The Alkaloids—Volume 2

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The Alkaloids

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Foreword

The first volume in this series was, perhaps, *sui generis*, in that it comprised reviews of developments in alkaloid chemistry over an eighteen-month period instead of the twelve-month period adopted for subsequent Reports. There was also included sufficient background material to enable the new work to be placed in perspective in its own particular area, as well as three summaries of a more extended kind; these were concerned with the biosynthesis of the terpenoid indole alkaloids, the bisindole alkaloids, and alkaloids of current pharmacological or clinical interest.

This second volume, which reviews the alkaloid literature from July 1970 to June 1971, approaches more closely the standard Specialist Periodical Report originally envisaged by the Chemical Society and adopts a form which, with minor variations, will very probably be followed in subsequent volumes. Once again the whole field of alkaloid chemistry has been reviewed, with the exception of the Steroidal Alkaloids of the *Solanum* and *Veratrum* Groups. The omission of these groups in the first volume was deliberate; their inclusion in the second volume was intended, but proved to be impracticable, and we hope to remedy this omission in the third volume. It is fortunate, however, that this particular area can quite properly be discussed in a volume devoted to alkaloids or in one devoted to steroids; and for a brief review of recent developments in this subject the reader is meanwhile referred to the Specialist Periodical Report on Terpenoids and Steroids, Volume One (Senior Reporter Dr. K. H. Overton).

Once again it is a pleasure to acknowledge the ready co-operation of my colleagues in the preparation of this Report, and my indebtedness to them for the efforts they made to ensure the punctual submission of their manuscripts.

Suggestions concerning the presentation of subsequent Reports in this series will, as always, be welcomed.

J. E. Saxton

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Biosynthesis

BY J. STAUNTON

The main emphasis of research on alkaloid biosynthesis has shown a significant move away from recently fashionable problems. The terpenoid indole family of alkaloids no longer dominates the scene and the benzylisoquinoline and ergot alkaloids have also lost their prominent position.

It seems unlikely that any new area will achieve in the future the dominant role enjoyed in the recent past by the indole alkaloid family, and the major advances this year have been spread over several unrelated fields. For example the middle and late stages in the biosynthesis of the *Ipecac* and *Cinchona* alkaloids have been largely elucidated although important gaps remain to be filled. The interesting work of several groups on the role of lysine in alkaloid biosynthesis continues apace and much further work will be necessary before one can be sure of understanding the overall picture in this complex field. A major breakthrough on the peyote cactus alkaloids has solved a longstanding puzzle in isoquinoline biosynthesis and should stimulate fresh interest in the early stages of isoquinoline formation in other systems.

As the body of knowledge accumulates, it becomes increasingly unlikely that many pathways remain to be discovered. Thus, it is hardly surprising that many of the compounds under investigation this year have been found to arise by modification of already established pathways. However, there is promising evidence that the mesembrine alkaloids are biosynthesized by an unexpected, novel route and the past year has produced its full quota of surprises and puzzling results from both new and established pathways.

Terpenoid Indole Alkaloids.—A surprising development has taken place since the comprehensive review was published in last year's Report.[1] The result came not from the biosynthetic study but from further investigation of the configuration at C(3) of vincoside (3).[2,3] The stereochemistry at this position was uncertain[1] because past research gave conflicting results. However, it has now been convincingly established that in vincoside the hydrogen at C(3) has the β-orientation.

[1] A. R. Battersby, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1, p. 31.
[2] K. T. D. De Silva, G. N. Smith, and K. E. H. Warren, *Chem. Comm.*, 1971, 905.
[3] W. P. Blackstock, R. T. Brown, and G. K. Lee, *Chem. Comm.*, 1971, 910.
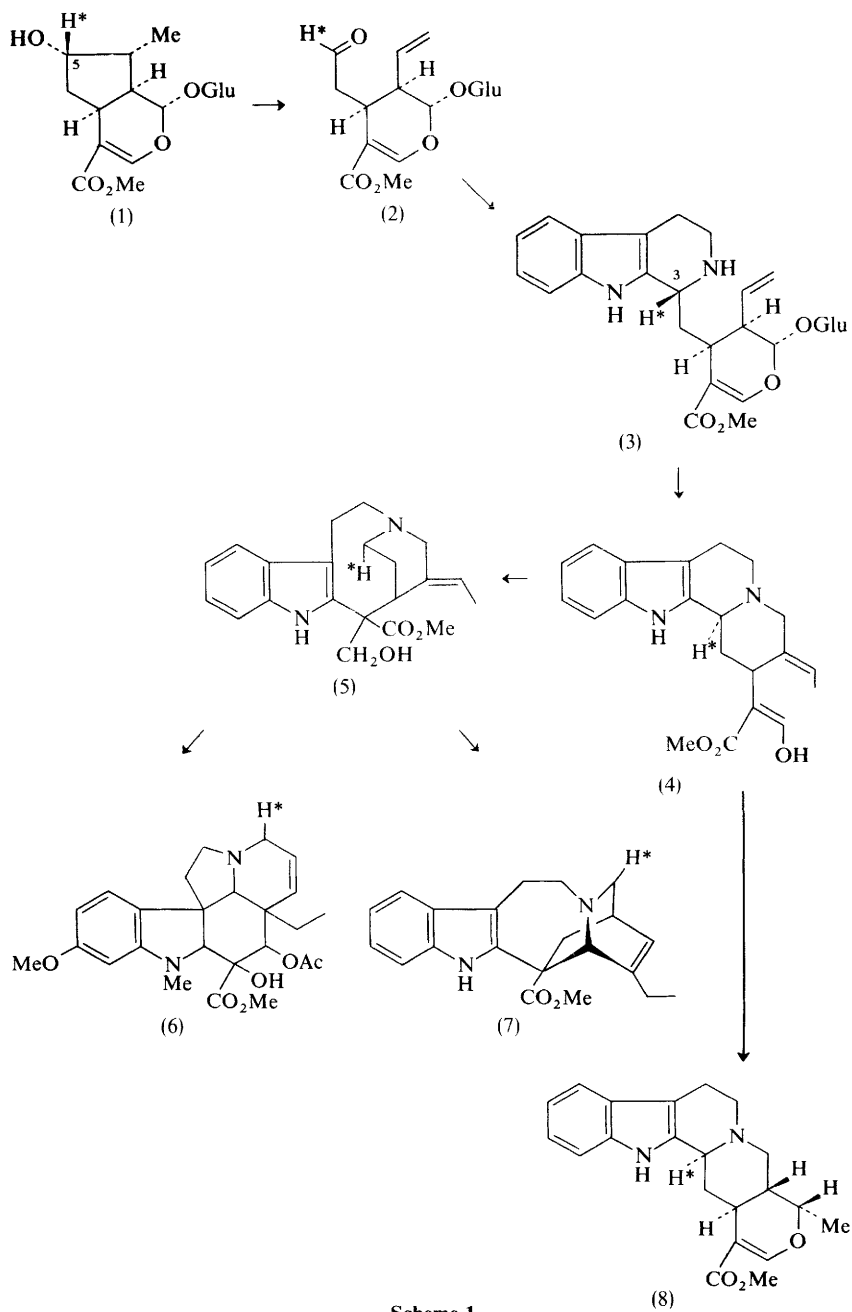
Scheme 1

This result is unexpected from the point of view of the biosynthetic chemist because the configuration at C(3) of vincoside is now opposite to that at the corresponding carbon of the next established intermediate, geissoschizine (4). It is not yet clear how this centre becomes epimerized in the biosynthesis but the following experimental facts have to be accounted for: (*a*) isovincoside [the C(3) epimer of vincoside] is not biologically active,[4] and (*b*) the hydrogen at C(5) of loganin (1) [C(5) of loganin corresponds to C(3) of vincoside] is completely retained[4] in the biosynthesis of the three main classes of indole alkaloid, represented in Scheme 1 by vindoline (6) [*Aspidosperma*], catharanthine (7) [*Iboga*], and ajmalicine (8) [*Corynanthe*].

The retention of the hydrogen from C(5) of loganin implies that the epimerization takes place without cleavage of a carbon–hydrogen bond and thus provides a valuable clue to the mechanism of this intriguing process. In view of the importance of this result, it is essential to show that the hydrogen has not undergone an unexpected migration prior to the epimerization step. The predicted destination of the hydrogen from C(5) of loganin in the absence of a migration is marked by an asterisk in the structures in Scheme 1. The earlier experiment was repeated[5] by administering [5-^{3}H,*O-methyl*-^{3}H]loganin to *Vinca rosea* plants. The three alkaloids (6), (7), and (8) were each found to retain both tritium labels without change in isotopic ratio and it was proved by degradation that, for each alkaloid, the activity incorporated into the skeleton resided specifically at the expected position. Thus, it is very probable that the epimerization process involves cleavage of a carbon–carbon or carbon–nitrogen bond. A similar process seems to operate in the biosynthesis of the *Ipecac* alkaloids and the problem will be discussed further in that section.

Eburnamine–Vincamine Alkaloids.—So far most of the effort on indole alkaloid biosynthesis has been concentrated on the *Corynanthe*, *Aspidosperma*, and *Iboga* systems. It is welcome, therefore, to see the preliminary results of an investigation of the biosynthesis of vincamine (10).[6] Comparable incorporations were observed for [*ar*-^{3}H]tryptophan, [*ar*-^{3}H]stemmadenine (5), and [*ar*-^{3}H]tabersonine (9). These results support the proposal[7] that vincamine is a transformation

(9)   (10)
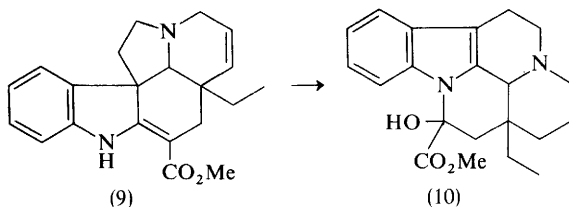
4 A. R. Battersby, A. R. Burnett, E. S. Hall, and P. G. Parsons, *Chem. Comm.*, 1968, 1582.
5 A. R. Battersby and K. H. Gibson, *Chem. Comm.*, 1971, 902.
6 J. P. Kutney, J. F. Bick, V. R. Nelson, and R. S. Sood, *J. Amer. Chem. Soc.*, 1971, **93**, 255.
7 E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, 1965, **87**, 1580.

product of the *Aspidosperma* system, and it will be interesting to see if further work supports the detailed mechanism proposed for the transformation.

Cinchona **Alkaloids.**—The biosynthetic route (Scheme 2) to the *Cinchona* alkaloids quinine (22), cinchonidine (21), and cinchoninine (23) is of exceptional complexity. Earlier work established that quinine is derived by combination of an indolic unit derived from tryptophan[8] with a monoterpenoid unit derived from geraniol[9,10] *via* loganin.[11] The close relationship to indole alkaloid biosynthesis implied by these results has been confirmed by the demonstration that vincoside succeeds loganin in the biosynthesis.[12] In feeding experiments with *C. ledgeriana* shoots [*ar*-³H]vincoside was incorporated into each of the *Cinchona* bases (21), (22), and (23). By analogy with indole alkaloid biosynthesis it is likely that secologanin (2) is an intermediate between loganin and vincoside.

The proposal that the next stages of the pathway would involve intermediates of the *Corynanthe* type has received experimental support. Corynanthealdehyde (12) was not incorporated but the closely related corynantheal (13) did serve as an efficient precursor for all three *Cinchona* bases.[12] Thus, the close parallel between the early stages of quinine biosynthesis and the corresponding stages (Scheme 1) of indole alkaloid biosynthesis is established.

From corynantheal onwards the pathways diverge completely. The generation of the skeleton of the *Cinchona* bases requires not only a further reorganization of the terpenoid moiety but also a fundamental rearrangement of the indolic portion of the molecule to generate the quinoline residue. The currently favoured working hypothesis for this transformation is shown in Scheme 2: (13) → (14) → (15) → (16) → (17) and (18). With the required skeleton in hand, only relatively trivial biochemical reactions are required to produce the known *Cinchona* alkaloids (21), (22), and (23).

The very late stages from (17) and (18) onwards have been intensively investigated.[13] When [11-³H]cinchonidinone (17) was administered to *C. ledgeriana* shoots, activity was incorporated efficiently into the corresponding alkaloids cinchonidine (21) and cinchonine (23). The incorporation was shown to be specific for cinchonine, by degradation. A low but possibly significant incorporation of (17) into quinine (22) was also observed. Thus, it is possible that the methoxy-group of quinine is introduced after generation of the quinoline system in (17).

The presence of the keto base (17) in *Cinchona* plants was confirmed by dilution analysis. *C. ledgeriana* shoots were allowed to metabolize [1-¹⁴C] tryptamine and were then worked up for alkaloids after the addition of inactive (17). The recovered carrier was radioactive, which confirms that the keto-base

[8] N. Kowanko and E. Leete, *J. Amer. Chem. Soc.*, 1962, **84**, 4919.
[9] A. R. Battersby, R. T. Brown, R. S. Kapil, J. A. Knight, J. A. Martin, and A. O. Plunkett, *Chem. Comm.*, 1966, 888.
[10] E. Leete and J. N. Wemple, *J. Amer. Chem. Soc.*, 1969, **91**, 2698.
[11] A. R. Battersby and E. S. Hall, *Chem. Comm.*, 1970, 194.
[12] A. R. Battersby and R. J. Parry, *Chem. Comm.*, 1971, 30.
[13] A. R. Battersby and R. J. Parry, *Chem. Comm.*, 1971, 31.

(11)

(3)

(12)

(14)

(13)

(16)

(15)

(17) R = H
(18) R = OMe

(19) R = H
(20) R = OMe

(21) R = H
(22) R = OMe

(23) R = H
(24) R = OMe
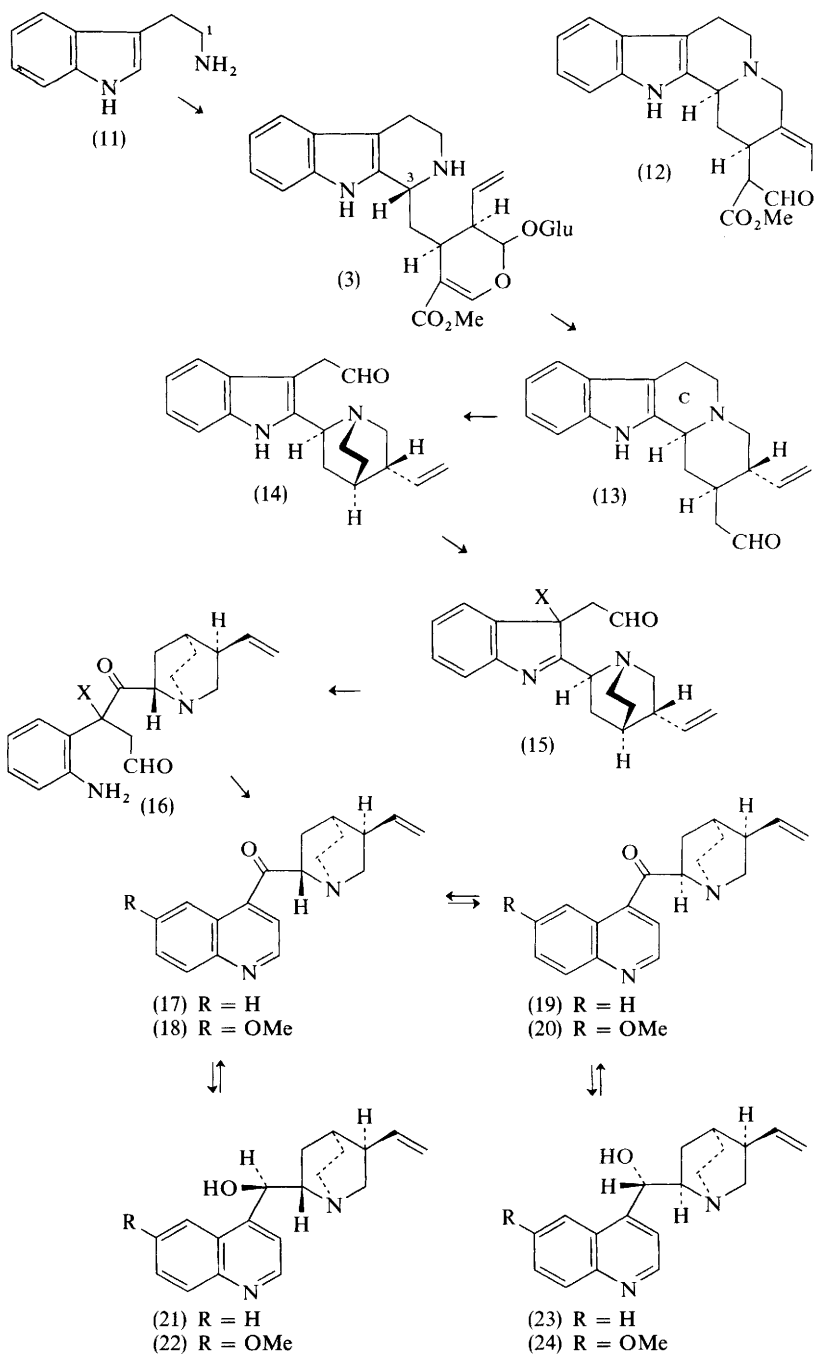
Scheme 2

(17) is a natural product of the *Cinchona* plants and is, therefore, a true intermediate in the biosynthesis of the alkaloids. The presence of the ketone (20) was also demonstrated by dilution analysis of *Cinchona* plants which had metabolized [*ar*-³H]vincoside.

The reversibility of the reduction step (17) → (21) was examined by feeding [11-³H]cinchonidine (21) to *C. ledgeriana* shoots and isolating the corresponding ketone (17) after addition of a carrier. The recovered cinchonidinone was radioactive, which proves that reversal does occur [*i.e.* (21) → (17)]. In view of this result, it is reasonable to suppose that all the late steps are reversible after generation of the quinoline system in (17) and (18) but obviously many more tracer experiments would be required to prove every detail implied in the scheme.

Thus, the early and late stages of *Cinchona* alkaloid biosynthesis are well worked out. However, the really unique steps in the pathway lie between (13) and (17) or (18); it is this stage of the biosynthesis that sees the profound skeletal reorganization of the indolic unit to a quinoline. The sequence of intermediates proposed in Scheme 2 is intellectually appealing but, at this stage, remains purely speculative.

Indirect evidence to support the intermediacy of the aldehyde (14) has come from experiments which rule out the corresponding alcohol and the corresponding acid, respectively.[13] The alcohol cinchonamine [(14) but CH_2OH instead of CHO] was tested directly by administering the tritiated compound to *C. ledgeriana* shoots. None of the *Cinchona* bases showed a significant incorporation of activity. The carboxylic acid corresponding to (14) was not tested directly but was ruled out by an incorporation experiment with [1-¹⁴C,1,1-³H₂]tryptamine (11). Each of the alkaloids showed an isotopic ratio corresponding to the retention of half the tritium. Thus, one of the two hydrogens residing at C(1) of tryptamine survives the biosynthesis, which rules out the acid corresponding to (14) as an intermediate. The elimination of the alcohol and the acid increases the probability that the aldehyde (14) is involved in the biosynthesis, but it must be emphasized that there is no direct support for this proposal.

The elucidation of the steps between (13) and (17) represents a formidable challenge to both chemical skill and biosynthetic intuition and it can be expected that this area will provide more exciting results in the future.

Ipecac **Alkaloids.**—Earlier tracer results[14] on the alkaloids emetine (29), cephaeline (28), and ipecoside (27) of *Cephaelis ipecacuanha* have established that a C_{9-10} unit (thickened bonds) is derived from geraniol *via* loganin. The suggested pathway (Scheme 3)[15] shows a parallel, in the early stages, to indole alkaloid biosynthesis. Secologanin (2) derived in the usual way from loganin, is condensed with a unit of dopamine to furnish one of the epimeric isoquinolines desacetylipecoside (26) or desacetylisoipecoside (25). Structural reorganization of the terpenoid unit is followed by condensation with a second dopamine unit to generate the alkaloids cephaeline (28) and emetine (29).

