derivatives of vindoline have been prepared[117] as intermediates in the synthesis of model vinblastine derivatives.

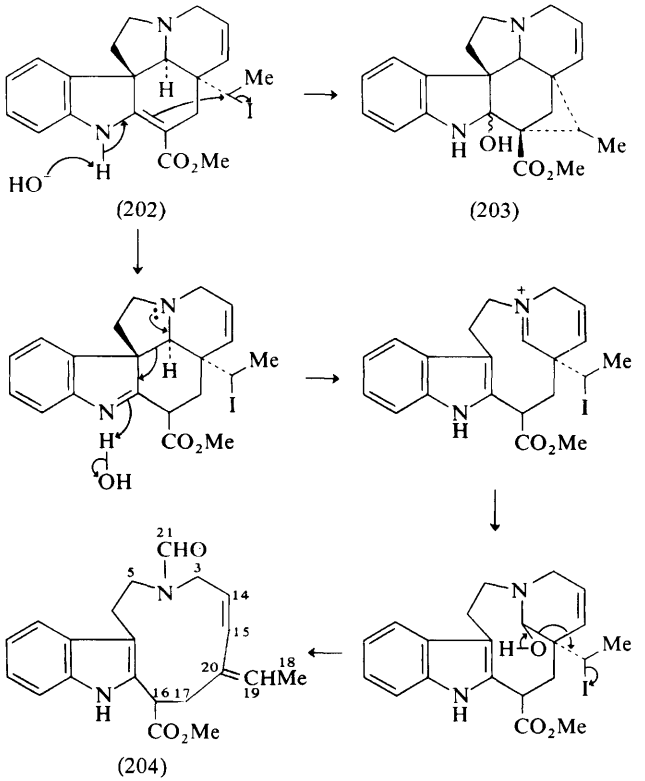
Yet another rearrangement of a tabersonine derivative has been reported. 19-Iodotabersonine (202), prepared from vindolinine, when heated with diazabicycloundecene in DMSO, gives mainly the expected Δ^{18}-tabersonine, together with the cyclobutane derivative (203) and an optically inactive non-basic indole derivative, for which the structure (204) has been proposed.[118] A much-improved yield of (204) (78%) can be obtained if the reaction is conducted in DMF in the presence of sodium acetate. One of the possible mechanisms for the formation of (204) is illustrated; if correct, this requires the presence of water in the reaction mixture.

The generation of a compound containing an N_b-formyl group in an eleven-membered ring is of considerable interest in view of the fact that bis-indole alkaloids are known (*e.g.* vinamidine) that contain a similar structural unit. It is apparent, therefore, that one possible genesis of this unit may be *via* the fragmentation of ring D in an appropriate precursor in which a leaving group is situated in the γ-position to N_b.

The c.d. spectra of vincamine and of its C-16 and C-21 epimers afford a simple and unequivocal method for the assignment of configuration at these positions.[119]

The major product in Ziegler's 1969 synthesis[120a] of 16,17-dehydroquebrachamine was subsequently suggested[120b] to be the tetrahydro-β-carboline derivative (205) (stereochemistry not assigned). The structure and sterochemistry of (205) have now been established[121] by examination of its n.m.r. spectrum (not

[116] C. Riche and C. Pascard-Billy, *Acta Cryst.*, 1976, **B32**, 1975.
[117] J. P. Kutney, K. K. Chan, W. B. Evans, Y. Fujise, T. Honda, F. K. Klein, and J. P. de Souza, *Heterocycles*, 1977, **6**, 435.
[118] L. Diatta, R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron*, 1976, **32**, 2839.
[119] B. Danieli, B. Gabetta, G. Gottarelli, and B. Samori, *Gazzetta*, 1976, **106**, 39.
[120] (*a*) F. E. Ziegler, J. A. Kloek, and P. A. Zoretic, *J. Amer. Chem. Soc.*, 1969, **91**, 2342; (*b*) F. E. Ziegler and G. B. Bennett, *ibid.*, 1973, **95**, 7458.
[121] S. Takano, M. Sato, S. Hatakeyama, M. Hirama, and K. Ogasawara, *Heterocycles*, 1976, **5**, 221.



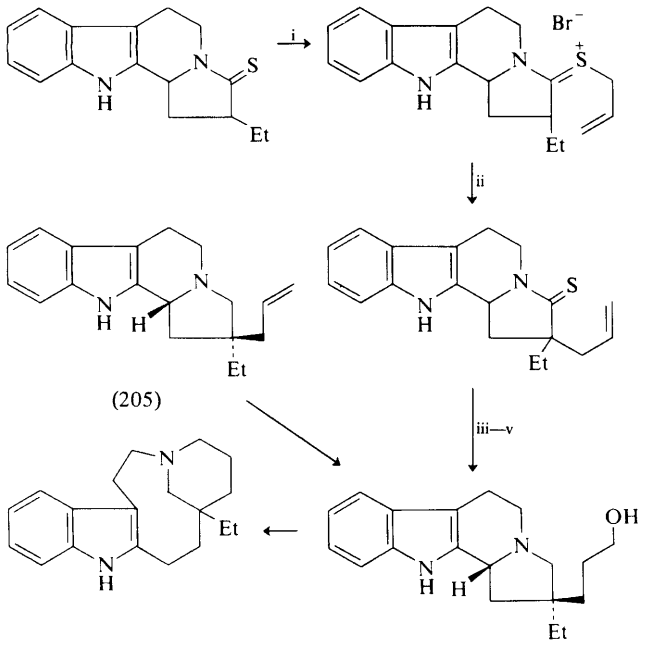
previously recorded) and by its conversion into the known related primary alcohol (206) by anti-Markovnikov hydration (diborane–oxidation).

A summary of Takano's recent synthesis of (±)-quebrachamine (200), mentioned in last year's Report,[22h] is now accessible.[122] The critical stages leading to a mixture of (206) and its epimer are outlined in Scheme 20; the remaining stages were carried out according to established methods.

A minor modification to Ban's synthesis of N_a-acetylaspidoalbidine[33j] has allowed the first synthesis of (±)-fendleridine (aspidoalbidine) to be completed.[123]

A second synthesis of (±)-deoxyaspidodispermine (207) has been developed[124] in which an attempt has been made to follow more closely a possible biosynthetic route to this alkaloid. Again the vital intermediate was the tetracyclic unsaturated amino-ketone (208), in which N_a was protected by formation of a urethane; the product was then converted into the diene (209) by conventional steps. A photosensitized oxygenation of this diene gave a cyclic peroxide (210) in which the peroxide bridge was *trans* with respect to the ethanamine bridge. Hydrogenation then afforded a mixture of products containing the required hydroxy-group at

[122] S. Takano, S. Hatakeyama, M. Hirama, T. Araki, S. Yamada, M. Sato, T. Sugahara, K. Shishido, and K. Ogasawara, *J. Amer. Chem. Soc.*, 1976, **98**, 7084.
[123] Y. Honma, T. Ohnuma, and Y. Ban, *Heterocycles*, 1976, **5**, 47.
[124] Y. Honma and Y. Ban, *Heterocycles*, 1977, **6**, 129.



Reagents: i, CH_2=$CHCH_2Br$–EtOH; ii, $KOBu^t$–THF; iii, B_2H_6–THF, heat; iv, H_2O_2–NaOH; v, Raney Ni–EtOH, heat

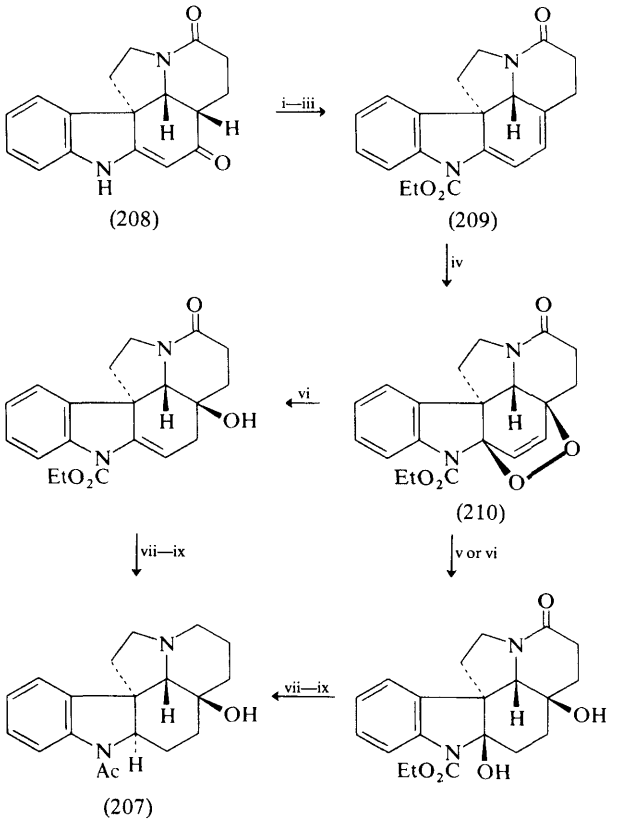
Scheme 20

C-20, which were converted into (±)-deoxyaspidodispermine (207) by standard processes (Scheme 21).

Details of the synthesis of cylindrocarine, cylindrocarpidine, and cylindrocarpine have now been published,[125] as have details of an earlier synthesis of vincamine.[126]

New work in the eburnamine–vincamine area includes new syntheses of eburnamonine[127] and eburnamenine.[128] The synthesis of eburnamonine (214) (Scheme 22) involves the Michael addition–cyclization reaction of 2-chloroacrylonitrile with the known enamine (211). Reduction of the product gave two separable C-16 epimeric mixtures, (212) and (213); the former gave (±)-eburnamonine (214) following oxygenation in the presence of strong base. Similarly, the C-20 epimeric series (213) gave rise to (±)-20-epi-eburnamonine (215).[127]

[125] G. Lawton, J. E. Saxton, and A. J. Smith, *Tetrahedron*, 1977, **33**, 1641.
[126] K. H. Gibson and J. E. Saxton, *Tetrahedron*, 1977, **33**, 833.
[127] A. Buzas, C. Herisson, and G. Lavielle, *Compt. rend.*, 1976, **283**, *C*, 763.



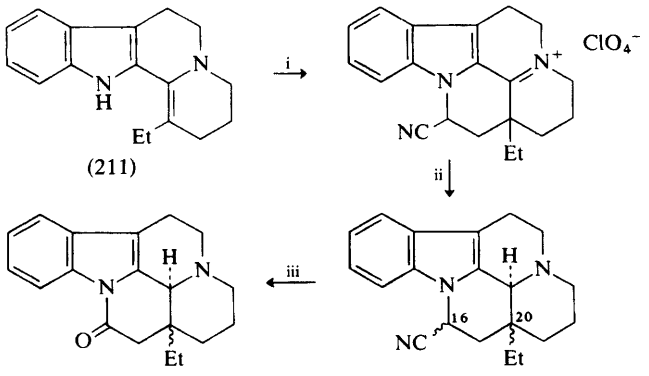
Reagents: i, NaH–$ClCO_2Et$–DMF; ii, $NaBH_4$–EtOH–THF; iii, PBr_3–py; iv, O_2–EtOH–eosin, $h\nu$; v, H_2–PtO_2–EtOH; vi, H_2–PtO_2–EtOAc; vii, 10% NaOH–H_2O–MeOH; viii, $LiAlH_4$–THF; ix, Ac_2O–py, r.t.

Scheme 21

In the synthesis of eburnamenine (216) (Scheme 23), Takano's group make further use of the thioacetal keto-ester (217), earlier prepared during their recent synthesis of quebrachamine.[22i] Reduction of the dehydro-salt (218) followed by thioacetal hydrolysis gave a good yield of (±)-eburnamenine (216); however, if these last two stages were reversed, and if the final reduction stage was carried out by means of $NaBH_4$, a good yield of 20-epi-eburnamenine [20-epi-(216)] could be obtained.[128]

Appropriate modification of Szántay's synthesis of vincamine has enabled the synthesis of 10-methoxyvincamine (isovincine) to be completed.[129] Although it is not yet known as a natural product, it was clearly of interest to prepare isovincine in order to be able to examine the relationship between structure and pharmacological activity.

[128] S. Takano, S. Hatakeyama, and K. Ogasawara, *J.C.S. Chem. Comm.*, 1977, 68.
[129] G. Kalaus, L. Szabó, J. Horváth, and Cs. Szántay, *Heterocycles*, 1977, **6**, 321.



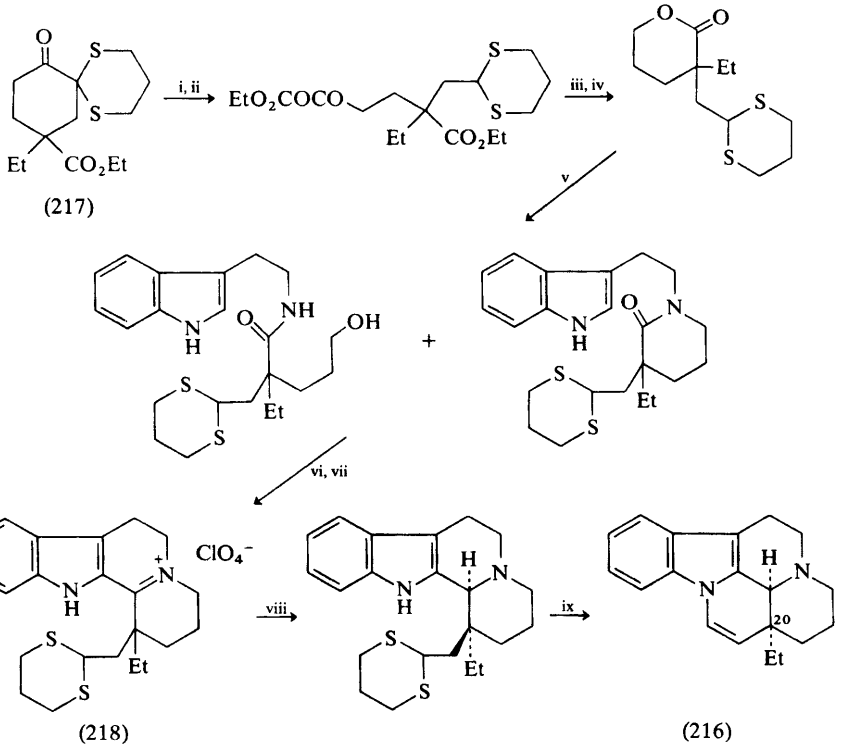
(211)

Eburnamonine (214) 20α-Et
Epieburnamonine (215) 20β-Et

(212) 20α-Et
(213) 20β-Et

Reagents: i, CH_2=CClCN–CH_2Cl_2; ii, Zn–EtOH–HCl; iii, $C_6H_{11}NPr^iLi$–THF–HMPA–O_2, −78 °C

Scheme 22



(217)

(218)

(216)

Reagents: i, NaH–Et_2O–H_2O; ii, $ClCO_2Et$–NEt_3; iii, $NaBH_4$–THF; iv, H_3O^+; v, tryptamine, 160 °C; vi, MeCN–$POCl_3$; vii, $LiClO_4$; viii, $LiAlH(OBu^t)_3$–THF; ix, MeI–MeCN–H_2O, r.t., 30 h

Scheme 23

Ibogamine–Catharanthine–Cleavamine Group. Of the known alkaloids of this group, ibogamine and isovoacangine have been found[64a] in *Hazunta costata* and *H. modesta* var. *modesta* subvar. *modesta*; ibogamine also occurs in *H. coffeoides*, *H. membranacea* forma *pilifera*, *H. modesta* var. *methuenii* subvar. *methuenii*, and *H. silicicola*; and isovoacangine in *H. modesta* var. *methuenii* and *H. modesta* var. *modesta*. The stem bark of *Tabernaemontana wallichiana* Steud. contains[130] voacangine, coronaridine, and voacristine, and the leaves contain voacangine, voacristine, and isovoacangine.

The genus *Pagiantha* has not previously been seriously investigated, although the presence of alkaloids in the leaves of *P. cerifera* Mgf. (*Tabernaemontana cerifera* Panch. et Seb.) has been noted.[131] Extraction of these leaves has now yielded[132] (−)-voacangine, (−)-voacangine hydroxy-indolenine, and (−)-ibogaine, while the seeds of *P. macrocarpa* (Jack) Mgf. (*Ervatamia macrocarpa* Merrill ≡ *T. macrocarpa* Jack) have been shown [111b] to contain (−)-voacangine, coronaridine, and voacangine hydroxy-indolenine.

The iboga drug, which is used by the natives of Gabon in small quantities as a stimulant and in larger quantities as a hallucinogen, is derived from the root bark of *Tabernanthe iboga* and of *T. subsessilis* Stapf. In spite of the fact that the leaves of *T. iboga* were reported[133] as long ago as 1941 to have a more pronounced physiological activity than the roots, no thorough investigation of the leaves was undertaken until recently. The leaves of both *T. iboga* and *T. subsessilis* have now been shown to contain[134] ibogamine and two new alkaloids, (+)-ibophyllidine (219) and (+)-iboxyphylline (220).

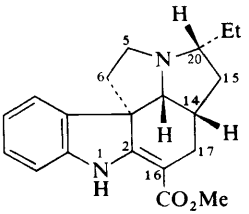
Ibophyllidine , $C_{20}H_{24}N_2O_2$, $[\alpha]_D + 134°$, is an amorphous base which exhibits an anilino-acrylate chromophore. In contrast to vincadifformine, which gives in the mass spectrum a prominent peak at *m/e* 124, the mass spectrum of ibophyllidine exhibits a peak at *m/e* 110, attributed to the lower homologue (221) of the vincadifformine fragment. An ethyl group is present (^{1}H n.m.r.), attached to one of the three methine carbon atoms (^{13}C n.m.r.) in the molecule, two of which, including the one carrying the ethyl group, are attached to nitrogen. Only one quaternary carbon is contained in the molecule, *i.e.* C-7, which, from the sign of rotation, presumably has the same absolute configuration as in (+)-vincadifformine. The structure thus deduced for ibophyllidine is (219). The structure of iboxyphylline, $C_{21}H_{26}N_2O_3$, m.pt. 245 °C, $[\alpha]_D + 444°$, which clearly belongs to the same stereochemical series, was shown by *X*-ray crystal structure analysis to be (220).

Biogenetically, these alkaloids may well arise from a base such as pandoline (223) by oxidative fission of the 20,21-bond, followed by Mannich re-cyclization of the hypothetical intermediate (222) [→(220)], or by loss of C-21 followed by cyclization and reduction [→(219)].[134]

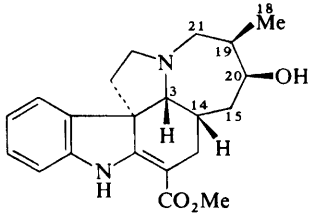
Pandoline and epipandoline, for which new sources have been found[135] in *Melodinus polyadenus* (Baillon) Boiteau and *Ervatamia obtusiuscula* Mgf., had

[130] S. K. Talapatra, S. S. Gupta, M. Bhattacharya, and B. Talapatra, *Indian J. Chem.*, 1976, **14B**, 385.
[131] E. Abisch and T. Reichstein, *Helv. Chim. Acta*, 1960, **43**, 1844.
[132] A. Harmouche, H. Mehri, M. Koch, A. Rabaron, M. Plat, and T. Sévenet, *Ann. pharm. franc.*, 1976, **34**, 31.
[133] Raymond-Hamet, *Bull. Acad. Méd.*, 1941, **124**, 243.
[134] F. Khuong-Huu, M. Cesario, J. Guilhem, and R. Goutarel, *Tetrahedron*, 1976, **32**, 2539.
[135] J. Bruneton, A. Cavé, E. W. Hagaman, N. Kunesch, and E. Wenkert, *Tetrahedron Letters*, 1976, 3567.

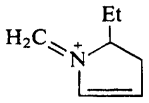
previously been shown to have the structure and absolute configuration shown in (223) and (224) respectively; only the configuration at C-20 was left undetermined.



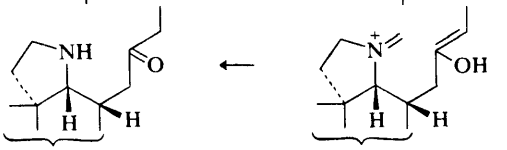
Ibophyllidine (219)



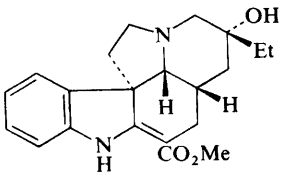
Iboxyphylline (220)



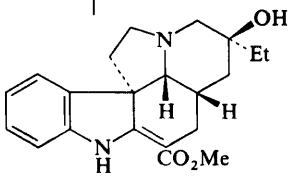
(221)



(222)

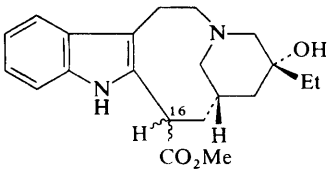


Pandoline (223)

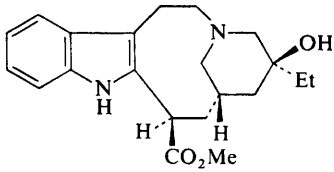


Epipandoline (224)

This remaining uncertainty has now been resolved by the correlation of pandoline and epipandoline with velbanamine derivatives, coupled with a study of their ^{13}C n.m.r. spectra.[135,136] Thus, reduction of pandoline with sodium borohydride gave 3,7-*seco*-pandolines A and B [(225) and (226)], and the corresponding reduction of epipandoline gave mainly one 3,7-*seco*-epipandoline (227), together with a



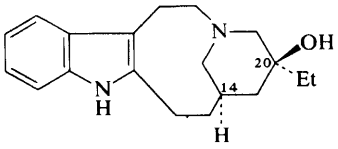
(225) 16β-H
(226) 16α-H



(227)

small amount of unstable isomer. Comparison of the ^{13}C n.m.r. data of 3,7-*seco*-pandoline A (225) with those of velbanamine (228) revealed that the two bases possess the same relative stereochemistry at positions 14 and 20. Further, in *seco*-pandoline A there must be a *cis* disposition of hydrogens[115] at positions 14

[136] G. Hugel, M. Zeches, M. J. Hoizey, L. Le Men-Olivier, and J. Lévy, *Compt. rend.*, 1976, **283**, *C*, 759.



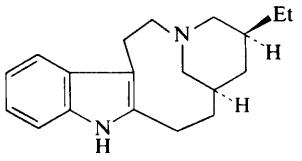
Velbanamine (228)

and 16. *seco*-Pandoline A is thus (225), *seco*-pandoline B is (226), and *seco*-epipandoline must have a *trans* arrangement of the hydrogen at C-14 and the ethyl group, as shown in (227); the assignment of configuration at C-16 is based on the ^{1}H n.m.r. signal for the proton attached to it, and is tentative. Pandoline is therefore (223), and epipandoline is (224).[135]

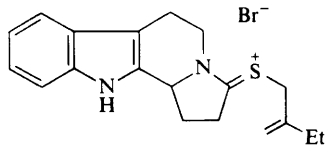
An independent, and perhaps more secure, proof of configuration at C-20 results from the direct correlation of pandoline with velbanamine.[136] Hydrogenation of pandoline (223) in the presence of palladized charcoal and trifluoroacetic acid affords (+)-16-methoxycarbonylvelbanamine, almost certainly identical with Wenkert's 3,7-*seco*-pandoline B (226). Hydrolysis and decarboxylation of (226) then gave the laevorotatory enantiomer of velbanamine (228). No trace of isovelbanamine (C-20 epimer) could be found. Similarly, epipandoline (224) was converted into the enantiomer of isovelbanamine, although a trace of (−)-velbanamine was formed, presumably by the already observed acid-catalysed epimerization.

The ^{13}C n.m.r. spectra of a number of cleavamine derivatives[115] and iboga alkaloids[137] have been discussed in detail, and complete assignments made. A similar situation obtains here as with the vincadine isomers (see above; p. 192). For example, 16α-methoxycarbonyl-15,20βH-dihydrocleavamine (229) adopts the same conformation as epivincadine (198); similarly, 16β-methoxycarbonyl-15,20βH-dihydrocleavamine (230) adopts the same conformation as vincadine (119). This analysis of the ^{13}C n.m.r. data has also confirmed[137] the configuration at C-19 in heyneanine and 19-epiheyneanine recently deduced by other workers.[22j]

New synthetic work in this area includes a description of the synthesis of dihydrocleavamine[122] and an ingenious, brief synthesis of desethylibogamine.[138] Takano's synthesis of (±)-20αH-dihydrocleavamine (231) involves an appropriate modification of the synthesis of (±)-quebrachamine, reported simultaneously. The essential starting material (232) was converted into (231) by the route outlined for the synthesis of quebrachamine in Scheme 20.



(231)

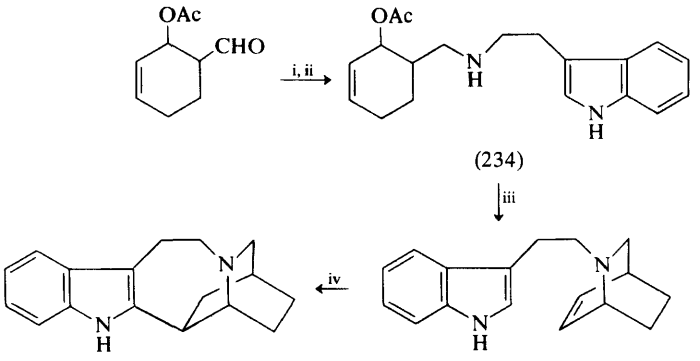


(232)

[137] E. Wenkert, D. W. Cochran, H. E. Gottlieb, E. W. Hagaman, R. Braz Filho, F. J. de Abreu Matos, and M. I. L. M. Madruga, *Helv. Chim. Acta*, 1976, **59**, 2437.

[138] B. M. Trost and J. P. Genêt, *J. Amer. Chem. Soc.*, 1976, **98**, 8516.

Trost's synthesis[138] of desethylibogamine (233) illustrates the application of a new approach to alkaloid synthesis, in which the two vital cyclization processes involve catalysis by palladium complexes; protection of the nitrogen by formation of an amide, so often necessary in conventional syntheses, is here unnecessary. The first of the cyclization processes, (234)→(235), results in a very neat formation of the isoquinuclidine ring system *via* a palladium-catalysed S_N2' cyclization of the tryptamine derivative (234) (Scheme 24).



Reagents: i, Tryptamine–PhMe–$MgSO_4$, −25 °C; ii, $NaBH_4$–MeOH; iii, $(Ph_3P)_4Pd$–NEt_3–MeCN, 70 °C; iv, Li derivative–$HgCl_2$–$PdCl_2$–THF, then quench with $NaBH_4$

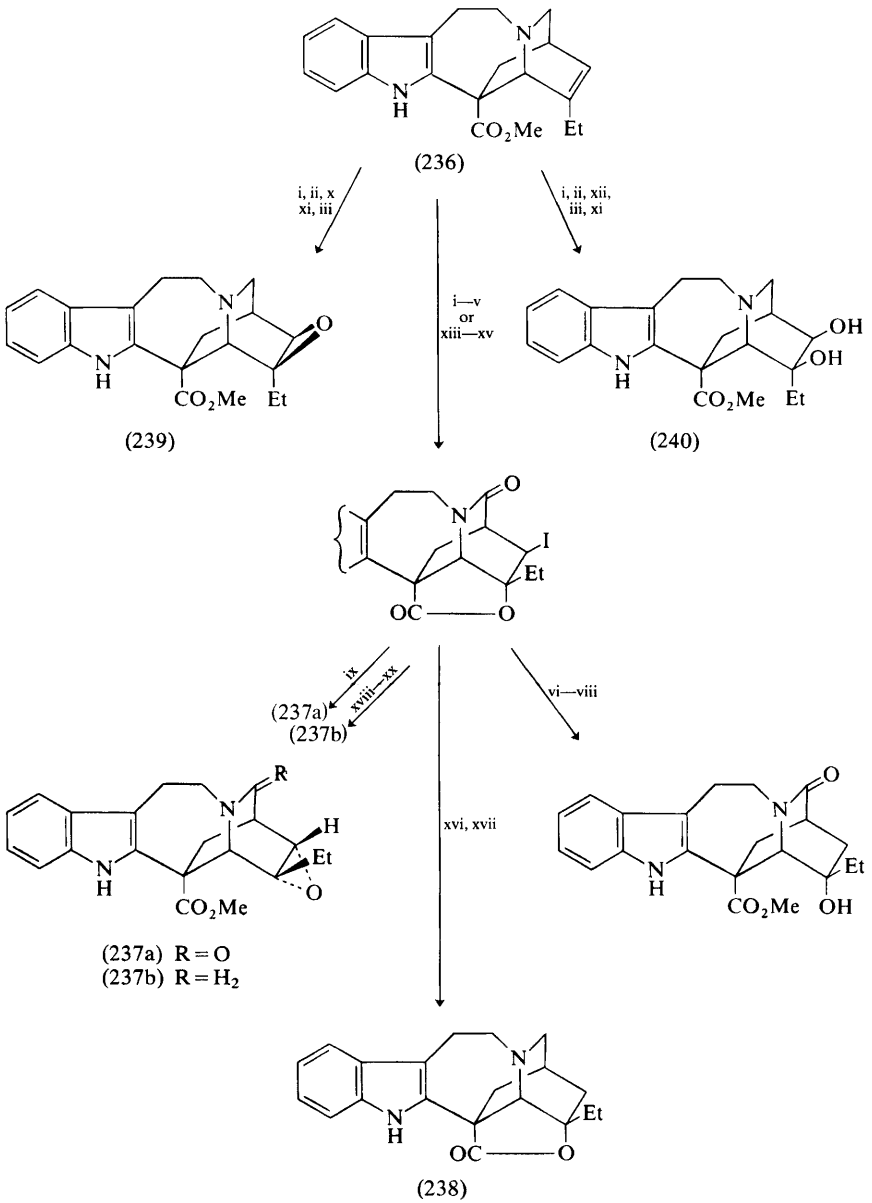
Scheme 24

Most of the transformations carried out on catharanthine have naturally been concerned with the preparation of potential precursors of dimeric bases related to vinblastine. For example, 15-acetoxydihydrocatharanthine (configuration at C-15 unknown) is also obtained, together with the recently reported[22k] 20-acetoxydihydrocatharanthine, when catharanthine is subjected to the modified Prévost reaction.[139] The conversion of catharanthine (236) into the potentially useful epoxides (237a), (237b), and (239), the lactone (238), and the diol (240) (stereochemistry at C-15 and C-20 not rigorously proved) has also been described (Scheme 25).[140,141]

4 Bis-indole Alkaloids

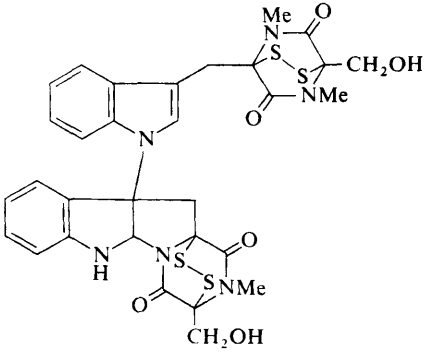
Calycanthine and chimonanthine have been found to occur in *Palicourea fendleri*;[142] this is the second report of the occurrence of calycanthine in the genus *Palicourea*. The structure of the antibiotic chetomin (241) has been elucidated,[143] mainly by ^{15}N and ^{13}C n.m.r. spectroscopy on ^{15}N-enriched material obtained from the culture of *Chaetomium cochliodes* in a nutrient medium containing $Na^{15}NO_3$.

[139] Atta-ur-Rahman, *Z. Naturforsch.*, 1976, **31b**, 1303.
[140] J. P. Kutney, G. H. Bokelman, M. Ichikawa, E. Jahngen, A. V. Joshua, P. Liao, and B. R. Worth, *Heterocycles*, 1976, **4**, 1267.
[141] Y. Honma and Y. Ban, *Heterocycles*, 1977, **6**, 285.
[142] T. Nakano and A. Martin, *Planta Med.*, 1976, **30**, 186 (*Chem. Abs.*, 1976, **85**, 139 786).
[143] A. G. McInnes, A. Taylor, and J. A. Walter, *J. Amer. Chem. Soc.*, 1976, **98**, 6741.



Reagents: i—xii are described in ref. 140, and the others in ref. 141: i, KH–$ClCO_2Me$; ii, I_2–base; iii, KOH–MeOH; iv, KOH–H_2O; v, I_2–KI–NaOH; vi, Bu^n_3SnH; vii, KOH–EtOH; viii, CH_2N_2; ix, NaOMe–MeOH; x, *m*-$ClC_6H_4CO_3H$; xi, B_2H_6; xii, OsO_4; xiii, $Hg(OAc)_2$–dioxan; xiv, 20% KOH–MeOH; xv, I_2–KI–$NaHCO_3$; xvi, Bu^n_3SnH; xvii, B_2H_6; xviii, NaOMe–MeOH; xix, $Et_3O^+ BF_4^-$; xx, $NaBH_4$

Scheme 25

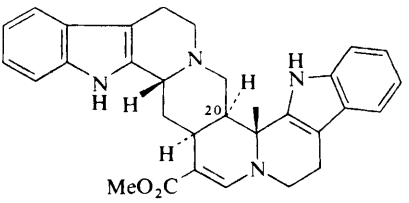


Chetomin (241)

Chetomin is an N_a,3′-bis-tryptamine derivative in which both N_b atoms are present in an epidithiodioxopiperazine unit; in the tryptamine moiety, in which N_a is unsubstituted, further cyclization has occurred to give an eserine-like ring system.

Trichotomine, the blue pigment isolated from the fruits of *Clerodendron trichotomum*, can be very simply synthesized *via* the condensation of L-tryptophan with α-ketoglutaric acid under conditions which permit the aerial oxidative dimerization of the initial cyclization product.[144]

The configuration of roxburghine B, for which the *normal* ajmalicinoid stereochemistry had been postulated earlier, has now been re-examined by means of 300 MHz ^{1}H n.m.r. spectroscopy (combined with INDOR experiments),[145] and ^{13}C n.m.r. spectroscopy.[146] Whereas the ^{13}C n.m.r. spectra of roxburghines D and E (*pseudo*), and C (*normal*) supported the previous assignments, neither the ^{13}C nor the 300 MHz ^{1}H n.m.r. spectrum supported the *normal* stereochemistry for roxburghine B, for which the *epiallo*-configuration (242) has now been established.



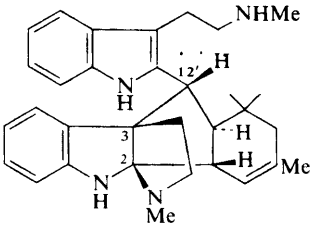
Roxburghine B (242)

The conversion of roxburghine E into B by means of zinc in acetic acid thus requires an epimerization at C-20, rather than the simpler epimerization at C-3, as previously envisaged.

Borreverine (243) is a bis-indole alkaloid of novel structural type, isolated from *Borreria verticillata*;[147] it is formed by the combination of two 2-isopentenyl-N_b-

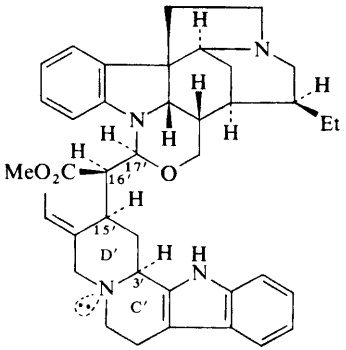
[144] G. J. Kapadia and R. E. Rao, *Tetrahedron Letters*, 1977, 975.
[145] C. Cistaro, R. Mondelli, and M. Anteunis, *Helv. Chim. Acta*, 1976, **59**, 2249.
[146] L. Merlini, R. Mondelli, G. Nasini, F. W. Wehrli, E. W. Hagaman, and E. Wenkert, *Helv. Chim. Acta*, 1976, **59**, 2254.
[147] J. L. Pousset, A. Cavé, A. Chiaroni, and C. Riche, *J.C.S. Chem. Comm.*, 1977, 261.

methyltryptamine components. The structure of borreverine (243) was elucidated by *X*-ray crystal structure analysis, as was the structure of its N_bN_b-diacetyl derivative, the formation of which is accompanied by a rearrangement in which the 2,N_b- and 3,12′-bonds are severed, and a new ring is formed by attachment of C-12′ to N_a.



Borreverine (243)

Although the gross structure of geissospermine has been known for some considerable time, the configuration at positions 16′ and 17′ remained to be elucidated; further, the absence of Bohlmann bands in its i.r. spectrum, together with the position of the n.m.r. signal owing to the proton at C-3′, were inconsistent with the *trans* C′/D′ ring junction hitherto accepted. An *X*-ray crystal structure determination has now shown[148] that geissospermine (224) contains a *cis* C′/D′ ring junction, the molecule unexpectedly adopting the conformation in which ring D′ is a chair, and the 15′,16′-bond is axial.

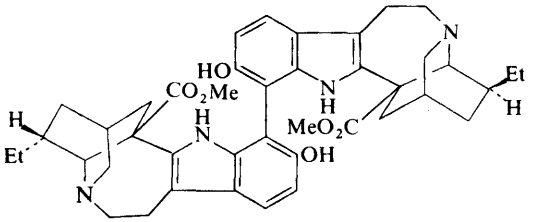


Geissospermine (244)

Of the numerous alkaloidal constituents (~60) of the stem bark of *Strychnos dolichothyrsa*, six have so far been identified, including five bis-strychninoid ones;[102] these are bisnordihydrotoxiferine, bisnor-C-curarine, bisnordihydrotoxiferine mono- and di-N_b-oxides, and (tentatively) bisnor-C-alkaloid D.

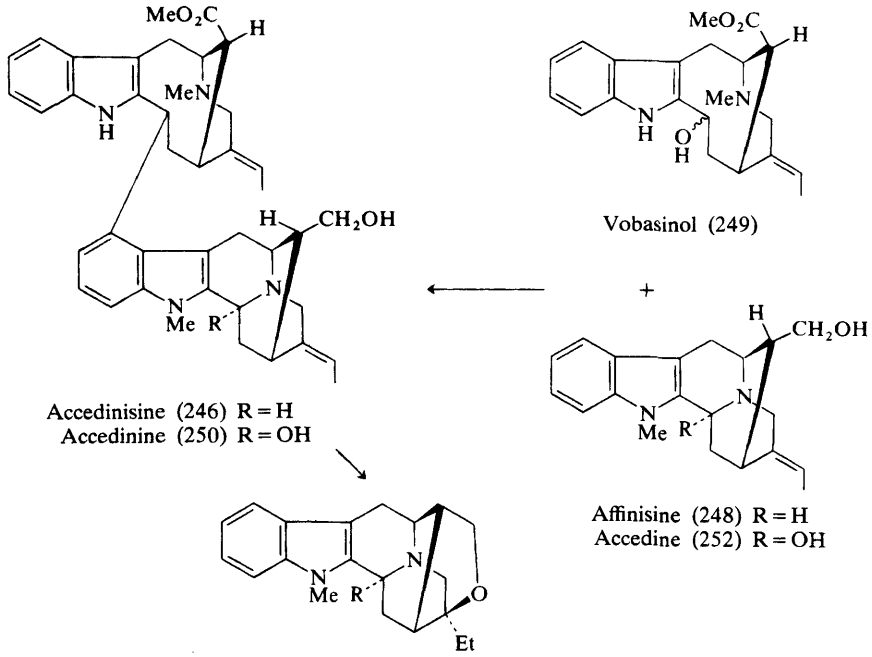
In the *Voacanga* series, conodurine and voacamine are among the alkaloids of *Peschiera laeta*,[62] and the symmetrical dimer 12,12′-bis-11-hydroxycoronaridine (245) occurs in the leaves of *Bonafousia tetrastachya*.[149]

[148] A. Chiaroni, C. Riche, M. Païs, and R. Goutarel, *Tetrahedron Letters*, 1976, 4729.
[149] M. Damak, C. Poupat, and A. Ahond, *Tetrahedron Letters*, 1976, 3531.



(245)

The root bark of *Tabernaemontana accedens* contains[150] six alkaloids, namely voacamine, voacamidine, voacamine N_b-oxide, and three new alkaloids, which are *N*-demethylvoacamine, accedinisine, and accedinine. Accedinisine (246) suffers cleavage by mineral acid to cycloaffinisine (247), which presumably originates from an affinisine unit in the alkaloid, since accedinisine contains two ethylidene (but no ethyl) groups. The spectral data for accedinisine are consistent with the presence of an affinisine unit combined with a vobasine residue, the latter being a common component in alkaloids of this group. In fact, accedinisine (246) may be synthesized by the condensation of affinisine (248) with vobasinol (249) in the presence of acid. Accedinine (250) behaves in all respects as a 3-hydroxy-accedinisine. Thus, acid fission gives cycloaccedine (251), and the alkaloid itself may be synthesized by the combination of accedine (252) with vobasinol.[150]



Vobasinol (249)

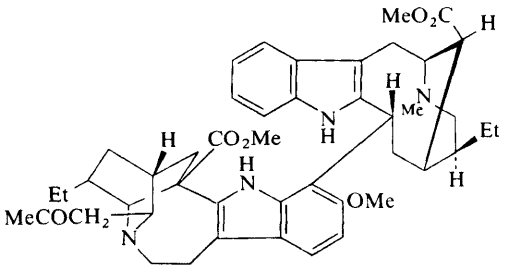
Accedinisine (246) R = H
Accedinine (250) R = OH

Affinisine (248) R = H
Accedine (252) R = OH

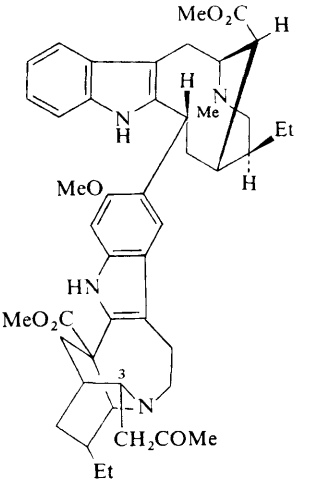
Cycloaffinisine (247) R = H
Cycloaccedine (251) R = OH

[150] H. Achenbach and E. Schaller, *Chem. Ber.*, 1976, **109**, 3527.

The detailed evidence (almost entirely spectral) on which the structures of the tabernaelegantines A—D are based[22l] has now been published,[151] and the structures of tabernaelegantinines A (253) and B (254) have also been elucidated.



Tabernaelegantinine A (253)



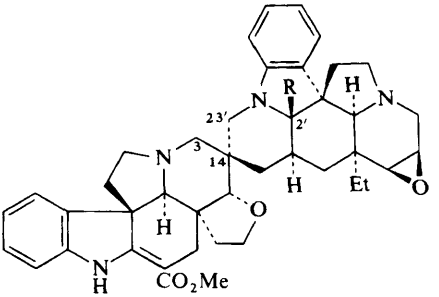
Tabernaelegantinine B (254)

These last two bases may well be formed by condensation of a 3,N_b-dehydroibogamine derivative with a biochemical equivalent of acetone; however, since acetone was used in the extraction process, the possibility that these bases are artefacts cannot be excluded. This study involved detailed discussion of the ^{13}C n.m.r. spectra of voacangine, dregaminol, and tabernaemontanol, and served to confirm the revised configurations of these last two bases.

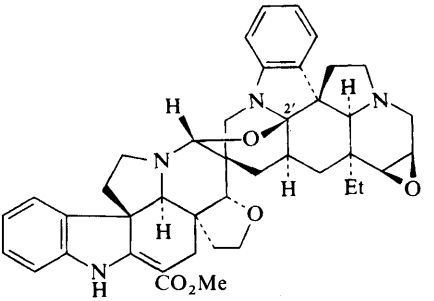
A thorough analysis of the ^{13}C n.m.r. data for a number of dimeric *Voacanga* bases, and comparison with the spectra of vobtusine, vobtusine lactone, and 2′-deoxyvobtusine lactone, has resulted in the confirmation of the structures deduced for vobtusine 3-lactam, vobtusine 3-lactam N_b′-oxide, voafolidine, and voafoline.[152] Isovoafoline, previously formulated as an isomer of voafoline, the origin of the isomerism being unknown, proves to be simply the C-14 epimer (255a) of voafoline. Other bases, whose structures were previously unknown and which have now been shown also to have the opposite configuration at C-14 to that in vobtusine, are folicangine (256), subsessiline (amataine) (257), and subsessiline lactone (258). The reduction ($NaBH_4$) of folicangine to isovoafolidine (255b) proves the presence of oxygen at position 2′; since folicangine is an internal carbinolamine ether, this oxygen atom must also be attached to position 23′, 3, or 5. The earlier structure, in which it was presumed to be attached to C-23′, has now been shown to be incorrect, the oxygen instead being present in a six-membered ring, as in (256). For exactly similar reasons, the structures containing the four-

[151] E. Bombardelli, A. Bonati, B. Gabetta, E. M. Martinelli, G. Mustich, and B. Danieli, *J.C.S. Perkin I*, 1976, 1432.

[152] Y. Rolland, N. Kunesch, J. Poisson, E. W. Hagaman, F. M. Schell, and E. Wenkert, *J. Org. Chem.*, 1976, **41**, 3270.

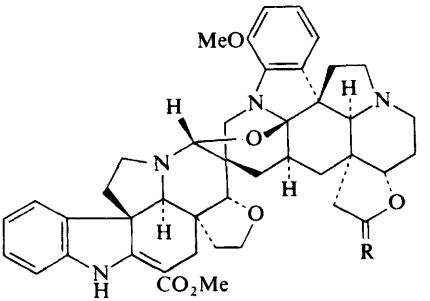


Isovoafoline (255a) R = H
Isovoafolidine (255b) R = OH



Folicangine (256)

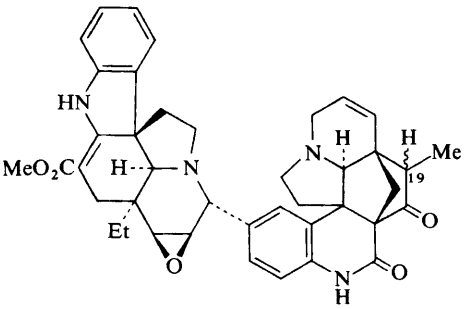
membered carbinolamine ether ring that were earlier proposed for subsessiline and subsessiline lactone are incorrect, the correct structures being (257) and (258), respectively.[152]



Subsessiline (257) R = H_2
Subsessiline lactone (258) R = O

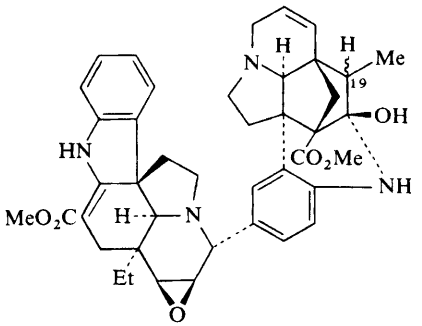
That ^{13}C n.m.r. spectroscopy is indispensable in structure elucidation is convincingly demonstrated in yet another contribution from Wenkert and his collaborators.[153] Scandomelonine (259) and episcandomelonine (260) form a C-19 epimeric

[153] M. Daudon, M. H. Mehri, M. M. Plat, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, 1976, **41**, 3275.



Scandomelonine (259) 19α-H
Episcandomelonine (260) 19β-H

pair of bases composed of tabersonine β-epoxide (pachysiphine) and meloscandonine components. A second C-19 epimeric pair, scandomeline (261) and episcandomeline (262), differ from (259) and (260) by the elements of a methoxy-group, and can be imagined to arise by methanolysis of the quinolone function in (259) and (260), followed by carbinolamine formation. In support of these formulations, treatment of scandomeline (261) with acetic anhydride gives the *N*-acetyl derivative, together with some scandomelonine (259); similarly, episcandomeline (262) gives its *N*-acetyl derivative, together with episcandomelonine (260).[153]

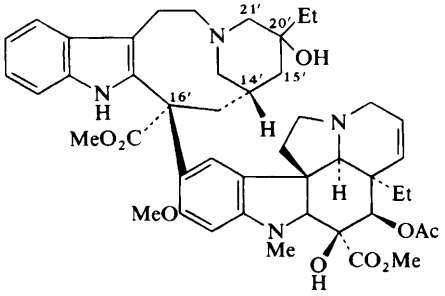


Scandomeline (261) 19α-H
Episcandomeline (262) 19β-H

The ^{13}C n.m.r. spectra of the vinblastine group of alkaloids have also been discussed,[154] and a method for the analysis of *ar.*-tritiated vinblastine by ^{3}H n.m.r. spectroscopy has been developed.[155]

The continuation of a systematic study of the constituents of *Catharanthus ovalis* has resulted in the isolation of three further alkaloids.[156] Vincovaline (263) is a new stereoisomer of vinblastine that is formulated (o.r.d. evidence) as being stereoisomeric at positions 14′ and 16′; the configuration at C-20′ is not specified. Vincovalinine appears to be 16′-demethoxycarbonyl-leurosine, and vincovalicine

[154] D. E. Dorman and J. W. Paschal, *Org. Magn. Resonance*, 1976, **8**, 413.
[155] J. P. Bloxsidge, J. A. Elvidge, J. R. Jones, R. B. Mane, V. M. A. Chambers, E. A. Evans, and D. Greenslade, *J. Chem. Res.* (*S*), 1977, 42.
[156] R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron Letters*, 1976, 2849.



Vincovaline (263)

contains N_a-demethyl-N_a-formylvindoline as the indoline component; however, no further information concerning these alkaloids is available at present.

The accelerating pace of research into the preparation of vinblastine and its derivatives has become very evident during the past year, and the volume of work reported is such that space does not allow a detailed discussion here. The dehydration of deacetylvinblastine, deacetylvincristine, and related bases generally gives mixtures of products resulting from formation of 15′,20′-dehydro- and the two geometrically isomeric 19′,20′-dehydro-derivatives; of these, 15′,20′-dehydro-deacetylvincristine showed lower toxicity and greater antitumour potency when compared with vincristine.[157]

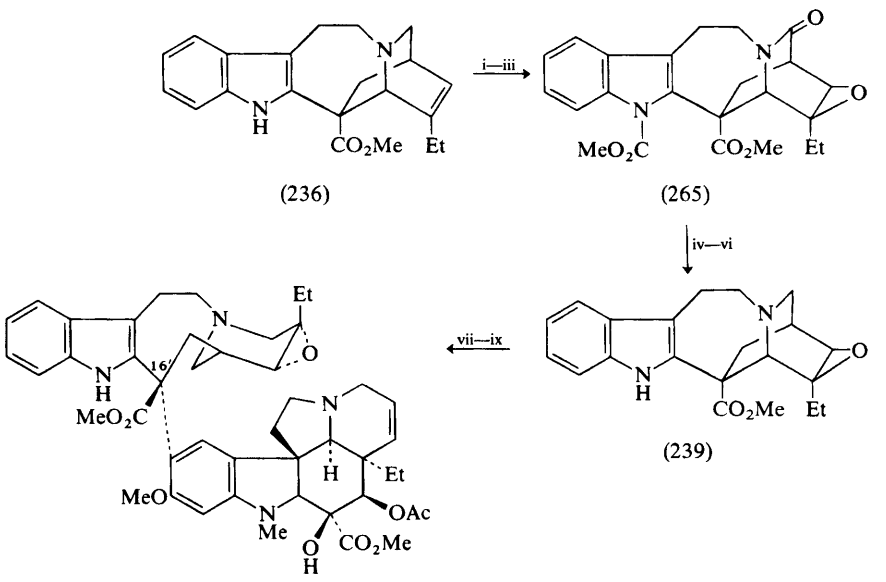
The difficulties inherent in the synthesis of vinblastine, and in particular the generation of the natural stereochemistry at C-16′, have been discussed by Atta-ur-Rahman, and the various possible synthetic approaches adopted up to mid-1976, which culminated in the first partial synthesis of vinblastine, have also been described.[158]

The pioneering application of the Polonovski reaction to the synthesis of anhydrovinblastine by Potier's group[22m] has been described in detail;[159] the work of Kutney's group in this same area has also been published *in extenso*.[160]

The known lack of reactivity of the vindoline nucleus towards peracid (owing to the hydrogen-bonding of N_b with the hydroxy-group at C-16) has allowed the partial synthesis of leurosine (264) to be completed.[161] Thus, oxidation of partially synthetic anhydrovinblastine by means of *p*-nitroperbenzoic acid in HMPA results in regiospecific oxidation, with the formation of pleurosine (leurosine N_b'-oxide) by 15′,20′-epoxidation and N_b-oxidation; some anhydrovinblastine N_b'-oxide is also obtained. Reduction of the mixture (Zn–AcOH) then leads to leurosine and anhydrovinblastine. Alternatively, the synthesis can be accomplished *via* (15*R*,20*S*)-epoxycatharanthine (catharanthine β-epoxide) (239), which is the stereospecific epoxidation product of catharanthine. Further oxidation to the N_b-oxide, followed by a Polonovski reaction [$(CF_3CO)_2O$–CH_2Cl_2] in the presence of vindoline, and reduction (a sequence exactly analogous to the partial synthesis of

[157] J. C. Miller, G. E. Gutowski, G. A. Poore, and G. B. Boder, *J. Medicin. Chem.*, 1977, **20**, 409.
[158] Atta-ur-Rahman, A. Basha, M. Ghazala, and N. Waheed, *Z. Naturforsch.*, 1976, **31b**, 1416.
[159] N. Langlois, F. Guéritte, Y. Langlois, and P. Potier, *J. Amer. Chem. Soc.*, 1976, **98**, 7017.
[160] J. P. Kutney, T. Hibino, E. Jahngen, T. Okutani, A. H. Ratcliffe, A. M. Treasurywala, and S. Wunderly, *Helv. Chim. Acta*, 1976, **59**, 2858.
[161] Y. Langlois, N. Langlois, P. Mangeney, and P. Potier, *Tetrahedron Letters*, 1976, 3945.

anhydrovinblastine) affords some leurosine (264) (Scheme 26); the yield, however, is very low.[161]



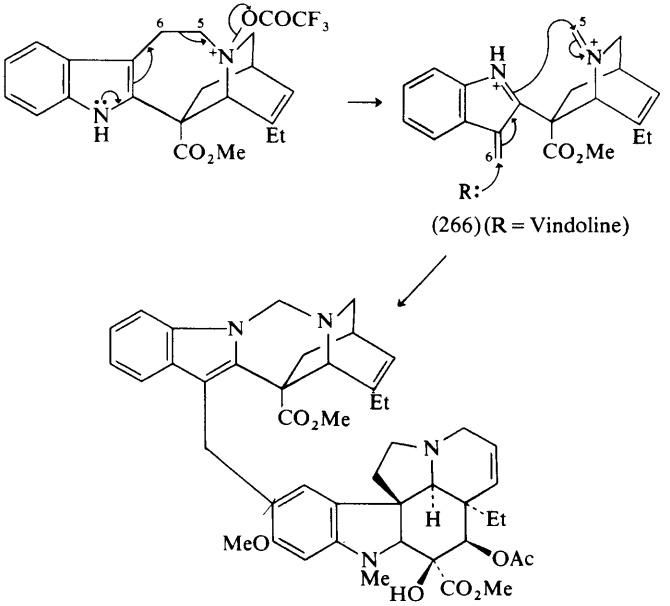
Reagents: i, KH–$ClCO_2Me$; ii, I_2–base; iii, *m*-$ClC_6H_4CO_3H$; iv, mild hydrolysis; v, P_2S_5; vi, Raney Ni; vii, *p*-$O_2NC_6H_4CO_3H$ or *m*-$ClC_6H_4CO_3H$; viii, vindoline–$(CF_3CO)_2O$; ix, $NaBH_4$

Scheme 26

The same sequence of reactions has also been accomplished by Kutney *et al.*,[162] from the β-epoxide (239); the process is described as efficient, but the yield of leurosine obtained is unspecified. In the course of this synthesis, an improved preparation of the epoxide (239) from catharanthine (236) *via* the lactam epoxide (265) was developed (Scheme 26).[162]

The critical dependence of the stereochemical and regiochemical course of the modified Polonovski reaction on the oxygen functionality in the catharanthine derivative has been well exemplified in recent synthetic studies. Indeed, in the reaction that ultimately provided the first synthesis of anhydrovinblastine, a minor product proved to be the result of an alternative fragmentation of the catharanthine N_b-oxide derivative in which the 5,6-bond was cleaved [→(266)] and subsequent coupling of vindoline occurred at position 6, with formation of the dimeric species (267).[159] When an attempt was made to couple the *N*-oxide of the lactone (238) with vindoline under Polonovski conditions, this type of coupling occurred exclusively, and the products were the lactone (268) (major product)[163—165], the

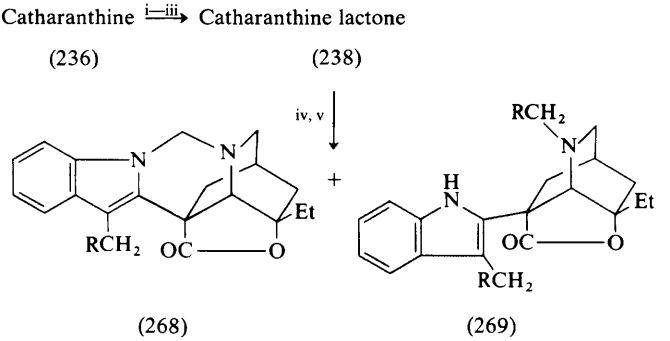
[162] J. P. Kutney and B. R. Worth, *Heterocycles*, 1976, **4**, 1777.
[163] J. P. Kutney, A. V. Joshua, and P. Liao, *Heterocycles*, 1977, **6**, 297.
[164] Y. Honma and Y. Ban, *Heterocycles*, 1977, **6**, 291.
[165] P. Mangeney, R. Costa, Y. Langlois, and P. Potier, *Compt. rend.*, 1977, **284**, *C*, 701.