[14] A. R. Battersby and B. Gregory, *Chem. Comm.*, 1968, 134.
[15] A. R. Battersby and R. J. Parry, *Chem. Comm.*, 1971, 901.
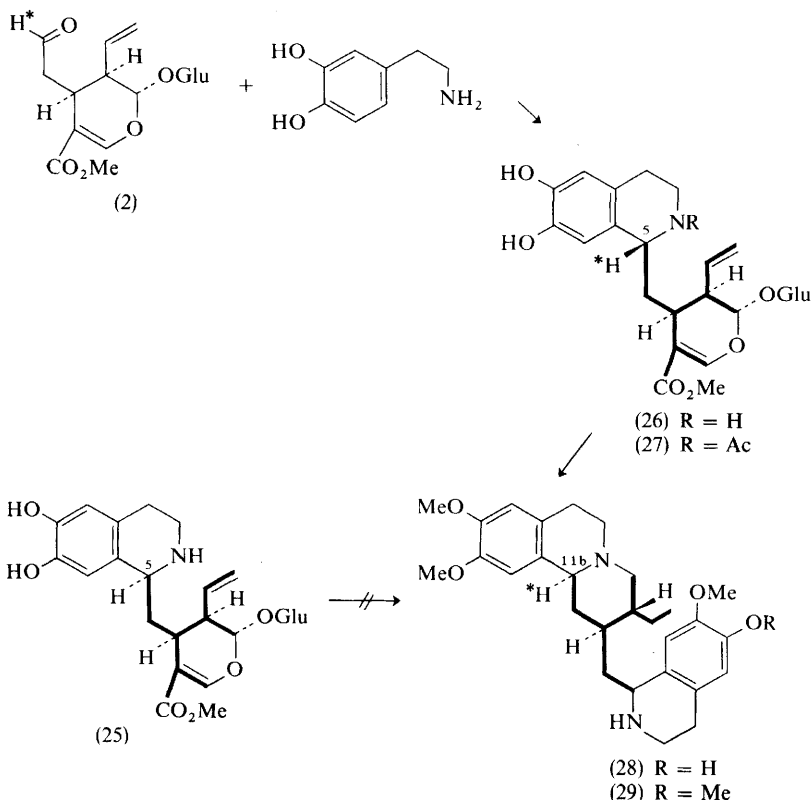
Scheme 3

The role of secologanin was studied[15] by feeding [*O-methyl*-^{3}H,6,6-^{3}H$_2$]secologanin to *C. ipecacuanha* plants; activity was incorporated into all three alkaloids and in the case of ipecoside the distribution of activity was shown by degradation to correspond to an intact incorporation.

A highly significant result emerged when the epimeric isoquinolines (25) and (26) were tested *in vivo*.[15] Both compounds are available from the *in vitro* condensation of dopamine with secologanin. [3'-^{14}C]Desacetylipecoside (26) was found to be an efficient and specific precursor of all three alkaloids (27), (28), and (29) whereas the epimer, desacetylisoipecoside (25), was biologically inactive.

The specific incorporation of (26) rather than its epimer (25) into cephaeline (28) and emetine (29) is surprising when one compares the configuration at C(5) of (25) with that at the corresponding position [C(11b)] of (28) and (29). The absolute configuration of (25) is rigorously established by relation to ipecoside.[16]

[16] Olga Kennard, P. J. Roberts, N. W. Isaacs, W. D. S. Motherwell, K. H. Gibson, and A. R. Battersby, *Chem. Comm.*, 1971, 899.

Thus, the transformation (26) → (28) requires inversion of the configuration at C(5) of (25).

The situation is reminiscent of the transformation of vincoside into geissoschizine in indole alkaloid biosynthesis. In the case of the indole alkaloid pathway it was proved by feeding [5-³H]loganin that the C—H bond at the relevant asymmetric centre is not broken in the epimerization step. A similar experiment[15] in *C. ipecacuanha* with [5-³H]loganin has established that the hydrogen at C(5) of loganin is again retained and that it resides in the alkaloids specifically at the corresponding position, C(11b). Thus, the two biosynthetic pathways show the same puzzling feature: when the heterocyclic ring is formed by condensation of an arylethylamine with an aldehyde, the new asymmetric centre is generated in the 'wrong' configuration; epimerization of this centre is therefore necessary and it is known that the mechanism does not involve cleavage of the C—H bond. It will be interesting to see whether this is a general pattern for biosynthetic pathways involving secologanin; also, the mechanism of the epimerization deserves further investigation.

The sequence of intermediates after (26) is still an open question. Evidence has been obtained that the ethyl group of (28) is not generated directly by reduction of the vinyl group, but that the double bond first migrates to generate an ethylidene group.[15] Thus, when [2,2-³H₂,2-¹⁴C]geraniol was administered to the plant the tritium was found to be completely lost in the alkaloids (28) and (29).

An earlier report[17] that glycine is incorporated specifically into the terpenoid unit of cephaeline has stimulated similar research in the indole alkaloid series. However, glycine was found not to be a specific precursor of either strychnine[18] or ajmalicine.[19]

Ergot Alkaloids.—The tryptophan and tryptamine derivatives (30) and (31) respectively, labelled in each case with ¹⁴C at the carbinol carbon, have been shown[20] to be precursors of the alkaloids agroclavine (32) and elymoclavine (33). These results throw further light on the sequence of intermediates leading from tryptophan to the ergoline system.

(30)   (31)   (32) R = Me
                                                            (33) R = CH₂OH
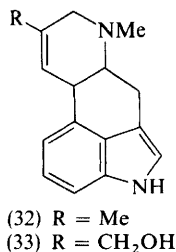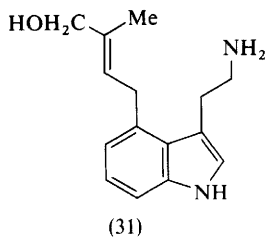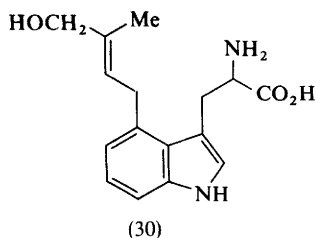
[17] J. R. Gear and A. K. Garg, *Tetrahedron Letters*, 1968, 141.
[18] D. Gröger, W. Maier, and P. Simchen, *Experientia*, 1970, **26**, 820.
[19] J. P. Kutney, J. F. Beck, V. R. Nelson, K. L. Stuart, and A. K. Bose, *J. Amer. Chem. Soc.*, 1970, **92**, 2174.
[20] H. Plieninger, C. Wagner, and H. Immel, *Annalen*, 1971, **743**, 95.

Several papers have appeared on the biosynthesis of the peptide side-chains of the various ergot alkaloids. In the case of ergotamine (34), activity was incorporated from $[1\text{-}^{14}C]$alanine into the 2-hydroxyalanyl residue.[21] An investigation[22] of ergotoxine (35) biosynthesis produced no surprises; DL-$[2\text{-}^{14}C]$tryptophan was specifically incorporated into the lysergic acid moiety and L-proline served as precursor of the proline unit of the side-chain. In contrast, the origin of the hydroxyethyl side-chain of N-(α-hydroxyethyl))lysergamide (36) is still obscure.[23] The following precursors have been administered to *Claviceps paspali*: $[1\text{-}^{14}C]$acetate, $[^{14}C]$formate, $[2\text{-}^{14}C]$mevalonic acid, $[2\text{-}^{14}C]$indole, DL-$[3\text{-}^{14}C]$tryptophan, DL-$[3\text{-}^{14}C]$serine, DL-$[2\text{-}^{14}C]$alanine, and DL-$[2\text{-}^{14}C]$-pyruvate. Activity was incorporated from each of these compounds but only the last two introduced activity into the hydroxyethyl group. However, the incorporation into this group was non-specific so that none of the compounds tested in this investigation qualified as a direct precursor of the hydroxyethyl side chain.

RNH·CO — NMe

(34) RNH =
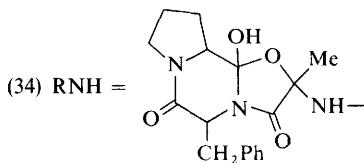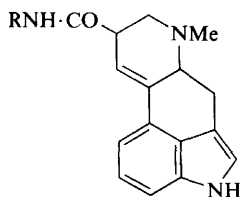
(35) RNH = a mixture of peptide units

(36) RNH =
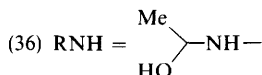
Miscellaneous Indole Alkaloids.—Echinulin (38) is known to be assembled from tryptophan, mevalonic acid, and alanine.[24—26] The indole derivative (37) has now been shown[27] to be converted efficiently by *Aspergillus amstelodami* into echinulin and is, therefore, probably an intermediate.

The fungal metabolite cyclopiazonic acid 1 (40) has been shown to derive from tryptophan, mevalonic acid, and acetate. The corresponding bis-seco-derivative (39) also gave an incorporation when administered to *Penicillium cyclopium* Westling and is, therefore, probably an intermediate.[28]

[21] R. A. Bassett, E. B. Chain, and K. Corbett, *Biochem. J.*, 1971, **122**, 58P.
[22] D. Gröger and D. Erge, *Z. Naturforsch.*, 1970, **25b**, 196.
[23] N. Castagnoli, K. Corbett, E. B. Chain, and R. Thomas, *Biochem. J.*, 1970, **117**, 451.
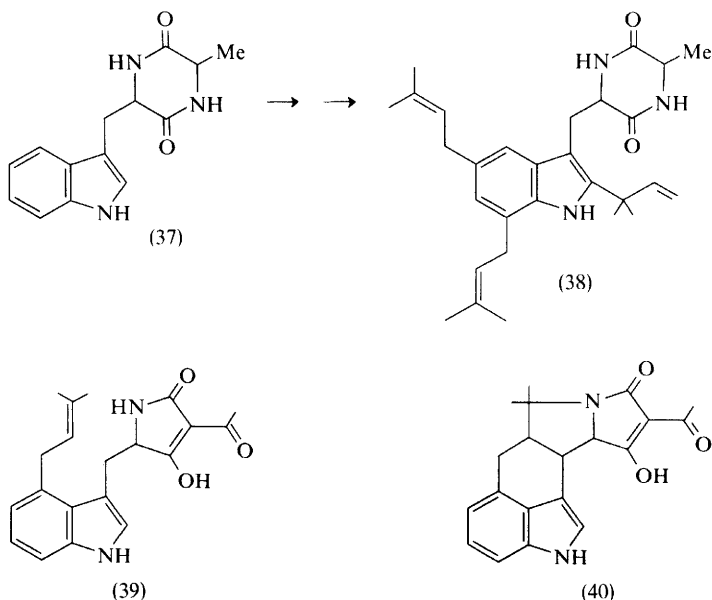[24] A. J. Birch and K. R. Farrar, *J. Chem. Soc.*, 1963, 4277.
[25] J. C. MacDonald and G. P. Slater, *Canad. J. Microbiol.*, 1966, **12**, 455.
[26] A. J. Birch, G. E. Blance, S. David, and H. Smith, *J. Chem. Soc.*, 1961, 3128.
[27] G. P. Slater, J. C. MacDonald, and R. Nakashima, *Biochemistry*, 1970, **9**, 2886.
[28] C. W. Holzapfel and D. C. Wilkins, *Phytochemistry*, 1971, **10**, 351.

(37)   (38)   (39)   (40)

Isoquinoline Alkaloids.—This year has seen the solution of a longstanding mystery in alkaloid biosynthesis: the origin of the 'extra' skeletal carbons of the peyote cactus alkaloids, anhalonidine (43) and anhalamine (47). The major portion of the skeleton is derived in each case from tyrosine, by a well established[29,30] pathway leading to the intermediate phenethylamine (41) but, despite much research, the origin of C(1) of (47) and C(1) + C(9) of (43) remained unsolved.
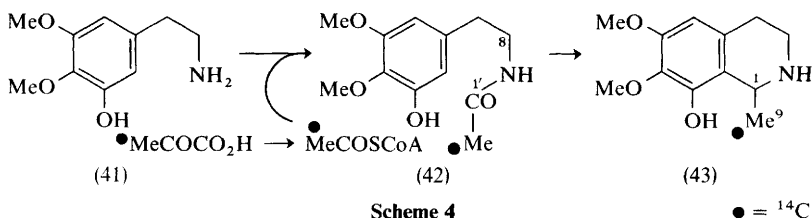
Considering (43) first, the obvious candidate for precursor of the mysterious C_2 unit is acetate, but although activity was incorporated from [1-^{14}C]acetate and [2-^{14}C]acetate the labelling pattern was in each case non-specific.[31] The initial breakthrough on this problem came from the discovery that activity was incorporated from the methyl group of pyruvate preferentially, though not specifically, into C(9) of anhalonidine.[32] To accommodate the success of pyruvate with the failure of acetate the pathway shown in Scheme 4 was suggested; pyruvate is converted to acetyl CoA and this 'active' acetate is then condensed with the phenethylamine (41) to produce the amide (42). Cyclization of the amide would produce an isoquinoline system and ultimately the alkaloid (43). The failure of the feeding experiments with acetate would be attributed to a lack of (or possibly inconvenient siting of) the enzyme required to convert acetate to acetyl CoA.

[29] J. Lundstrom and S. Agurell, *Tetrahedron Letters*, 1969, 3371.
[30] A. G. Paul, K. L. Khanna, H. Rosenberg, and M. Takido, *Chem. Comm.*, 1969, 838.
[31] A. R. Battersby, R. Binks, and R. Huxtable, *Tetrahedron Letters*, 1968, 611.
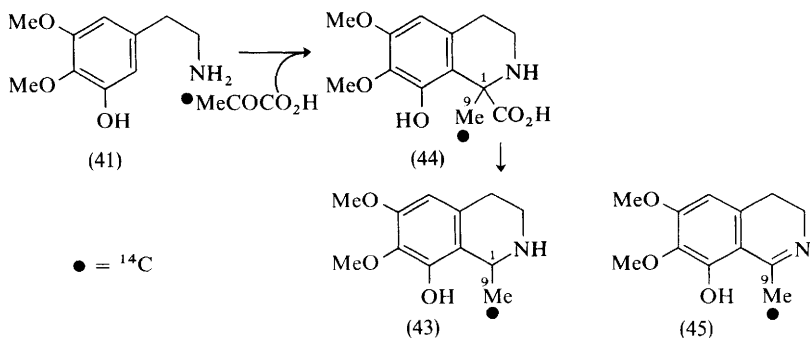[32] E. Leete and J. D. Braunstein, *Tetrahedron Letters*, 1969, 451.

Scheme 4 ● = ¹⁴C

MeO, MeO, OH NH₂ → MeO, MeO, OH ₈NH CO → MeO, MeO, OH Me⁹ NH

●MeCOCO₂H → MeCOSCoA ●Me

(41) (42) (43)

The pathway in Scheme 4 was tested[33] by feeding to the cactus the amide (42) multiply labelled with ¹⁴C at both C(8) and the carbonyl group. The alkaloid (43) was isolated in radioactive form but the distribution of the label ruled out an intact incorporation. Thus, the amide (42) is not an intermediate.

Ironically, the answer to this problem has rested in the literature since Hahn published in 1935 his theory of isoquinoline biosynthesis.[34] In his hypothesis (illustrated for anhalonidine in Scheme 5) the phenethylamine is condensed with the appropriate pyruvic acid to form an amino-acid (44) which is decarboxylated to provide the alkaloid (43).

This pathway to anhalonidine has now been shown to be essentially correct by *in vivo* experiments.[33] Administration of [1,9-¹⁴C]peyoruvic acid (44) to peyote cacti resulted in an efficient and specific incorporation of activity into the alkaloid, without a change in isotopic ratio. The status of the amino-acid as a true intermediate was confirmed by chemical analysis to show that it is present in the peyote cactus. Further support for Scheme 5 was provided by incubation of [9-¹⁴C]peyoruvic acid (44) with fresh peyote slices. Carbon dioxide was evolved and on work-up the decarboxylation product was found to be the imine (45), specifically labelled with ¹⁴C at C(9). The production of the imine rather than the tetrahydroisoquinoline (43) suggests that the decarboxylation may be an oxidative process and this interesting reaction deserves further investigation.

MeO, MeO, OH NH₂ ●MeCOCO₂H → MeO, MeO, HO Me CO₂H ● ₉ ₁ NH

(41) (44) ↓

● = ¹⁴C

MeO, MeO, OH Me ● ₉ ₁ NH MeO, MeO, OH Me ● ₉ N

(43) (45)

Scheme 5

[33] 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.
[34] G. Hahn, L. Barnard, O. Schales, and H. Werner, *Annalen*, 1935, **520**, 107; G. Hahn and H. Werner, *ibid.*, p. 123; G. Hahn and K. Stiehl, *Ber.*, 1936, **69**, 2627; G. Hahn and F. Rumpf, *ibid.*, 1938, **71**, 2141.

The extra carbon [C(1)] of anhalamine (47) is derived in a similar way.[33] In this case the corresponding carboxylic acid, peyoxylic acid (46), labelled with ^{14}C at C(1), was incorporated specifically into the alkaloid. The amino-acid was also identified as a natural product of the peyote cactus. Presumably peyoxylic acid is derived in the plant by condensation of the phenethylamine (41) with glyoxylic acid (Scheme 6).

In view of the importance of the isoquinoline system in biosynthesis it is surprising that so little effort has been devoted in the past to the biosynthesis of the basic ring system. No doubt the success of this investigation in the peyote cactus will stimulate further work in other systems. It is likely that the normal pattern will involve condensation of a phenethylamine with the appropriate pyruvic acid. However, reference has already been made to ipecoside (27) (Scheme 3) in which the isoquinoline system is formed by condensation of the phenethylamine with an aldehyde [secologanin]. Presumably the corresponding aldehyde, rather than a pyruvic acid, will be found to serve as precursor for the phenethylisoquinolines,[35] and also for the isoquinoline alkaloids of the *Lophophora* cactus such as lophocerine (66).
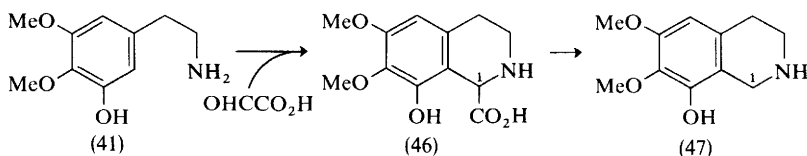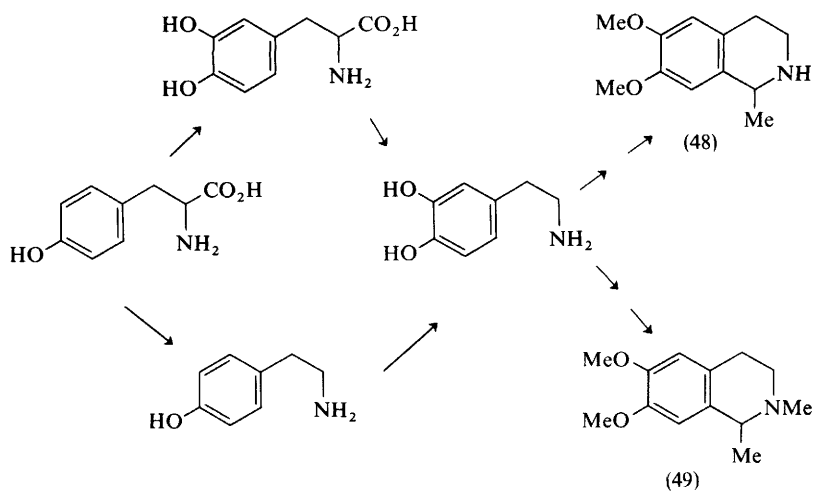

Scheme 6

The alkaloids salsolidine (48) and carnegine (49) show an obvious structural relationship to the peyote alkaloids (43) and (47) and evidence[36] has been obtained for a related biosynthesis. Thus, in both systems alternative routes from tyrosine to dopamine are in operation involving tyramine and dopa respectively (Scheme 7).[29,30,36] By analogy with peyote alkaloid biosynthesis, the C_2 unit C(1) + C(9) would be expected to derive from pyruvic acid, and therefore the failure of this residue to incorporate activity from methionine is not unexpected.