(266) (R = Vindoline)

(267)

corresponding lactol [also obtainable by the reduction of (268) with $NaBH_4$], and an apparently trimeric species, derived from the condensation of two vindoline units with the catharanthine derivative.[163] This product, formulated by Ban[164] as (269), is clearly obtained by nucleophilic attack at both positions 5 and 6 in (266) by vindoline molecules (Scheme 27). During the course of their work in this area, the French group developed a new and efficient preparation of the lactone (238) from catharanthine (236) (Scheme 27)[165] which proceeded in 55% overall yield.



(268) (269)

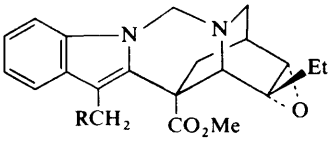
R = 10-Vindolinyl

Reagents: i, $Ba(OH)_2$–dioxan; ii, $HgCl_2$; iii, $NaBH_4$; iv, *p*-$O_2NC_6H_4CO_3H$ or *m*-$ClC_6H_4CO_3H$; v, vindoline–$(CF_3CO)_2O$

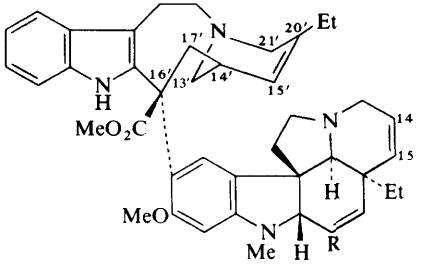
Scheme 27

A dimeric product (270) of the undesired type was also obtained from the Polonovski coupling of the α-epoxide (237b) with vindoline; in this reaction, however, (270) was the only dimeric species isolated.[163]

Further use of the modified Polonovski reaction has been made[166] in the synthesis of four model vinblastine derivatives (271)—(274) from the vindoline relatives mentioned earlier;[117] all four products have the natural stereochemistry at C-16′.

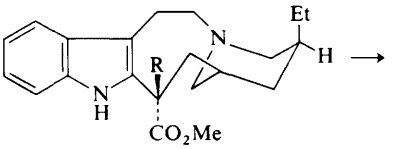


(270) R = 10-Vindolinyl

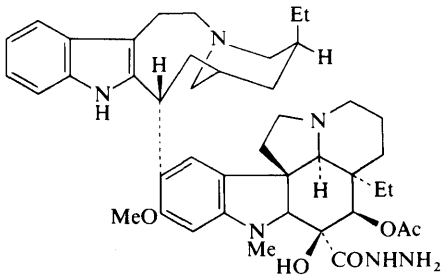


(271) R = CO_2Me
(272) R = CO_2Me; 14,15-dihydro
(273) R = CONHMe
(274) R = CONHMe; 14,15-dihydro

Two further contributions on vinblastine chemistry deserve mention. Prolonged treatment of vinblastine with hydrazine results in the removal of the 16′-methoxycarbonyl group; however, the stereochemistry at C-16′ is retained.[167a] Similarly, synthetic relatives of vinblastine lacking the ester group at C-16′ but possessing the unnatural configuration at C-16′ are also configurationally stable to hydrazine. However, the synthetic dimer (275), on hydrazinolysis, suffers loss of the ester group attached to C-16′, but it also epimerizes at C-16′ to give [167a] the hydrazide (276) with the natural configuration at C-16′.



(275) R = 10-(14,15-Dihydrovindolinyl)

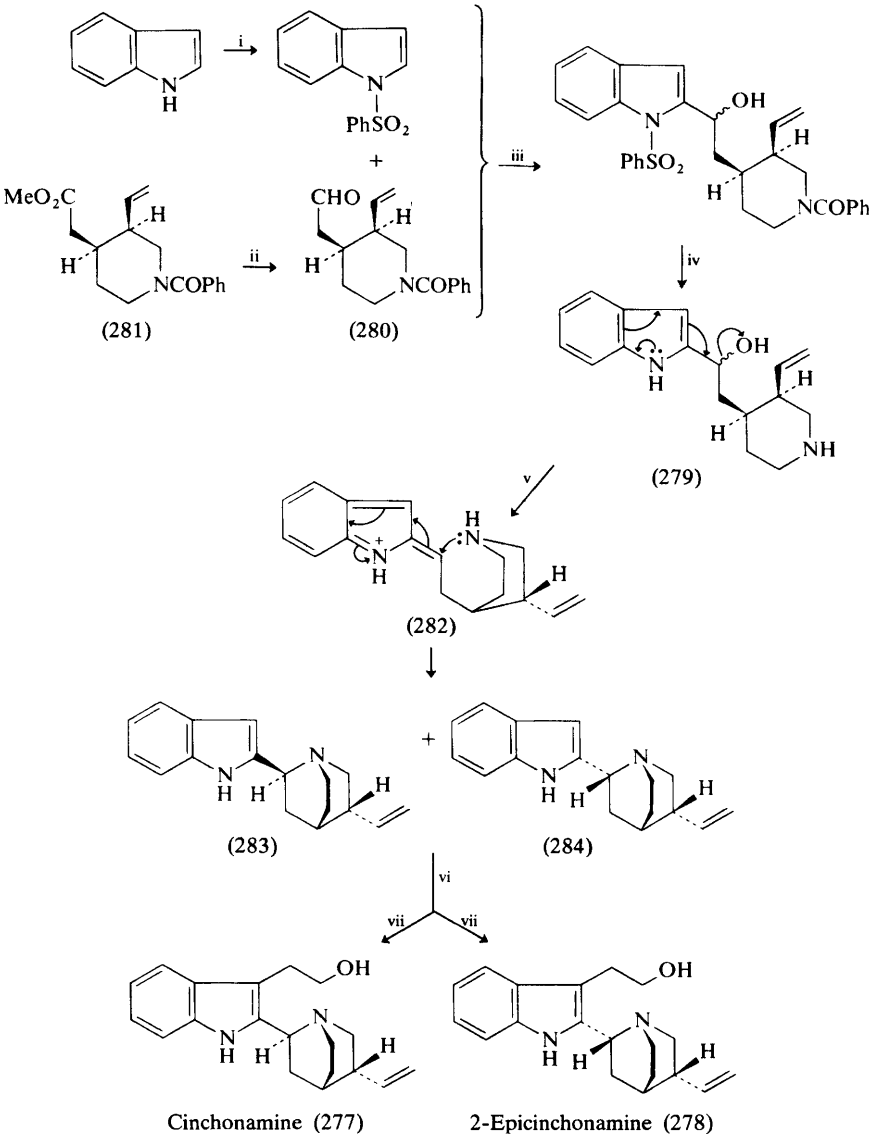


(276)

The action of three oxidizing agents on the velbanamine component in vinblastine and related compounds has also been studied.[167b] Osmium tetroxide hydroxylates the double bond between positions 15′ and 20′, if present, but also

[166] J. P. Kutney, W. B. Evans, and T. Honda, *Heterocycles*, 1977, **6**, 443.
[167] (*a*) J. P. Kutney, E. Jahngen, and T. Okutani, *Heterocycles*, 1976, **5**, 59; (*b*) J. P. Kutney, J. Balsevich, and G. H. Bokelman, *ibid.*, 1976, **4**, 1377.

oxidizes the C-3′ methylene group, with formation of a lactam carbonyl group at this position. Iodine in the presence of sodium bicarbonate also results in the formation of 3′-lactams; however, in contrast, oxygen in the presence of trifluoroacetic acid gives rise to products containing a 21′,N_b'-lactam function.[167b]



Reagents: i, NaH–DMSO–$PhSO_2Cl$; ii, Bu^i_2AlH–PhMe, −70 °C; iii, Bu^nLi–THF–TMEDA; iv, KOH–MeOH–H_2O; v, *o*-$C_6H_4Cl_2$, 155 °C; vi, separation of isomers; vii, MeMgI–ethylene oxide

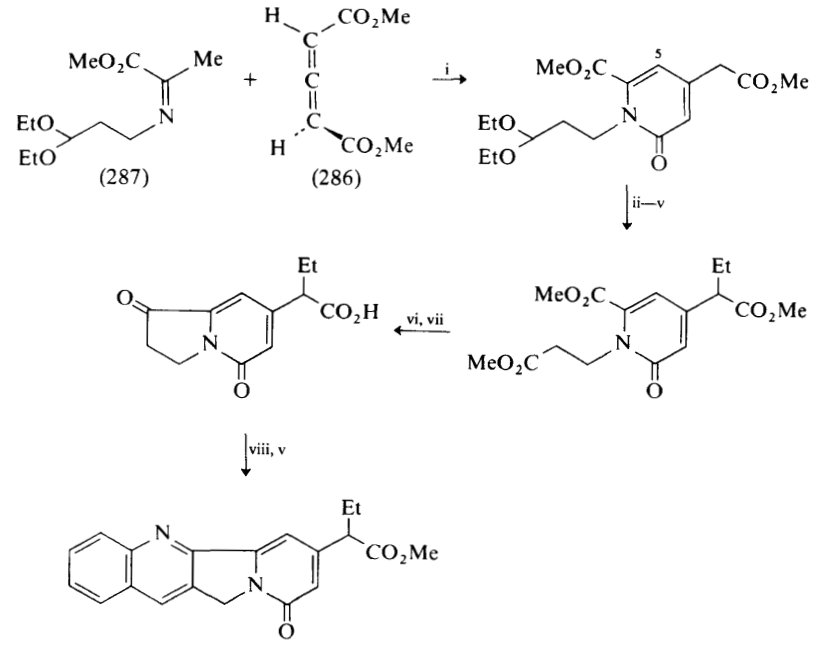
Scheme 28

5 Biogenetically Related Quinoline Alkaloids

A second group of workers has concurred[168] that one of the major metabolites of quinidine in man[22n] is the 5′-hydroxy-derivative.

The first total synthesis of cinchonamine (277) and 2-epicinchonamine (278) proceeds *via* the epimers (279), which were prepared by two independent methods.[169] Scheme 28 illustrates the more efficient of the two syntheses, which involves as its first stage the condensation of 2-lithio-*N*-benzenesulphonyl-indole with *N*-benzoylmeroquinene aldehyde (280), itself obtained by reduction of the readily available *N*-benzoylmeroquinene ester (281). The critical cyclization stage [(279)→(283)+(284)] that occurs on prolonged heating at 155 °C presumably proceeds *via* the immonium ion (282), since separation of the epimers of (279) followed by dehydration and cyclization affords the same mixture of (283) and (284). Finally, the hydroxyethyl group was introduced by the reaction of the Grignard derivatives of (283) and (284) with ethylene oxide.[169]

A new synthesis[170] of the tetracyclic pyridone ester (285) (Scheme 29) represents another formal total synthesis of camptothecin, since (285) has already been



Reagents: i, Et_3N–DME, −78 °C; ii, EtI–$KOBu^t$–DME; iii, 5% HCl–Me_2CO; iv, Jones oxidation; v, MeOH–HCl; vi, NaOMe–MeOH; vii, 10% HCl, reflux; viii, *o*-$H_2NC_6H_4CHO$–NaOH

Scheme 29

[168] B. Beermann, K. Leander, and B. Lindström, *Acta Chem. Scand.* (*B*), 1976, **30**, 465.
[169] G. Grethe, H. L. Lee, and M. R. Uskokovic, *Helv. Chim. Acta*, 1976, **59**, 2268.
[170] J. Quick, *Tetrahedron Letters*, 1977, 327.

converted into camptothecin by other workers. This synthesis makes use of a new preparation of pyridones unsubstituted at position 5 which involves the condensation of allenedicarboxylic diester (286) with an imine (287), presumably *via* the enamine tautomer.

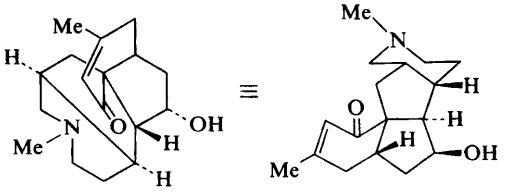
12

Lycopodium Alkaloids

BY W. A. AYER

Since the last Report, two years ago,[1] relatively few papers have appeared concerning this group of alkaloids. The alkaloids of *Lycopodium magellanicum*, the concentrations of which appear to show seasonal variation, have been examined[2] and a new alkaloid, magellanine, was isolated, along with the known alkaloids lycopodine, fawcettiine, deacetylfawcettiine, α-obscurine, and clavolonine. Magellanine, an $\alpha\beta$-unsaturated ketone (λ_{max} 237 nm) has been shown, by an *X*-ray crystallographic study,[2] to have structure (1), and thus to possess the same skeleton as paniculatine.[1] Alkaloids with this skeleton show distinctive mass spectral fragmentation patterns, and thus may be differentiated from other skeletal types by this method of analysis.[2] Two species of *Lycopodium* indigenous to Africa, *L. gnidioides* and *L. verticillatum*, have been the subject of isolation studies.[3] *L. gnidioides* yielded the known alkaloids lucidioline, anhydrolycodoline, selagine, and lycoclavine (2) along with the new substances lycognidine (3) (closely related to lycoclavine) and gnidioidine (4), which is a 11,12-dehydroclavolonine. The major alkaloid of *L. verticillatum* proved to be anhydroaposerratinine (5), a transformation product of serratinine which had not previously been obtained from natural sources. A minor alkaloid isolated from *L. verticillatum* and named lycoverticine was shown to have structure (6), *i.e.* a hydroxylated flabelline (7). Hydrolysis of lycoverticine gave lycodoline (8); the reverse transformation (8)→(6) was achieved by catalytic hydrogenation of the oxime of (8) in acetic anhydride.

A new short and elegant total synthesis of (±)-luciduline, utilizing a novel intramolecular addition of an *N*-alkenyl-nitrone to a double bond, has been reported[4] and is summarized in Scheme 1. The *cis*-octalone (9), along with some of



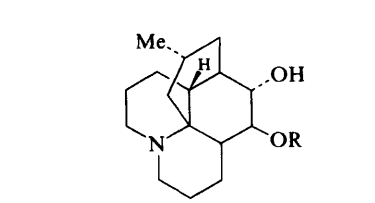
(1)

[1] W. A. Ayer, in 'The Alkaloids', ed. M. F. Grundon (Specialist Periodical Reports), The Chemical Society, London, 1975, Vol. 6, Ch. 11.

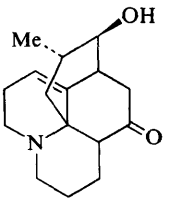
[2] M. Castillo, L. A. Loyola, G. Morales, I. Singh, C. Calvo, H. L. Holland, and D. B. MacLean, *Canad. J. Chem.*, 1976, **54**, 2893.

[3] L. Nyembo, N. Kahindo, J. C. Braekman, and C. Hootele, *Bull. Soc. chim. belges*, 1976, **85**, 595.

[4] W. Oppolzer and M. Petrzilka, *J. Amer. Chem. Soc.*, 1976, **98**, 6722.



(2) R = COMe
(3) R = $CO(CH_2)_2$



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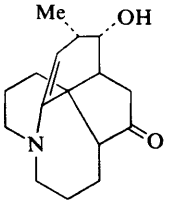

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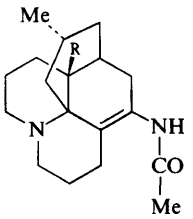
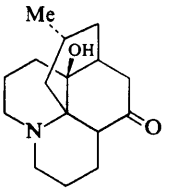
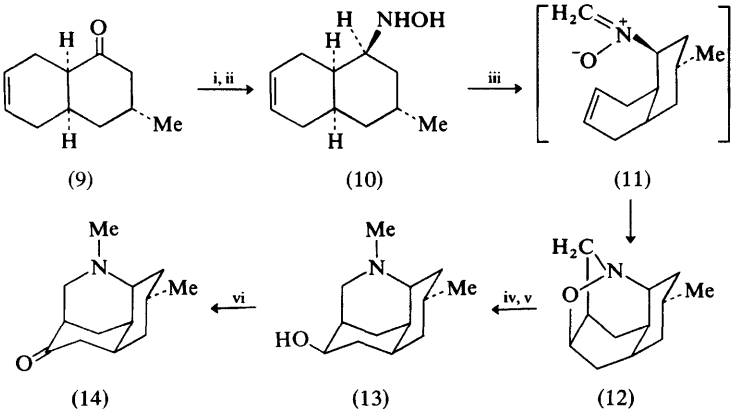


(6) R = OH
(7) R = H



(8)

the *trans*-isomer, was prepared by Lewis-acid-catalysed Diels–Alder addition of butadiene to 5-methylcyclohex-2-enone. The octalone (9) was transformed, in two steps, into the hydroxylamine (10), and this in turn was transformed into the bridged isoxazoline (12) by treatment with paraformaldehyde in toluene, the reaction presumably involving the highly regioselective intramolecular 1,3-addition of the intermediate nitrone (11) to the double bond. *N*-Methylation of (12) followed by



(9) (10) (11)

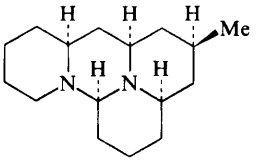
(14) (13) (12)

Reagents: i, H_2NOH,HCl–NaOAc–MeOH; ii, $NaBH_3CN$–MeOH; iii, $(CH_2O)_x$–toluene, molecular sieves; iv, FSO_3Me–ether; v, $LiAlH_4$–THF; vi, Jones' oxidation

Scheme 1

hydride reduction gave (±)-dihydroluciduline (13), which on Jones' oxidation afforded (±)-luciduline (14).

The details of a new synthesis of dihydrodeoxyepiallocernuine (15), a transformation product of the alkaloid cernuine (16), have been reported,[5] and are



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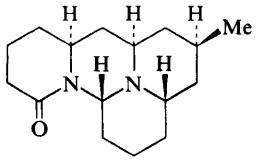
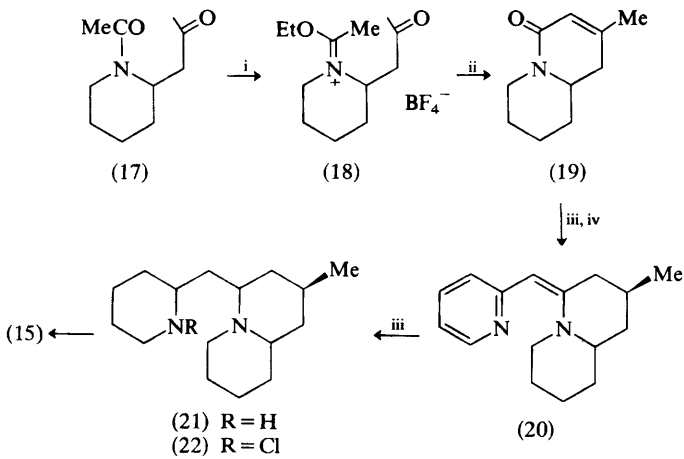


(16)

summarized in Scheme 2. *N*-Acetylpelletierine (17), prepared from 2-piperidone by a new procedure, was transformed into the immonium salt (18) by treatment with triethyloxonium fluoroborate. When the crude product (18) was treated with potassium t-butoxide in refluxing t-butyl alcohol, the unsaturated lactam (19) was obtained. Catalytic hydrogenation of (19) followed by condensation of the resulting saturated lactam with α-picolyl-lithium gave (20). Catalytic hydrogenation of (20) afforded the diamine (21). When (21) was transformed into the chloro-amine (22) and this was subjected to photolysis in strong acid solution (normal Hoffmann–Löffler conditions), no product was obtained. However, when (22) was generated *in situ* in ether and irradiated immediately, dihydrodeoxyepiallocernuine was obtained in 30% yield, along with the dihydrochloride of the diamine (21).[5] The generality of this method for the synthesis of 1,3-diaza-heterocycles in the presence of an amine has been demonstrated.[6]



Reagents: i, $Et_3O^+ BH_4^-$–CH_2Cl_2; ii, KOBu^t–Bu^{t}OH; iii, H_2–Pt–$MeCO_2H$; iv, α-picolyl-lithium–THF; v, *N*-chlorosuccinimide–ether, $h\nu$

Scheme 2

[5] Y. Ban, M. Kimura, and T. Oishi, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 1490.
[6] M. Kimura and Y. Ban, *Synthesis*, 1976, 201.

13

Diterpenoid Alkaloids

BY S. WILLIAM PELLETIER AND S. W. PAGE

1 Introduction

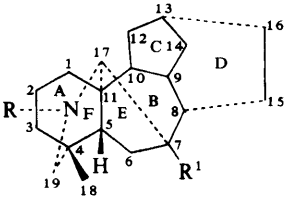
Interest in the chemistry of diterpenoid alkaloids has continued, as shown by the volume of publication during the past year. In spite of the increased reliance on physical methods of structure determination, especially on *X*-ray crystallography and ^{13}C n.m.r. spectroscopy, interesting chemical transformations of these complex bases have been reported.

Five new diterpenoid alkaloids have been isolated from *Aconitum* species (Ranunculaceae) and five from *Delphinium* species (Ranunculaceae). Four new *Anopterus* (Escalloniaceae) bases have been identified. The most significant synthetic achievement has been the total synthesis of racemic chasmanine. A detailed review of the alkaloids of *Delphinium staphisagria* has appeared.[1]

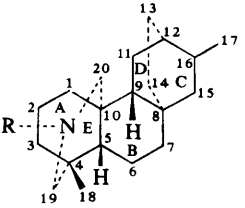
Several papers on the taxonomy of the Ranunculaceae have been published.[2—8] These clarify some of the nomenclatural and taxonomic problems of this Family, particularly of those species found in the eastern and south-eastern United States.

The limited reports of work on the *Daphniphyllum* alkaloids include the description of the isolation of two new compounds from *D. humile.*

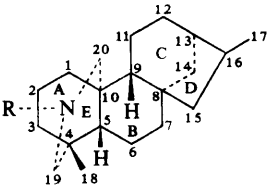
The numbering systems used for the aconitine, lycoctonine, atisine, and veatchine skeletons are indicated in structures (A), (B), (C), and (D), respectively.



(A) Aconitine skeleton; $R^1 = H$
(B) Lycoctonine skeleton; $R^1 = OR^2$



(C) Atisine skeleton

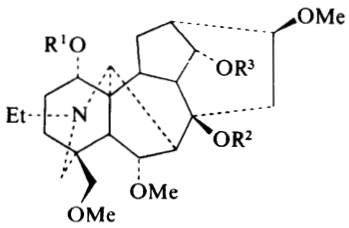


(D) Veatchine skeleton

[1] S. W. Pelletier and N. V. Mody, *Heterocycles*, 1976, **5**, 771.
[2] C. S. Keener, *Castanea*, 1976, **41**, 12.
[3] C. S. Keener, *SIDA Contrib. Bot.*, 1976, **6**, 266.
[4] R. Kral, *SIDA Contrib. Bot.*, 1976, **6**, 243.
[5] T. S. Rostovtseva, *Bot. Zhur. (Leningrad)*, 1976, **61**, 1133 (*Biol. Abs.*, 1977, **63**, 036 826).
[6] R. V. Kamelin, *Byull. Mosk. O-va. Ispyt. Prir. Otd. Biol.*, 1975, **8C**, No. 6, p. 136 (*Biol. Abs.*, 1976, **62**, 041 339).
[7] L. A. Malakhova, A. A. Kozlova, and N. N. Kartashova, *Bot. Zhur. (Leningrad)*, 1976, **61**, 1137 (*Biol. Abs.*, 1977, **63**, 036 829).
[8] T. A. Aseeva and B.-O. Badaraev, *Rastit. Resur.*, 1976, **12**, 96 (*Biol. Abs.*, 1977, **64**, 006 937).

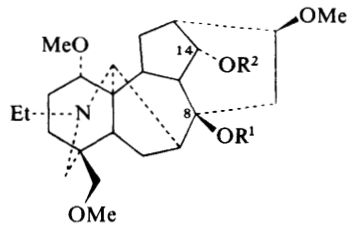
2 C_{19} Diterpenoid Alkaloids

Structure and Absolute Configuration of Chasmanine 14α-Benzoate Hydrochloride.—The full report on the *X*-ray crystallographic structure determination of this derivative of chasmanine, isolated from the roots of *Aconitum chasmanthum* Stapf, has appeared[9] (*cf.* Vol. 7, p. 253). The structure was computed to be (1) by direct methods. The absolute configuration as determined by the *R*-ratio test is 1*S*, 4*S*, 5*R*, 6*R*, 7*R*, 8*S*, 9*R*, 10*R*, 11*S*, 13*R*, 14*S*, 16*S*, 17*R*.[10] This structure determination confirmed the structures of chasmanine (2) and homochasmanine (3) that had previously been proposed on the basis of chemical and spectral data.[11]



(1) R^1 = Me, R^2 = H, R^3 = benzoyl, HCl
Chasmanine (2) R^1 = Me, R^2 = R^3 = H
Homochasmanine (3) R^1 = R^2 = Me, R^3 = H

Alkaloids of *Aconitum confertiflorum*: Monoacetyltalatisamine.—The tubers of *A. confertiflorum* (DC.) Voroschilov were extracted with dichloroethane to yield 1.98% of total alkaloids.[12] Thin-layer chromatographic analysis indicated that this alkaloid fraction contained at least nine components. Two of the bases were isolated by column chromatography on aluminium oxide. The first alkaloid was an amorphous base, reported to be a monoacetyltalatisamine (4). Neither structure



Monoacetyltalatisamine (4) R^1, R^2 = H, Ac

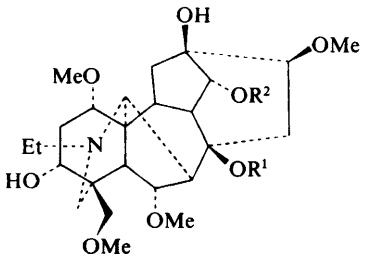
nor data were given in this report to enable assignment of the acetoxy-group to either C-8 or C-14.

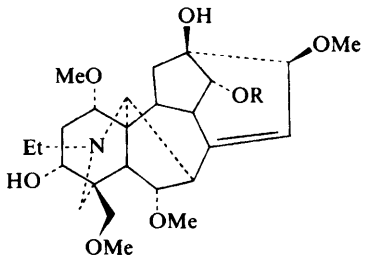
[9] W. H. De Camp and S. W. Pelletier, *Acta Cryst.*, 1977, **B33**, 722.
[10] The absolute configuration at C-8 is incorrect as stated in the original article for chasmanine. The correct Cahn–Ingold–Prelog notation is 8*S* for the molecule corresponding to our published coordinates and drawings. The absolute configuration at the remaining chiral centres is correctly stated in both cases. We express appreciation to Prof. E. F. Meyer of Texas A. and M. University for bringing the error to our attention.
[11] S. W. Pelletier, Z. Djarmati, S. Lajšić, and W. H. De Camp, *J. Amer. Chem. Soc.*, 1976, **98**, 2617.
[12] B. Sh. Ibragimov, G. M. Mamedov, and H. M. Ismailov, *Doklady Akad. Nauk Azerb. S. S. R.*, 1976, **32**, No. 10, p. 58.

The second amorphous compound isolated had a molecular weight of 421. From the spectral data, these workers concluded that this alkaloid contained a lycoctonine skeleton, an *N*-ethyl group, and three methoxy-groups.

Alkaloids of *Aconitum falconeri*: Falaconitine and Mithaconitine. In addition to the previously known veratroylpseudaconine (5), pseudaconitine (6) and indaconitine (7), two new C_{19} diterpenoid alkaloids, falaconitine and mithaconitine, have been isolated from the roots of *Aconitum falconeri* Stapf.[13,14] Singh and co-workers[15] had reported a preliminary study of the two alkaloids, 'bishatisine' and 'bishaconitine', isolated from this species. However, in the recent work,[13,14] no 'bishatisine' or any atisine-type alkaloid was identified, and the data reported for 'bishaconitine' were consistent with a mixture of falaconitine and several closely related bases. The identities of (5), (6), and (7) were determined primarily by ^1H and ^{13}C n.m.r. techniques and confirmed by comparison with authentic samples.[14]

Falaconitine, an amorphous base, $C_{34}H_{47}NO_{10}$, is a major constituent of the alkaloidal fraction isolated from the roots. Mithaconitine, $C_{32}H_{43}NO_8$, was isolated in an amorphous form as a minor component. The spectral data indicate that these alkaloids are indentical except for the presence of a benzoyl group in mithaconitine instead of the veratroyl group in falaconitine. Comparison of the ^{13}C n.m.r. spectra of pseudaconitine (6), indaconitine (7), veratroylpseudaconine (5), and pyrodelphinine with those of falaconitine and mithaconitine enabled assignment of structures (8) and (9), respectively, to these new alkaloids. Falaconitine and mithaconitine were found to be identical with the pyrolysis products (8) and (9) of pseudaconitine and indaconitine, respectively. These are the first naturally occurring pyrodelphinine-type alkaloids. It was proposed that these bases might be biogenetic precursers for the C_{19} diterpenoid alkaloids containing hydroxyl or acetoxyl functionalities attached to C-8 or C-15.





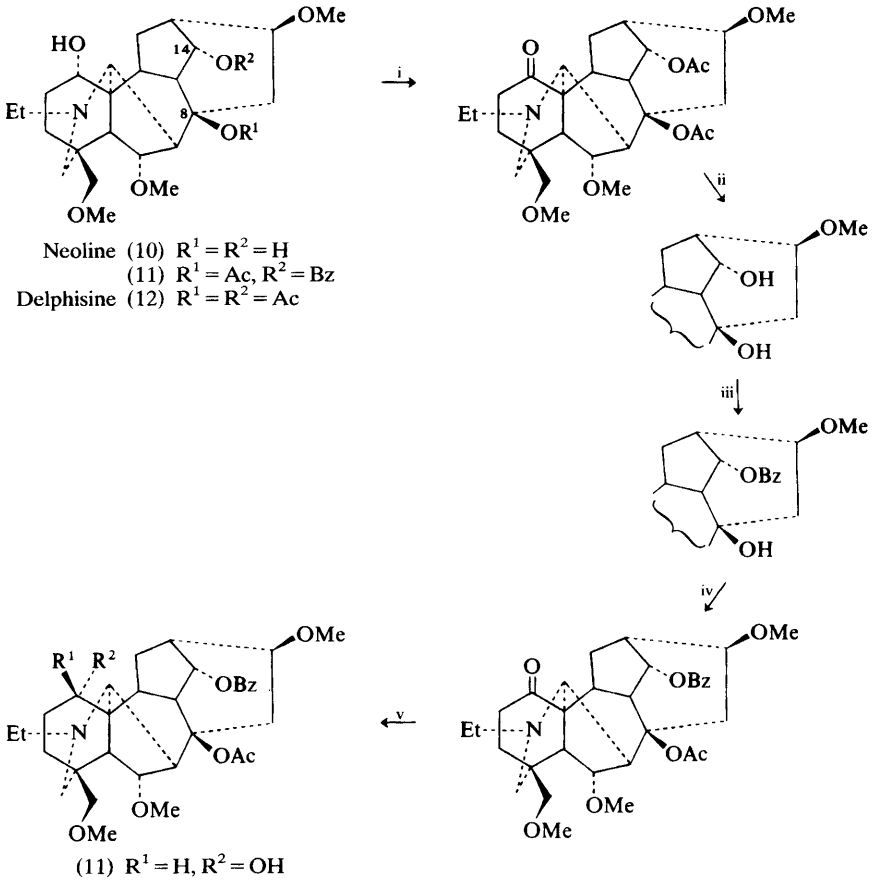
Veratroylpseudaconine (5) $R^1 = H$, R^2 = veratroyl
Pseudaconitine (6) $R^1 = Ac$, R^2 = veratroyl
Indaconitine (7) $R^1 = Ac$, R^2 = benzoyl

Falaconitine (8) R = veratroyl
Mithaconitine (9) R = benzoyl

Further Studies of 'Neopelline'.[16]—This alkaloid, $C_{32}H_{45}NO_8$, m.pt. 80 °C, had been reported as an impurity in crude aconitine from *Aconitum napellus*.[17] On alkaline hydrolysis, 'neopelline' afforded neoline (10), benzoic acid, and acetic acid.

[13] S. W. Pelletier, N. V. Mody, and H. S. Puri, *J.C.S. Chem. Comm.*, 1977, 12.
[14] S. W. Pelletier, N. V. Mody, and H. S. Puri, *Phytochemistry*, 1977, **16**, 623.
[15] N. Singh, G. S. Bajwa, and M. G. Singh, *Indian J. Chem.*, 1966, **4**, 39.
[16] S. W. Pelletier, J. Bhattacharyya, and N. V. Mody, *Heterocycles*, 1977, **6**, 463.
[17] H. Schulze and G. Berger, *Arch. Pharm.*, 1924, **262**, 553.

Later workers[18] were unable to isolate 'neopelline' under the same conditions, and suggested that it was hydrolysed during the basic isolation procedures which were employed. Since the structure of neoline (10), $C_{24}H_{39}NO_6$, has been determined,[19] the molecular formula for 'neopelline' from the previous work must be revised to $C_{33}H_{45}NO_8$. Of the six possible monoacetyl-monobenzoyl-neoline structures, 8-acetyl-14-benzoylneoline (11) is the most biogenetically plausible. To test this possibility, delphisine (12) was converted into (11) as outlined in Scheme 1.[16] However, none of the properties of (11) agreed with those published for 'neopelline', suggesting that they are not identical.



Neoline (10) $R^1 = R^2 = H$
(11) $R^1 = Ac, R^2 = Bz$
Delphisine (12) $R^1 = R^2 = Ac$

(11) $R^1 = H, R^2 = OH$

Major product: $R^1 = OH, R^2 = H$

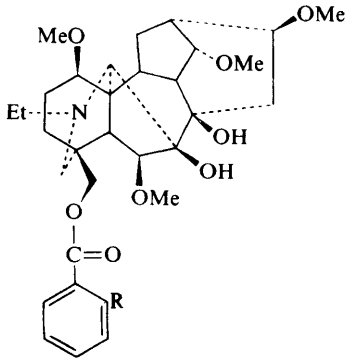
Reagents: i, CrO_3–H_2O–pyridine; ii, MeOH–5% KOH; iii, PhCOCl–pyridine; iv, Ac_2O–TsOH; v, $NaBH_4$

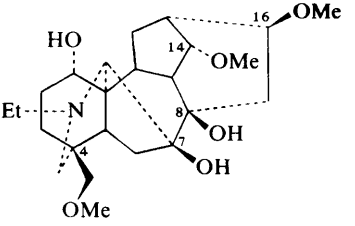
Scheme 1

[18] W. Freudenberg and E. F. Rogers, *J. Amer. Chem. Soc.*, 1937, **59**, 2572.
[19] K. Wiesner, H. W. Brewer, D. L. Simmons, D. R. Badin, F. Bickelhaupt, J. Kallos, and T. Bogri, *Tetrahedron Letters*, 1960, No. 3, p. 17.

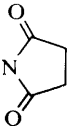
Alkaloids of *Aconitum nasutum*.–Plekhanova and Murav'eva have reported studies of the alkaloids from *A. nasutum*.[20] From the aerial parts of this species, they obtained 0.42% total alkaloids. The roots yielded 1.6% alkaloid fraction, which was shown to contain at least five components. One of these was isolated as a base, $C_{22}H_{35}NO_4$, m.pt. 148 °C, $[\alpha]_D^{20} = -20.7°$.

Alkaloids of *Aconitum umbrosum*: Umbrosine.—From roots of *Aconitum umbrosum*, workers at Tashkent have isolated lycaconitine (13), anthranoyl-lycoctonine (14), ajacine (15), and a new alkaloid, umbrosine (16), $C_{24}H_{39}NO_6$, m.pt. 150—151 °C.[21]





Umbrosine (16)



Lycaconitine (13) R = –N

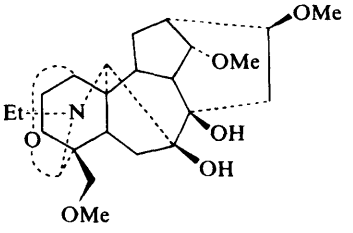
Anthranoyl-lycoctonine (14) R = NH_2

Ajacine (15) R = NHAc

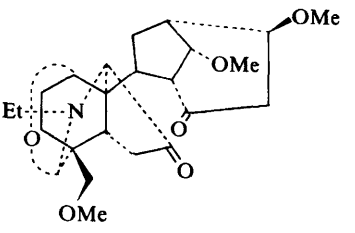
The ^{1}H n.m.r. and mass spectral data of umbrosine and its monoacetyl derivative indicate that umbrosine contains a lycoctonine skeleton with an *N*-ethyl, three methoxy-groups (one located at C-14, and having an α-configuration), and a hydroxy-group in the α-configuration at C-1. On oxidation of (16) with potassium permanganate, the α-carbinol amine internal ether (17) was obtained, further confirming the α-hydroxy-group at C-1. The loss of acrolein and methoxyl radical in the mass spectrum of (17) suggested the location of a methoxymethyl group at C-4. On oxidation of umbrosine with periodic acid, (18) was formed. This diketone was reduced to (19) in the presence of Adams catalyst. On further hydrogenation of (19) in acid solution, (20) was obtained. These structures were assigned on the basis of spectral comparisons with the analogous seco-products from known lycoctonine-type alkaloids. The locations of the diol system at C-7 and C-8 and of the β-methoxy-group at C-16 were assigned on the basis of these transformations.

[20] T. I. Plekhanova and D. A. Murav'eva, *Aktual. Vopr. Farm.*, 1974, **2**, 49 (*Chem. Abs.*, 1976, **84**, 102 350).

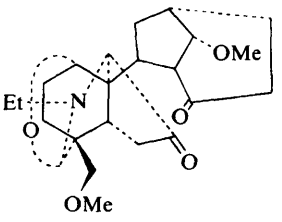
[21] V. A. Tel'nov, N. M. Golubev, and M. S. Yunusov, *Khim. prirod. Soedinenii*, 1976, 675.



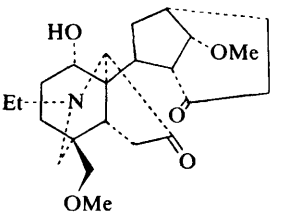
(17)



(18)

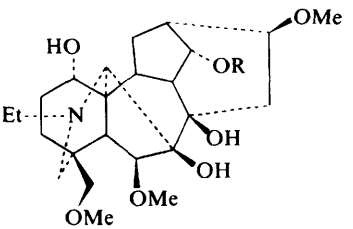


(19)



(20)

Phytochemical Screening of *Delphinium ajacus* and *D. belladonna*.—Egyptian workers[22,23] have examined the seeds, flowers, leaves, pericarps, stems, and roots of *D. ajacus* L. and *D. belladonna* Kelw, growing in Egypt, for total alkaloids. They reported that the seeds contain ajacine (15) as the major alkaloid, as well as delcosine (delphamine) (21), monoacetyldelcosine (22), and ajacinoidine (no structure indicated).

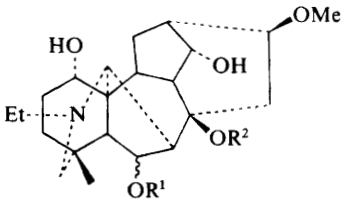


Delcosine (Delphamine) (21) R = H
Monoacetyldelcosine (22) R = Ac

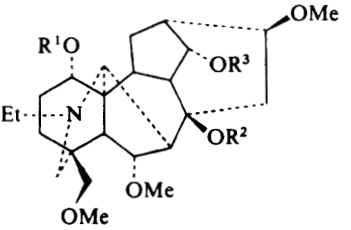
Alkaloids of *Delphinium bicolor* Nutt.—The structure of Alkaloid A from this plant has been revised on the basis of additional ^{13}C n.m.r. data.[24] Alkaloids A and B formerly had been assigned structures (23) and (24), respectively, as a result of a pyrolysis study of Alkaloid A and from ^{13}C n.m.r. data.[25] Comparison of the spectra of these alkaloids with those of neoline (10), 8-acetylneoline (25), delphisine (12), trimethoxyneoline (26), heteratisine (27), and 6-acetylheteratisine

[22] F. M. Hashem, S. M. Abdel-Wahab, M. Salah Ahmed, and A. A. Seida, *Bull. Fac. Pharm., Cairo Univ.*, 1974, **13**, 205 (*Chem. Abs.*, 1977, **86**, 40 214).
[23] F. M. Hashem, S. M. Abdel-Wahab, M. Salah Ahmed, and A. A. Seida, *Bull. Fac. Pharm., Cairo Univ.*, 1974, **13**, 217 (*Chem. Abs.*, 1977, **86**, 40 215).
[24] S. W. Pelletier, N. V. Mody, A. J. Jones, and M. H. Benn, *Tetrahedron Letters*, 1976, 3025.
[25] A. J. Jones and M. H. Benn, *Canad. J. Chem.*, 1973, **51**, 486.

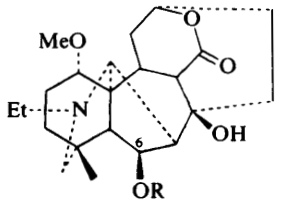
(28) has shown that the assignment of the methoxy-group at C-6 and of the acetoxy-group at C-8 in Alkaloid A is incorrect; it is actually the reverse. The structures of Alkaloids A and B are as indicated in (29) and (30), respectively. A number of the chemical shifts of Alkaloids A and B listed in the earlier report have been revised.



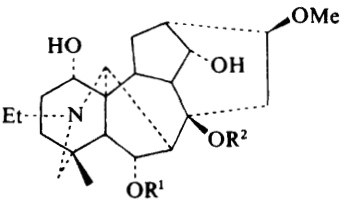
(23) R^1 = Me, R^2 = Ac
(24) $R^1 = R^2$ = H



Neoline (10) $R^1 = R^2 = R^3$ = H
8-Acetylneoline (25) $R^1 = R^3$ = H, R^2 = Ac
Delphisine (12) R^1 = H, $R^2 = R^3$ = Ac
Trimethoxyneoline (26) $R^1 = R^2 = R^3$ = Me

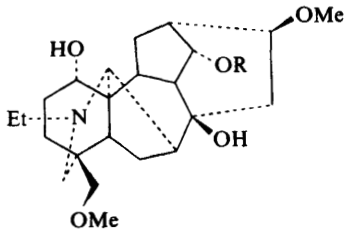


Heteratisine (27) R = H
6-Acetylheteratisine (28) R = Ac

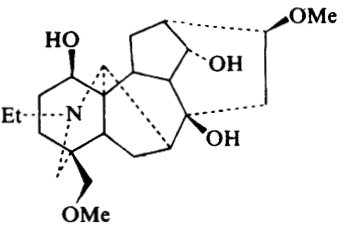


Alkaloid A (29) R^1 = Ac, R^2 = Me
Alkaloid B (30) $R^1 = R^2$ = H

Structure and Absolute Configuration of Condelphine Hydroiodide.—Condelphine, $C_{25}H_{39}NO_6$, m.pt. 158—159 °C, has been isolated from *Delphinium denudatum* and from *D. confusum*. This alkaloid was correlated with isotalatizidine (31) and talatizidine (32). On treatment with methyl iodide in a sealed tube at 80 °C, the hydroiodide derivative, rather than the methiodide, was obtained. *X*-Ray crystallographic structural investigations of this hydroiodide have shown the structure of condelphine to be (33), refined to $R = 0.100$, based on 3828 observed reflections.[26]



Isotalatizidine (31) R = H
Condelphine (33) R = Ac



Talatizidine (32)

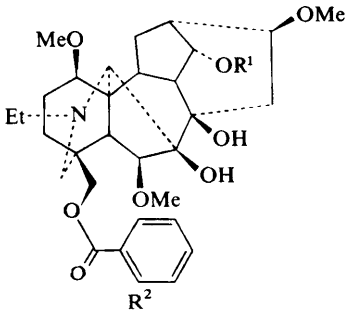
[26] S. W. Pelletier, W. H. De Camp, D. L. Herald, jun., S. W. Page, and M. G. Newton, *Acta Cryst.*, 1977, **B33**, 716.

The absolute configuration was established as 1*S*, 4*S*, 5*R*, 7*S*, 8*S*, 9*R*, 10*R*, 11*S*, 13*R*, 14*S*, 16*S*, 17*R*, by examination of Friedel pairs of reflections.

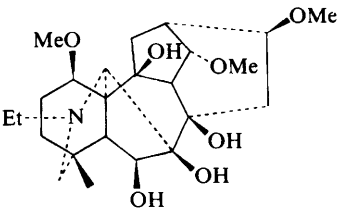
This work confirmed the location and β-orientation of the methoxy-group at C-16 in condelphine. Since isotalatizidine was obtained by saponification of condelphine, and talatizidine is the C-1 epimer of isotalatizidine, the structures and absolute configurations of these alkaloids have now also been confirmed.

Alkaloids of *Delphinium dictyocarpum*: *N*-Acetyldelectine and Demethylenedeltamine.—Further investigations of the aerial parts of *D. dictyocarpum* DC. have yielded a new base (34), $C_{26}H_{41}NO_8$, m.pt. 116—118 °C.[27] Spectral analyses (i.r., n.m.r., and mass) indicate the presence of an *N*-ethyl and three methoxy-groups, and an *N*-acetyl anthranilate ester, on a lycoctonine-type skeleton. Saponification of (34) gave anthranilic acid and a base identical with that obtained from delectine (35). Therefore, this new alkaloid was assigned the structure of *N*-acetyldelectine (34).

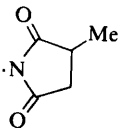
Methyl-lycaconitine (36), anthranoyl-lycoctonine (14), and a new alkaloid, $C_{24}H_{39}NO_7$, m.pt. 98—100 °C, were isolated from the alkaloid fraction of the roots of *D. dictyocarpum* collected in the Kuyandysa region.[27] The i.r., n.m.r., and mass spectral data indicate that the new alkaloid is most probably demethylenedeltamine (37). This conclusion was confirmed by comparison with the demethylene derivative of deltamine (eldelidine) (38).

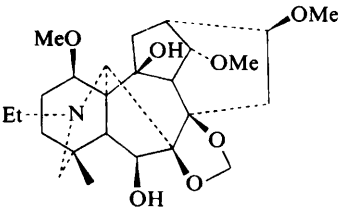


N-Acetyldelectine (34) $R^1 = H$, $R^2 = NHAc$
Delectine (35) $R^1 = H$, $R^2 = NH_2$



Demethylenedeltamine (37)

Methyl-lycaconitine (36) $R^1 = Me$, $R^2 =$ 



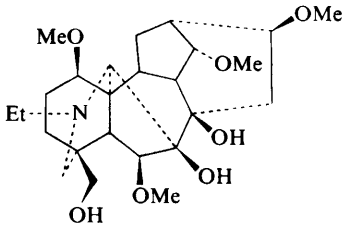
Anthranoyl-lycoctonine (14) $R^1 = Me$, $R^2 = NH_2$

Deltamine (Eldelidine) (38)

Alkaloids of *Delphinium elisabethae*.—Soviet researchers[28] have reported the isolation of an alkaloid fraction from the roots of this species by extraction with methanol–acetic acid–water. From this mixture they separated five alkaloids. On

[27] B. T. Salimov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1977, 128.
[28] L. V. Beshitaishvili, M. N. Sultankhodzhaev, M. S. Yunusov, and K. S. Mudzhiri, *Soobshch. Akad. Nauk Gruz. S. S. R.*, 1975, **79**, 617 (*Chem. Abs.*, 1976, **84**, 86 723).

the basis of i.r. and n.m.r. data, they identified methyl-lycaconitine (36), anthranoyl-lycoctonine (14), and lycoctonine (39). Two other bases, having molecular weights of 676 and 535, were also reported.



Lycoctonine (39)

Alkaloids of *Delphinium formosum*.—Tanker and Ozden[29] obtained an alkaloid fraction from the roots of this species, growing in Turkey, by treatment with ammonium hydroxide and benzene percolation. Thin-layer-chromatographic separation afforded six alkaloids. Two of these were identified as lycoctonine (39) and delsemine (see 'Alkaloids of *D. tricorne*', p. 228).

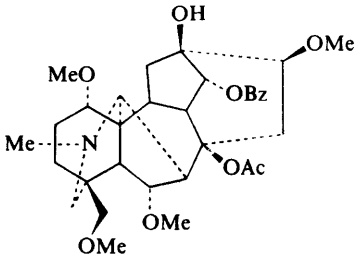
Alkaloids of *Delphinium grandiflora*.—Savchenko[30] has reported the isolation of four alkaloids from *D. grandiflora*. The total alkaloid content of the plant was 0.71%. The major alkaloid, methyl-lycaconitine (36), was isolated as its perchlorate salt. Delpyrine (no structure indicated), anthranoyl-lycoctonine (14), and a minor alkaloid were isolated by counter-current distribution methods.

Alkaloids of *Delphinium staphisagria*: Delphidine[31] and Delphirine.[32]—These new bases were isolated from the mother liquors accumulated from the large-scale separation of delphinine (40) from the seeds of *D. staphisagria* L.

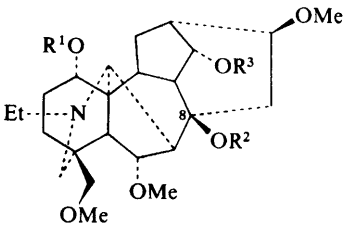
Delphidine, $C_{26}H_{41}NO_7$, m.pt. 98—100 °C, on hydrolysis with methanolic potassium carbonate, gave neoline (10). Treatment of delphidine with acetic anhydride–pyridine yielded neoline triacetate (41). On the basis of this behaviour and by comparison of its spectral data with those of neoline and delphisine (12), delphidine has been assigned the structure of 8-acetylneoline (25).[31] It was noted that when delphisine was allowed to stand in hexane on an alumina column for three days, it was quantitatively converted into delphidine.

Delphirine, $C_{24}H_{39}NO_6$, m.pt. 95—100 °C, has been assigned structure (42) from spectral data and a chemical correlation.[32] The ^{13}C n.m.r. spectrum of delphirine resembles that of neoline except for the shifts of the carbons in ring A and of C-19. These shifts resemble those of 1-epidelphisine (43), suggesting that delphirine is 1-epineoline. This idea was confirmed by Cornforth oxidation of delphisine to 1-ketodelphisine (44), which was hydrolysed to 1-ketoneoline (45). Reduction of 1-ketoneoline with borohydride gave a mixture of neoline (20%) and 1-epineoline

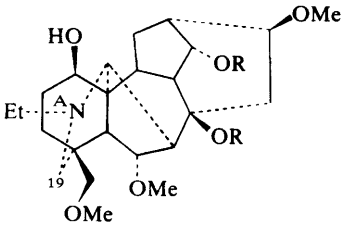
[29] M. Tanker and S. Ozden, *Ankara Univ. Eczacilik Fak. Mecm.*, 1975, **5**, 113 (*Chem. Abs.*, 1976, **85**, 198 082).
[30] Ya. S. Savchenko, *Aktual. Vopr. Farm.*, 1974, **2**, 22 (*Chem. Abs.*, 1976, **84**, 147 613).
[31] S. W. Pelletier, J. K. Thakkar, N. V. Mody, Z. Djarmati, and J. Bhattacharyya, *Phytochemistry*, 1977, **16**, 404.
[32] S. W. Pelletier and J. Bhattacharyya, *Tetrahedron Letters*, 1976, 4679.



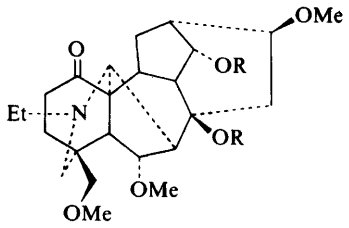
Delphinine (40)



Neoline (10) $R^1 = R^2 = R^3 = H$
(41) $R^1 = R^2 = R^3 = Ac$
Delphisine (12) $R^1 = H$, $R^2 = R^3 = Ac$
Delphidine (25) $R^1 = R^3 = H$, $R^2 = Ac$



Delphirine (42) R = H
1-Epidelphisine (43) R = Ac



(44) R = Ac
(45) R = H

(60%); the latter compound was identical with delphirine. The absolute configurations of delphirine and delphidine can be related to the absolute configuration previously derived for delphisine.[33]

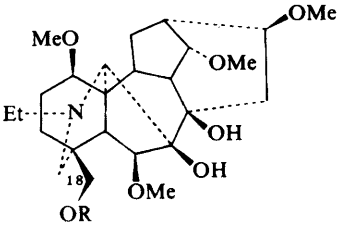
Alkaloids of *Delphinium tricorne*: Tricornine.—Examination of the alkaloid fraction of the whole-plant extract from *D. tricorne* Michaux revealed lycoctonine (39), 'Alkaloid A' (36), 'Alkaloid B' ('delsemine'), and a new base, tricornine (46), $C_{27}H_{43}NO_8$, m.pt. 187—189 °C.[34,35]

For tricornine,[35] the i.r. and ^1H n.m.r. data indicate the presence of an *N*-ethyl, an acetoxy-, four methoxy-, and two hydroxy-groups. The ^{13}C n.m.r. spectrum is very similar to that of lycoctonine, except for a downfield shift for C-18 and the presence of two additional carbon atoms in the spectrum of tricornine. This result suggests that tricornine is the 18-acetate of lycoctonine. This structure assignment was confirmed by mild hydrolysis of tricornine with alkali to give a product identical with lycoctonine. Treatment of the latter with acetic anhydride–pyridine at room temperature acetylated the only primary hydroxyl function, to yield a product identical with tricornine (46).