A surprising result has emerged[37] from an investigation of the biosynthesis of corydine (52), glaucine (60), and dicentrine (61), the aporphine alkaloids of *Dicentra eximia*. The methylation pattern of ring A of (52) strongly (but misleadingly) suggests a biosynthesis involving either reticuline (50) (path *a* in Scheme 8) or orientaline (51) (path *b* in Scheme 8). The other two alkaloids (60) and (61) would be derived by standard modification of the phenol coupling step, so that an integrated biosynthesis leading to all three alkaloids is possible for either pathway. However, both routes were quickly disproved by feeding experiments which
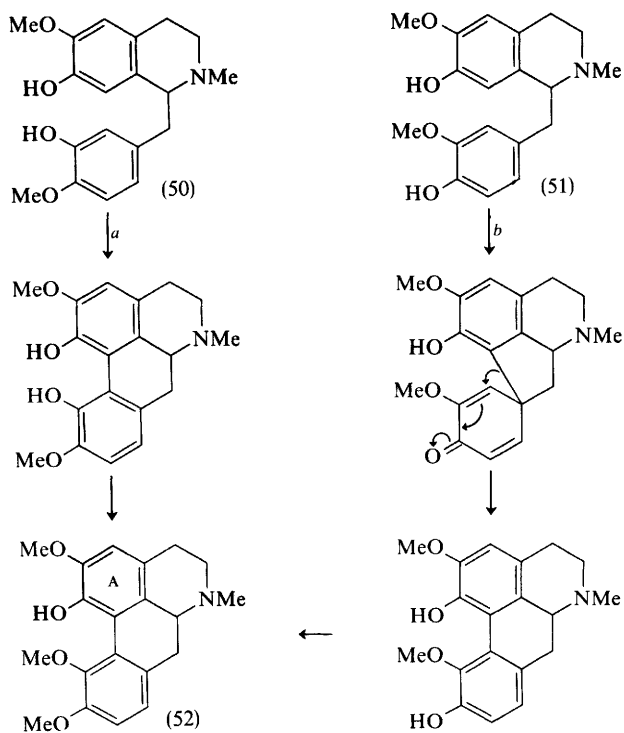
[35] A. R. Battersby, R. B. Herbert, and F. Santavy, *Chem. Comm.*, 1965, 415.
[36] J. G. Bruhn, U. Svensson, and S. Agurell, *Acta Chem. Scand.*, 1970, **24**, 3775.
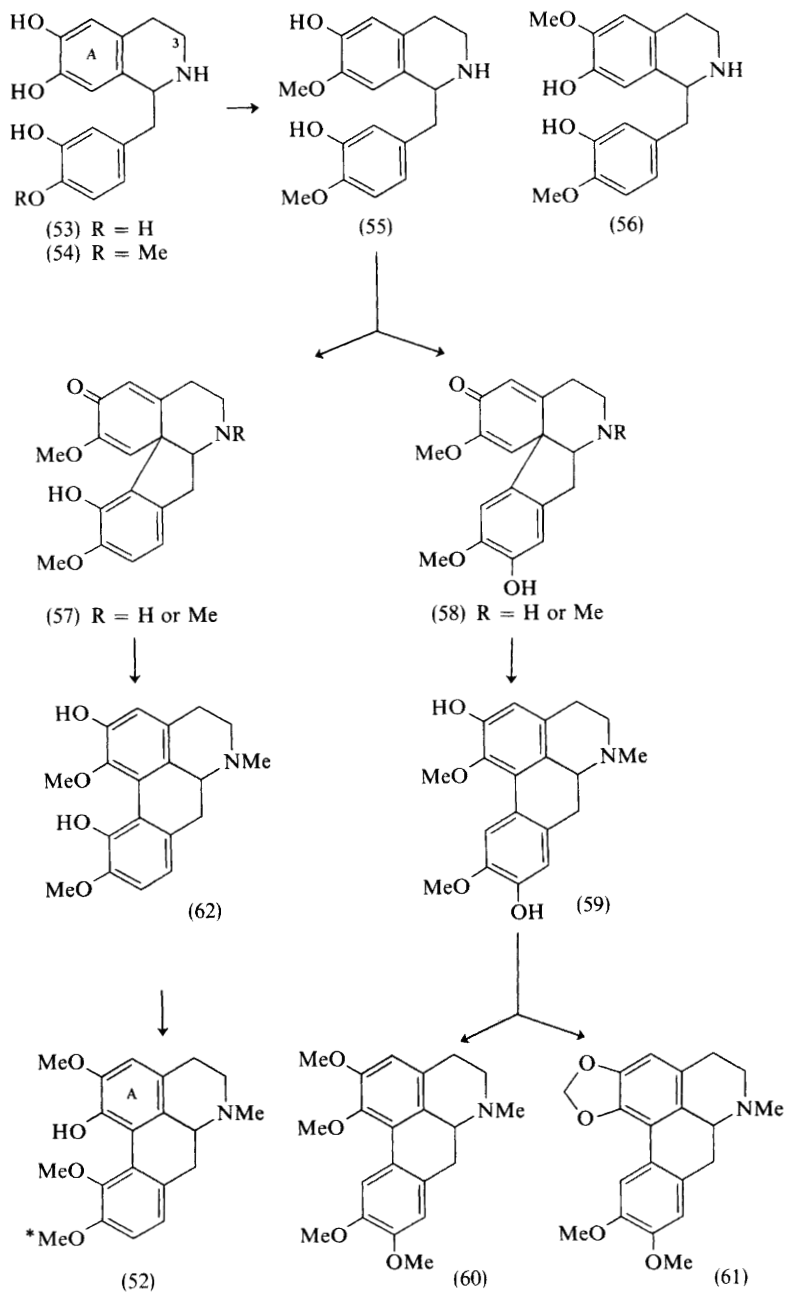[37] A. R. Battersby, J. L. McHugh, J. Staunton, and M. Todd, *Chem. Comm.*, 1971, 985.

Scheme 7

Scheme 8

(53) R = H
(54) R = Me

(55)

(56)

(57) R = H or Me

(58) R = H or Me

(62)

(59)

(52)

(60)

(61)

Scheme 9

showed that neither reticuline nor orientaline is a precursor of the alkaloids. Of course, negative incorporation results are of questionable significance but parallel feedings were carried out with tyrosine to prove that the alkaloids were being produced at the time of the experiment.

Faced with the failure of the two 'obvious' pathways, the investigators were forced to elucidate the pathway step by step. The results of this patient detective work revealed the unexpected pathway shown in Scheme 9. It can be seen from this scheme that the methylation pattern of ring A of corydine (52) provided a false clue because it is the opposite of that in the early precursor (55).

The detective story begins with norlaudanosoline (53), which gave a positive incorporation and thus established that the aporphines are modified benzyliso-quinolines. The corresponding *N*-methyl derivative gave a negative result so the next step involves methylation on oxygen rather than nitrogen. All four possible mono-*O*-methyl derivatives of (53) were tested; only one (54) was an effective precursor. Before going further it was essential to establish that this *O*-methyl group remains intact throughout the biosynthesis. This was proved by feeding the doubly labelled [*O-methyl-*^{3}H,3-^{14}C] compound (54). The labels were incorporated without change in isotopic ratio and the tritium activity in corydine (52) was shown to reside exclusively in the starred methyl group.

The most probable next step is methylation of one of the hydroxy-groups of ring A in (54). Accordingly, the two possible isomers (55) and (56) were synthe-sized; only the former was an effective precursor.

It is not yet clear whether the next stage of the biosynthesis involves an *N*-methylation or phenol coupling. However, given the pattern of *O*-methylation in (55), phenol coupling can take place in two senses leading to the dienones (57) and (58) respectively. Rearrangement of dienone (58) as indicated would lead *via* boldine (59) to glaucine (60) and dicentrine (61). Boldine was tested as a precursor and was efficiently incorporated into both alkaloids.

The remaining alkaloid corydine (52) would derive from the alternative dienone (57), presumably *via* the aporphine (62). In ring A this aporphine has the opposite methylation pattern to corydine. It would be interesting to know if this aporphine is in fact a precursor of corydine and if so how the methylation pattern of ring A is altered to produce the misleading pattern in the alkaloid.

Crotonosine (64) has been observed to incorporate activity when tritiated linearisine (65) was administered to *Croton linearis* plants.[38] The significance of this result is not clear; intuitively one would not expect that (65) would be a true intermediate on the pathway from the accepted[39] precursor, (+)-coclaurine (63).

The cactus alkaloid pilocerine (67) had earlier been shown to incorporate activity from [*N-methyl-*^{14}C]lophocerine (66). This result has been confirmed[40] by feeding [1-^{14}C,*N-methyl-*^{3}H]lophocerine to *Lophocereus schlottii*; the pre-cursor was incorporated intact without change in isotopic ratio.

[38] K. L. Stuart and L. Graham, *Chem. Comm.*, 1971, 392.
[39] L. J. Haynes, K. L. Stuart, D. H. R. Barton, D. S. Bhakuni, and G. W. Kirby, *Chem. Comm.*, 1965, 141.
[40] B. G. O'Donovan, E. Barry, and H. Horan, *J. Chem. Soc. (C)* 1971, 2398.

(63)   (64)   (65)

(66)

● = ^{14}C
* = ^{3}H

(67)
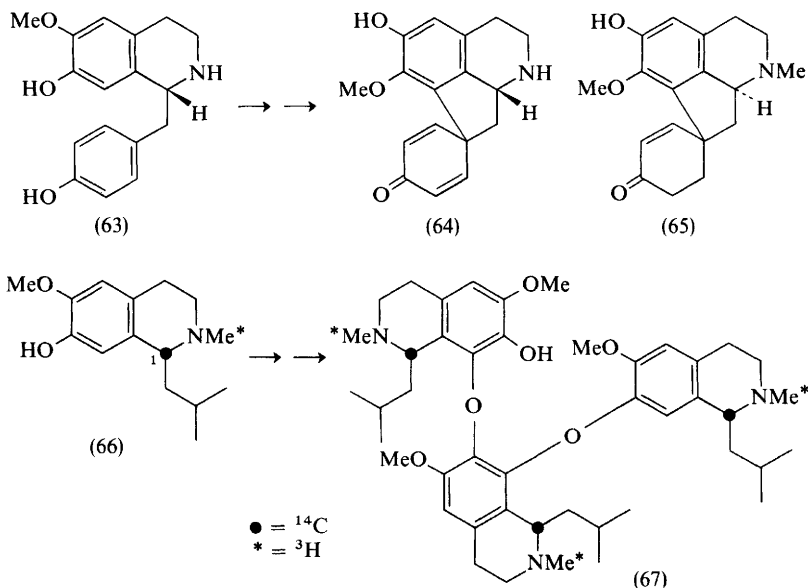
Amaryllidaceae Alkaloids.—Narciclasine (73) occurs in *Narcissus* plants along with the Amaryllidaceae alkaloids haemanthamine (70), lycorine (71), and nor-pluviine (72). The three alkaloids (70), (71), and (72) are derived[41,42] from *O*-methylnorbelladine (68) following pathways outlined in Scheme 10. In path *a* phenol coupling of (68) in the *para–para* direction leads ultimately to haemanthamine (70); *ortho–para* coupling as in path *b* leads to lycorine (71) and nor-pluviine (72).

In view of its structural affinity to both haemanthamine and lycorine, narciclasine could be derived by either pathway. The biosynthesis has now been shown[43] to follow path *a* in Scheme 10 with intermediates related to oxocrinine (69). When *O*-methylnorbelladine (68), multiply labelled with radiocarbon and tritium as indicated, was administered to daffodil plants all four alkaloids incorporated activity. The isotopic ratio [^{3}H:^{14}C] for norpluviine and lycorine was, as expected, 50 % that of the precursor, whereas in haemanthamine the ratio was unchanged. These results prove that (*i*) the *O*-methyl group of (68) is completely retained in the three alkaloids and thus provides a satisfactory internal standard, and (*ii*) the degree of tritium retention is a reliable guide to the direction of phenol coupling. Narciclasine (73) showed an isotopic ratio (75 %) higher than that of lycorine and norpluviine though lower than that of haemanthamine.

[41] A. R. Battersby, H. M. Fales, and W. C. Wildman, *J. Amer. Chem. Soc.*, 1961, **83**, 4098; A. R. Battersby, R. Binks, S. W. Breuer, H. M. Fales, W. C. Wildman, and R. J. Highet, *J. Chem. Soc.*, 1964, 1595.
[42] D. H. R. Barton, G. W. Kirby, J. B. Taylor, and G. M. Thomas, *J. Chem. Soc.*, 1963, 4545.
[43] C. Fuganti, J. Staunton, and A. R. Battersby, *Chem. Comm.*, 1971, 1154
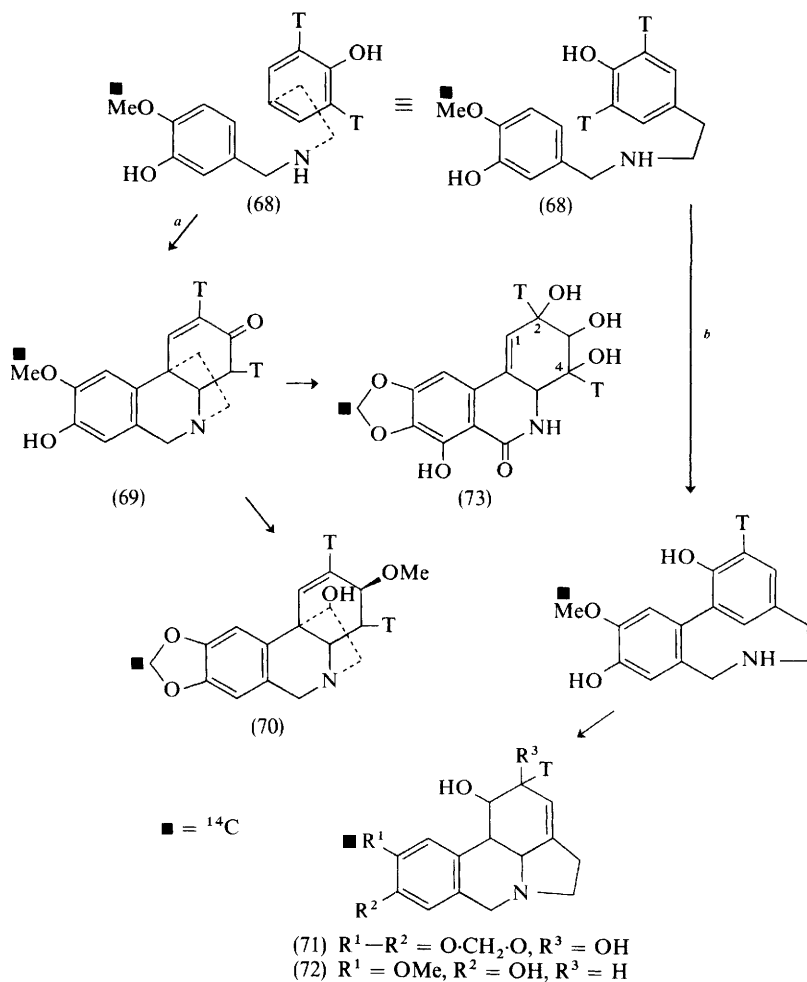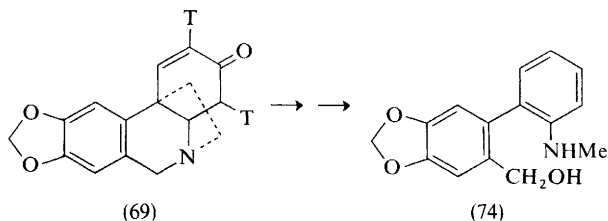
Scheme 10

The fact that more than 50% of the tritium is retained suggests that *O*-methyl-norbelladine is incorporated into narciclasine *via* path *a* rather than path *b* and this conclusion was confirmed by degradation to show that the tritium in narciclasine resides at both C(2) and C(4) as would be expected.

Further evidence for the operation of path *a* to narciclasine was obtained by feeding [³H]oxocrinine (69). The precursor was labelled specifically with tritium as indicated and was incorporated into narciclasine to label the corresponding positions C(2) and C(4).

The alkaloid ismine (74) has also been shown[44] to be a transformation product of oxocrinine (69) (Scheme 11). The precursor (69), labelled with tritium as indicated, was administered to *Sprekelia formosissima* plants. Radioactive ismine was isolated and shown to be specifically labelled with tritium at the expected positions.

Scheme 11

The research on mesembrine (76) has been much less straightforward but after several setbacks it has now reached a particularly interesting stage. The story of this problem so far shows how frustrating biosynthetic work can be when a persuasive structural relationship gives a false lead to the biosynthesis.

Previous studies[45] have demonstrated that tyrosine and phenylalanine follow separate pathways in providing the hydroaromatic C_6—C_2—N unit and the aromatic C_6 unit of mesembrine. In this respect mesembrine follows the pattern, already established for the biosynthesis of the structurally related Amaryllidaceae alkaloids derived from *O*-methylnorbelladine, *e.g.* haemanthamine (70). The present investigation[46] followed this lead and started with a reasonable working hypothesis (Scheme 12) in which the biosynthesis proceeds *via O*-methylnor-belladine (68) and intermediates of the crinine type such as (75). However, feeding
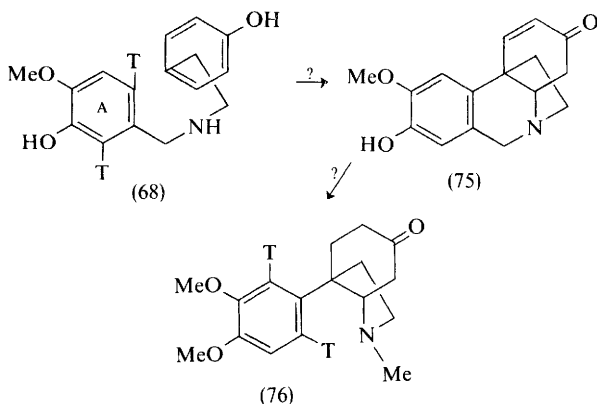
Scheme 12

[44] C. Fuganti and M. Mazza, *Chem. Comm.*, 1970, 1466.
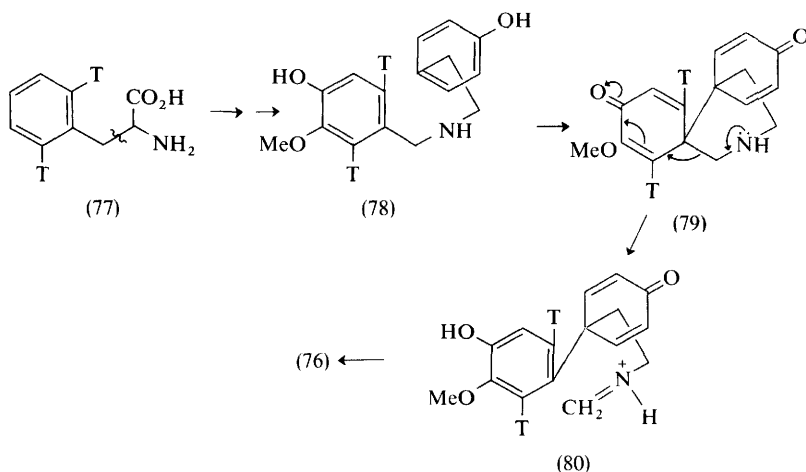[45] P. W. Jeffs, W. C. Archie, and D. S. Farrier, *J. Amer. Chem. Soc.*, 1967, **89**, 2509.
[46] P. W. Jeffs, H. F. Campbell, D. S. Farrier, and G. Molina, *Chem. Comm.*, 1971, 228.

experiments with norbelladine and variously methylated derivatives including (68) gave inconclusive results. For example, activity was incorporated from (68) but the isomer with the reversed methylation pattern in ring A produced a higher incorporation.