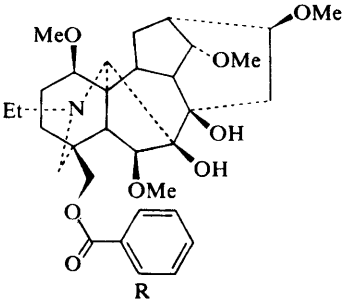
'Alkaloid A', which forms lycoctonine on mild alkaline hydrolysis, was identified as methyl-lycaconitine (36) from ^{13}C n.m.r. data. 'Alkaloid B' also forms lycoctonine on similar hydrolysis. However, the ^{13}C n.m.r. spectrum of 'Alkaloid B'

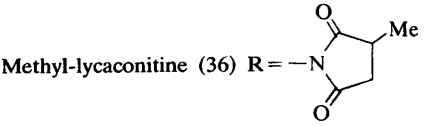
[33] S. W. Pelletier, Z. Djarmati, S. Lajšić, and W. H. De Camp, *J. Amer. Chem. Soc.*, 1976, **98**, 2617.
[34] S. W. Pelletier and J. Bhattacharyya, *Tetrahedron Letters*, 1977, 2735.
[35] S. W. Pelletier and J. Bhattacharyya, *Phytochemistry*, 1977, **16**, 1464.

indicates that it is a mixture of (47) and (48). Kuzovkov and Platonova[36] had earlier assigned alternative structures (47) and (48) to 'delsemine', isolated from *D. semibarbatum*.[37] These structures were proposed on the basis of the formation of



Lycoctonine (39) R = H
Tricornine (46) R = Ac





Methyl-lycaconitine (36)

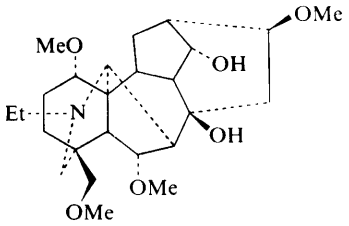
'Delsemine' (47) $R = NHC(O)CHMeCH_2C(O)NH_2$
(48) $R = NHC(O)CH_2CHMeC(O)NH_2$

Anthranoyl-lycoctonine (14) $R = NH_2$

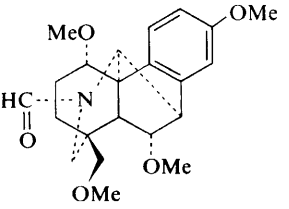
'delsemine' from methyl-lycaconitine on treatment with ammonium hydroxide and on the hydrolysis of 'delsemine' to anthranolyl-lycoctonine (14). Treatment of 'Alkaloid A' with ammonium hydroxide gave 'Alkaloid B', the mixture of compounds resulting from attack at both carbonyl centres in the methyl-succinimido-group. Hydrolysis of 'Alkaloid B', following the published procedure[36] for the hydrolysis of 'delsemine', gave anthranoyl-lycoctonine (14). These results demonstrate that 'Alkaloid B' is identical with the mixture called 'delsemine'. Since the methods of isolation of these alkaloidal fractions involved the use of ammonium hydroxide, 'delsemine', or 'Alkaloid B', is probably an artefact. It should be noted that without the use of ^{13}C n.m.r. techniques this problem would have been very difficult to resolve.

Total Synthesis of Chasmanine.—Wiesner and his co-workers[38,39] have accomplished a landmark in diterpenoid alkaloid chemistry in their completion of the total synthesis of racemic chasmanine (49), a hexacyclic base with six oxygen functionalities. The synthesis of the intermediate (50) was reviewed in the previous Report (Vol. 7, pp. 257—259).

[36] A. D. Kuzovkov and T. F. Platonova, *J. Gen. Chem.* (*U.S.S.R.*), 1959, **29**, 2746.
[37] S. Yu. Yunusov and N. K. Abubakirov, *Doklady Akad. Nauk Uzbek S.S.R.*, 1949, No. 8, p. 21.
[38] K. Wiesner, I. H. Sanchez, K. S. Atwal, and S. F. Lee, *Canad. J. Chem.*, 1977, **55**, 1091.
[39] T. Y. R. Tsai, C. S. J. Tsai, W. W. Sy, M. N. Shanbhag, W. C. Liu, S. F. Lee, and K. Wiesner, *Heterocycles*, 1977, **7**, 217: we wish to thank Professor Wiesner for a pre-publication copy of this manuscript.

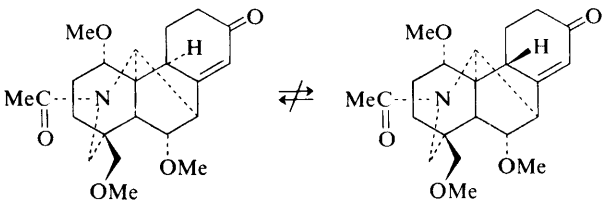


Chasmanine (49)



(50)

The reactions by which (50) is converted into chasmanine were studied in model systems.[38] An earlier scheme[40] (*cf.* Vol. 7, p. 258) was found to be unsatisfactory due to the unfavourable equilibrium between (51) and (52). The next model

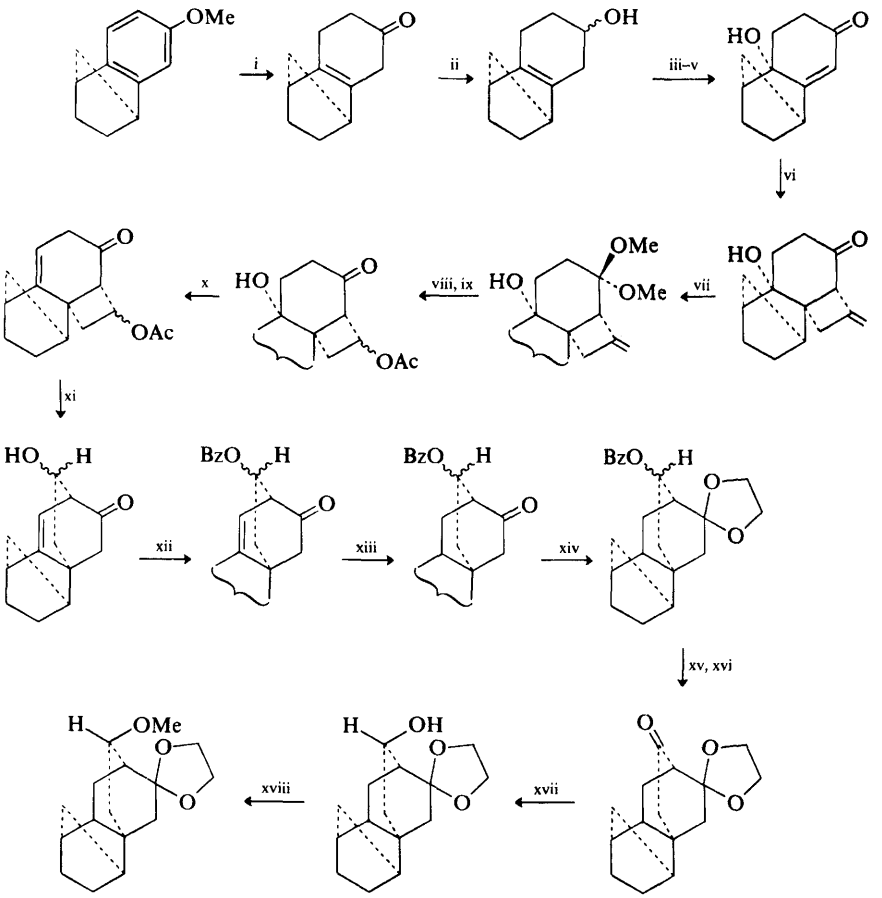


(51) (52)

variant attempted is outlined in Scheme 2. However, when compound (53) was prepared, it could not be dehydrated. This lack of reactivity was attributed to the non-bonded interaction of the tertiary hydroxy-group and the methoxy-group attached to ring A. Therefore, the development of a third variant was necessary. This was accomplished as outlined in Scheme 3. This route is particularly notable in that it turns out to be simpler than the previous routes, and, more important, it worked (with slight modification) in the real system.[39]

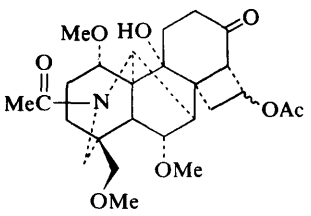
Reduction of (50) with lithium in THF and liquid ammonia followed sequentially by acetylation and treatment with methanolic hydrochloric acid under reflux gave (54). Photoaddition of allene to this compound produced (55) in 85% yield. Conversion of (55) into the acetal and subsequent ozonolysis, with borohydride work-up, gave (56). This crude alcohol was acetylated, and the product (57) was treated with aqueous methanolic hydrochloric acid to afford (58). Bromination of (58) with pyridine hydrobromide perbromide gave (59). Dehydrobromination with lithium bromide–lithium carbonate in DMF yielded (60). This $\alpha\beta$-unsaturated ketone was treated with aqueous methanolic sodium hydroxide to afford the epimeric aldols (61), which were converted into the corresponding acetates (62). Hydrogenation of (62) with rhodium on alumina followed by oxidation with chromium trioxide–pyridine in methylene chloride gave the epimeric acetates (63). These were converted into (64) by formation of the ethylene glycol acetal, saponification, and oxidation with chromium trioxide–pyridine. Reduction with sodium borohydride proceeded stereospecifically to give (65), which was methylated with sodium hydride–methyl iodide to yield (66).

[40] K. Wiesner, P.-T. Ho, W.-C. Liu, and M. N. Shanbhag, *Canad. J. Chem.*, 1975, **53**, 2140.

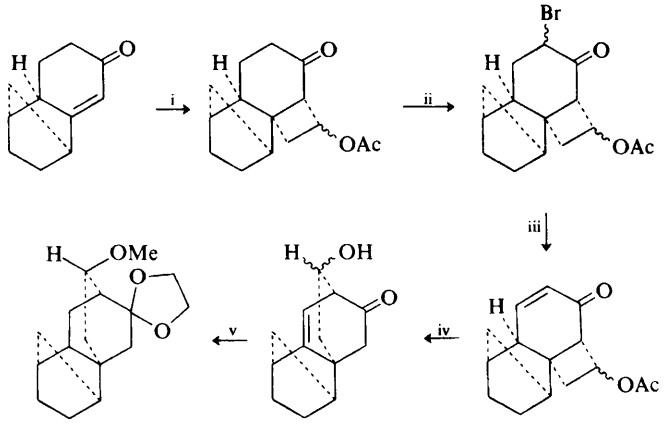


Reagents: i, Li–NH_3–THF–Bu^{t}OH–oxalic acid; ii, $NaBH_4$; iii, *m*-chloroperbenzoic acid; iv, tetramethylpiperidine hydrochloride–*m*-chloroperbenzoic acid; v, NaOMe–MeOH; vi, allene–*hν*; vii, trimethyl orthoformate; viii, O_3–$NaBH_4$; ix, Ac_2O–pyridine; x, $SOCl_2$–pyridine; xi, KOH–MeOH; xii, PhCOCl–pyridine; xiii, H_2–Rh, preparative t.l.c.; xiv, ethylene glycol–TsOH; xv, KOH–MeOH; xvi, CrO_3–pyridine; xvii, $NaBH_4$; xviii, MeI–NaH.

Scheme 2



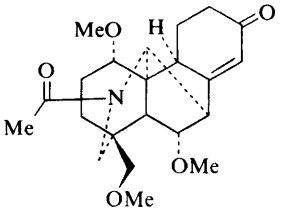
(53)



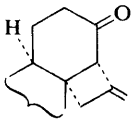
Reagents: i, vinyl acetate–$h\nu$; ii, pyridinium hydrobromide perbromide–THF; iii, LiBr–$LiCO_3$–DMF; iv, KOH–MeOH; v, same as reagents xii to xviii in Scheme 2

Scheme 3

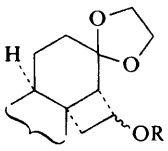
Unlike the model system, (66) could not be brominated directly. Therefore, it was converted into the ketone (67) by heating in 80% acetic acid, and this ketone was brominated with excess bromine in ether to give (68). Conversion of (68) into the acetal (69) was accomplished with diethylene orthocarbonate and toluene-*p*-sulphonic acid. Rearrangement of (69) to (70) was effected by heating with excess 1,5-diazabicyclo[3,4,0]nonene in xylene–DMSO. On comparison of i.r., n.m.r., and mass spectral data, this synthetic racemate was identical with the corresponding derivative from natural chasmanine.



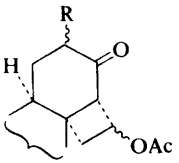
(54)



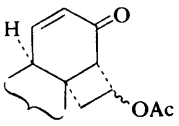
(55)



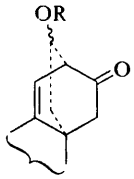
(56) R = H
(57) R = Ac



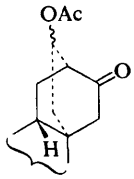
(58) R = H
(59) R = Br



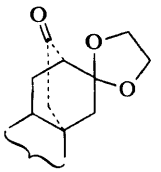
(60)



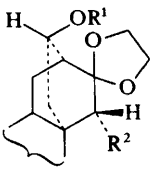
(61) R = H
(62) R = Ac



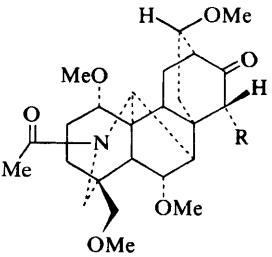
(63)



(64)

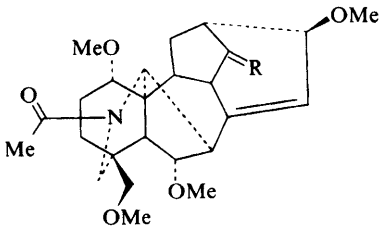


(65) $R^1 = R^2 = H$
(66) $R^1 = Me$, $R^2 = H$
(69) $R^1 = Me$, $R^2 = Br$

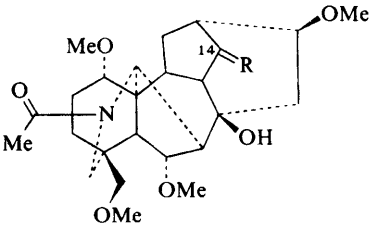


(67) R = H
(68) R = Br

Oxymercuration of (70) gave (71), which was then heated in 80% acetic acid to give 14-dehydro-α-oxochasmanine (72). Reduction of (72) with lithium aluminium hydride gave racemic chasmanine – identical with the natural material by t.l.c., i.r., n.m.r., and mass spectral analyses.



(70) R =



(71) R =

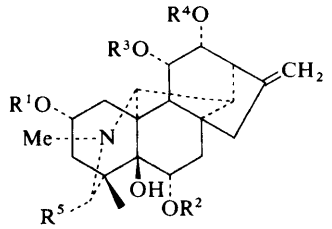
(72) R = O

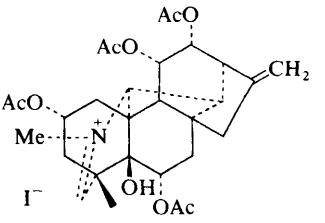
3 C_{20} Diterpenoid Alkaloids

Alkaloids of *Anopterus* Species (Escalloniaceae): Anopterimine, Anopterimine *N*-Oxide, Hydroxyanopterine, and Dihydroxyanopterine.—Some Australian workers[41,42] have studied the alkaloids of *Anopterus macleayanus* F. Muell. (Queensland) and *A. glandulosus* Labill. (Tasmania). Extracts of these plants have shown some preliminary anticancer activity.

The structures of anopterine (73) and its hydrolysis product, anopteryl alcohol (74), had previously been assigned on the basis of an *X*-ray crystallographic study of the azomethine iodide (75) formed on treatment of tetra-acetylanopteryl alcohol (76) with methyl iodide. The structure of the original alkaloid was derived from this azomethine by an n.m.r. study[43] (*cf.* Vol. 4, p. 325).

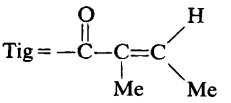
[41] N. K. Hart, S. R. Johns, J. A. Lamberton, H. Suares, and R. J. Willing, *Austral. J. Chem.*, 1976, **29**, 1295.
[42] N. K. Hart, S. R. Johns, J. A. Lamberton, H. Suares, and R. J. Willing, *Austral. J. Chem.*, 1976, **29**, 1319.
[43] W. A. Denne, S. R. Johns, J. A. Lamberton, A. Mc L. Mathieson, and H. Suares, *Tetrahedron Letters*, 1972, 2727.





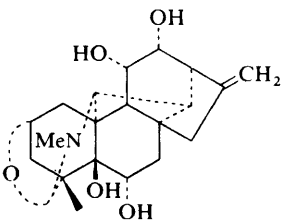
(75)

Anopterine (73) $R^1 = R^2 = R^5 = H$, $R^3 = R^4 =$ Tig
Anopteryl alcohol (74) $R^1 = R^2 = R^3 = R^4 = R^5 = H$
(76) $R^1 = R^2 = R^3 = R^4 =$ Ac, $R^5 = H$
(77) $R^1 = R^2 = R^3 = R^4 =$ Ac, $R^5 = OH$
(82) $R^1 = R^3 = R^4 =$ Ac, $R^2 = R^5 = H$
(83) $R^1 = R^5 = H$, $R^2 = R^3 = R^4 =$ Ac
(84) $R^1 = R^2 = R^5 = H$, $R^3 = R^4 =$ Ac

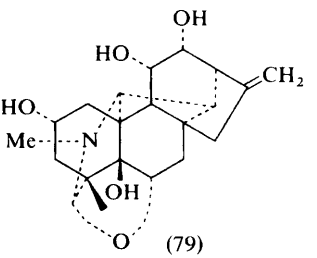


As might be expected from this novel skeleton, a full report of the chemical and spectral investigations has revealed some interesting results.[41] In order to verify that no skeletal rearrangement had occurred on formation of the azomethine iodide (75), its conversion into anopteryl alcohol was attempted. On treatment of (75) with aqueous ammonia or sodium bicarbonate, an epimeric mixture (5:1) having the presumed structure (77) was obtained. On alkaline hydrolysis, the major product was a carbinolamine ether, having either structure (78) or (79). However, reduction of (75) with cold sodium borohydride, followed by alkaline hydrolysis, did afford anopteryl alcohol in good yield.

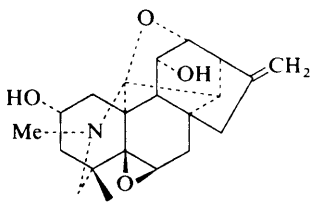
Oxidation of anopteryl alcohol (74) with potassium ferricyanide gave an 8% yield of a compound with either structure (78) or (79). The major product of this reaction (following purification by acetylation and then alkaline hydrolysis of the acetylated product) was determined to be (80) by an *X*-ray crystallographic analysis. Acetylation of (80) gave (81).



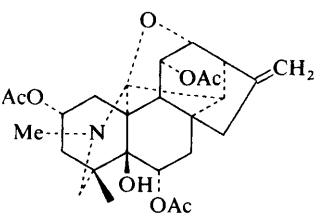
(78)



(79)



(80)

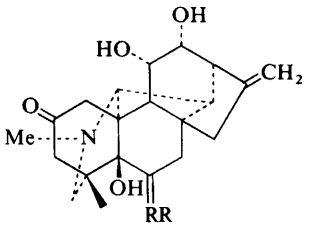


(81)

Acetylation of anopteryl alcohol with acetic anhydride–pyridine at 100 °C for four hours gave (76). Less drastic conditions produced a mixture of products, including (76), (82), (83), and (84). These assignments were based on ^{1}H n.m.r. data.

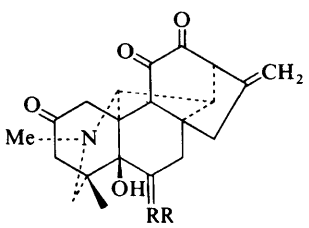
Oxidation of anopterine with chromic acid–pyridine followed by hydrolysis afforded (85). Oxidation of anopterine with Jones reagent, followed by hydrolysis, was shown to yield a monoketone, which was assigned probable structure (86). Reduction of (86) with sodium borohydride gave a 4:1 mixture, with anopteryl alcohol as the major product. Jones oxidation of anopteryl alcohol gave a mixture of (87) and (88). On oxidation of (85) (from anopterine) with Jones reagent, the tetraketone (89) was obtained.

On acetylation of (89), (87), and (88) with acetic anhydride–pyridine, *O*-acetyl-, *OO*-diacetyl-, and *OOO*-triacetyl-compounds, respectively, were obtained. In these derivatives, there was an acetoxy-group at a tertiary centre. However, n.m.r. spectral comparisons with the parent ketones indicated that a rearrangement or a major conformational change had occurred. On the basis of these studies, structure (90) was proposed for the diacetyl derivative from (87). The conformational argument presented was that if ring A assumed a boat form, the formation of an acetal at C-2 with an oxygen bridge between C-2 and C-5 could occur. Ring B could then assume a boat conformation, with the nitrogen-containing ring changing from a boat to a chair form to relieve ring strain. The supposition that no skeletal rearrangement was involved was supported by the formation of (87) on mild alkaline hydrolysis of (90).



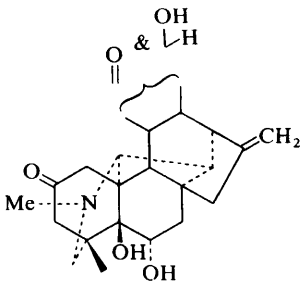
(85) RR = O

(86) RR = H, OH

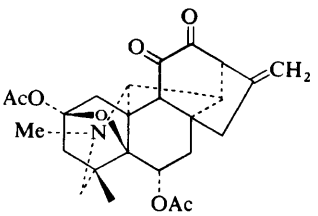


(87) RR = H, OH

(89) RR = O



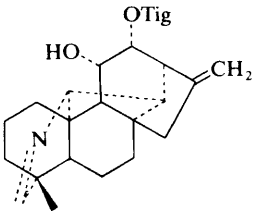
(88)

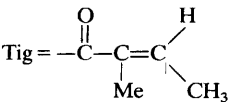


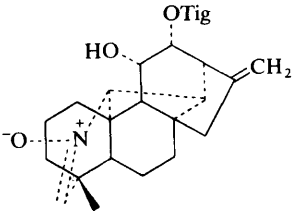
(90)

These studies were supported by detailed ^{1}H and ^{13}C n.m.r. data, ^{13}C n.m.r. shielding data for anopterine, anopteryl alcohol, (76), (83), (80), and (81) being presented in tabular form.

Anopterimine, $C_{25}H_{33}NO_3$, m.pt. 235—238 °C, and anopterimine *N*-oxide, $C_{25}H_{33}NO_4$, m.pt. 233—235 °C, were isolated as minor alkaloids from the leaves of *A. macleayanus*.[42] These bases were assigned structures (91) and (92), respectively, from the spectral data.



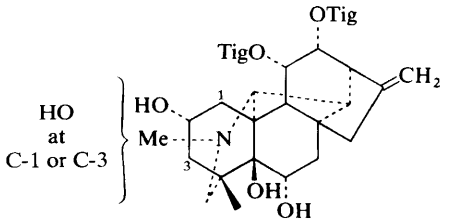


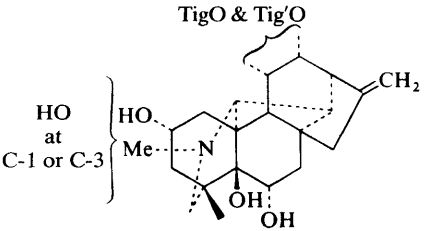


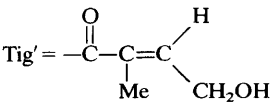
Anopterimine (91)

Anopterimine *N*-oxide (92)

Hydroxyanopterine, $C_{31}H_{43}NO_8$, m.pt. 247—249 °C, was isolated from the bark and leaves of *A. macleayanus* and *A. glandulosus*.[42] Dihydroxyanopterine, $C_{31}H_{43}NO_9$, m.pt. 242—244 °C, was isolated from the bark of *A. glandulosus* as a very minor component. From comparison of their spectral data (especially n.m.r.) with those of anopterine, the partial structural formulae (93) and (94) were proposed for hydroxyanopterine and dihydroxyanopterine, respectively.







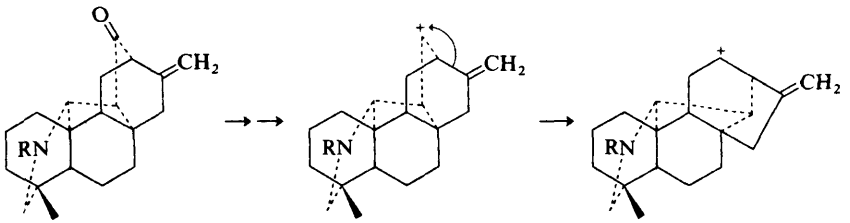
Hydroxyanopterine (93)

Dihydroxyanopterine (94)

A biosynthetic pathway to the unique C-20–C-14 bond in anopterine involving a hetisine-type precursor, as shown in Scheme 4, has been proposed.

Alkaloids of *Aconitum karakolicum*: 12-Acetylnapelline.—In further studies of the alkaloid fraction of the aerial parts of *Aconitum karakolicum*, Yunusov and co-workers[44] identified songorine (95), napelline (96), and a new base, $C_{24}H_{35}NO_4$,

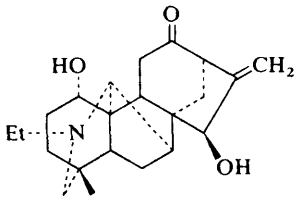
[44] M. N. Sultankhodzhaev, L. V. Beshitaishvili, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 681.



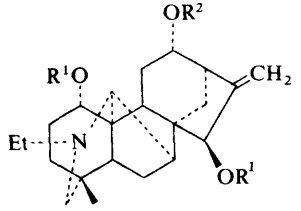
Scheme 4

m.pt. 205—206 °C. While napelline was the major alkaloid isolated from the above-ground parts of the plant, aconitine (97) was the main alkaloidal component of the roots.

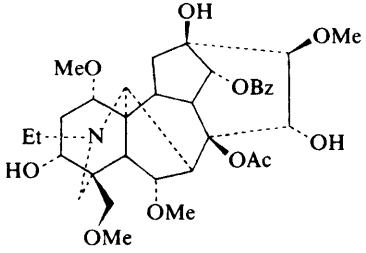
From the spectral data and the formation of a diacetate on treatment with acetic anhydride–pyridine, the partial formula $C_{16}H_{20}$(*N*-Et)(*C*-Me)(C=CH_2)(OAc)-$(OH)_2$ was assigned to the new alkaloid. On alkaline hydrolysis, a compound identical with napelline was obtained. The assignment of the acetoxy-group in the new alkaloid (98) was based on chemical and mass spectral data. Oxidation of (98) with silver oxide gave (99), a result which served as evidence for a free hydroxy-group at C-1. The choice between attachment at one of positions 12 and 15 was made on the basis of the mass spectral data of (98) and of its diacetate derivative (100). Previous mass spectral investigations had indicated that in compounds with an acetoxy-group attached to C-15, the $M-$Ac ion is a major fragment. In compound (98), $M-$Ac accounted for 6%; in the diacetate (100) it was 36%. By making this comparison, the acetoxy-group was assigned to position 12.



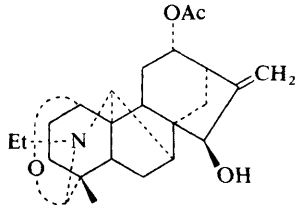
Songorine (95)



Napelline (96) $R^1 = R^2 = H$
12-Acetylnapelline (98) $R^1 = H$, $R^2 = Ac$
(100) $R^1 = R^2 = Ac$

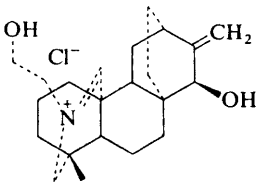


Aconitine (97)

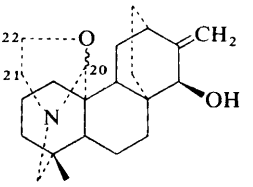


(99)

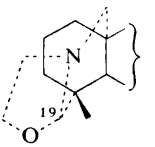
Conformational Studies on the E and F Rings of Atisine, Veatchine, and Related Alkaloids.—Recent ^{13}C n.m.r. studies have elucidated the chemistry of the oxazolidine ring system in atisine,[45,46] an amorphous base which is usually isolated as the salt, atisinium chloride (101). Atisine (102) undergoes facile isomerization to isoatisine (103) on heating in methanol or on treatment with methanolic base. To explain the ^1H n.m.r. spectra, it was assumed earlier that atisine exists as two different conformers, (104) and (105), in solution.[47] However, Pradhan and Girijavallabhan[48] later postulated that, to account for these and additional ^1H n.m.r. data, atisine in solution must exist as an equilibrium mixture of the C-20 epimers (106) and (107), which are interconvertible through a zwitterion (108). The ^{13}C n.m.r. spectra for atisine (102), isoatisine (103), atisinone (109), veatchine (110), and garryine (111) were determined and the resonances for all individual carbon



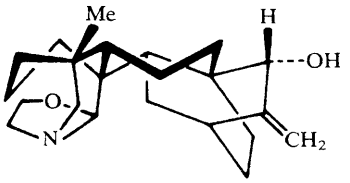
Atisinium chloride (101)



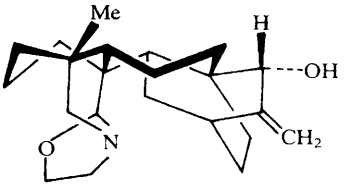
Atisine (102)



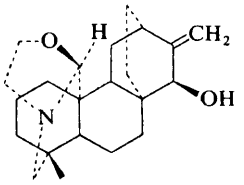
Isoatisine (103)



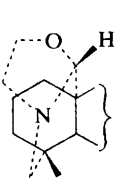
(104)



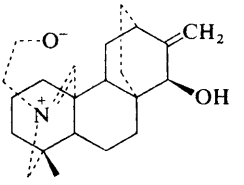
(105)



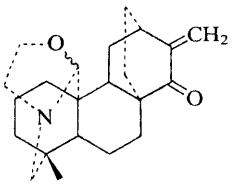
(106)



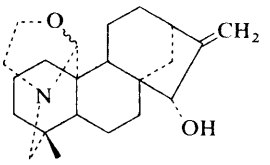
(107)



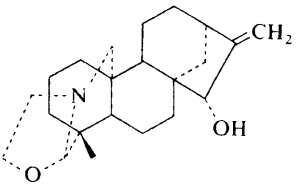
(108)



Atisinone (109)



Veatchine (110)

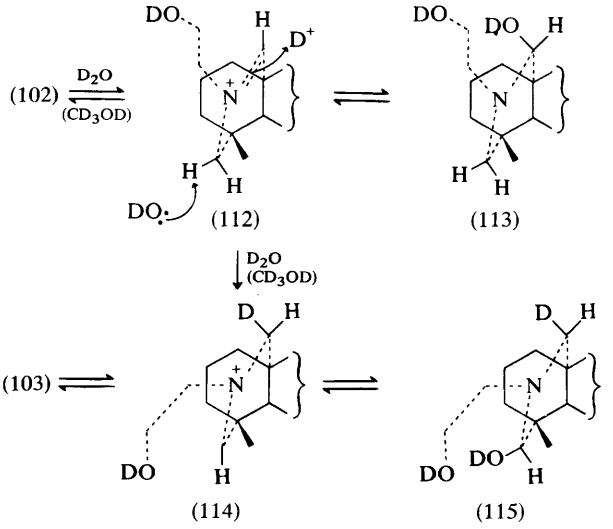


Garryine (111)

[45] S. W. Pelletier and N. V. Mody, *J. Amer. Chem. Soc.*, 1977, **99**, 284.
[46] S. W. Pelletier and N. V. Mody, *Tetrahedron Letters*, 1977, 1477.
[47] S. W. Pelletier and T. N. Oeltmann, *Tetrahedron*, 1968, **24**, 2019.
[48] S. K. Pradhan and V. M. Girijavallabhan, *J.C.S. Chem. Comm.*, 1970, 644.

atoms were assigned.[46] Two different sets of signals for the carbon atoms in rings E and F and for the 18-methyl group in atisine were observed. It was concluded that the difference in free energy between the conformers (104) and (105) would be small; therefore it is not likely that there should be two different sets of signals for these conformers. The existence of the C-20 epimers was also supported by a ^{13}C n.m.r. temperature-dependence study. The isomerization of atisine to isoatisine occurred at temperatures as low as 56 °C, but, even at higher temperatures, the sets of signals did not coalesce. Atisine could also be isomerized to isoatisine in 10% D_2O in [$^2H_6$]acetone. On comparison of the ^{13}C n.m.r. spectra taken in 10% D_2O–[$^2H_6$]acetone and 10% H_2O–[$^2H_6$]acetone, no differences were found. In CD_3OD, the ^{13}C chemical shifts of carbons-20, -21, and -22 were moved upfield, supporting the existence of species such as (112), (113), (114), and (115). Following the replacement of the CD_3OD solvent with $CDCl_3$, the ^{13}C n.m.r. spectrum showed that, although some isoatisine was present, there was no deuterium exchange at C-20 in atisine or at C-19 in isoatisine. These results were confirmed by the ^1H n.m.r. spectrum.

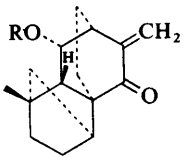
In another study[45] of the temperature dependence of the ^{13}C n.m.r. spectrum of atisine in deuteriated toluene, the progressive formation of isoatisine was noted from 56 to 90 °C. The two sets of signals from the atisine epimers did not coalesce, and the ratio of signals from these epimers remained constant. The Indian workers' interpretation[48] of the broadening of the signal of the C-20 proton as indicating equilibration between the C-20 epimers in 10% D_2O in [$^2H_6$]acetone or in CD_3OD is incorrect, because there is actually isomerization of atisine to isoatisine and the formation of species (112)–(115). The conclusion by Pradhan and Girijavallabhan[48] that these epimers are interconvertible *via* a zwitterion is thus in error.



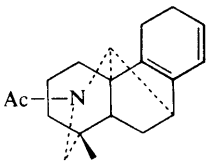
The ^{13}C n.m.r. spectra of atisinone (104) and veatchine (105) also showed two sets of signals for the carbons of rings E and F, indicating that these compounds also exist as C-20 epimers. Because atisine and veatchine are isolated as the ternary

iminium salts, which on treatment with base regenerate the respective alkaloids, it is not known which C-20 epimer of each alkaloid exists naturally in the plant.

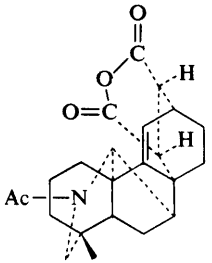
Syntheses Directed Toward C_{20} Diterpenoid Alkaloid Systems.—A denudatine model (116) has been prepared by the New Brunswick group,[49] based on their previous demonstration that maleic anhydride adds stereospecifically to the diene (117) to give (118)[50] (*cf.* Vol. 5, p. 238). Alkylation of the model compound (119)



(116) R = H
(116a) R = *p*-Bromobenzoyl

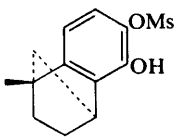


(117)

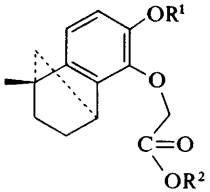


(118)

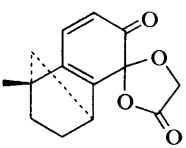
with bromomethyl acetate and potassium carbonate in acetone gave (120). This compound was hydrolysed to the acid (121). The reaction of (121) in dichloromethane with aqueous sodium acetate–*N*-bromosuccinimide afforded the masked quinone (122). Treatment of (122) with ethyl vinyl sulphide gave (123),



(119)

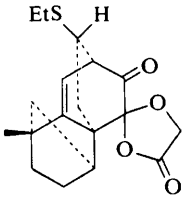


(120) R^1 = Ms, R^2 = Me
(121) $R^1 = R^2$ = H

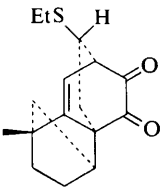


(122)

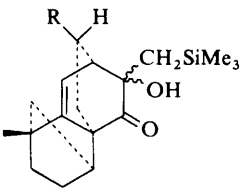
which was then hydrolysed to the diketone (124) with aqueous methanolic potassium carbonate. The reaction of (124) with trimethylsilylmethylmagnesium chloride in THF afforded (125). Desulphurization of (125) with Raney nickel to



(123)



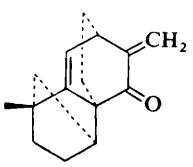
(124)



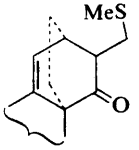
(125) R = SEt
(126) R = H

[49] K. Wiesner, T. Y. R. Tsai, G. I. Dmitrienko, and K. P. Nambiar, *Canad. J. Chem.*, 1976, **54**, 3307.
[50] K. Wiesner, P.-T. Ho, and S. Oida, *Canad. J. Chem.*, 1974, **52**, 1042.

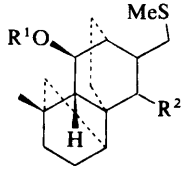
(126), followed by oxidation with perchloric acid, gave (127). Treatment of (127) with methanethiol furnished (128). Hydroboration followed by oxidation with hydrogen peroxide gave an epimeric product (129). This was converted into (130) by sequential acetylation, partial hydrolysis, and oxidation with dicyclohexylcarbodi-imide and DMSO. Saponification of (130) gave (131). On treatment of (131) with methyl iodide under reflux, followed by aqueous potassium carbonate, the hydroxy-ketone (116) was obtained. An *X*-ray crystallographic structure determination of the *p*-bromobenzoyl derivative (116a) confirmed this structure and configuration. This method has considerable potential as a simpler route to polysubstituted denudatine-type (132) alkaloids, as well as, *via* rearrangement, alkaloids of the delphinine type (*cf.* 'Total Synthesis of Chasmanine', p. 229).



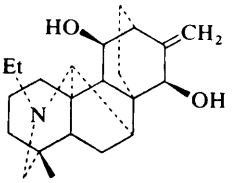
(127)



(128)

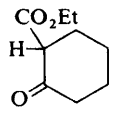


(129) $R^1 = H, R^2 =$ ~OH
(130) $R^1 = Ac, R^2 = O$
(131) $R^1 = H, R^2 = O$

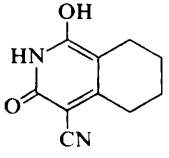


Denudatine (132)

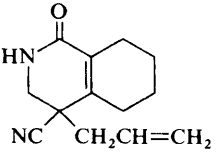
A new approach to the ABE ring system of the pentacyclic C_{20} diterpenoid alkaloids has been reported by van der Baan and Bickelhaupt.[51] For the model system of major interest, (134) was prepared from (133) by reaction with cyanoacetamide. Treatment of (134) with allyl bromide gave almost exclusively *C*-alkylation, to afford (135). On heating (135) at 100—110 °C, a Cope-type rearrangement to (136) was effected. This compound was then *N*-alkylated with ethyl iodide–DMF, the product being (137). Treatment of (137) with *N*-bromosucc-



(133)



(134)



(135)

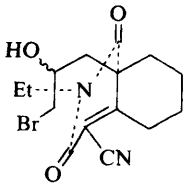
(136) R = H
(137) R = Et

inimide in water–DMSO gave (138) in 51% yield. Protection of the hydroxy-group in (138) as the tetrahydropyranyl ether, followed by treatment with sodium hydride in DMF, afforded (139). Removal of the protecting group, followed by Jones oxidation, gave (140).

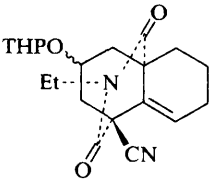
Ghatak and co-workers[52] have reported an interesting approach to the preparation of key intermediates in the syntheses of C_{20} diterpenoid alkaloids and C_{20}

[51] J. L. van der Baan and F. Bickelhaupt, *Recueil, J. Royal Netherlands Chem. Soc.*, 1975, **94**, No. 5, p. 109.

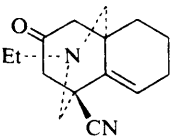
[52] U. R. Ghatak, B. Sanyal, and S. Ghosh, *J. Amer. Chem. Soc.*, 1976, **98**, 3721.



(138)

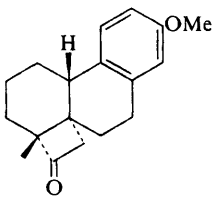


(139)

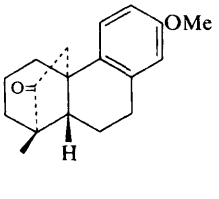


(140)

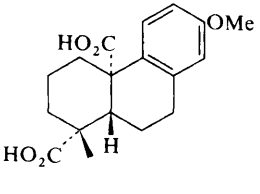
gibberellins. On treatment of the cyclobutanone (141)[53] with excess triethyloxonium fluoroborate in methylene chloride, the bridged ketone (142) was obtained in yields of 90—95%. The intramolecular course of this reaction was demonstrated by deuterium-labelling studies. This ketone has been converted into the diacid (143) through the corresponding hydroxy-methylene derivative, followed by oxidation with alkaline hydrogen peroxide.[53]



(141)

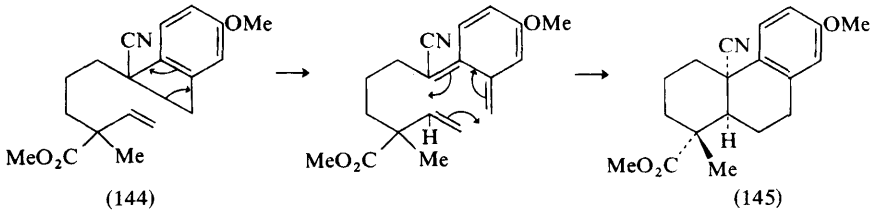


(142)



(143)

Kametani *et al.*[54] have published a full account of their synthesis of (149) (*cf.* Vol. 7, p. 263). The key step in this synthesis was the thermolytic intramolecular cycloaddition of (144), to produce (145) (Scheme 5). In order to obtain the

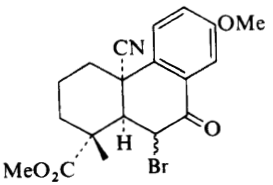


(144) (145)

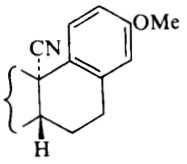
Scheme 5

trans-fused system (147), the *cis*-fused octalin (145) was oxidized with chromium trioxide in acetic acid, and the resulting ketone treated with bromine to yield (146). Dehydrobromination to the $\alpha\beta$-unsaturated ketone followed by catalytic hydrogenation with 10% Pd on carbon gave (147). Reduction of (147) with Raney nickel in ethanol under hydrogen at 110 atm produced (148). Treatment of (148) with lithium aluminium hydride in boiling dioxan gave (149).

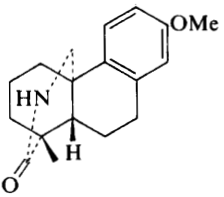
[53] U. R. Ghatak and S. Chakrabarty, *J. Org. Chem.*, 1976, **41**, 1089.
[54] T. Kametani, Y. Kato, T. Honda, and K. Fukumoto, *J. Amer. Chem. Soc.*, 1976, **98**, 8185.



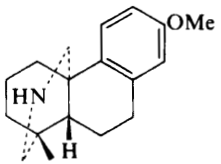
(146)



(147)



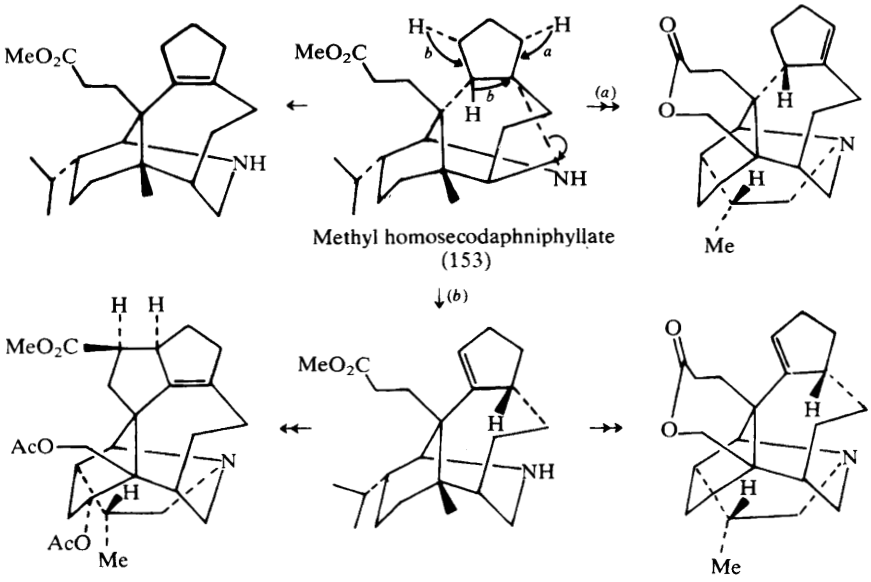
(148)



(149)

4 *Daphniphyllum* Alkaloids

The Alkaloids of *Daphniphyllum humile*: Deoxy-yuzurimine and Isodaphnilactone-B.–Yamamura and Terada[55] have isolated two new alkaloids from the leaves of *D. humile* M. Deoxy-yuzurimine (150), $C_{27}H_{37}NO_6$, m.pt. 132 °C, was found to be identical with the previously reported product[56] of the reduction of yuzurimine



Deoxy-yuzurimine (150)

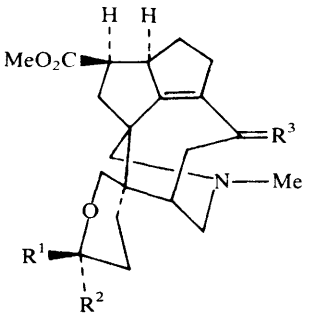
Daphnilactone-B (152)

Scheme 6

[55] S. Yamamura and Y. Terada, *Chem. Letters*, 1976, 1381.
[56] H. Irikawa, S. Yamamura, and Y. Hirata, *Tetrahedron*, 1972, **28**, 3727.

with zinc. Isodaphnilactone-B, $C_{22}H_{31}NO_2$, a colourless liquid, formed a monomethiodide derivative, m.pt. 196—198 °C. The spectral data for this alkaloid are similar to those for daphnilactone-B. On the basis of the ^1H n.m.r. data, the structure of isodaphnilactone-B was indicated to be (151), a double-bond isomer of daphnilactone-B (152). A biogenetic route for the formation of these nitrogenous bases from methyl homosecodaphniphyllate (153) has been suggested (Scheme 6).

Alkaloids of *Daphniphyllum macropodum* and *D. gracile*.—A further report on the structures of yuzurine (154)[57] (*cf.* Vol. 6, p. 268), daphnigracine (155), daphnigraciline (156), oxodaphnigracine (157), oxodaphnigraciline (158), and epioxodaphnigraciline (159)[58] (*cf.* Vol. 7, p. 265) has appeared.[59] Yuzurine was isolated

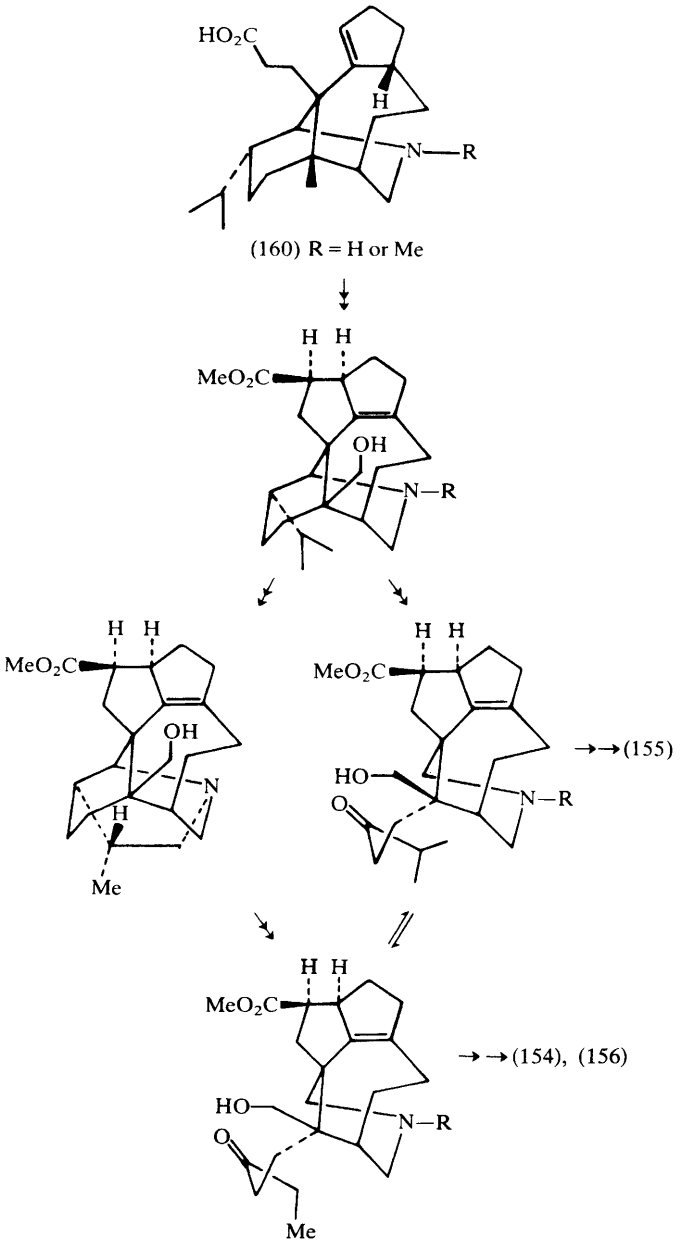


Yuzurine (154) $R^1 = OMe$, $R^2 = Et$, $R^3 = H_2$
Daphnigracine (155) $R^1 = OH$, $R^2 = Pr^i$, $R^3 = H_2$
Daphnigraciline (156) $R^1 = OH$, $R^2 = Et$, $R^3 = H_2$
Oxodaphnigracine (157) $R^1 = OH$, $R^2 = Pr^i$, $R^3 = O$
Oxodaphnigraciline (158) $R^1 = OH$, $R^2 = Et$, $R^3 = O$
Epioxodaphnigraciline (159) $R^1 = Et$, $R^2 = OH$, $R^3 = O$

from the bark and leaves of *D. macropodum* Miquel (Japan), while the other alkaloids were obtained from *D. gracile* Gage (New Guinea). Biogenetic pathways to these alkaloids from the intermediate (160) have been proposed (Scheme 7).

Acknowledgment: The authors wish to express appreciation to Dr. Naresh V. Mody for reviewing the manuscript and making several helpful suggestions.

[57] S. Yamamura, J. A. Lamberton, H. Irikawa, Y. Okumura, M. Toda, and Y. Hirata, *Bull. Chem. Soc. Japan*, 1977, **50**, 1836.
[58] S. Yamamura, K. Sasaki, M. Toda, and Y. Hirata, *Tetrahedron Letters*, 1974, 2023.
[59] S. Yamamura, J. A. Lamberton, H. Irikawa, Y. Okumura, and Y. Hirata, *Chem. Letters*, 1975, 923.


HO2C
H
N—R
(160) R = H or Me
H H
MeO2C
OH
N—R
MeO2C
OH
N
H
Me
MeO2C
HO
O
N—R
→→(155)
MeO2C
HO
O
N—R
Me
→→(154), (156)

Scheme 7

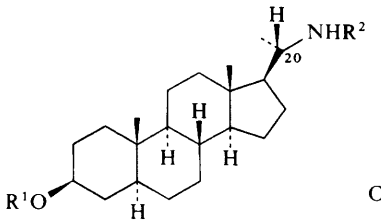
14

Steroidal Alkaloids

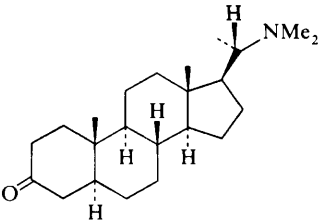
BY D. M. HARRISON

1 Alkaloids of the Apocynaceae

A new alkaloid, holacetine (1a), has been isolated in 0.04% yield from the root bark of *Holarrhena antidysenterica*, together with the known component conessine.[1] Acetylation of holacetine gave an *O*-acetyl derivative (1b), vigorous acid-catalysed hydrolysis of which yielded the (20*S*)-20-amino-pregnane (1c). The identity of the latter, and hence of holacetine, was established by its conversion *via* standard methods into the known alkaloid funtumafrine C (2), and by its preparation from (20*S*)-3β-hydroxypregn-5-ene-20-carboxylic acid.[1] Conessine has been identified in tissue cultures of *H. antidysenterica*.[2]

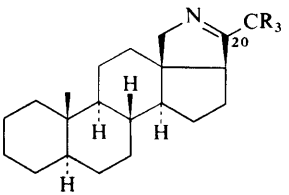


(1a) $R^1 = H$; $R^2 = Ac$
(1b) $R^1 = R^2 = Ac$
(1c) $R^1 = R^2 = H$



(2)

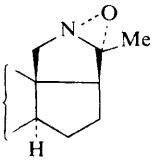
Bromination of *N*-demethyl-20(*N*)-conenine (3a) in the presence of sodium carbonate gave the tribromo-derivative (3b).[3] The reaction of (3a) with chlorinating agents under a variety of conditions gave the trichloro-derivative (3c) together with



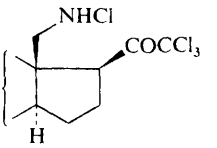
(3a) R = H
(3b) R = Br
(3c) R = Cl

[1] R. N. Rej, P. Ghosh, and J. Banerji, *Phytochemistry*, 1976, **15**, 1173.
[2] M. R. Heble, S. Narayanaswamy, and M. S. Chadha, *Phytochemistry*, 1976, **15**, 681.

mono- and di-chloro-derivatives; the oxaziran (4) was also formed. Treatment of the trichloro-derivative (3c) with chlorine and sodium carbonate yielded the *N*-chloro-amine (5), which reverted to the starting trichloro-compound on treatment with acetone.[3]



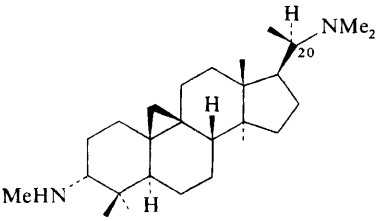
(4)



(5)

2 *Buxus* Alkaloids

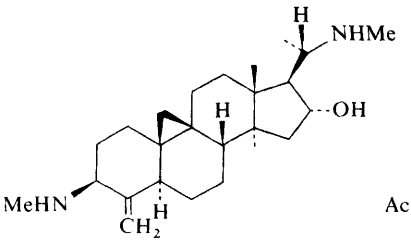
An alkaloid originally isolated from *Buxus sempervirens*, and designated *l*-cycloprotobuxine C,[4] has been assigned the unusual (20*R*) structure (6),[5] following mass



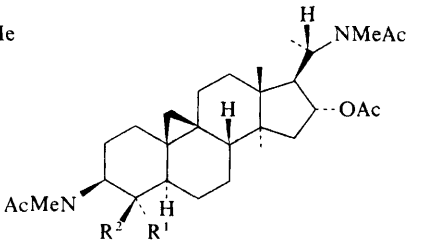
(6)

spectroscopic and n.m.r. comparison with cycloprotobuxine C. The 3-methylamino substituent was assigned the α-configuration since 3-*N*-acyl derivatives of *l*-cycloprotobuxine C were hydrolysed less rapidly than model compounds containing a 3β-*N*-acyl substituent.[5]

Catalytic hydrogenation of cyclobuxine D (7), followed by acetylation of the dihydro-product, gave the 4β-methyl-steroid (8a), while acetylation of (7) prior to hydrogenation yielded the 4α-methyl-derivative (8b). The epimeric steroids (8a)