The investigators then tested *ortho*-tritiated phenylalanine, which would be expected to label the intermediate (68) with tritium as indicated. If intermediates of the crinine type are involved, a 50% loss of tritium with respect to an internal standard would be expected as a result of the phenol coupling process. Surprisingly, mesembrine was produced without loss of tritium and the alkaloid was found to have the tritium labelling pattern shown in (76) (Scheme 12).

This highly significant result definitely excludes the crinine hypothesis. A second working hypothesis was then adopted (Scheme 13) in which a different O-methyl derivative (78) of norbelladine undergoes phenol coupling to give the spirodienone (79). This scheme nicely accounts for the retention of both *ortho*-hydrogens of phenylalanine (77) and has the added attraction that the fragmentation step (79) → (80) provides an elegant mechanism for the loss of the C_1 unit. The scheme was tested by feeding norbelladine and variously methylated derivatives. A significant incorporation was observed as before for norbelladine and for (78) but, disappointingly, double-labelling experiments proved that neither precursor was incorporated intact. This surprising result would seem to rule out not only the spirodienone route in Scheme 13 but also any scheme based on the proposed biosynthetic relationship with the Amaryllidaceae alkaloids. Fortunately, the experiment with *ortho*-tritiated phenylalanine provides an invaluable guide for the design of future experiments and there is the promise that the investigators will be rewarded for their painstaking and frustrating work by the discovery of an extremely interesting and novel biosynthetic pathway.
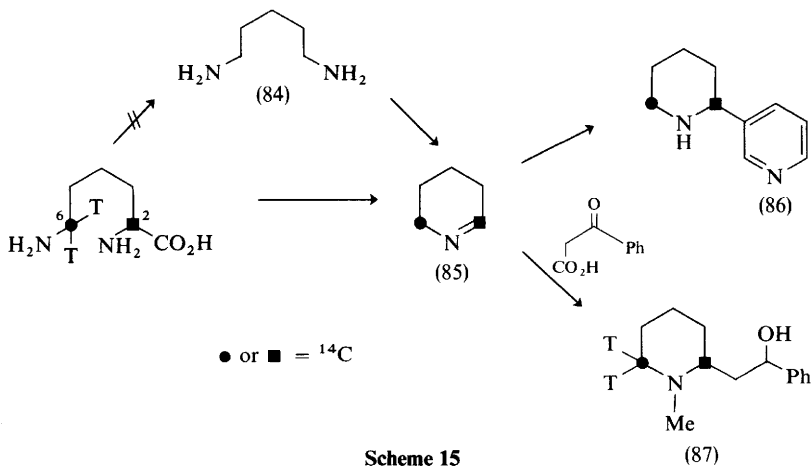

Scheme 13

There is a developing interest in the stereochemistry and mechanism of reactions involved in biosynthesis, particularly those reactions which involve the removal of a hydrogen and can, therefore, be investigated by feeding precursors labelled with deuterium or tritium. The introduction of the hydroxy-group residing at the marked carbon (●) of haemanthamine (83) (Scheme 14) provides a typical example of this type of problem. The stereochemistry of this reaction has been investigated by two groups and it has been shown that the hydroxylation proceeds with retention of configuration (*i.e.* the incoming hydroxy-group adopts the same configuration as the displaced hydrogen).

The first group[47] synthesized the late precursor O-methylnorbelladine (82) stereospecifically labelled with tritium on the marked carbon. The (R)- and (S)-isomers were fed separately to daffodil plants in admixture with a ^{14}C standard; the former isomer (82; H_R = T) largely lost its tritium, in the biosynthesis, whereas with the latter (82; H_S = T) the tritium was largely retained. Since the stereochemistry of the hydroxy-group of haemanthamine is known, this result shows that hydroxylation has occurred with retention of configuration.

However, before mechanistic conclusions can be drawn from this experiment it is essential to determine whether the neighbouring methylene, C(1) of O-methyl-norbelladine (82), is involved in the hydroxylation process. This possibility was ruled out by showing that no tritium was lost with respect to an internal standard on incorporation of O-methyl-[1,1-$^3H_2$]norbelladine (82). Thus, the hydroxyla-tion reaction corresponds to a direct insertion of an oxygen species into a C—H bond.

The second group[48] used L-tyrosine (81) stereospecifically labelled at C(3) with tritium to determine the stereochemistry of the hydroxylation reaction. Both the (3R)- and (3S)-isomers were tested and it was shown that H_R of (81) was lost whereas H_S was retained.

Scheme 14

Lysine and the Piperidine Alkaloids.—The amino-acid lysine serves as the precursor of a piperidine ring in the biosynthesis of a large number of alkaloids. Several alkaloid families are under active investigation and because the attack on this problem is taking place on several fronts, progress is difficult to follow.

[47] A. R. Battersby, J. Kelsey, and J. Staunton, *Chem. Comm.*, 1971, 183.
[48] G. W. Kirby and J. Michael, *Chem. Comm.*, 1971, 187, 415.

Therefore, a brief outline of the salient features of past work is desirable to help to put current results in perspective.

The alkaloids anabasine (86) and sedamine (87) are typical representatives of one such alkaloid family; past results suggest that they are both formed by condensation of a suitable nucleophile with a unit of Δ^1-piperideine (85) derived from lysine (Scheme 15). The nucleophile is possibly benzoylacetic acid for sedamine[49] and has been shown to be derived from nicotinic acid for anabasine.[50] The origin of the different side-chains will be discussed in detail later under the individual alkaloids. For the moment this account will focus on the pattern of incorporation of lysine and will try to correlate the results from different systems.

Some earlier results for sedamine and anabasine are illustrated in Scheme 15. Activity was incorporated from cadaverine (84) into the piperidine ring of anabasine.[51] However, the incorporation from lysine was specific for both sedamine[52] and anabasine[53] as indicated in Scheme 15, so that the two ends of the lysine chain must retain their separate identities throughout the biosynthesis.

Scheme 15

Therefore, cadaverine (84), because of its symmetry, cannot serve as an intermediate between lysine and the alkaloids. Other significant findings are that the nitrogen on C-6 of lysine is retained in anabasine[54] and that both hydrogens on

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[49] R. N. Gupta and I. D. Spenser, *Canad. J. Chem.*, 1967, **45**, 1275.

[50] M. L. Solt, R. F. Dawson, and D. R. Christman, *Plant Physiol.*, 1960, **35**, 887.

[51] E. Leete, *J. Amer. Chem. Soc.*, 1958, **80**, 4393.

[52] R. Bentley, in 'Biogenesis of Antibiotic Substances'; ed. Z. Vanek and Z. Hostalik, Publishing house of the Czechoslovak Academy of Sciences, Prague, 1965, p. 241.

[53] J. R. Hanson and B. Achilladelis, *Tetrahedron Letters*, 1967, 1295; L. G. Paleg, *Ann. Rev. Plant Physiol.*, 1965, 16; B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J. Chem. Soc.*, 1964, 295.

[54] B. E. Cross and K. Norton, *Chem. Comm.*, 1965, 535; E. Leete, *J. Amer. Chem. Soc.*, 1964, **86**, 3907.

C(6) are retained in sedamine.[55] All these results can be accommodated by the sequence of intermediates in path *a* of Scheme 16.

Further work[56] has now disproved this pathway, at least for sedamine. When [2-³H,6-¹⁴C]lysine was administered to *Sedum acre* the alkaloid incorporated both labels with an unchanged isotopic ratio. Thus, the hydrogen at C(2) of lysine is not lost in the biosynthesis as would be required for pathway *a*. An alternative sequence, path *b* (Scheme 16) satisfactorily accommodates the fresh evidence. Decarboxylation at C-2 now precedes rather than follows the oxidation step. To avoid the generation of a symmetrical diamine, the amino-group at C(6) is differentiated by methylation in the first step.
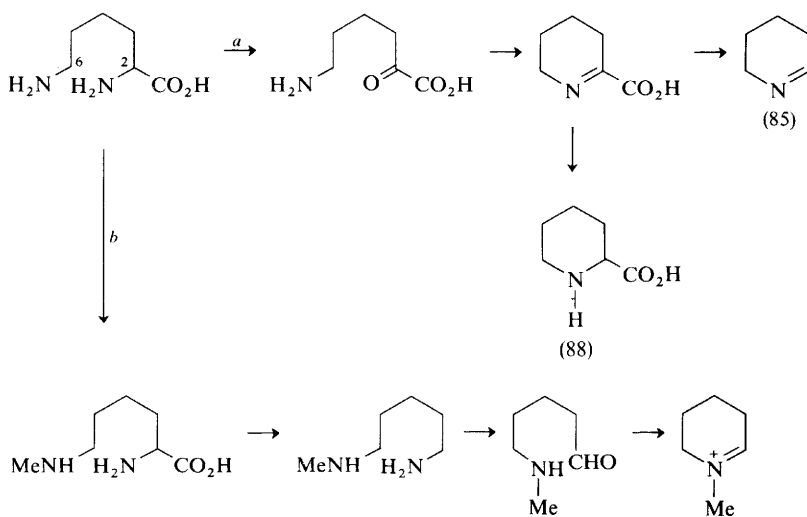
Scheme 16

It will be interesting to see if the hydrogen at C(2) of lysine is retained in the biosynthesis of the other alkaloids of this family, such as anabasine (86) and pelletierine (89), where the nitrogen atom is not methylated. It is significant that the pipecolic acid (88) produced along with the sedamine in this experiment, was devoid of tritium. Therefore, the pathway *a* could be in operation for this natural product and it may be the normal route for some of the alkaloids also.

The alkaloids *N*-methylpelletierine (90) and pseudopelletierine (91) of *Punica granatum* and also anaferine (92) of *Withania somnifera* are probably related in biosynthesis to sedamine and anabasine. The proposed biosynthesis (Scheme 17) has received support from recent tracer studies.[57]

[55] R. N. Gupta and I. D. Spenser, *J. Biol. Chem.*, 1969, **244**, 88.
[56] R. N. Gupta and I. D. Spenser, *Phytochemistry*, 1970, 9, 2329.
[57] M. F. Keogh and D. G. O'Donovan, *J. Chem. Soc. (C)*, 1970, 1792.
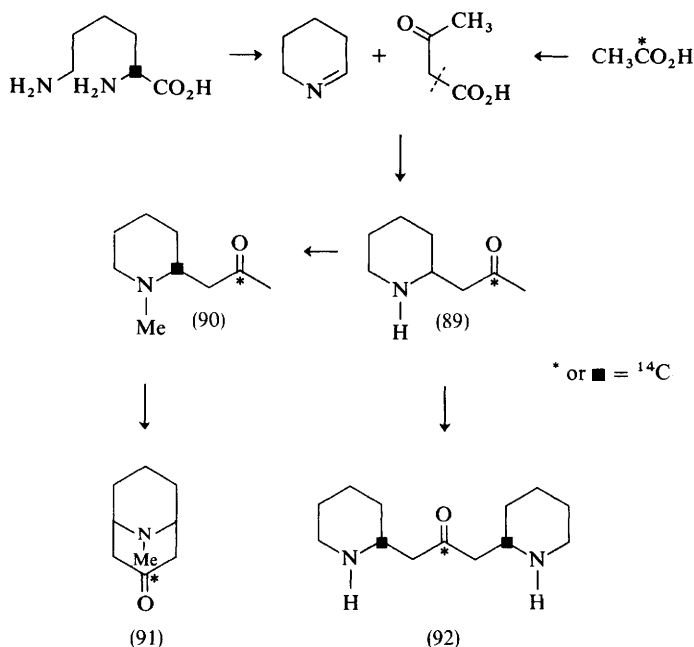
Scheme 17

In experiments with intact plants, the activity from [1-^{14}C]acetate was found to be incorporated specifically into the predicted position for each alkaloid. In parallel experiments with [2-^{14}C]acetate, N-methylpelletierine was degraded and shown to have, as expected, 50% of the activity located in the C-methyl group. The sequence of intermediates in the late stages of the pathway were investigated with the following results; (i) N-methylpelletierine (90) is incorporated into pseudopelletierine (91), and (ii) pelletierine (89) is a precursor of anaferine (92).

The results on the pattern of incorporation of lysine in this system are of general interest. Activity from [2-^{14}C]lysine was incorporated specifically, as indicated, into both anaferine (92) and N-methylpelletierine (90). Thus, no symmetrical intermediate is involved in the biosynthesis, although it is not clear at this stage which of the two pathways from lysine (Scheme 16) is in operation in these plants.

The alkaloid (93) which is produced by *Haloxylon salicornicum* shows a structural resemblance to pelletierine (89). A feeding experiment[58] with [6-^{14}C]-lysine in intact plants has supported the related biosynthesis in Scheme 18. Activity was incorporated at C(6) of the alkaloid as shown. Surprisingly, no activity was incorporated from [2-^{14}C]acetate but this negative result could be due to the failure of acetate to reach the site of synthesis.

[58] D. G. O'Donovan and P. B. Greedon, *Tetrahedron Letters*, 1971, 1341.

$\bullet = {}^{14}C$

Scheme 18

(93)
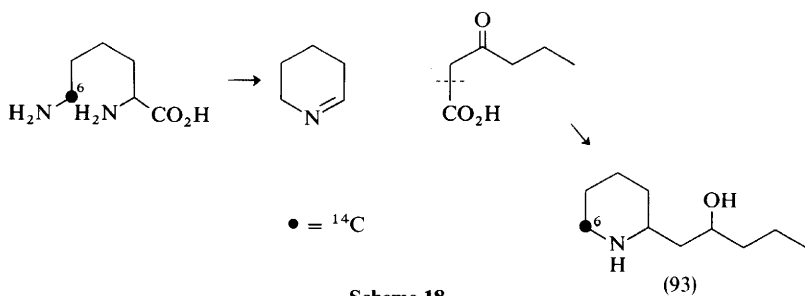
In each of the alkaloids discussed so far, lysine has been found to be incorporated into the piperidine ring without the intervention of a symmetrical intermediate. However, examples have been discovered recently where lysine is incorporated symmetrically, *e.g.* cernuine,[59] decodine (97),[60] and now lobeline (96).[61] It is possible, though not yet proven, that cadaverine is an intermediate in the biosynthesis of these alkaloids.

The evidence[61] for a symmetrical intermediate in the biosynthesis of lobeline came from an incorporation experiment with [2-^{14}C]lysine. The alkaloid was degraded to show that C(2) probably carries 50% of the activity; the remaining activity was assumed to reside at C(6). If this assumption is valid, then lysine is incorporated symmetrically into lobeline.

The pattern of incorporation is in marked contrast with that observed for the closely related alkaloid sedamine (see Scheme 15). However, there is a potentially symmetrical intermediate (95, Scheme 19) in the late stages of the proposed pathway to lobeline so that lysine may still be incorporated non-symmetrically into the early piperidine intermediate (94) by one of the two paths in Scheme 16.

In the working hypothesis the side-chains are derived by successive condensation of two units of benzoylacetate. The proposal was tested[61] by administration of [2,3-^{14}C$_2$]phenylalanine, a plausible precursor of benzoylacetate. A good incorporation was observed and it was shown by degradation that the phenylalanine was incorporated as an intact C$_6$—C$_2$ unit to provide at least one and possibly both of the side chains.

Earlier work[60] on the Lythraceae alkaloid decodine (97) had shown that lysine is incorporated symmetrically into the piperidine ring A. The contribution of phenylalanine has been further investigated[62] by incorporation experiments with multiply-labelled [1,3-^{14}C]phenylalanine. The alkaloid incorporated activity at three positions and the results are summarized in Scheme 20. The ratio of the activities at C(1) and C(3) was the same as that of the precursor so that ring D together with C(1'), C(2'), and C(3') comprise an intact C$_6$—C$_3$ unit. Activity was also present at C(1) but not at C(3); thus a C$_6$—C$_3$ unit is not involved in this

[59] R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *Chem. Comm.*, 1970, 409.
[60] S. H. Koo, R. N. Gupta, I. D. Spenser, and J. T. Wrobel, *Chem. Comm.*, 1970, 396.
[61] M. F. Keogh and D. G. O'Donovan, *J. Chem. Soc. (C)*, 1970, 2470.
[62] S. H. Koo, F. Comer, and I. D. Spenser, *Chem. Comm.*, 1970, 897.
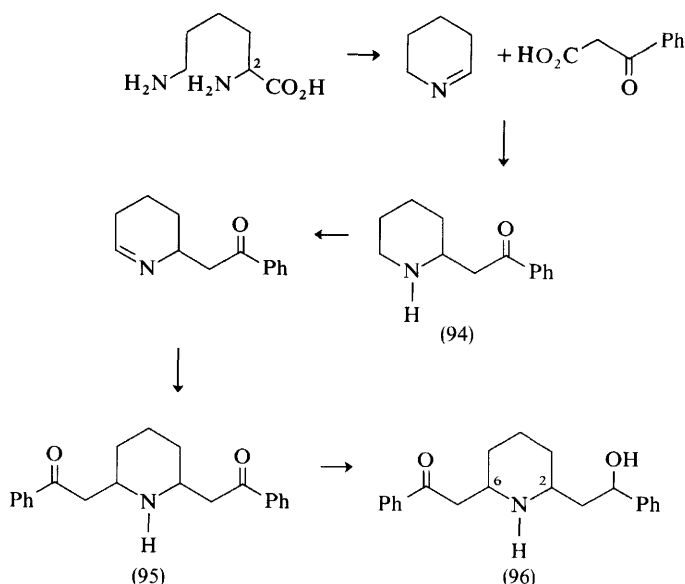
Scheme 19
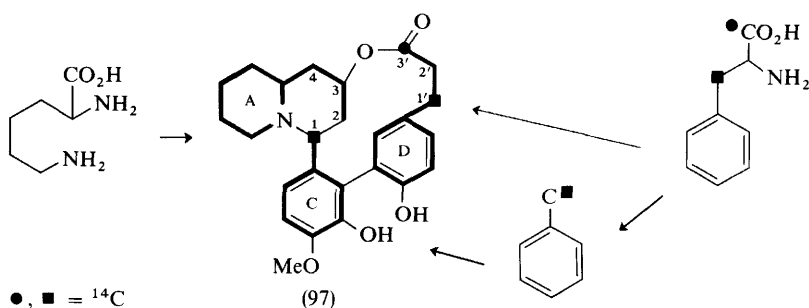
Scheme 20

case and ring C must derive from a C_6—C_1 unit or a C_6—C_2 unit. Intuitively, the former possibility would seem more probable because the remaining carbons [ring A plus C(4), C(3), and C(2)] then correspond to a pelletierine (89) unit. If pelletierine is an intermediate the symmetrical incorporation of lysine in this plant contrasts with the non-symmetrical incorporation into the pelletierine unit of anaferine (92) in *Withania somnifera*.

Thus, no clear pattern has yet emerged for the role of lysine in alkaloid biosynthesis. It is possible that at least three pathways can operate from lysine to Δ^1-piperideine or its *N*-methyl derivative; one would involve a symmetrical

intermediate such as cadaverine, the other two (Scheme 16) would not. A further complication arises from the fact that a particular alkaloid, such as pelletierine, might be derived by different pathways in different plants. Much further work will be required to clarify this complex situation.

The lupin alkaloids sparteine (98) and lupanine (99) are both derived from lysine, and it is possible on the basis of past work that either one may be a precursor of the other.[63] However, recent work suggests that they are derived by divergent pathways.[64]

(98)   (99)
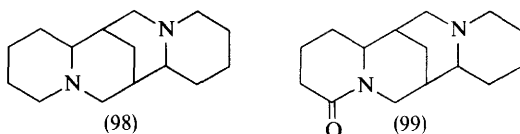
The evidence that lupanine is not an intermediate in sparteine biosynthesis came from experiments in which *Lupinus arboreus* plants were exposed to radio-active carbon dioxide for varying periods; the sparteine became radioactive in every experiment but the lupanine remained consistently non-radioactive.

The evidence against sparteine being an intermediate in lupanine biosynthesis is less convincing. When *L. polyphyllus* plants were exposed to radioactive carbon dioxide the lupanine became radioactive. Attempts to detect sparteine in the extracts by chemical and radiochemical analysis gave negative results. This result suggests that sparteine is not present in this plant and is not, therefore, an intermediate in lupanine biosynthesis. However, it is possible that sparteine is involved but that the pool size is too small to be detected.

Coniine.—In each of the piperidine alkaloids discussed so far the piperidine ring was derived from lysine. However, in the case of coniine (100) all the carbon atoms are derived from acetate and lysine is not a precursor.[65] The discovery[66]

MeCO$_2$H → HO$_2$C ... → OHC ...

(100)
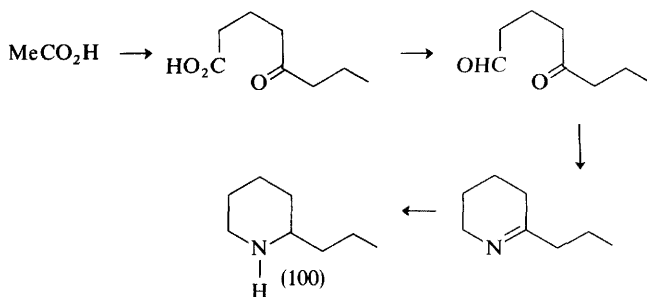
Scheme 21

[63] For review see I. D. Spencer, in 'Metabolism of Cyclic Compounds', ed. M. Florkin and E. H. Stotz, Elsevier Publishing Company, Amsterdam, 1968, p. 262.

[64] V. D. Cho, R. O. Martin, and J. N. Anderson, *J. Amer. Chem. Soc.*, 1971, **93**, 2087.

[65] E. Leete, *J. Amer. Chem. Soc.*, 1964, **86**, 2509.

[66] E. Leete, *J. Amer. Chem. Soc.*, 1970, **92**, 3835.

that octanoic acid is also a specific precursor of coniine in the hemlock plant, *Conium maculatum*, has been followed up by incorporation experiments[67] with 5-keto-[6-^{14}C]octanoic acid and the corresponding [6-^{14}C]aldehyde (Scheme 21). Both compounds were found to be efficient and specific precursors of coniine. In addition, a dilution analysis experiment showed that the radioactive keto-acid is present in the hemlock plant after administration of [1-^{14}C]octanoate. The sequence of intermediates in Scheme 21 is consistent with these findings.

Hyoscyamine.—Hyoscyamine (103) is a member of a large family of alkaloids in which a pyrrolidine ring is derived from ornithine. The biosynthetic pathway to hyoscyamine shown in Scheme 22 is supported by a wealth of evidence from past work.[68] It is noteworthy that the route from ornithine to (102) parallels exactly the corresponding sequence (path *b*, Scheme 16) by which lysine is converted to Δ^1-piperideine in the currently favoured route to sedamine. Further support[69] for this sequence has come from the administration of N^δ-methyl-ornithine (101) to *Datura stramonium* plants. The precursor was multiply labelled with ^{14}C as indicated and the activity was incorporated specifically into the corresponding positions of the alkaloid, without change in isotopic ratio. In contrast, the N^α-methyl isomer of ornithine was biologically inert.
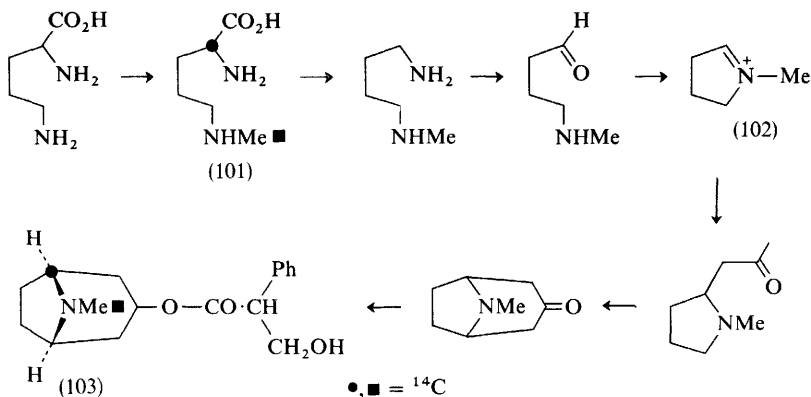
Scheme 22

Tylophorine.—As a result of current work,[70] the biosynthesis illustrated in Scheme 23 has been proposed for tylophorine (104). The evidence came from incorporation experiments in *Tylophora asthmatica* plants with [2-^{14}C]phenyl-alanine and [2-^{14}C]tyrosine respectively. The alkaloid from each feeding was degraded to establish the labelling pattern shown in (104). Thus, tyrosine and phenylalanine are incorporated by completely separate pathways, probably as a

[67] E. Leete and J. O. Olson, *Chem. Comm.*, 1970, 1651.
[68] For recent reviews see ref. 63, p. 246 and ref. 73, p. 9.
[69] A. Ahmad and E. Leete, *Phytochemistry*, 1970, 9, 2345.
[70] N. B. Mulchandani, S. S. Iyer, and L. P. Badheka, *Phytochemistry*, 1971, 10, 1047.

C_6—C_2 unit in each case, to provide ring A + C(10) + C(6) and ring B + C(9) + C(7), respectively. The scheme employs a Δ^1-pyrrolidine unit derived from ornithine; specifically labelled ornithine gave rise to radioactive tylophorine but the pattern of incorporation has not yet been established.

$\bullet$, $\blacksquare$ = ^{14}C
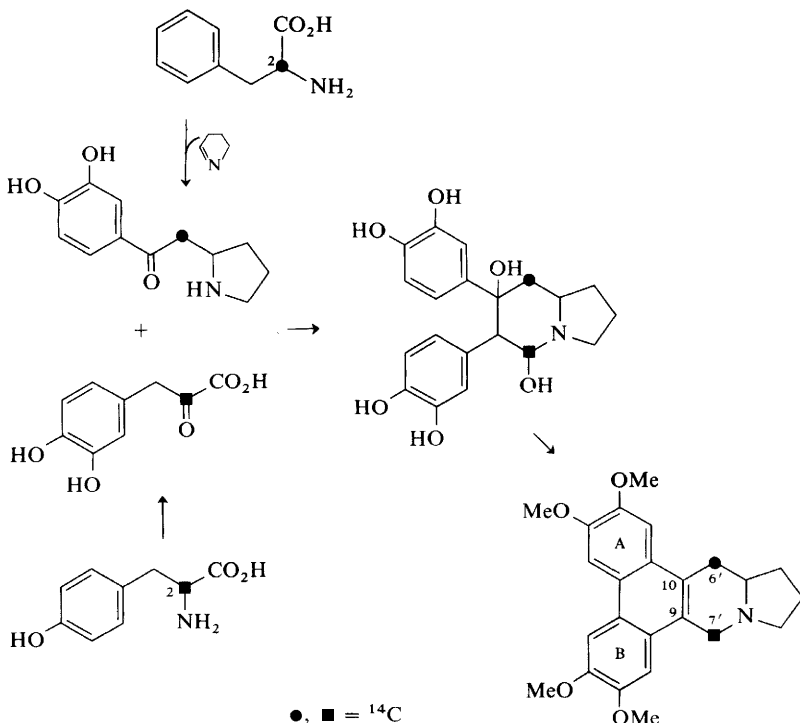
Scheme 23   (104)

Quinoline Alkaloids.—The pseudans, *e.g.* (105), have now been shown to be biosynthesized by combination of a unit of anthranilate with a β-keto-acid (Scheme 24).[71] [1-^{14}C]Acetate, [2-^{14}C]acetate, and [1-^{14}C]malonate were administered to *Pseudomonas aeruginosa* and the metabolite produced in each case was degraded to determine the labelling pattern at four key positions: C(2), C(3), C(6'), and C(7'). These precursors were incorporated into the side chain together with C(2) and C(3) and the results were consistent with the alternating labelling pattern expected for an acetate–polymalonate biosynthesis. In contrast with earlier results,[72] C(3) was found to derive from the methylene group of malonate. Anthranilic acid was shown to be a precursor of the anthranilic moiety. Thus, all

[71] C. Ritler and M. Luckner, *European J. Biochem.* 1971, **18**, 391.
[72] M. Luckner, *Abhandl, Deut. Akad. Wiss., Berlin, K. Chem. Geol. Biol.*, 1966, **3**, 445.

the carbons are accounted for and the results support the biosynthesis outlined in Scheme 24.
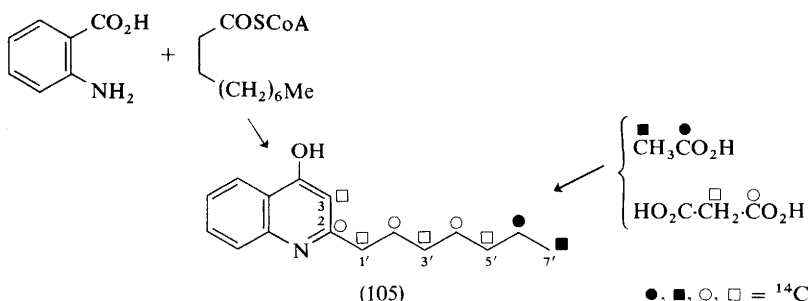
Scheme 24

The biosynthesis is closely related to the already established route to the quinoline system of the furanoquinoline alkaloids such as skimmianine (107) (Scheme 25). Two papers have been published this year on the biosynthesis of (107) but they add nothing new to the earlier work reviewed last year.[73] Briefly, the results confirm that (*i*) C(2) and C(3) of the furan ring of (107) are derived in *Fagara coco* plants from C(4) and C(5) respectively of mevalonic acid,[74] (*ii*) in the same plant, activity is incorporated specifically at C(3) of the furan from C(1) of dimethylallyl alcohol,[75] and (*iii*) 2,4-dihydroxy[3-^{14}C,^{15}N]quinoline (106) is an efficient and specific precursor of the quinoline system of (107) in *Ruta graveolens* and is incorporated without randomization.[75] Surprisingly, the isomer kokusaginine (108) showed a random incorporation in this experiment.

(107) R^1 = H, R^2 = OMe
(108) R^1 = OMe, R^2 = H
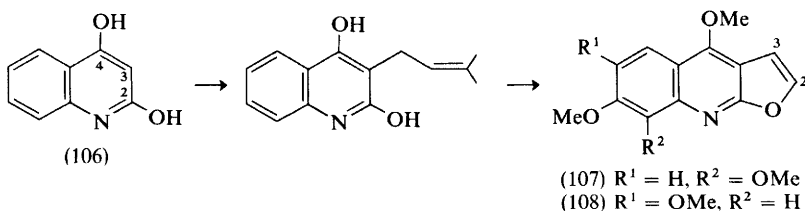
Scheme 25

Arborine.—The biosynthesis of arborine in *Glycosmis arborea* plants has been studied by two groups. The results are to some extent in conflict so that it is not clear which of the two pathways, *a* or *b*, in Scheme 26 is correct. In view of this dichotomy the two sets of results will be presented separately.

[73] R. B. Herbert, in ref. 1, p. 12.
[74] A. O. Colonna and E. G. Gros, *Phytochemistry*, 1971, **10**, 1515.
[75] M. Cobet and M. Luckner, *Phytochemistry*, 1971, **10**, 1031.
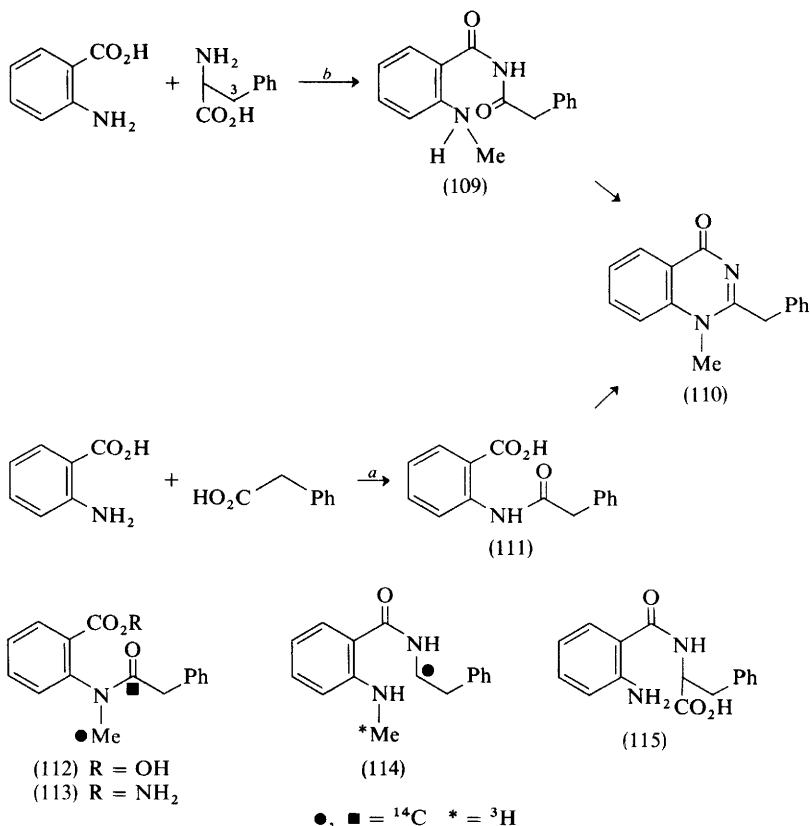
Scheme 26

The first group[76] report results consistently in favour of path *a*. Administration of [*carboxy*-^{14}C]anthranilic acid to intact plants produced a low but specific incorporation into the anthranilate part of the molecule. DL-[3-^{14}C]Phenylalanine, [1-^{14}C]phenethylamine, and [1-^{14}C]phenylacetic acid were each incorporated specifically into the phenylacetic acid residue; although each of these results is compatible with path *a*, the incorporation levels were low and there was no detectable trend to indicate the sequence of intermediates. However, very strong support for path *a* came from feeding experiments with (112) and (114) multiply labelled with carbon or carbon and tritium as indicated. The former substance, (112), was incorporated efficiently and specifically to label the expected two positions with an unchanged isotopic ratio; the latter, (114), exhibited low biological efficiency and a changed isotopic ratio on incorporation. Thus, all these results are consistent with, or support, path *a*.

[76] D. G. O'Donovan and H. Horan, *J. Chem. Soc. (C)*, 1970, 2466.

In the second investigation[77] the specific incorporation of an anthranilate unit was confirmed by feeding [Me-^{14}C]N-methylanthranilic acid. In further work (115) and (113) labelled with ^{3}H and ^{14}C respectively were fed to *Glycosmis arborea* plants; the latter was incorporated well, whereas the former was not. These results again argue for path *a* and against path *b*.

The conflicting evidence came from the demonstration that activity is incorporated from [3-^{14}C, ^{15}N]phenylalanine without change in isotopic ratio. This result would argue against degradation of the amino-acid to phenylacetic acid prior to incorporation, as implied in path *a*. However, one cannot rule out the possibility that phenylalanine is degraded to singly labelled species (*e.g.* ammonia and phenylacetic acid) and that these are later recombined to give a true precursor with, fortuitously, the same isotopic ratio as the administered amino-acid.

It is significant that both groups observed the efficient incorporation of a phenylacetamide derivative, (112) and (113) respectively, and on balance the evidence at this stage of the investigation is weighted in favour of path *a*.

Annuloline.—The unique oxazole alkaloid annuloline (119), produced by the annual rye grass *Lolium multiflorum*, is derived by the unexceptional biosynthetic route shown in Scheme 27.[78] Activity was incorporated into both halves of the

Scheme 27

[77] S. Johne, K. Waiblinger, and D. Gröger, *European J. Biochem.*, 1970, **15**, 415.
[78] D. G. O'Donovan and H. Horan, *J. Chem. Soc.* (*C*), 1971, 331.

molecule to label the marked positions when [3-^{14}C]phenylalanine was admini-stered to whole plants; the same labelling pattern was produced by incorporation of [3-^{14}C]tyrosine. In the later stages of the biosynthesis the routes leading to the two halves of the molecule are completely discrete. Thus, tyramine (116) labelled only the left-hand side of the molecule, whereas dopa (117) and cinnamic acid (118) were incorporated only into the right-hand side.

Dolichotheline.—The biosynthesis of dolichotheline (120) in intact *Dolichothele sphaerica* cacti plants is straightforward.[79] An experiment with DL-[2-^{14}C]hista-mine (123) showed that the histamine residue arises specifically from this pre-cursor. The isovaleryl unit incorporated activity efficiently from DL-[2-^{14}C]-leucine (121) and [1-^{14}C]isovalerate (122) to label in each case the carbonyl group of (120) (Scheme 28); mevalonic acid was a specific but less efficient precursor of this residue.
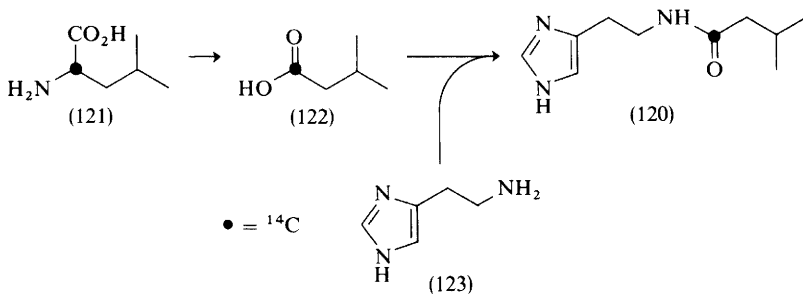
Scheme 28

In incorporation studies[80] with intact *Withania somnifera* plants, the pyrazole alkaloid withasomnine (124) incorporated activity from DL-[3-^{14}C]phenylalanine (0.002 %) and DL-[2-^{14}C]ornithine (0.004 %). No degradations were carried out so the significance of these very low incorporations is not clear.

(124)
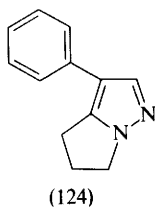
[79] H. Horan and D. G. O'Donovan, *J. Chem. Soc. (C)*, 1971, 2083.
[80] D. G. O'Donovan and T. J. Forde, *Tetrahedron Letters*, 1970, 3637.