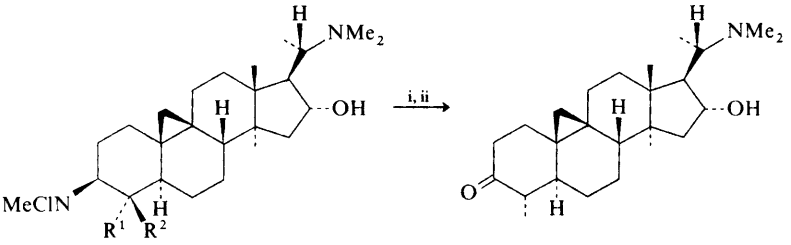
(7)



(8a) $R^1 = H$, $R^2 = Me$
(8b) $R^1 = Me$, $R^2 = H$

[3] A. Picot, M. Dendane, and X. Lusinchi, *Tetrahedron*, 1976, **32**, 2899.
[4] B. U. Khodzhaev, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 266 (*Chem. Abs.*, 1975, **83**, 128 654).
[5] B. U. Khodzhaev, R. Shakirov, and S. Yu. Yunusov *Khim. prirod. Soedinenii*, 1976, 554 (*Chem. Abs.*, 1977, **86**, 121 587).

and (8b) were converted into *N*-chloro-derivatives (9a) and (9b) respectively, each of which yielded the same 4α-methyl ketone (10) on Ruschig degradation (Scheme 1).[6] This demonstration that epimerization of a 4β-methyl substituent may occur during Ruschig degradation provides indirect confirmation for the currently accepted[7] formulation of cyclobuxamine as having a 4α-methyl group.[6]



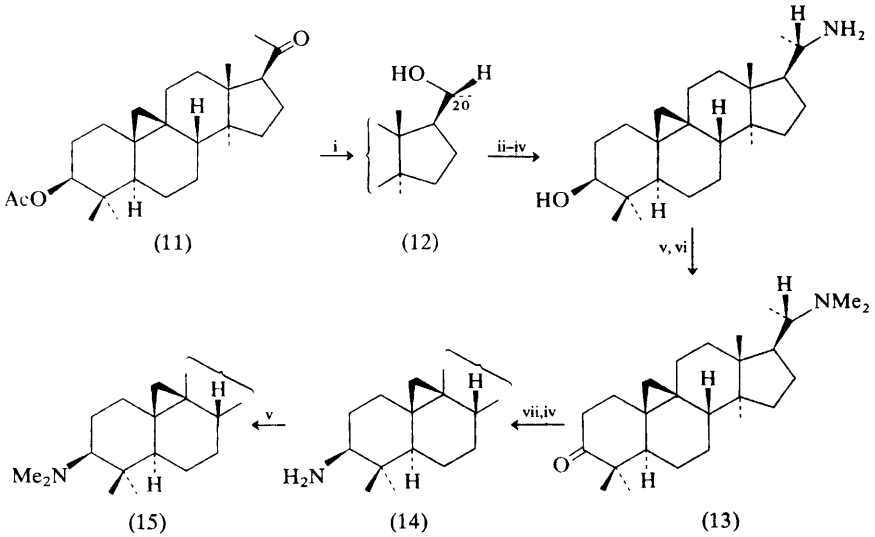
(9a) $R^1 = H$, $R^2 = Me$
(9b) $R^1 = Me$, $R^2 = H$

(10)

Reagents: i, Na–MeOH; ii, H^+

Scheme 1

Syntheses of buxandonine (13), cycloprotobuxine F (14), and cycloprotobuxine A (15) from the acetoxy-ketone (11) have been achieved by the route summarized in Scheme 2.[8] The major product (12) of the reduction of (11) with sodium



(11) (12) (15) (14) (13)

Reagents: i, $NaBH_4$; ii, TsCl; iii, N_3^-; iv, $LiAlH_4$; v, H_2CO–HCO_2H; vi, CrO_3; vii, NH_2OH

Scheme 2

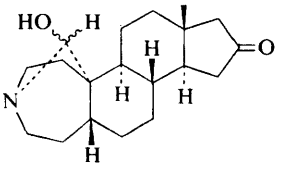
[6] Z. Votický and V. Paulík, *Coll. Czech. Chem. Comm.*, 1977, **42**, 541.
[7] T. Nakano and Z. Votický, *J. Chem. Soc.* (*C*), 1970, 590; *cf.* discussion by J. Tomko and Z. Votický in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1973, Vol. 14, p. 76.
[8] C. Singh and S. Dev, *Tetrahedron*, 1977, **33**, 1053.

borohydride was assigned the 20*R* configuration by analogy with the reduction of 20-oxopregnane derivatives. The acetoxy-ketone (11) was prepared by degradation of the triterpene cycloartenol, which was earlier the subject of a formal total synthesis. Hence the present work represents, in a formal sense, the total synthesis of alkaloids (13), (14), and (15).[8]

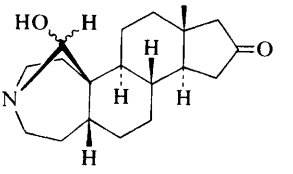
The intramolecular hydrogen exchange that occurs during fragmentation of 3-dimethylamino-steroids in the mass spectrometer has been studied.[9] The chemistry of those *Buxus* alkaloids which are based on the 19-nor-B-homopregna-9a(10),9(11)-diene nucleus has been reviewed.[10]

3 *Salamandra* Alkaloids

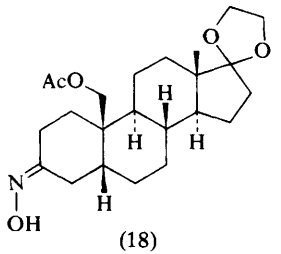
Cycloneosamandione was originally assigned structure (16), which contains an unusual A/B ring junction. Subsequently, the unexceptional structure (17) was favoured.[11] The latter formulation has now received further confirmation from the total synthesis of cycloneosamandione.[12] Beckmann rearrangement of the oxime (18) led to the ε-lactam (19), from which cycloneosamandione (17) was prepared in four steps. The structural revision mentioned above necessitated similar revision of the structure of cycloneosamandaridine. Accordingly, the carbinolamine (20) also was synthesized from the ε-lactam (19), but (surprisingly) it was not identical with cycloneosamandaridine. The structure of the latter therefore remains in doubt.[12]



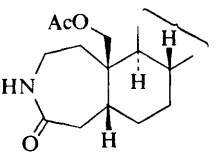
(16)



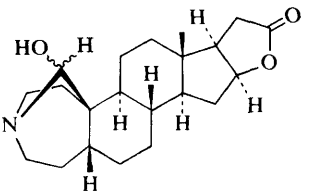
(17)



(18)



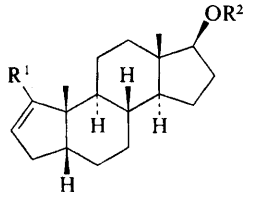
(19)



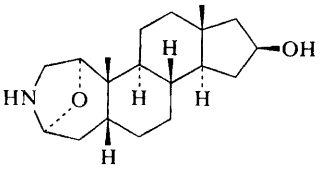
(20)

An intermediate (21a) that might be useful in the synthesis of samandarine (22) has been prepared from the A-norandrostane derivative (21b).[13] Full details

[9] P. Longevialle and C. Marazano, *Org. Mass Spectrometry*, 1976, **11**, 964.
[10] W. Turowska-Jones and U. Wrzeciono, *Wiad. Chem.*, 1976, **30**, 107 (*Chem. Abs.*, 1976, **85**, 21 695).
[11] G. Habermehl and A. Haaf, *Z. Naturforsch.*, 1968, **23b**, 1551.
[12] K. Oka and S. Hara, *J. Amer. Chem. Soc.*, 1977, **99**, 3859.
[13] K. Oka and S. Hara, *Tokyo Yakka Daigaku Kenkyu Nempo (Japan)*, 1975, **25**, 530 (*Chem. Abs.*, 1977, **86**, 121 606).



(21a) $R^1 = CH_2NHAc$, $R^2 = Ac$
(21b) $R^1 = CHO$, $R^2 = H$

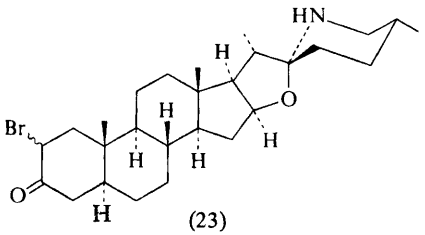


(22)

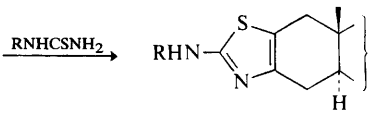
of the previously reported synthesis of samandaridine from 17β-hydroxy-2-hydroxymethylene-5β-androstan-3-one are now available.[14]

4 *Solanum* Alkaloids

The preparation of the amino-thiazole (24a) by the condensation of 2-bromosolasodan-3-one (23) with thiourea has been described.[15] A number of related derivatives (24b) were similarly prepared in a search for new physiologically active



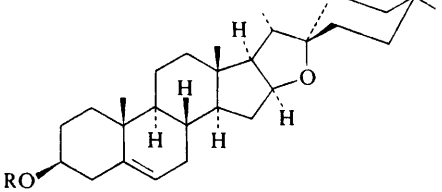
(23)



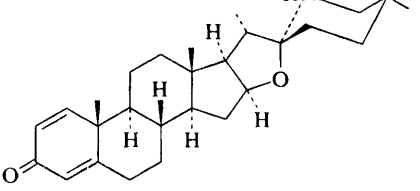
(24a) R = H
(24b) R = N=CR^{1}R^2

steroids.[15] Solasodine (25a) and its 5,6-dihydro-derivative soladulcidine underwent microbiological oxidation to yield solasoda-1,4-dien-3-one (26).[16]

Solasodine and related compounds may serve as useful starting materials for the commercial preparation of steroid hormones,[17] and the search for suitable



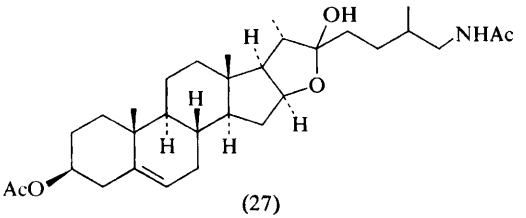
(25a) R = H
(25b) R = Ac



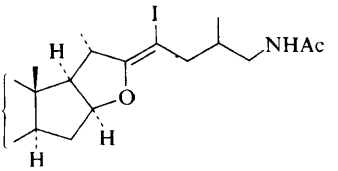
(26)

[14] (*a*) Y. Shimizu, *J. Org. Chem.*, 1976, **41**, 1930; (*b*) F. Khuong-Huu and R. Goutarel, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4, p. 366.
[15] M. P. Irismetov, V. V. Kurilskaya, and M. I. Goryaev, *Izvest. Akad. Nauk. Kazakh. S.S.R., Ser. khim.*, 1976, **26**, No. 4, p. 41 (*Chem. Abs.*, 1977, **86**, 16 840).
[16] I. Belic, V. Gaberc-Porekar, and H. Socic, *Vestnik. Slov. Kem. Drus.*, 1975, **22**, 49 (*Chem. Abs.*, 1977, **86**, 68 109).
[17] D. M. Harrison, in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6, p. 285.

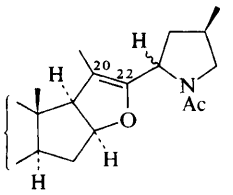
degradative pathways continues. Iodination of the cyclic hemiketal (27) derived from solasodine gave the vinyl iodide (28). Acetolysis of the latter gave the diastereoisomeric mixture (29) of *N*-acetyl-pyrrolidines.[18] The same diastereoisomeric mixture was formed on direct iodination of diacetyl-pseudosolasodine A[19] and on acetolysis of the allylic alcohol (30), which is a product of the autoxidation of diacetyl-pseudosolasodine A.[20] Oxidation of the $\Delta^{20(22)}$ bond of (29) with chromic acid, followed by hydrolysis of the keto-ester that was produced, gave the pregnane derivative (31).[19] Other transformations of solasodine derivatives have been the subjects of recent patents.[21]



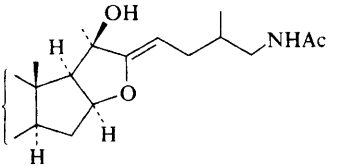
(27)



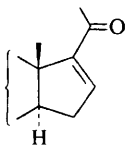
(28)



(29)



(30)



(31)

Tomatillidine[22] was originally assigned the structure (32), while the so-called 24-oxosolacongestidine[23] was thought to be the C-25 epimer of 5,6-dihydro-

[18] G. G. Malanina, L. I. Klimova, L. M. Morozovskaya, and G. S. Grinenko, *Khim. Farm. Zhur.*, 1976, **10**, No. 6, p. 92 (*Chem. Abs.*, 1977, **86**, 43 895).

[19] G. G. Malanina, L. I. Klimova, L. M. Morozovskaya, O. S. Anisimova, K. F. Turchin, T. Ya. Filipenko, and G. S. Grinenko, *Khim. Farm. Zhur.*, 1976, **10**, No. 4, p. 90 (*Chem. Abs.*, 1976, **85**, 78 260).

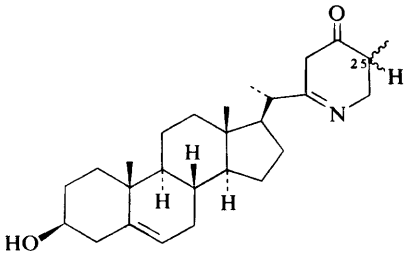
[20] G. G. Malanina, L. I. Klimova, L. M. Morozovskaya, and G. S. Grinenko, *Khim. Farm. Zhur.*, 1976, **10**, No. 8, p. 98 (*Chem. Abs.*, 1977, **86**, 111 114).

[21] L. M. Morozovskaya, L. I. Klimova, G. G. Malanina, N. N. Suvorov, I. A. Andreeva, V. N. Milovanov, L. K. Fedotova, and T. P. Radina, U.S.S.R.P. 507 583 (*Chem. Abs.*, 1976, **85**, 21 726); E. S. Belen'kaya, L. M. Morozovskaya, L. I. Klimova, and G. S. Grinenko, U.S.S.R.P. 514 848 (*Chem. Abs.*, 1976, **85**, 78 271).

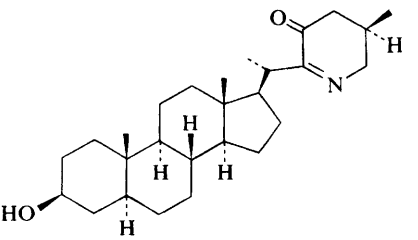
[22] E. Bianchi, C. Djerassi, H. Budzikiewicz, and Y. Sato, *J. Org. Chem.*, 1965, **30**, 754.

[23] (*a*) Y. Sato, Y. Sato, H. Kaneko, E. Bianchi, and H. Kataoka, *J. Org. Chem.*, 1969, **34**, 1577; (*b*) R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3, p. 280.

tomatillidine. These assignments have been rendered untenable by the observation that 23-oxosolacongestidine (33) undergoes isomerization to dihydrotomatillidine

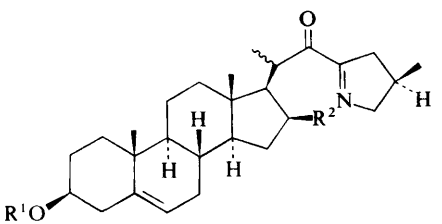


(32)

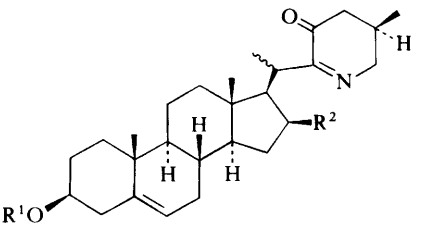


(33)

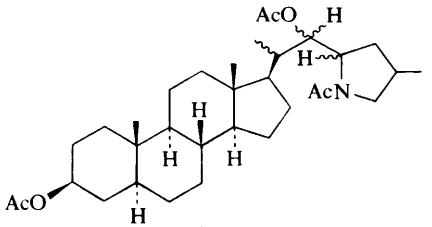
and '24-oxosolacongestidine' during t.l.c. on silica gel.[24] Tomatillidine has been assigned[24] the revised structure (34a) on the basis of the following observations: (i) conjugated ketone (35a) underwent ring contraction during chromatography on silica gel to give the isomeric ketone (34b) in 60% yield; (ii) reduction of 5,6-dihydrotomatillidine with sodium borohydride and acetylation of the product yielded three isomeric triacetyl derivatives, each of which was shown by n.m.r. double-irradiation experiments to possess the gross structure (36) rather than the piperidine structure (37) that was expected on the basis of the original formulation



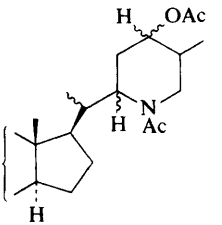
(34a) $R^1 = R^2 = H$
(34b) $R^1 = Ac$, $R^2 = OAc$



(35a) $R^1 = Ac$, $R^2 = OAc$
(35b) $R^1 = R^2 = H$



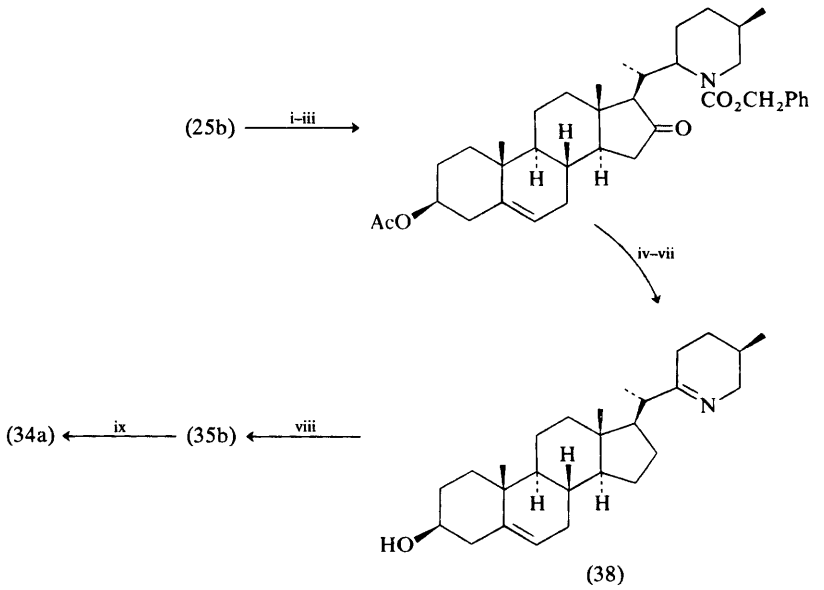
(36)



(37)

of tomatillidine; (iii) the synthesis of tomatillidine from solasodine was achieved by the route shown in Scheme 3, the last step of which involves the indicated ring contraction, which is catalysed by silica gel; (iv) the spectroscopic data reported[22] for tomatillidine and its derivatives are consistent with the revised structure (34a).[24]

[24] G. Kusano, T. Takemoto, Y. Sato, and D. F. Johnson, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 661 (*Chem. Abs.*, 1976, **85**, 46 936).



Reagents: i, $NaBH_4$; ii, $PhCH_2OCOCl$; iii, Killiani oxidation; iv, $(CH_2SH)_2$; v, Raney Ni; vi, *N*-chlorosuccinimide; vii, NaOMe; viii, MnO_2; ix, silica gel

Scheme 3

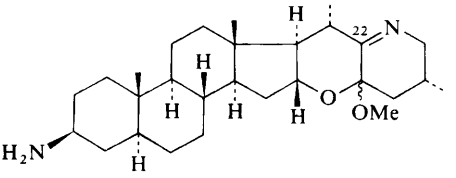
The structure (32) originally proposed for tomatillidine was deduced, in part, after considering the products obtained by the Wolff–Kishner reduction of the alkaloid, these including 22,26-epiminocholesta-5,22(N)-dien-3β-ol (38).[22] It was suggested[24] that the formation of this degradation product is consistent also with the new formulation (34a) of tomatillidine, since expansion of the pyrrolidine ring may conceivably occur during Wolff–Kishner reduction of the alkaloid. Further clarification of this point and of the relationship between tomatillidine and '24-oxosolacongestidine' would be desirable.

A number of new *Solanum* alkaloids containing the rare 3β-amino-group have been isolated.[25–28] The antimicrobial alkaloid solacasine ($C_{28}H_{46}N_2O_2$) was isolated in 0.006% yield from flowering tops of *Solanum pseudocapsicum*.[25] The mass spectrum of this compound displayed significant peaks at *m/e* 56 and 82, characteristic of a 3β-aminocholestane derivative, while a peak at *m/e* 410 (M^+-32) suggested the presence of a methoxy-group. The i.r. spectrum (ν_{max} 1660 cm^{-1}) of solacasine and the formation of a dihydro-derivative on treatment with sodium borohydride suggested that the alkaloid contained a C=N linkage. Further evidence concerning the nature of the two nitrogen functions was revealed by the

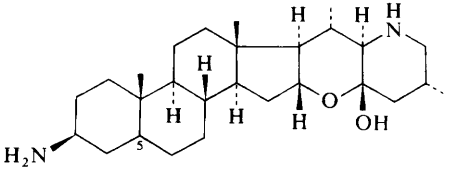
[25] L. A. Mitscher, J. V. Juvarkar, and J. L. Beal, *Experientia*, 1976, **32**, 415. The structures displayed in this paper contain a number of errors.
[26] E. Ali, A. K. Chakravarty, S. C. Pakrashi, K. Biemann, and C. E. Hignite, *Tetrahedron*, 1977, **33**, 1371.
[27] S. C. Pakrashi, A. K. Chakravarty, and E. Ali, *Tetrahedron Letters*, 1977, 645, 814.
[28] G. J. Bird, D. J. Collins, F. W. Eastwood, B. M. K. C. Gatehouse, A. J. Jozsa, and J. M. Swan, *Tetrahedron Letters*, 1976, 3653.

formation of a tri-*N*-methyldihydro-derivative on treatment of the natural product with formaldehyde in the presence of sodium borohydride. Structure (39) was assigned to solacasine by analogy with the earlier established structure of solanocapsine[29] (40a), and was confirmed by the preparation of 22,*N*-dihydrosolacasine by acid-catalysed methanolysis of solanocapsine.[25]

A related 3β-amino-alkaloid, solanoforthine ($C_{27}H_{44}H_2O_2$), was isolated in the free state from *S. seaforthianum* together with solanocapsine (40a) and artefacts consisting of the condensation products of solanocapsine with acetone, and of solanoforthine with acetone or acetaldehyde.[26] The structure of solanoforthine (40b) was established by spectroscopic and degradative evidence paralleling that

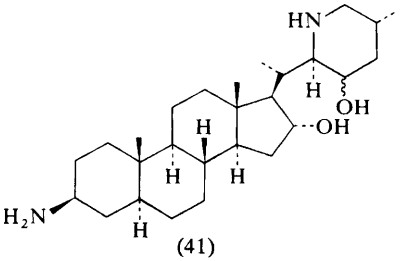


(39)



(40a) 5α-H
(40b) Δ^5

for solanocapsine, and was confirmed by the formation of the latter on catalytic hydrogenation of solanoforthine. The mass spectrum of pure solanocapsine isolated from *S. seaforthianum* displayed no significant peak at *m/e* 114,[26] in contrast to that reported for solanocapsine isolated from *S. pseudopersicum*.[29] This discrepancy was resolved by the demonstration that solanocapsine from the latter species was accompanied by a difficultly removable mixture of diols of gross structure (41) which displayed a strong fragment ion of *m/e* 114 in its mass spectrum.[26]

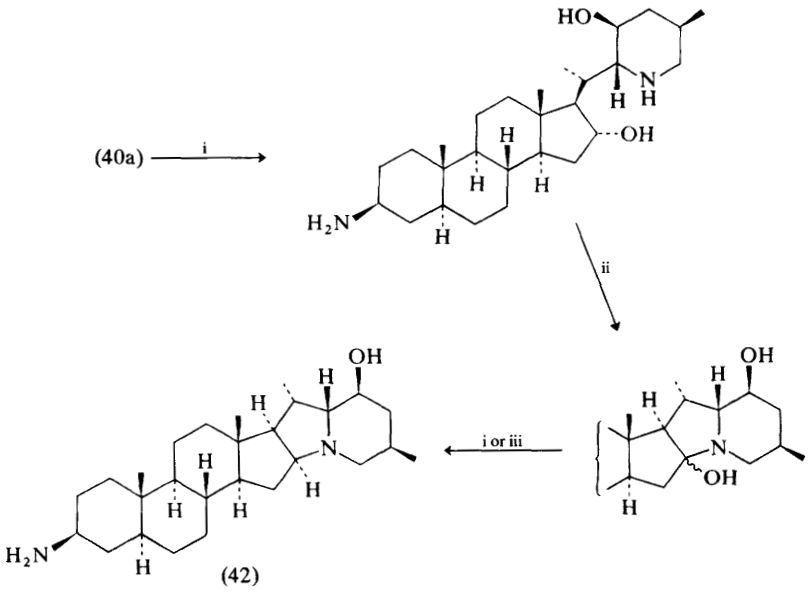


(41)

The first naturally occurring 3β-amino-solanidane alkaloid, solanogantine ($C_{27}H_{46}N_2O$), has been isolated from *S. giganteum*.[27] This non-crystalline base was

[29] H. Budzikiewicz, *Tetrahedron*, 1964, **20**, 2267; for recent references see R. B. Herbert in ref. 23*b*.

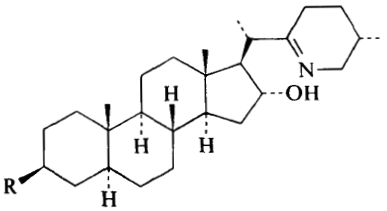
characterized as its *NN*-dimethyl and *NO*-diacetyl derivatives. Solanogantine was shown to possess the 3β-amino-23β-hydroxy-22βH-solanidane structure (42) by spectroscopic studies and by its partial synthesis from solanocapsine as outlined in Scheme 4.[27]



Reagents: i, $NaBH_4$; ii, CrO_3–AcOH; iii, catalytic hydrogenation

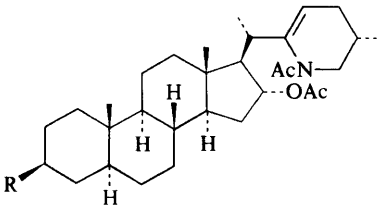
Scheme 4

Two new steroidal alkaloids, 25-isosolafloridine (43a) and solacallinidine (43b), were isolated from among the hydrolysis products of the crude glycoalkaloids of *S. callium*.[28] The two alkaloids had similar formulae, $C_{27}H_{45}NO_2$ and $C_{27}H_{46}N_2O$



(43a) R = OH
(43b) R = NH_2

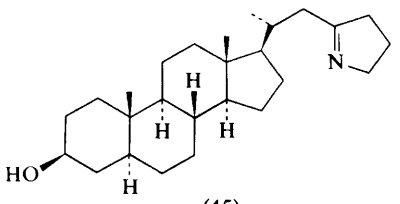
respectively, suggesting that solacallinidine was the 3-deoxy-3β-amino-analogue of 25-isosolafloridine. The mass spectrum of each alkaloid showed a major fragmentation peak at *m/e* 125, which implies that each compound possesses a side-chain of formula $C_8H_{15}N$. Spectroscopic evidence showed that both 25-isosolafloridine and solacallinidine contained a C=N linkage (λ_{max} 239 nm and ν_{max}



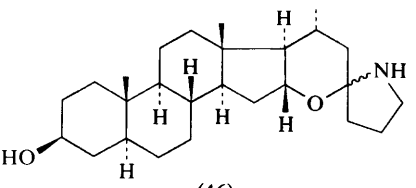
(44a) R = OAc
(44b) R = NHAc

1650 cm^{-1}), and each formed an *N*-acetyl-enamine, (44a) and (44b) respectively, on acetylation. The structure and stereochemistry of 25-isosolafloridine (43a) were deduced from *X*-ray diffraction studies on its hydrochloride. The structure of solacallinidine (43b) followed from the similarities noted above, the identity of the c.d. curves of the two compounds, and the differences in shifts of the carbon atoms of ring A in the natural-abundance ^{13}C n.m.r. spectra of the two compounds, which parallel those for 3β-hydroxy- and 3β-amino-cholestane.[28] The natural-abundance ^{13}C n.m.r. spectra of a number of *Solanum* alkaloids[30] and glycoalkaloids[31] have been reported.