2
Pyrrolidine, Piperidine, and Pyridine Alkaloids

BY V. A. SNIECKUS

Introductory surveys of these groups form parts of two chapters in an excellent general volume on the chemistry of alkaloids.[1,2] A short review dealing with selected alkaloids of potential medicinal interest includes mention of a pyridine alkaloid.[3] A review on the use of n.m.r. spectroscopy in structural and conformational elucidation of piperidine, pyridine, and monoterpenoid alkaloids is not readily accessible.[4]

Consideration to the interesting group of pyrrole antibiotics obtained from *Pseudomonas aeruginosa* is not given in this Report, but is given elsewhere.[5]

1 Pyrrolidine Alkaloids

The structure $(1; R^1 = Me, R^2 = OH, R^3 = OMe)$ previously assigned[6] to codonopsine has been discarded and a new structure $(1; R^1 = OH, R^2 = Me, R^3 = OMe)$ has been deduced on the basis of n.m.r. spectral and Hofmann degradation studies.[7] Another alkaloid, codonopsinine, isolated from the same species, *Codonopsis clematidea*, has been assigned structure $(1; R^1 = OH, R^2 = Me, R^3 = H)$.[8]

Relatively few new alkaloids have been isolated. Two groups have obtained *trans*-3-ethylidene-2-pyrrolidone ('alkaloid P') (2) from *Corydalis pallida* var. *tenuis*.[9,10] The structure was deduced from spectral data and by hydrogenation

[1] A. Brossi and B. Pecherer in 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, p. 11.
[2] R. K. Hill in 'Chemistry of the Alkaloids,' ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, p. 385.
[3] M. Shamma, *Ann. Reports Medicin. Chem.*, 1969, 323.
[4] M. Vlassa, *Studii Cercetari Chim.*, 1970, **18**, 1109 (*Chem. Abs.*, 1971, **74**, 125 875y).
[5] D. M. Bailey and R. E. Johnson, *Tetrahedron Letters*, 1970, 3555; S. Umio, K. Kariyone, K. Tanaka, T. Kishimoto, H. Nakamura, and M. Nishida, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1414; S. Umio and K. Kariyone, *J. Japanese Chem.*, 1970, **24**, 809 (*Chem. Abs.*, 1970, **73**, 130 804h); S. Umio and K. Kariyone, *ibid.*, 1970, **24**, 903 (*Chem. Abs.*, 1971, **74**, 22 639v).
[6] S. F. Matkhalikova, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 30 (*Chem. Abs.*, 1969, **71**, 13 245z).
[7] S. F. Matkhalikova, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 606 (*Chem. Abs.*, 1970, **73**, 15 050x).
[8] S. F. Matkhalikova, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 607 (*Chem. Abs.*, 1970, **73**, 25 712d).
[9] H. Kaneko and S. Naruto, *J. Pharm. Soc. Japan*, 1971, **91**, 101 (*Chem. Abs.*, 1971, **74**, 142 108t).
[10] T. Kametani, M. Ihara, and T. Honda, *J. Chem. Soc. (C)*, 1970, 1060.

to a dihydro-derivative. The latter was shown not to be 5-ethyl-2-pyrrolidone by synthesis. Final confirmation of the assigned structure (2) was obtained by total synthesis (Scheme 1) from compounds (3) and (5) *via* the common intermediate (4).[11]

Two cinnamoylpyrrolidine alkaloids (6; $R^1 = R^2 = H$, $n = 1$) and (6; $R^1 = OMe$, $R^2 = H$, $n = 1$) have been isolated from *Piper methysticum* (kava roots) for the first time.[12] A detailed re-investigation of the constituents in black pepper (*Piper nigrum*) has been published.[13] Aside from several piperidine alkaloids, piperyline (6; $R^1 + R^2 = OCH_2O$, $n = 2$) was isolated and fully characterized by spectral and chemical means and by synthesis, utilizing a Wittig reaction as the key step.

(1)

(2)

iii—v

(3)   i, ii → (4) ← i, vi   (5)
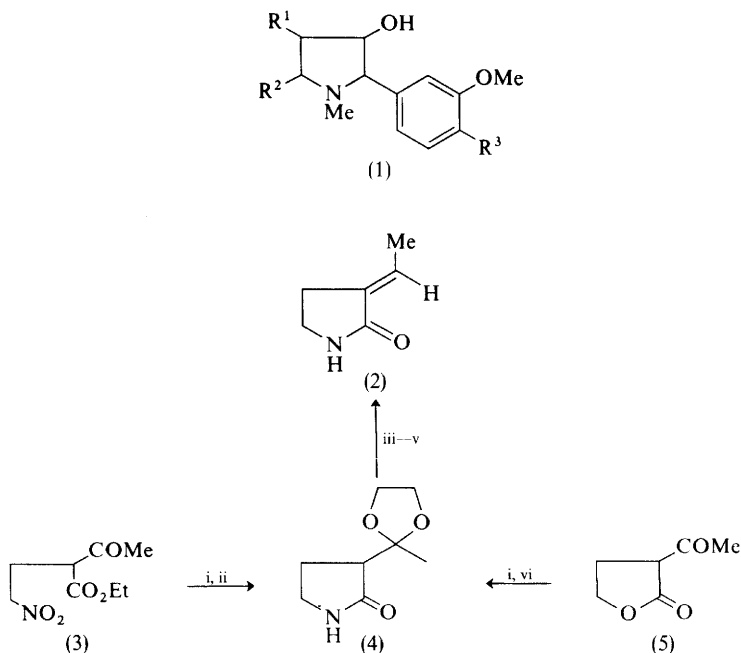
Reagents: i, $HOCH_2CH_2OH$, TsOH; ii, H_2, PtO_2; iii, TsOH; iv, $NaBH_4$; v, $POCl_3$;
    vi, NH_3, 210 °C.

Scheme 1

(6)
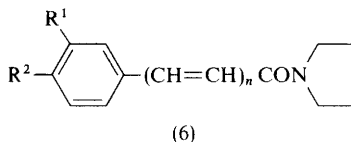
[11] T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), 1971, 999.
[12] H. Achenbach and W. Karl, *Chem. Ber.*, 1970, **103**, 2535.
[13] R. Grewe, W. Freist, H. Neumann, and S. Kersten, *Chem. Ber.*, 1970, **103**, 3752.

2 Piperidine Alkaloids*

The mass spectra of the alkaloids cassine (7), bicyclocassine (8), and closely related derivatives were shown to exhibit ions resulting from an anomalous expulsion of the acetonyl group.[14] For example, in cassine the mass spectrum exhibits a base peak corresponding to the ion (m/e 114) resulting from cleavage of the alkyl chain adjacent to the nitrogen. However, the strongest ion at m/e greater than 114 is that at m/e 240 resulting by loss of CH_2COMe from the molecular ion. This was confirmed by accurate mass measurements and by inspection of the spectrum of pentadeuteriocassine. Interestingly, peaks due to the McLafferty rearrangement were not observed, in agreement with recent results demonstrating that it occurs to an insignificant extent when the ionic charge is localized far from the keto-group.[15] Furthermore, the spectrum of (8) showed an even more abundant ion resulting from loss of acetonyl, presumably due to the less favourable nature of the cleavage adjacent to the nitrogen (Bredt's rule violation).

The isolation of campedine (9) from *Campanula medium*[16] and piperoleine A (10; $n = 6$) and piperoleine B (10; $n = 4$) from *Piper nigrum*[13] constitute the only reports of isolation of new alkaloids from land plant sources. The structures of the last two alkaloids were determined by spectral and chemical means. For example, piperoleine A was hydrolysed to the corresponding carboxylic acid, which was identical with synthetic material prepared by a route involving the Wittig reaction of the phosphorane (11) with $OHC(CH_2)_6CO_2Et$. Another alkaloid, piperoleine C, was isolated but its structure remains unknown. It has long been believed that chavicine, also isolated from *P. nigrum*, possesses the structure (12; *cis, cis*) and that this alkaloid is responsible for the hot taste of pepper. Re-examination of earlier work has shown that chavicine is in fact a mixture of piperine (12; *trans, trans*) and some minor alkaloids.[13] In the course of defining the structure of piperine, all the possible geometrical isomers corresponding to (12) were synthesized. According to the authors' taste buds, the hot taste of pepper is due to piperine!

(7)   (8)
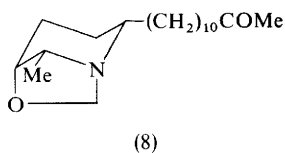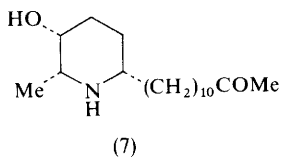
[14] R. J. Highet and P. F. Highet, *Tetrahedron Letters*, 1970, 1803.
[15] T. Wachs and F. W. McLafferty, *J. Amer. Chem. Soc.*, 1967, **89**, 5044; A. Mandelbaum and K. Biemann, *ibid.*, 1968, **90**, 2975.
[16] W. Doepke and G. Fritsch, *Pharmazie*, 1970, **25**, 128.

* Including Lythraceae alkaloids, some of which possess a quinolizidine skeleton.

(9)

CH=CH—(CH₂)ₙCON
trans
(10)

Structure (10): $CH=CH-(CH_2)_nCON$ (trans)

(11)

$CH=P(C_6H_5)_3$

(12)

$CH=CH-CH=CH-CON$
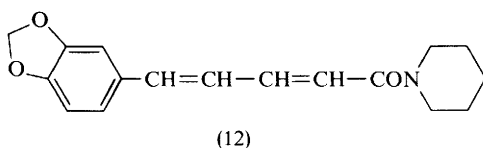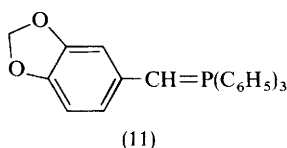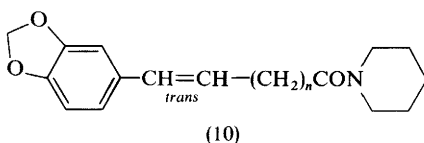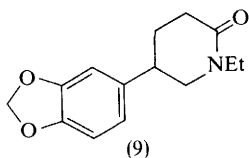
Of more than passing interest is the identification of L-baikiain (L-1,2,3,6-tetrahydropyridine-2-carboxylic acid) as a constituent of the red seaweed, *Corallina officinalis*.[17] Furthermore, in view of the recent intense interest in insect chemistry, attention should be drawn to a full report on the characteristics of five alkaloids corresponding to structures (13; $n = 10$, 12, and 14) and (14; $n = 3, 5$) obtained from the venom of the fire ant, *Solenopsis saevissima*.[18] 2,6-Disubstituted piperidines are not uncommonly found in plants (*e.g. Lobelia* species) but the only naturally-occurring *trans*-2,6-disubstituted alkaloids appear to be those found in *Nanophyton erinaceum*. The structures of the fire ant alkaloids were determined by application of combined gas chromatography–mass spectrometry, carbon skeleton chromatography, and finally by synthesis. Owing to the extremely small amounts of materials, new analytical techniques unfamiliar to many alkaloid chemists are being devised in this field. For example, the technique of carbon skeleton chromatography, a hydrogenolytic procedure which produces alkane fragments, deserves special mention.[19]

In continuation of extensive synthetic work on alkaloids, Schöpf and co-workers have prepared *meso*-1,3-di-(2-piperidyl)propan-2-one and shown that it is identical with anaferine (15), previously isolated from *Withania somnifera*.[20] Condensation of 2,3,4,5-tetrahydropyridine with acetonedicarboxylic acid at pH 11.5 gives a mixture of the *meso*- and racemic forms of (15). Their configurations were established by reduction to stereoisomeric mixtures of alcohols. An interesting reaction [(15) → (16)] was observed when anaferine was distilled at high vacuum. The preparation of (17), a compound related to the piperidine alkaloid anaferine, using a well-travelled reaction sequence, has been reported.[21]

The structures of the novel alkaloids lythranine (18; $R^1 = R^3 = H, R^2 = Ac$), lythranidine (18; $R^1 = R^2 = R^3 = H$), and lythramine (19; $R^1 = R^2 = H$,

[17] J. C. Madgwick, B. J. Ralph, J. S. Shannon, and J. J. H. Simes, *Arch. Biochem. Biophys*, 1970, **141**, 766.
[18] J. G. MacConnell, M. S. Blum, and H. M. Fales, *Tetrahedron*, 1971, **27**, 1129.
[19] M. Beroza, *Accounts Chem. Res.*, 1970, **3**, 33.
[20] C. Schöpf, G. Benz, F. Braun, H. Hinkel, G. Krueger, R. Rokohl, and A. Hutzler, *Annalen*, 1970, **737**, 1.
[21] M. J. Bishop, *Z. Naturforsch.*, 1970, **25b**, 1248.

Me$\cdots$(CH$_2$)$_n$Me
(13)

Me$\cdots$(CH$_2$)$_n$CH=CH(CH$_2$)$_7$Me
(14)

CH$_2$COCH$_2$
(15)

Me
X$^-$
(16)

CO$_2$Et
Me
Me
(17)
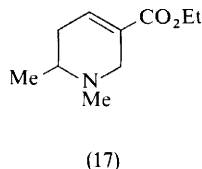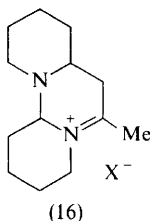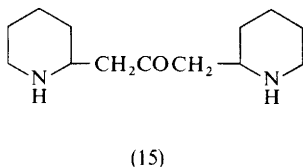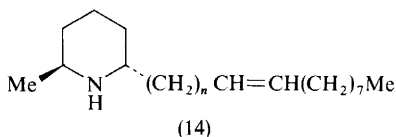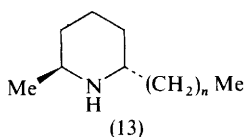
R^3 = OAc), isolated from *Lythrum anceps*, have been fully defined.[22—24] Lythranidine, C$_{26}$H$_{35}$O$_4$N, was shown to possess one aromatic methoxy-group, a phenolic hydroxy-function, two secondary alcohol groups, an imino-group, and six aromatic protons.[22] On methylation with diazomethane, lythranidine gave the amorphous *O*-methyl-lythranidine (18; R^1 = Me, R^2 = R^3 = H) and a crystalline *ON*-dimethyl derivative (18; R^1 = R^3 = Me, R^2 = H).[23] Alkaline permanganate oxidation of (18; R^1 = Me, R^2 = R^3 = H) gave acidic products which upon treatment with diazomethane yielded the symmetrical biphenyl system (20), as shown by n.m.r. spectral measurement and comparison with an authentic sample. The methiodide of *ON*-dimethyl-lythranidine was subjected to exhaustive Hofmann degradation to afford the des-N-base (21; R^1 = R^3 = OH, R^2 = R^4 = H) which on oxidation with chromium trioxide gave the diketone (21; R^1 + R^2 = R^3 + R^4 = O). The structure of the last compound was supported by spectral and chemical evidence. In the n.m.r. spectrum, signals were observed at δ 2.83 (4H, A$_2$B$_2$ type), assignable to the methylene protons (Ar—C*H*$_2$C*H*$_2$CO—), and at δ 2.32 (2H, triplet, J = 7 Hz). Since irradiation at δ 1.42 caused the δ 2.32 triplet to collapse to a singlet, this absorption was assigned to the other methylene group adjacent to the carbonyl (Ar—CH$_2$CH$_2$COC*H*$_2$-C*H*$_2$—). The mass spectrum exhibited a molecular ion at *m/e* 422, showing that the above ratio of protons obtained from the n.m.r. spectrum is half of the total number as a result of the completely symmetrical nature of the structure. Chemical confirmation of structure (21; R^1 + R^2 = R^3 + R^4 = O) was secured by its basic permanganate oxidation followed by reaction with diazomethane, to produce dimethyl esters of adipic and azelaic acids but no ester of sebacic acid.

The presence of a piperidine ring in these alkaloids was demonstrated by successive dehydrogenation, permanganate oxidation, and methylation of lythranine (18; R^1 = R^3 = H, R^2 = Ac) to yield the dimethyl ester of 2,6-pyridinedicarboxylic acid.[23] Treatment of *O*-methyl-lythranidine with ethyl

[22] E. Fujita, K. Bessho, K. Fuji, and A. Sumi, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2216.
[23] E. Fujita, K. Fuji, K. Bessho, and S. Nakamura, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2393.
[24] E. Fujita and K. Fuji, *J. Chem. Soc. (C)*, 1971, 1651.

R¹O OMe

H   OR²
₃ --OH   H--₁₁
        R³
        N
H ₅   ₉
        H

(18)

R¹O OMe

                R³
    ₁₁ O
H   ₂₆ R²--₃
        N
H ₉   ₅
            H

(19)

CO₂Me OMe

OMe   CO₂Me

(20)

MeO OMe

    R²   R³
  --R¹   R⁴--
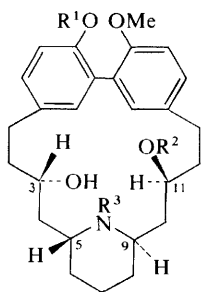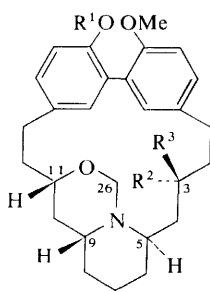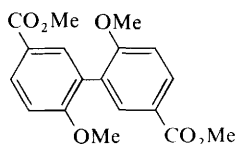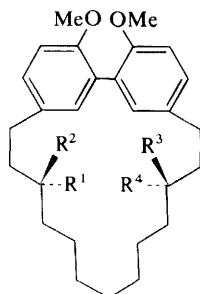
(21)

orthoformate and toluene-*p*-sulphonic acid gave the amido-acetal (22). A similar reaction occurred with lythranidine. The structure (22) is the most reasonable representation for the product of this reaction, although it was recognized that the alternative structures (23) and (24) for *O*-methyl-lythranidine could also form amido-acetals. The n.m.r. spectrum of lythramine, the alkaloid which had been previously shown to be identical with the product derived from the reaction of lythranine with formalin,[22] was more closely examined in order to exclude the alternative structure (25; R^1 = Me, R^2 = H or R^1 = H, R^2 = Me) for lyth-ramine, and therefore (23) for *O*-methyl-lythranidine.[23] Lythramine showed a two-proton signal at δ 4.80, assigned to an overlap of the $C(3)$-H signal with one of the AB-type protons of the $C(26)$-methylene group. A multiplet at δ 2.26 (2H), assigned to $C(4)$-CH$_2$, was shown to be coupled to $C(3)$-H. The latter was shown to be coupled to a signal at δ 1.42. On the basis of these observations, structure (25) for lythramine and therefore structure (23) for lythranidine were clearly ruled out. Structures (24) and (26; R^1 = Me, R^2 = H or R^1 = H, R^2 = Me; R^3 = H, R^4 = OH) for lythranidine and lythramine respectively were discarded on the basis of the following experiments. Oxidation of *O*-methyldeacetyl-lythramine (19; R^1 = Me, R^2 = H or OH, R^3 = OH or H; or 26; R^1 = R^2 = Me, R^3 = H, R^4 = OH) with chromium trioxide–pyridine gave a ketone whose n.m.r. spectrum

showed an AB-type pattern assignable to methylene protons adjacent to nitrogen. Treatment of the ketone with sodium deuteroxide in D_2O gave a product which had incorporated 4 deuterium atoms (mass spectral analysis). These results led to the reasonable assignment of structure (19; $R^1 = $ Me, $R^2 + R^3 = $ O) for the ketone and eliminated from consideration the alternative structure (26; $R^1 = R^2 = $ Me, $R^3 + R^4 = $ O). Thus it was concluded that structures (19; $R^1 = $ H, $R^2 = $ H or OAc, $R^3 = $ OAc or H) and (18; $R^1 = $ Me, $R^2 = R^3 = $ H) correctly represented lythramine and *O*-methyl-lythranidine respectively.

The *trans* relationship between $C(5)$- and $C(9)$-hydrogen atoms in (18) was assigned by taking advantage of the generalization that signals of hydrogen atoms in an antiparallel arrangement to the lone pair of an adjacent nitrogen in fixed ring systems appear 50—60 Hz to higher field in the n.m.r. spectrum than other proton signals which are simply adjacent to nitrogen.[24] This assignment was supported by the fact that bisdeoxy-*NO*-dimethyl-lythranidine [18; $R^1 = R^3 = $ Me; $C(3)$-OH, $C(11)$-OR^2 replaced by H] was obtained from a previous degradation of the corresponding alkaloid as an optically active compound. The *trans* stereochemistry between $C(3)$- and $C(11)$-hydrogen atoms was indicated by the optically active nature of (21; $R^1 = R^3 = $ OH, $R^2 = R^4 = $ H) in conjunction with the lack of optical activity of the diketone (21; $R^1 + R^2 = R^3 + R^4 = $ O). Finally, the *X*-ray analysis of bromolythranidine (18; $R^1 = R^3 = $ H, $R^2 = $ Ac; *ortho*-Br to phenolic OH) hydrobromide confirmed the overall structure of these alkaloids and established the absolute stereochemistry for lythranine (18; $R^1 = R^3 = $ H, $R^2 = $ Ac), lythranidine (18; $R^1 = R^2 = R^3 = $ H) and lythramine (19; $R^1 = R^2 = $ H, $R^3 = $ OAc), as indicated by the structural representations with *S*-configuration at both $C(3)$ and $C(11)$ and *R*-configuration at both $C(5)$ and $C(9)$ atoms.

Further examination of *Lythrum anceps* has yielded seven new alkaloids, all exhibiting part quinolizidine skeletons (27).[25] That the alkaloids possessed a common skeleton was shown by simple chemical interrelationships. The n.m.r.

MeO OMe

(22)

MeO OMe

OH

NH

OH

(23)
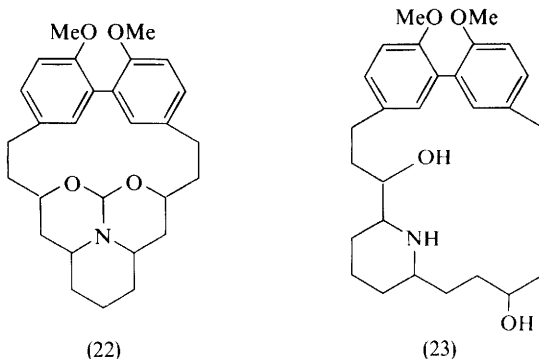
[25] E. Fujita and Y. Saeki, *Chem. Comm.*, 1971, 368.

(24)

(25)

(26)

(27)

(28)
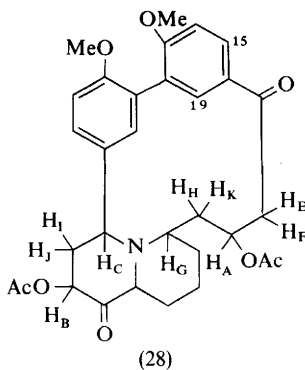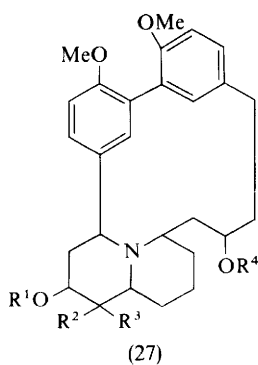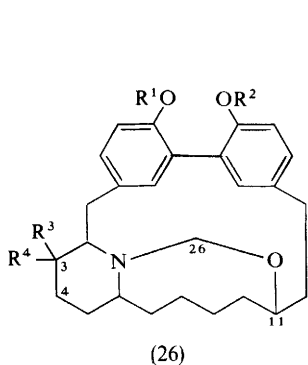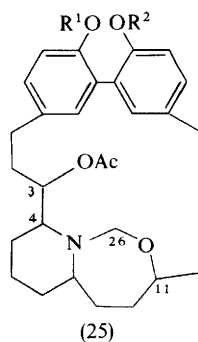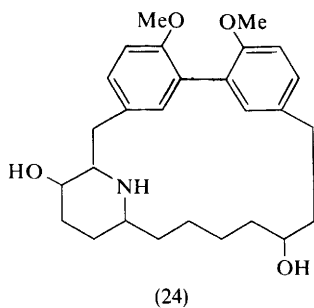
spectrum of lythrancine-II showed the presence of a secondary acetate function (δ 2.01, s, 3H and δ 5.35, m, 1H), two methoxy-groups (δ 3.87, s, 6H), and a proton on carbon which is both benzylic and adjacent to a nitrogen atom (δ 4.08, dd, 1H, $J = 4$ and 10.5 Hz). The n.m.r. spectrum of lythrancine-II *OO*-diacetate showed that the other hydroxy-group was also secondary in nature. That the two

hydroxy-groups are present as a *cis*-glycol was shown by the treatment of lythrancine-II with phosgene to give a five-membered cyclic carbonate (i.r. absorption at 1798 cm^{-1}). Successive chromic acid oxidation and methylation gave the biphenyl derivative (20) and *trans*-2-methoxycarbonyl-6-methoxy-carbonylhexahydropyridine, thus supplying evidence for the presence of these ring systems in the alkaloid. On the other hand, Jones oxidation of lythrancine-III gave a ketone (27; $R^1 = R^4 = Ac$, $R^2 + R^3 = O$) and a diketone (28). The latter yielded sufficient information to allow assignment of the complete structure, excluding stereochemistry. In its n.m.r. spectrum, an ABX pattern at δ 2.61 (H_E, dd, $J = 10$ and 14.5 Hz), 3.25 (H_F, d, $J = 14.5$ Hz), and 5.81 (H_A, m) was readily assigned and confirmed by irradiation studies. Simultaneous irradiation at δ 3.17 (br d, 1H, $J = 11$ Hz) and 2.61 (m, 1H) caused the octet at δ 1.47 (1H, $J = 3, 6$, and 15 Hz) to collapse to a doublet ($J = 15$ Hz). These absorptions could thus be assigned to interaction of protons H_G, H_A, and H_K respectively. A downfield shift of two aromatic protons [$C(15)$-H and $C(19)$-H] in the spectrum of (28) as compared with that of the monoketone (27; $R^1 = R^4 = Ac$, $R^2 + R^3 = O$) showed that the second oxidation had occurred at a benzylic position. Finally, double-irradiation studies also showed the presence of the carbon unit bearing protons H_B, H_I, H_J, and H_C. Hence the structure of the ketone (28) was secure, and on this basis lythrancine-III was assigned structure (27; $R^1 = R^4 = Ac$, $R^2 = OH$, $R^3 = H$). The structures of the other new alkaloids are as follows: lythrancine-I (27; $R^1 = R^2 = R^4 = H$, $R^3 = OH$), lythrancine-II (27; $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = Ac$), lythrancine-IV (27; $R^1 = R^4 = Ac$, $R^2 = H$, $R^3 = OAc$), lythrancepine-I (27; $R^1 = R^2 = R^3 = R^4 = H$), lythrancepine-II (27; $R^1 = R^2 = R^3 = H$, $R^4 = Ac$), and lythrancepine-III (27; $R^1 = R^4 = Ac$, $R^2 = R^3 = H$).[25]

An interesting biogenetic-type synthesis (Scheme 2) of an uncoupled precursor (33; $R = H$) to dihydrolyfoline (34) has been reported.[26] Benzylisovanillin (29) was transformed into the β-keto-ester (30) in several steps and the latter was condensed with Δ^1-piperideine to give the quinolizidine derivative (31) in 84 % yield. An extensive study of conditions for the ultimate hydrolysis–decarboxylation step was undertaken before it was found that the reaction gave optimum results in very dilute basic medium. Since it was known that 2-ketoquinolizidines are usually reduced to a mixture of epimeric alcohols in which the equatorial isomer predominates by *ca.* 10 : 1, it was expected that reduction of (31) would result largely in the production of the undesired alcohol for the synthesis of dihydrolyfoline (34). This expectation was realized with lithium aluminium hydride or sodium borohydride. However, when the sodium borohydride reduction was carried out in the presence of $AlCl_3$, $AlBr_3$, AlI_3, or sodium tetraphenylborate, increasing amounts of axial alcohol (32) were produced and reached a maximum with the last reagent (axial : equatorial = 1 : 1). Although it was thought that the Lewis acids complexed with the quinolizidine ring, the reason(s) for the shift in epimeric alcohol ratios in the presence of these reagents is not

[26] J. Rosazza, J. M. Bobbitt, and A. E. Schwarting, *J. Org. Chem.*, 1970, **35**, 2564.

clear. Reaction of the epimeric alcohol mixture (32) with methyl *p*-benzyloxy-hydrocinnamate led, by transesterification, to the epimeric esters (33; R = $CH_2 \cdot C_6H_5$), which were readily separated by column chromatography. Debenzylation gave the corresponding epimeric diphenols (33; R = H) in quantitative yield. Unfortunately, neither diphenol produced the desired oxidative-coupling products (34) when subjected to ferric chloride, potassium ferricyanide, electrolytic oxidation, or catalytic oxygenation.
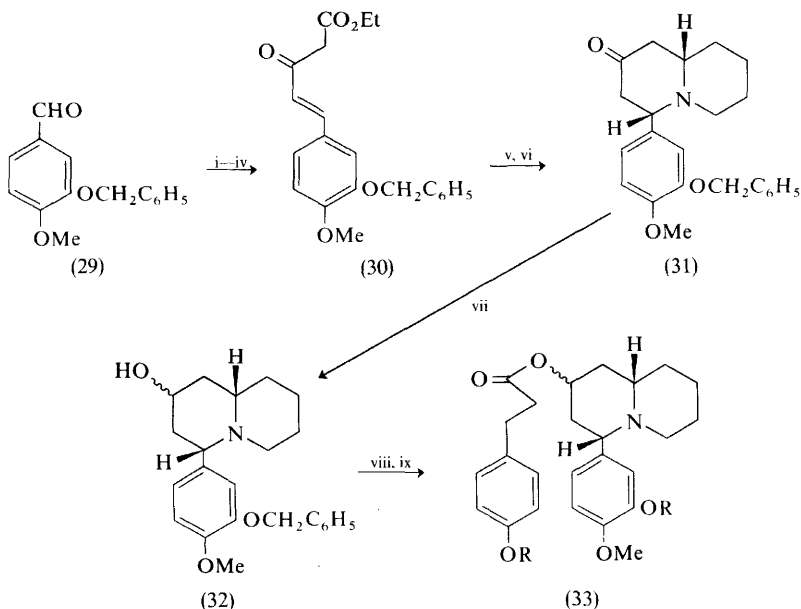
Reagents: i, $HO_2CCH_2CO_2H$, C_5H_5N, $C_5H_{11}N$; ii, $SOCl_2$, xylene; iii, Na, $MeCOCH_2$-CO_2Et, xylene; iv, NH_3, xylene; v, Δ^1-piperidine, EtOH, r.t.; vi, 0.5 % KOH, EtOH–H_2O; vii, $NaBH_4$, $NaBPh_4$; viii, *p*-MeO·$C_6H_4CH_2CH_2CO_2Me$, NaOMe, xylene; ix, H_2, Pd–C.

Scheme 2

(34)
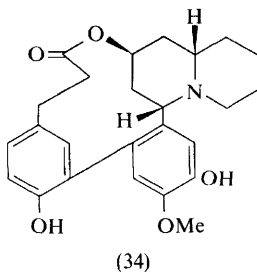
3 Pyridine Alkaloids

A new photometric determination of volatile bases in tobacco and tobacco smoke in terms of nicotine, which compares quantitatively with mass spectral and g.c. methods, has been developed.[27] A colorimetric method for the estimation of nicotine alkaloids in tobacco by reaction with cyanogen bromide and 4,4′-diaminostilbene-2,2′-disulphonic acid has also been reported.[28] Dilute sulphuric acid extraction of nicotine and anabasine from autopsy tissue appears to be a more efficient method than extraction with acidified ethanol, aqueous oxalic acid, and steam distillation.[29] Thin-layer chromatography has been effective in the analysis of nicotine and other alkaloids and drugs.[30] Two reports on the isolation of anabasine from anabasine–lupinine mixtures have appeared.[31] The pK_a values of some nicotine-type compounds have been determined.[32]

Relatively few new reports on isolation of alkaloids have been published. The leaves of *Acacia concinna* yielded nicotine[33] while the fruits and leaves of *Nicotiana glauca* grown in Egypt were shown to contain anabasine, nicotine, and two other undefined alkaloids.[34] Examination of *Priestleya elliptica* and *P. tomentosa* showed the presence of only anabasine; on the other hand, *P. hirsuta* and *P. vestita* were devoid of this alkaloid.[35] Ricinidine (35) was isolated from *Trewia nudiflora*.[36] The report of nicotine and nornicotine content from various parts of Burley tobacco may be noted.[37] The effect of boron and manganese fertilization[38] and of photoperiods and red to far red radiation on alkaloid content in tobacco[39] have been studied.

In the last few years, the impact of the use of ^{13}C n.m.r. spectroscopy in natural product chemistry has been substantial, and in this regard alkaloids have not escaped attention. The natural-abundance ^{13}C n.m.r. spectrum of nicotine has been determined at 15.8 MHz using both the noise-modulated total proton decoupling and the specific and off-resonance, single-frequency proton decoupling

[27] I. G. Mokhnachev, N. A. Sherstyanykh, and L. A. Dulan, *Ber. Inst. Tabakforsch., Dresden*, 1969, **16**, 83 (*Chem. Abs.*, 1970, **73**, 42 478z).
[28] W. R. Harvey and A. M. Palmer, *Tobacco Sci.*, 1971, **15**, 29 (*Chem. Abs.*, 1971, **75**, 1087u).
[29] S. I. Baik and V. F. Kramarenko, *Farm. Zhur. (Kiev)*, 1970, **25**, 49 (*Chem. Abs.*, 1971, **74**, 11 509b).
[30] R. Tulus and G. Iskender, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1969, **5**, 130 (*Chem. Abs.*, 1970, **73**, 69 887u).
[31] T. K. Kasymov, Kh. A. Aslanov, A. I. Ishbaev, and A. S. Sadykov, *Uzbek. khim. Zhur.*, 1970, **14**, 59 (*Chem. Abs.*, 1971, **74**, 54 064v); Yu. N. Forostyan, E. I. Efimova, and E. P. Kukhta, *Khim. prirod. Soedinenii*, 1970, **6**, 276 (*Chem. Abs.*, 1970, **73**, 45 648r).
[32] Ya. L. Gol'dfarb, F. M. Stoyanovich, A. P. Churilina, and V. G. Klimenko, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1970, 1883 (*Chem. Abs.*, 1971, **74**, 31 877y).
[33] G. L. Gupta and S. S. Nigam, *Planta Med.*, 1971, **19**, 55.
[34] S. M. Khafagy and A. M. Metwally, *J. Pharm. Sci., U.A.R.*, 1968, **9**, 83 (*Chem. Abs.*, 1971, **74**, 1253z).
[35] E. Steinegger, E. Schlunegger, F. Schnyder, and R. Frehner, *Pharm. Weekblad*, 1971, **106**, 245 (*Chem. Abs.*, 1971, **74**, 136 429g).
[36] S. N. Ganguly, *Phytochemistry*, 1970, **9**, 1667.
[37] J. L. Sims, L. P. Bush, and W. O. Atkinson, *J. Agric. Food Chem.*, 1970, **18**, 381.
[38] K. Krystyna, *Roczniki Wyzsz. Szk. Rolniczych Poznaniu*, 1969, No. 42, 91 (*Chem. Abs.*, 1970, **74**, 52 565k).
[39] T. C. Tso, M. J. Kasperbauer, and T. P. Sorokin, *Plant Physiol.*, 1970, **45**, 330.

procedures[40] which are now quite standard practice. In the noise-decoupled spectrum of nicotine a single peak was observed for each carbon atom, and it was possible to assign tentatively all of these atoms on the basis of known carbon chemical shifts. In the single-frequency off-resonance (SFOR) proton-decoupled spectrum, in place of a single peak for each carbon atom, a multiplet pattern was observed that had one more line than the number of hydrogen atoms attached to that carbon. The observed multiplicities allow for a check of the assignments made on the basis of chemical shifts. In this manner, a total analysis of the ^{13}C n.m.r. spectrum of nicotine was achieved.[40]

Very little significant synthetic work has been reported. An improved procedure for the preparation of nicotine N-oxide using m-chloroperbenzoic acid in chloroform has been developed.[41] Several simple reactions of anabasine (alkylation,[42] dehydrogenation,[43] hydrogenation,[44] reaction with phosgene[45]) and nicotine (alkylation,[46] pyrolysis[47]) have been investigated. The reaction of N-(β-hydroxyethyl)anabasine with $Ph_2P(O)Cl$ and $MeP(S)(Cl)OC_5H_{11}{}^i$ to produce the phosphorus-containing esters [36; R = $P(O)Ph_2$] and [36; R = $P(S)(Me)OC_5H_{11}{}^i$] respectively may be worthy of special mention.[48] Finally,
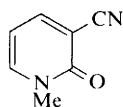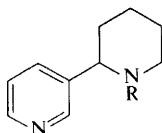
(35)   (36)

[40] J. D. Roberts, W. O. Crain, jun., and W. C. Wildman, *J. Amer. Chem. Soc.*, 1971, **93**, 990.

[41] C. J. Cymerman and K. K. Purushothaman, *J. Org. Chem.*, 1970, **35**, 1721.

[42] K. Toremuratov, A. A. Abduvakhabov, Kh. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1970, **6**, 771 (*Chem. Abs.*, 1971, **74**, 100 260*f*); L. S. Arutyunyan, M. A. Kaitandzhyan, V. A. Mnatsakanyan, and A. L. Mndzhoyan, *Armyan. khim. Zhur.*, 1970, **23**, 923 (*Chem. Abs.*, 1971, **74**, 142 132*w*): F. K. Kurbanov, A. B. Kuchkarov, A. N. Denisov, Kh. A. Aslanov, and A. S. Sadykov, *Doklady Akad. Nauk Uzbek. S.S.R.*, 1970, **27**, 32 (*Chem. Abs.*, 1971, **74**, 142 131*v*).

[43] O. S. Otroshchenko, A. S. Sadykov, V. K. Kiryukhin, M. Goshaev, and L. Srybnaya, *Trudy. Samarkand. Gosud. Univ.*, 1969, No. 167, p. 104 (*Chem. Abs.*, 1971, **74**, 31 878*z*); Yu. V. Kurbatov, A. S. Kurbatova, O. V. Zalyalieva, O. S. Otroshchenko, and A. S. Sadykov, *Nauch. Trudy Samarkand. Univ.*, 1969, No. 167, p. 9. From *Ref. Zhur., Khim.*, 1970, Abstr. No. 6Zh840 (*Chem. Abs.*, 1971, **74**, 142 111*p*); Yu. V. Kurbatov, S. V. Zalyalieva, O. S. Otroshchenko, and A. S. Sadykov, *Nauch. Trudy Samarkand. Univ.*, 1969, No. 167, p. 185. From *Ref. Zhur., Khim.*, 1970, Abstr. No. 6Zh842 (*Chem. Abs.*, 1971, **74**, 142 134*y*).

[44] Yu. N. Forostyan and E. I. Efimova, *Khim. prirod. Soedinenii*, 1970, **6**, 720 (*Chem. Abs.*, 1971, **74**, 106 969*r*).

[45] Yu. N. Forostyan, E. I. Efimova, and A. P. Oleinik, *Khim. prirod. Soedinenii*, 1970, **6**, 571 (*Chem. Abs.*, 1971, **74**, 54 065*w*).

[46] J. A. Schaefer and C. H. Jarboe, *J. Medicin. Chem.*, 1970, **13**, 1026.

[47] Y. Kaburaki, S. Sugawara, U. Kobashi, and T. Doihara, *J. Agric. Chem. Soc. Japan*, 1970, **44**, 224 (*Chem. Abs.*, 1970, **73**, 98 755*e*).