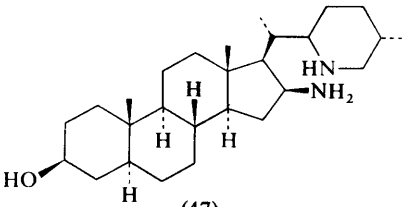
Syntheses have been reported of three analogues (45),[32] (46),[33] and (47)[34] of naturally occurring *Solanum* alkaloids.



(45)



(46)



(47)

The solasodine-based glycoalkaloids solamargine and solasonine were isolated from ripe fruits of *S. acculeatissimum*. The total solasodine content of these fruits was 3.8%.[35] The same glycoalkaloids were found in tissue cultures of *S. acculeatissimum*,[36] while solasodine was isolated from tissue cultures of five *Solanum*

[30] R. Radeglia, G. Adam, and H. Ripperger, *Tetrahedron Letters*, 1977, 903.
[31] R. J. Weston, H. E. Gottlieb, E. W. Hagaman, and E. Wenkert, *Austral. J. Chem.*, 1977, **30**, 917.
[32] G. Piancatelli and A. Scettri, *Tetrahedron*, 1976, **32**, 1745.
[33] G. Piancatelli and A. Scettri, *Gazzetta*, 1976, **106**, 167.
[34] R. Franzmair, *Monatsh.*, 1976, **107**, 501.
[35] P. G. Kadkade and C. Rolz, *Phytochemistry*, 1977, **16**, 1128.
[36] P. G. Kadkade and T. R. Madrid, *Naturwiss.* 1977, **64**, 147.

species.[37] The solasodine content of fruits of *S. mammosum*,[38] of fruits of the curved-spine mutant of *S. khasianum*,[39] and of all parts of seven other *Solanum* species[40] has been investigated. A study of the variation with time in the glycoalkaloid content of various parts of *S. persicum* has been reported.[41]

The distribution and concentration of solasodine and solafloridine in *S. umbellatum*[42] and *S. verbascifolium*[43] have been studied. The latter species also contains tomatidenol glycoalkaloids in its leaves.[43] The glycoalkaloid α-tomatine was isolated in 0.3% yield from the root bark of *Lycopersicum pruniforme*.[44] The mode of detoxification of α-tomatine by the fungus *Fusarium oxysporum* f. sp. *lycopersici* has been studied; a soluble enzyme is produced which hydrolyses tomatidine to the aglycone and lycotetraose.[45] The subcellular localization of steroidal glycoalkaloids in vegetative organs of *Lycopersicum esculentum* and *S. tuberosum* has been investigated.[46]

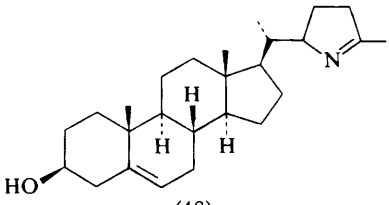
The effects of light[47] and of mechanical injury[48] on the glycoalkaloid content of potatoes have been studied. Solasodine has been shown to possess teratogenic properties.[49]

The utility of high-performance liquid chromatography (h.p.l.c.) has been demonstrated in the separation of *Solanum* and *Veratrum* steroidal alkaloids.[50] Methods have been described for the determination of *Solanum* alkaloids by paper chromatography[51] and of crude glycoalkaloids by t.l.c.[52]

5 *Veratrum* Alkaloids

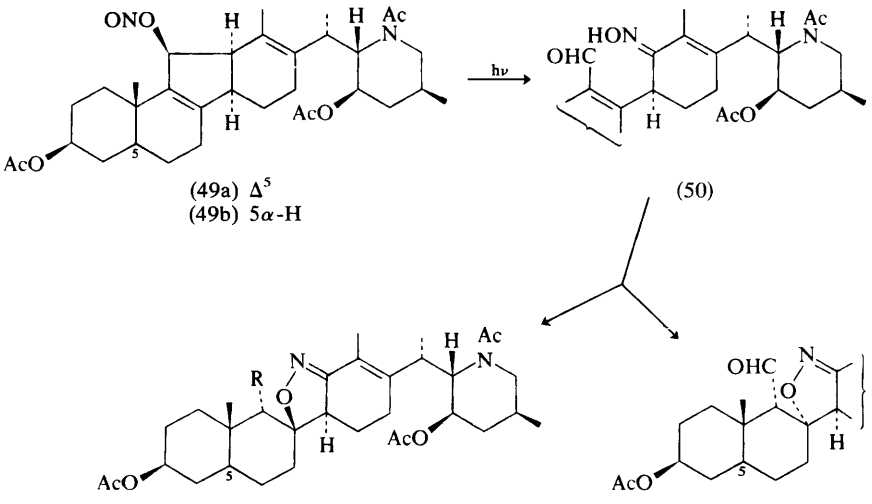
Additional degradative work and ^{13}C n.m.r. spectroscopic studies have been described in support of the structure (48) assigned earlier[53] to veracintine.[54]

[37] P. Khanna, A. Uddin, G. L. Sharma, S. K. Manot, and A. K. Rathove, *Indian J. Exp. Biol.*, 1976, **14**, 694 (*Chem. Abs.*, 1977, **86**, 40 211).
[38] D. N. Upadhyay, A. K. Shukla, and K. K. Singh, *Indian J. Pharm.*, 1976, **38**, 52 (*Chem. Abs.*, 1976, **85**, 74 907).
[39] M. R. Heble and B. Bhatt, *Indian J. Exp. Biol.*, 1976, **14**, 527 (*Chem. Abs.*, 1977, **86**, 1765).
[40] J. F. Verbist, R. Monnet, and J. F. Dobremez, *Plant. Med. Phytother.*, 1977, **11**, 40 (*Chem. Abs.*, 1977, **86**, 185 969).
[41] E. N. Novruzov, *Izvest. Akad. Nauk. Azerb. S.S.R., Ser. biol. Nauk.*, 1976, No. 5, p. 20 (*Chem. Abs.*, 1977, **86**, 136 331).
[42] W. Doepke, V. Jimenez, and U. Hess, *Pharmazie*, 1976, **31**, 488.
[43] W. Doepke, I. L. Mola, and U. Hess, *Pharmazie*, 1976, **31**, 656.
[44] M. M. Shabana, T. S. M. A. El-Alfy, and G. H. Mahran, *Bull. Fac. Pharm., Cairo Univ.*, (*Egypt*), 1973, **12**, 141 (*Chem. Abs.*, 1976, **85**, 37 127).
[45] J. E. Ford, D. J. McCance, and R. B. Drysdale, *Phytochemistry*, 1977, **16**, 545.
[46] J. G. Roddick, *Phytochemistry*, 1977, **16**, 805.
[47] N. F. Haard, *J. Food Biochem.*, 1977, **1**, 57 (*Chem. Abs.*, 1977, **86**, 185 970).
[48] M. T. Wu and D. K. Salunkhe, *J. Amer. Soc. Hortic. Sci.*, 1976, **101**, 329 (*Chem. Abs.*, 1976, **85**, 59 791).
[49] R. F. Keeler, D. Brown, D. R. Douglas, G. F. Stallknecht, and S. Young, *Bull. Environ. Contam. Toxicol.*, 1976, **15**, 522 (*Chem. Abs.*, 1976, **85**, 41 883); S. Chaube and C. A. Swinyard, *Toxicol. Appl. Pharmacol.*, 1976, **36**, 227 (*Chem. Abs.*, 1976, **85**, 41 881).
[50] I. R. Hunter, M. K. Walden, J. R. Wagner, and E. Heftmann, *J. Chromatog.*, 1976, **119**, 223.
[51] T. Adzet and J. L. Masso, *Rev. R. Acad. Farm. Barcelona*, 1976, **13**, 35 (*Chem. Abs.*, 1977, **86**, 67 711).
[52] V. N. Borisov, L. A. Pikova, G. L. Zachepilova, and A. I. Bankovskii, *Khim. Farm. Zhur.*, 1976, **10**, No. 12, p. 116 (*Chem. Abs.*, 1977, **86**, 127 147).
[53] J. Tomko, V. Brázdová, and Z. Votický, *Tetrahedron Letters*, 1971, 3041; R. B. Herbert, in ref. 23*b*, p. 294.
[54] A. Vassová, Z. Votický, J. Tomko, and A. Ahond, *Coll. Czech. Chem. Comm.*, 1976, **41**, 2964.



(48)

Photolysis of the nitrite ester (49a), which was derived from isojervine, gave the isoxazolines (51a) and (52a) in a ratio of 3 : 1. The structures of these products were determined by spectroscopic studies, and were confirmed, in the case of isoxazoline (51a), by *X*-ray diffraction studies on the derived iodomethyl compound (51c).[55] The 5,6-dihydro-derivative (49b) similarly gave isoxazolines (51b) and (52b) on irradiation.[56] In each case, the isoxazolines isolated appear to be secondary products which are formed by cyclization of the initially formed unstable formyloxime derivatives (50) during chromatography on silica gel.[55,56]



(49a) Δ^5
(49b) 5α-H

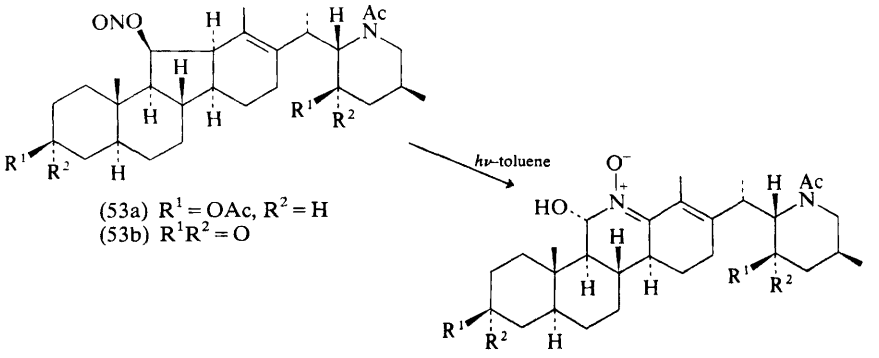
(50)

(51a) R = CHO, Δ^5
(51b) R = CHO, 5α-H
(51c) R = CH_2I, Δ^5

(52a) Δ^5
(52b) 5α-H

The nitrone (54a) was the sole product when nitrite ester (53a) was photolysed in toluene. When (53a) was labelled with ^{15}N in the nitrite ester group and photolysed in the presence of unlabelled (53b) the isotopic label was scrambled equally between the product nitrones (54a) and (54b); recovered nitrite ester (53b) remained unlabelled.[57] Nitrone (54a) was only a minor product when (53a) was

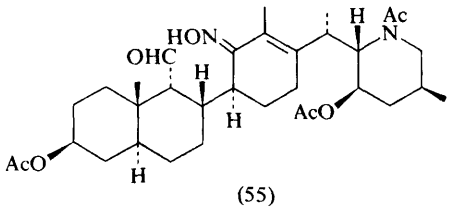
[55] H. Suginome, T. Tsuneno, N. Sato, N. Maeda, T. Masamune, H. Shimanouchi, Y. Tsuchida, and Y. Sasada, *J.C.S. Perkin I*, 1976, 1297.
[56] H. Suginome, N. Maeda, and T. Masamune, *J.C.S. Perkin I*, 1976, 1312.
[57] H. Suginome, T. Mizuguchi, and T. Masamune, *J.C.S. Perkin I*, 1976, 2365; *cf.* R. B. Herbert in ref. 23*b* p. 297.



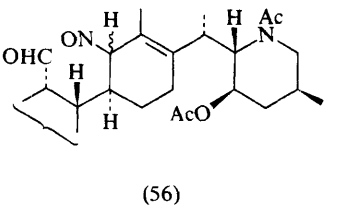
(53a) $R^1 = OAc$, $R^2 = H$
(53b) $R^1R^2 = O$

(54a) $R^1 = OAc$, $R^2 = H$
(54b) $R^1R^2 = O$

photolysed in THF;[58] the major product was the oxime (55), which was stable to these reaction conditions and so could not be the precursor of nitrone (54a). Presumably the first-formed *C*-nitroso-aldehyde (56) may undergo cyclization, leading to the nitrone (54a), or tautomerization, to give the oxime (55), in competing reactions. The nitroso-aldehyde was detected spectroscopically during photolysis of (53a) in a solid matrix at 77 K.[58]



(55)



(56)

The syntheses from jervine and the chemistry of some C-nor-D-homoandrostane derivatives have been reported.[59] The pharmacological properties of *Veratrum* alkaloids have been discussed.[60]

6 *Fritillaria* Alkaloids

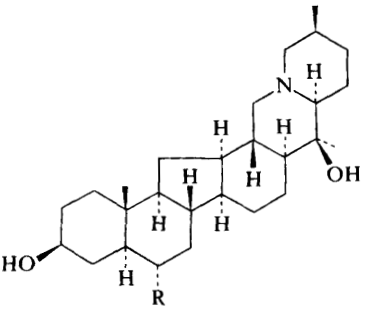
The total synthesis of verticine (57a) has been described.[61,62] The key intermediate, the diacetoxy-ketone (58), was prepared by degradation of hecogenin, which was earlier the subject of a total synthesis.[61] Ketone (58) was caused to react with 2-lithio-5-methylpyridine to give the desired product (59) together with its C-20

[58] H. Suginome, T. Mizuguchi, S. Honda, and T. Masamune, *J.C.S. Perkin I*, 1977, 927; *cf.* R. B. Herbert, in ref. 14*b*, p. 393.

[59] A. Murai, T. Nishimura, and T. Masamune, *Bull. Chem. Soc. Japan*, 1976, **49**, 1602, 1612; T. Masamune, A. Murai, K. Nishizakura, T. Orito, S. Numata, and H. Sasamori, *ibid.*, p. 1622; A. Murai, N. Iwasa, M. Takeda, H. Sasamori, and T. Masamune, *ibid.*, 1977, **50**, 429; A. Murai, H. Sasamori, and T. Masamune, *ibid.*, p. 437.

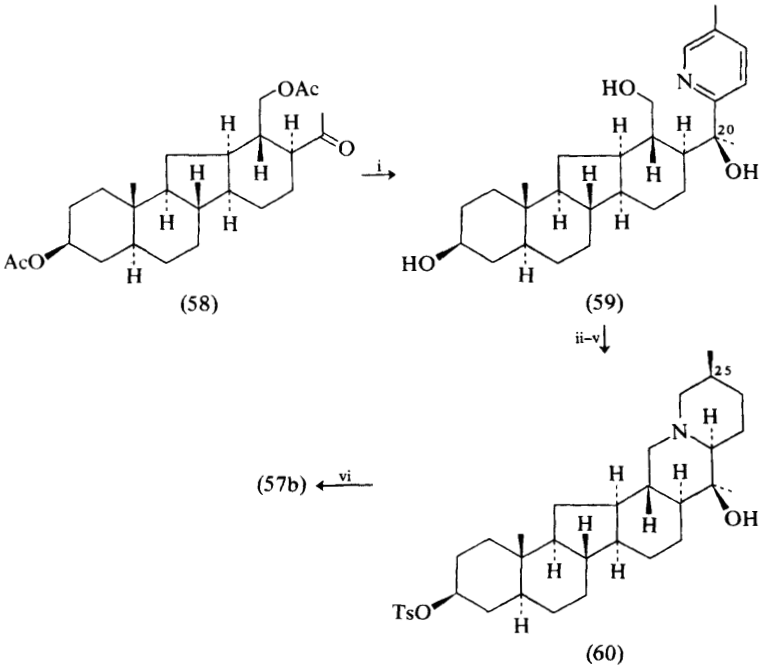
[60] H. P. Buech, *Ann. Univ. Sarav. Med.*, 1976, **23**, 76 (*Chem. Abs.*, 1976, **85**, 87 115).

[61] J. P. Kutney, R. W. Brookes, C. C. Fortes, Y. Murakami, A. Preston, and Y. Ueda, *J. Amer. Chem. Soc.*, 1977, **99**, 963.



(57a) R = OH
(57b) R = H

epimer. Subsequent cyclization and reduction (Scheme 5) led to the required hexacyclic intermediate (60) together with its C-25 epimer. Detosylation of (60) gave the desired diol (57b), which was converted into the derived Δ^5-enone by standard methods and thence, *via* hydroboration, into verticine (57a).[62]

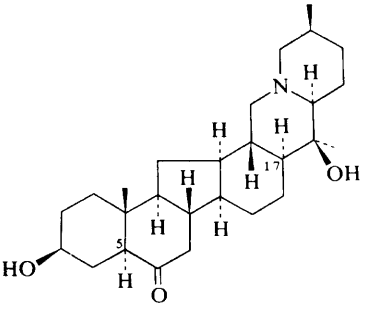


Reagents: i, 2-lithio-5-methylpyridine; ii, TsCl–pyridine; iii, Et_3N; iv, $NaBH_4$; v, H_2–Pt; vi, Na–naphthalene

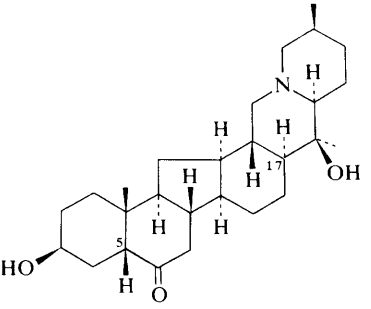
Scheme 5

[62] J. P. Kutney, C. C. Fortes, T. Honda, Y. Murakami, A. Preston, and Y. Ueda, *J. Amer. Chem. Soc.*, 1977, **99**, 964.

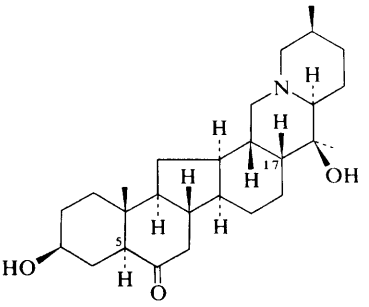
Imperialine and verticinone were assigned structures (61) and (62) respectively by Yunusov and his colleagues.[63] Subsequently, Itô and co-workers demonstrated that verticinone, and not imperialine, possessed structure (61).[64] The latter



(61) 5α-H, 17α-H



(62) 5β-H, 17α-H



(63) 5α-H, 17β-H

workers have now reinvestigated the structure of imperialine, to which they have assigned[65] the D/E-*cis* structure (63) on the basis of the following considerations: (i) both imperialine and verticinone are stable to base, and therefore are not C-5 epimers; (ii) a correlation of the changes of chemical shift of the C-19 protons in a series of corresponding derivatives of imperialine and verticinone demonstrated that these alkaloids possess identical rings A and B; (iii) o.r.d. studies also demonstrated that the structures of imperialine and verticinone differ at a position remote from rings A and B; (iv) *X*-ray crystallographic analysis of the methobromide derivative revealed that imperialine possesses the structure and stereochemistry shown in (63).[65] A 'new' alkaloid, kashmirine, was isolated from bulbs of *Fritillaria roylei* together with verticinone.[66] Kashmirine also was assigned structure (63) on the basis of spectroscopic evidence and an *X*-ray diffraction study! Fortunately this conflict should be readily resolved, since a comparison of the physical constants

[63] R. N. Nuriddinov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, 260 (*Chem. Abs.*, 1969, **70**, 685 89).
[64] S. Itô, Y. Fukazawa, T. Okuda, and Y. Iitaka, *Tetrahedron Letters*, 1968, 5373.
[65] S. Itô, Y. Fukazawa, and M. Miyashita, *Tetrahedron Letters*, 1976, 3161.
[66] A. Chatterjee, K. P. Dhara, C. Pascard, and T. Prange, *Tetrahedron Letters*, 1976, 2903.

quoted for kashmirine (m.pt. 262—265 °C, $[\alpha]_D^{CHCl_3} - 40.4°$)[66] with those of imperialine (m.pt. 267 °C, $[\alpha]_D^{CHCl_3} - 38.5°$)[67] suggests that these 'two' alkaloids are identical.

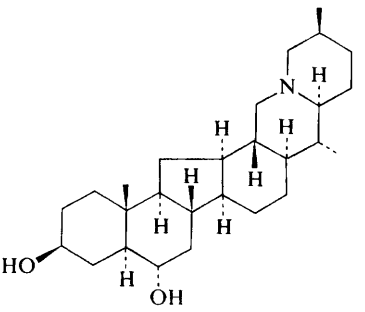
Four new cevanine derivatives, namely imperialine *N*-oxide,[68] eduardinine,[69] edpetisine,[70] and edpetisinine,[71] have been isolated from aerial parts of *Petilium eduardi*, (*Fritillaria* sp.). The structure of imperialine *N*-oxide ($C_{27}H_{43}NO_4$) was established from spectroscopic data, including the presence of a peak at *m/e* 429 ($M^+ - 16$) in its mass spectrum, and from the observation that reduction of the alkaloid with zinc and hydrochloric acid gave imperialine (63). Oxidation of imperialine with hydrogen peroxide gave an *N*-oxide which was not identical to the natural product, but which could also be reduced to imperialine; presumably the synthetic and natural *N*-oxides possess opposite chirality at nitrogen.[68]

Eduardinine ($C_{27}H_{45}NO_2$) was assigned structure (64) following spectroscopic studies on the alkaloid and its derivatives.[69] Treatment of eduardinine with chromic oxide gave a diketone which was identical to that formed from edpetilidine[72] on oxidation.[69]

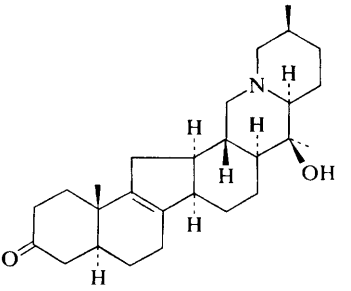
Edpetisine[70] (65) and edpetisinine[71] (66a) were assigned the indicated structures and stereochemistry solely on the basis of spectroscopic studies of these alkaloids and their simple derivatives. Edpetisinine was reported to form a 3,6-diketone (66b) together with two monoketones on treatment with chromic oxide. Surprisingly, the 3,6,15-trioxocevanine was not formed.[71]

Structural studies continue on the basic components extracted from *Korolkowia sewerzowi* (*Fritillaria sewerzowi*).[73–77] Sewertzidine (67)[73] and korsidine (68)[74] were assigned the structures that are indicated largely on the basis of spectroscopic investigations. Additional evidence for the structure and stereochemistry of korsidine was obtained by hydrogenation over Adams catalyst, followed by treatment of the dihydro-product with chromic oxide. The diketone so formed[74] was identical to that formed on oxidation of petilinine (69).[78] Oxidation of korseveridinine[75] gave a monoketone which was said to be identical with the oxidation product of

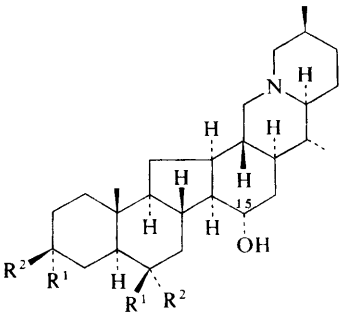
[67] H. G. Boit, *Chem. Ber.*, 1954, **87**, 472.
[68] A. Nabiev, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 676 (*Chem. Abs.*, 1977, **86**, 136 313).
[69] A. Nabiev, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 535 (*Chem. Abs.*, 1976, **84**, 44 480).
[70] A. Nabiev, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 403 (*Chem. Abs.*, 1977, **86**, 43 873).
[71] A. Nabiev, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 679 (*Chem. Abs.*, 1977, **86**, 190 294).
[72] R. N. Nuriddinov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, 333 (*Chem. Abs.*, 1970, **72**, 43 941).
[73] K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 367 (*Chem. Abs.*, 1977, **86**, 43 872).
[74] K. Samikov, R. Shakirov, D. N. Safaeva, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 780 (*Chem. Abs.*, 1977, **86**, 86 124).
[75] D. U. Abdullaeva, K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 796 (*Chem. Abs.*, 1977, **86**, 171 688).
[76] K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 827 (*Chem. Abs.*, 1977, **86**, 171 729).
[77] K. Samikov, R. Shakirov, D. U. Abdullaeva, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 269 (*Chem. Abs.*, 1976, **85**, 108 928).
[78] R. N. Nuriddinov, B. Babaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, 261 (*Chem. Abs.*, 1969, **70**, 68 588).



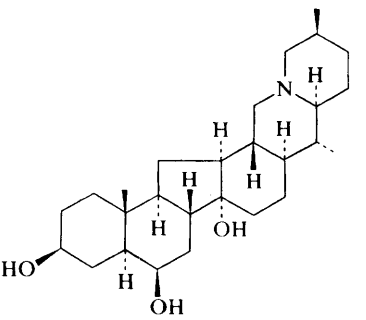
(64)



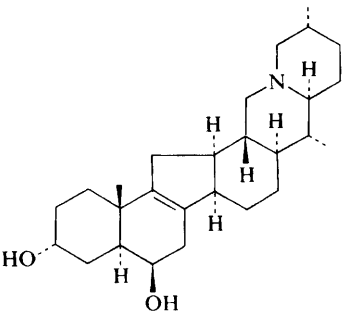
(65)



(66a) $R^1 = OH, R^2 = H$
(66b) $R^1R^2 = O$



(67)



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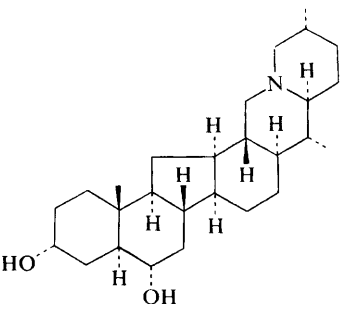
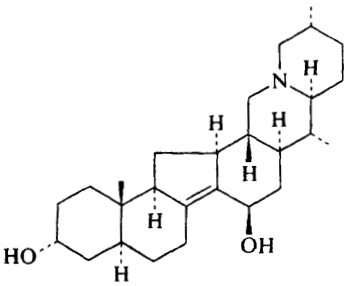


(69)

korseveridine, the structure of which had earlier been assigned by the same group of workers.[79] The stereochemical details of the structure (70) now assigned to korseveridinine[75] do not seem to be consistent with this correlation.

The alkaloid korsiline[76] and the glycoalkaloid sevcorine[77] have been assigned structures (71) and (72) respectively, following spectroscopic studies on the natural

[79] R. N. Nuriddinov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, 101 (*Chem. Abs.*, 1968, **69**, 77 560).



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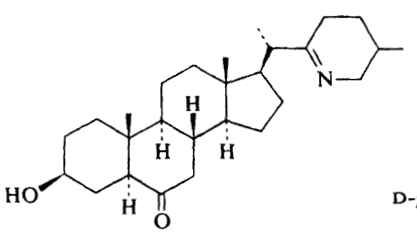

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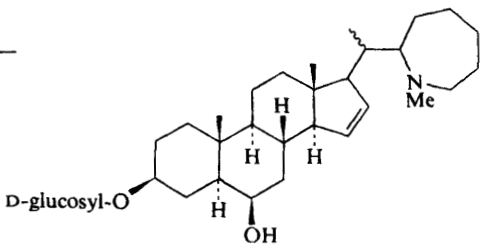

(72)

products and their derivatives. Firmer evidence for the biogenetically unlikely side-chain assigned to sevcorine would be desirable.

The c.d. spectra of a number of *Veratrum* and *Fritillaria* alkaloids have been discussed.[80]

[80] G. P. Moiseeva, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 630 (*Chem. Abs.*, 1977, **86**, 155 859).

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