[48] K. Toremuratov, A. A. Abduvakhabov, Kh. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1970, **6**, 722 (*Chem. Abs.*, 1971, **74**, 100 258*m*).

the synthesis of 6-bromo-*N*-methylanabasine from 6-amino-*N*-methylanabasine has been accomplished.[49]

4 Mono- and Sesqui-terpenoid Alkaloids

A review dealing with the stereochemistry of bridgehead nitrogen compounds, which discusses quinolizidine derivatives, may be useful in studies on alkaloids which exhibit this ring system.[50]

(37)
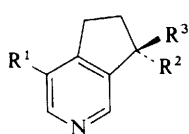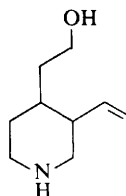
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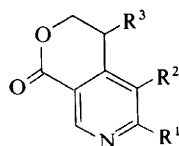
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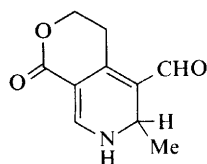
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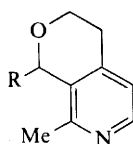
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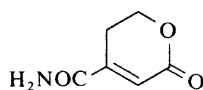
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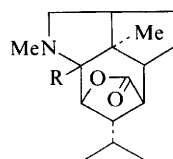
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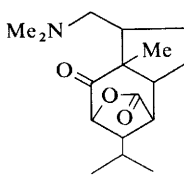
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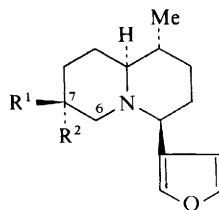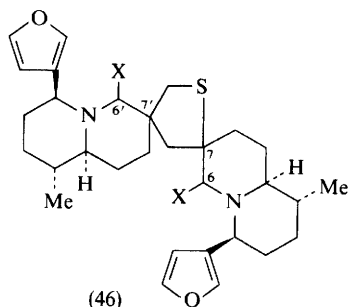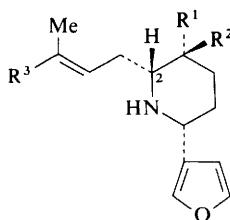
[49] M. Goshaev, O. S. Otroshchenko, and A. S. Sadykov, *Nauch. Trudy Samarkand. Univ.*, 1969, No. 167, p. 175. From *Ref. Zhur., Khim.*, 1970, Abstr. No. 6Zh841 (*Chem. Abs.*, 1971, **74**, 142110*n*).
[50] T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, 1971, **71**, 109.

Table *Isolation of mono- and sesqui-terpenoid alkaloids*

Species	Alkaloid (Structure)	Ref.
	Monoterpenoid Alkaloids	
Cantleya corniculata	Cantleyine (37; $R^1 = CO_2Me$, $R^2 = R^3 = H$)	51
Gentiana asclepiadea	Gentiabetin	
	Gentialutin (38)	
	Gentianidine (39; $R^1 = Me$, $R^2 = R^3 = H$)	52
	Gentianine* (39; $R^1 = R^3 = H$, $R^2 = CH{=}CH_2$)	
G. olgae	Gentianadine (39; $R^1 = R^2 = R^3 = H$)	
	Gentiananine	53
	Gentioflavine (40)	
G. olivieri	(Gentianadine, Gentianine)*	
	Gentianamine (39; $R^1 = H$, $R^2 = CH{=}CH_2$, $R^3 = CH_2OH$)	
	Gentioflavine	54
	Oliveridine (41; $R = OMe$)	
	Oliverine (41; $R = OMe$; additional OMe)	
	Alkaloid,† m.p. 159–160 °C	
G. tianshanica	Gentianine*	
	Gentiananine	53
	Gentioflavine	
G. vvedenskyi	Gentiananine	53
	Gentianine	
Gentiana and *Erythraea* spp.	Gentiocrucine (42)	
	Gentioflavine	
	Unnamed (41; $R = OH$)	55
	Alkaloid,‡ m.p. 249–252 °C	
	Alkaloid,‡ m.p. 240 °C (decomp.)	
	Alkaloid,‡ m.p. 189–191 °C (decomp.)	
Swertia connata	Gentiananine	
	Gentianine	53
	Gentioflavine	
Pedicularis olgae	Indicainine (37; $R^1 = CHO$, $R^2 = H$ or Me, $R^3 = Me$ or H; N-Et)	56
Valeriana officinalis	Valerianine (37; $R^1 = CH_2OMe$, $R^2 = Me$, $R^3 = H$)	57

[51] T. Sevenet, B. C. Das, J. Parello, and P. Potier, *Bull. Soc. chim. France*, 1970, 3120.

[52] F. Rulko and K. Nadler, *Diss. Pharm. Pharmacol.*, 1970, **22**, 329 (*Chem. Abs.*, 1971, **74**, 83 989*f*).

[53] T. U. Rakhmatullaev, *Khim. prirod. Soedinenii*, 1971, **7**, 128 (*Chem. Abs.*, 1971, **74**, 136 454*m*).

[54] T. U. Rakhmatullaev, S. T. Akramov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 608 (*Chem. Abs.*, 1970, **73**, 84 624*z*).

[55] N. Marekov and St. Popov, *Izvest. Otdel. Khim. Nauk., Bulg. Akad. Nauk.*, 1970, **2**, 575 (*Chem. Abs.*, 1970, **73**, 15 051*y*).

[56] S. Khakimdzhanov, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 126 (*Chem. Abs.*, 1971, **74**, 142 118*w*).

[57] B. Franck, U. Petersen, and F. Hueper, *Angew. Chem. Internat. Edn.*, 1970, **9**, 891.

Table (continued)

Species	Alkaloid (Structure)	Ref.
	Sesquiterpenoid Alkaloids	
Dendrobium	Dendrobine (43; R = H)	⎫
findlayanum	2-Hydroxydendrobine (43; R = OH)	⎬ 58
	Nobiline (44)	⎭
Jasminum fruticans	Alkaloids ¶ J-1 and J-2	59
Nuphar luteum	6,6'-Dihydroxythionuphlutine-A (46; X = OH)	⎫ 60
subsp. *macrophyllum*	6,6'-Dihydroxythionuphlutine-B (46; X = OH)	⎭
N. luteum subsp.	Deoxynupharidine (45; R^1 = Me, R^2 = H)	61
variegatum	7-Epideoxynupharidine (45; R^1 = H, R^2 = Me)	61—63
	3-Epinuphamine (47; R^1 = Me, R^2 = H, R^3 = CH$_2$OH)	63, 64
	Nuphamine (47; R^1 = H, R^2 = Me, R^3 = CH$_2$OH)	61

* Known alkaloid, previously isolated from the same species but usually in a different locality. *Cf.* J. J. Willaman and H.-L. Li, *Lloydia*, 1970, **33**, No. 3A (Suppl.) and R. A. Raffauf, 'A Handbook of Alkaloids and Alkaloid-Containing Plants', Wiley–Interscience, New York, 1970.
† Identical with an alkaloid isolated from *G. tibetica*.
‡ Gentioflavine skeleton with vinyl side-chain linked to other groups.
¶ Not fully characterized but possibly sesquiterpenoid alkaloids.

In comparison with the previous year, a considerably larger number of papers on isolation and structural elucidation of new alkaloids have appeared, and these are summarized in the Table. Cantleyine (37; R^1 = CO$_2$Me, R^2 = R^3 = H), from the trunk bark of *Cantleya corniculata*, was synthesized but appears to be an artifact of the ammoniacal extraction.[51] The structures proposed for oliveridine (41; R = OMe) and oliverine (41; R = OMe; additional OMe) do not conform to the gentianidine (39; R^1 = Me, R^2 = R^3 = H) structural type.[54] It was reported that the structure of indicainine (37; R^1 = CHO, R^2 = H or Me, R^3 = Me or H, *N*-Et) was elucidated on the basis of spectral data and by its oxidation with selenium dioxide to plantagonine (37; R^1 = CO$_2$H, R^2 = H or Me, R^3 = Me or H).[56] The oxidative removal of the *N*-ethyl function by selenium dioxide appears to be unprecedented. Valerianine (37; R^1 = CH$_2$OMe, R^2 = Me, R^3 = H), a new sedative alkaloid from *Valeriana officinalis*, was readily assigned the indicated structure on the basis of n.m.r. spectral and biogenetic considerations.[57] A neat synthesis was executed in order to confirm this structure. Diels–Alder reaction of aldehyde (48) with 1,3-dimethoxypropene gave the dihydropyranyl ether (49) as a mixture of three diastereomers. Since eventual conversion into the alkaloid involves destruction of three of the four centres of chirality, the isomeric mixture was not separated but subjected directly to successive treatment

[58] I. Granelli, K. Leander, and B. Luning, *Acta Chem. Scand.*, 1970, **24**, 1209.
[59] St. Popov, N. Marekov, and P. Panov, *Doklady Bolg. Akad. Nauk*, 1970, **23**, 1247 (*Chem. Abs.*, 1971, **74**, 50 505s).
[60] R. T. LaLonde, C. F. Wong, and W. P. Cullen, *Tetrahedron Letters*, 1970, 4477.
[61] C. F. Wong and R. T. LaLonde, *Phytochemistry*, 1970, **9**, 2417.
[62] C. F. Wong and R. T. LaLonde, *Phytochemistry*, 1970, **9**, 659.
[63] R. T. LaLonde, *U.S. Clearing House Fed. Sci. Tech. Inform.*, *PB Rep.*, 1970, No. 192810 (*Chem. Abs.*, 1971, **74**, 39 208b).
[64] C. F. Wong and R. T. LaLonde, *Phytochemistry*, 1970, **9**, 1851.

with acid and with hydroxylamine to give the racemic valerianine. Resolution was effected with dibenzoyltartaric acid. On the basis of comparison of the optical rotation of valerianine with those of actinidine (37; $R^1 = R^3 = H$, $R^2 = Me$) and tecostidine (37; $R^1 = CH_2OH$, $R^2 = Me$, $R^3 = H$), whose absolute configurations are known, valerianine was tentatively assigned the *S*-configuration. It would appear that similar monoterpenoid alkaloids have been readily prepared by adaptation of the above synthetic scheme.[57]

The structure of the new alkaloid 2-hydroxydendrobine (43; R = OH) was determined with the aid of i.r., n.m.r., and mass spectral data and by its hydrogenolysis in acetic acid to dendrobine (43: R = H).[58] An attempt to detect the amino-ketone of (43; R = OH) analogous to nobiline (44) by i.r. spectroscopy failed.
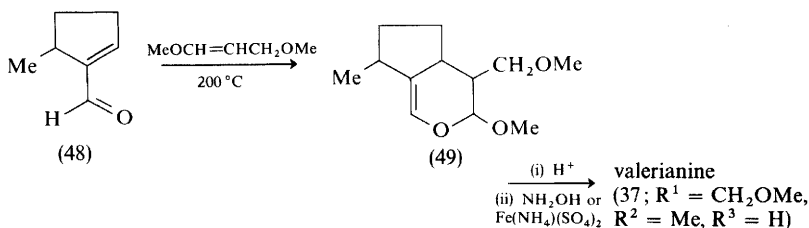
Continued investigations of alkaloids isolated from the aquatic plant *Nuphar luteum* subspecies *variegatum* have been presented in a series of papers by LaLonde and co-workers.[60—64] 7-Epideoxynupharidine has been isolated for the first time from natural sources and shown to possess structure and stereochemistry (45; $R^1 = H$, $R^2 = Me$) on the basis of spectral data and correlation with Δ^6-dehydrodeoxynupharidine (50), from which it was obtained by catalytic reduction.[62] The structure of 3-epinuphamine (47; $R^1 = Me$, $R^2 = H$, $R^3 = CH_2OH$) was indicated from a comparison of its mass spectrum with that of the known alkaloid nuphenine (47; $R^1 = R^3 = Me$, $R^2 = H$). The position of the 3-furanyl group accounting for one of the heteroatoms was established on the basis of n.m.r. evidence, and the involvement of the remaining two heteroatoms in alcohol and secondary amine functions was shown by the formation of a *NO*-dibenzoyl derivative. The n.m.r. spectrum also yielded complete information about the nature of the side-chain. In particular, the *trans* stereochemistry of the double bond was established by comparison of the absorption due to the vinyl proton at τ 5.41 with that of the same proton in *trans*-2-methylpent-2-en-1-ol. Manganese dioxide oxidation of 3-epinuphamine gave the $\alpha\beta$-unsaturated aldehyde (47; $R^1 = Me$, $R^2 = H$, $R^3 = CHO$) which showed u.v. absorption at 225 nm (ε 16 000) as expected for the proposed *trans* stereochemistry. The attachment of the *trans*-$HOCH_2(Me)CH\!:\!CHCH_2$ side-chain was indicated in the mass spectrum by the base peak at *m/e* 164 corresponding to the known facile α-cleavage in amines and, in this case, formation of a stable allyl radical. The piperidine substitution pattern was confirmed by the oxidation with osmium tetroxide and periodic acid of both the *NO*-dibenzoyl-3-epinuphamine and nuphenine (47;

$R^1 = R^3 = $ Me, $R^2 = $ H) *N*-benzamide to the structurally but not stereo-chemically identical aldehyde (51). The relative stereochemistry of 3-epinupha-mine (47; $R^1 = $ Me, $R^2 = $ H, $R^3 = CH_2OH$) as written was elucidated by detailed examination of its n.m.r. and i.r. spectra in comparison with those of other *Nuphar* alkaloids. Advantage was taken of the known n.m.r. correlation in methylquinolizidines, which showed that axial methyl groups consistently give rise to signals at lower fields than the corresponding equatorial methyl functions. Finally, Bohlmann bands were used to assign the stereochemistry at C(2).

(50)　　　　　(51)　　　　　(52)

m/e 358　(53)　m/e 178
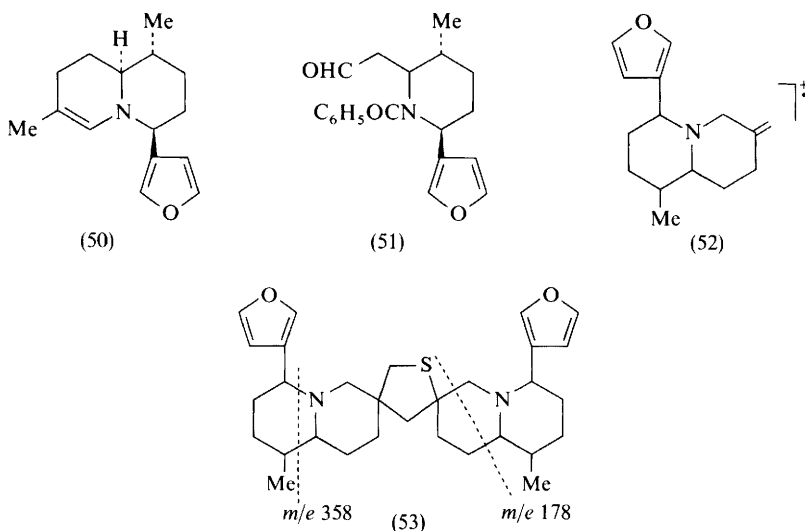
Although a number of C_{30} sulphur-containing *Nuphar* alkaloids have been isolated, the structure of only one of these, neothiobinupharidine (46; X = H), had been established, mainly on the basis of an *X*-ray analysis. Now the gross structures of two new C_{30} alkaloids, 6,6'-dihydroxythionuphlutine-A and -B (46; X = OH), have been elucidated, relying partly on the similarities and differences of their n.m.r. and mass spectral data in comparison with those of neothiobinupharidine.[60,63] The carbinolamine nature of the isomeric alkaloids A and B was indicated from their ready formation of bisimmonium diperchlorates and their reduction with sodium borohydride to thionuphlutine-A and -B (46; X = H). However, the physical properties of the reduction products were different from those of neothiobinupharidine, demonstrating that no two of the three alkaloids were identical. The symmetrical nature of the thionuphlutine isomers A and B was indicated by the presence of an intense peak in their mass spectra at m/e 230, which may be attributed to double cleavage in the thiaspiran ring with loss of hydrogen and sulphur or, in the case of the dihydroxythio-nuphlutines-A and -B, hydrogen, sulphur, and $C(6,6')$-oxygen, to give the fragment (52). Support for this pathway was obtained from the mass spectrum of the

dideuteriated compounds (46; X = D), obtained by sodium borodeuteride reduction of the alkaloids, which showed a shift of the ion at m/e 230 to 231. Additionally, the thionuphlutines showed a peak at m/e 178 and other peaks in the m/e 357–359 region which were shifted to 179 and 359—361 respectively in the spectra of the deuteriated alkaloids. These were interpreted by the fragmentations indicated in structure (53). The observation in the m/e 357—359 region was consistent with an analogous major fragmentation previously defined for deoxynupharidine (45; R^1 = Me, R^2 = H) and its $6\beta,7\beta$-dideuteriated derivative. Further evidence for the incorporation of the carbinolamine functions at C(6) and C(6′) was obtained from the n.m.r. spectra of the alkaloids measured in deuteriochloroform–D_2O. The thiomethylene protons were observed as a two-proton AB-quartet, demonstrating that only two protons are adjacent to sulphur and requiring that the thiaspiran ring be incorporated across C(7) and C(7′). Therefore, 6,6′-dihydroxythionuphlutine-A and -B (46; X = OH) are stereo-isomeric structures exhibiting the neothiobinupharidine (46; X = H) skeleton.

The identity of RW-47 and venoterpine, two alkaloids previously isolated from *Rauwolfia verticillata* and *Alstonia venenata* respectively, has been established by direct comparison.[65] Both alkaloids are represented by structure and absolute configuration (54), as deduced from o.r.d.–c.d. spectral comparison with L-(–)-actinidine (37; R^1 = R^2 = Me, R^3 = H), whose absolute configuration was unambiguously known. The significance of the fact that the absolute configuration of the actinidine alkaloids is opposite to that found in the glycosides which have been implicated in indole alkaloid biosynthesis remains to be clarified. It has been found that α- and β-skytanthines (55) were not present in the original extract of the roots, leaves, green stalks, woody parts, and ripe fruit of *Skytanthus acutus* and they must thus be considered as artifacts.[66]

The structure and absolute configuration (45; R^1 = Me, R^2 = H) previously deduced for deoxynupharidine by chemical degradation[67] has now been confirmed by X-ray analysis.[68] The mass spectral fragmentation patterns of pedicularine (56) and its methyl ester have been determined and compared with

(54)   (55)   (56)
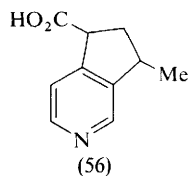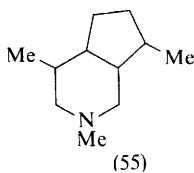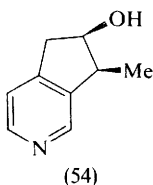
[65] L. A. Mitscher, A. B. Ray, and A. Chatterjee, *Experientia*, 1971, **27**, 16.

[66] H. H. Appel and P. M. Streeter, *Rev. Latinoamer. Quim.*, 1970, **1**, 63 (*Chem. Abs.*, 1971, **74**, 72 815*v*).

[67] See 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, vol. 1, p. 54.

[68] K. Oda and H. Koyama, *J. Chem. Soc. (B)*, 1970, 1450.

(57)

(58)

(59)

(60)
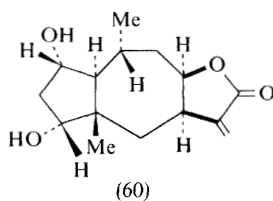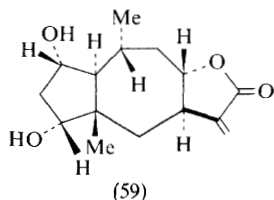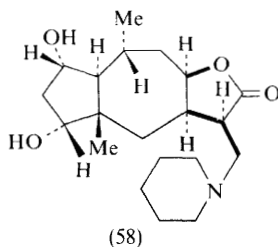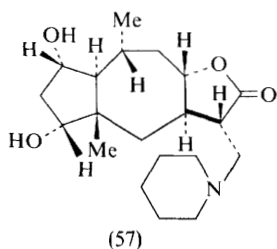
those observed for indicaine (37; R^1 = CHO, R^2 = H or Me, R^3 = Me or H) and plantagonine (37; R^1 = CO_2H, R^2 = H or Me, R^3 = Me or H).[69]

Over the past four years, a series of novel sesquiterpene alkaloids, some possessing anti-inflammatory activity, have been isolated from *Gaillardia pulchella*.[70] The structures of pulchellidine (57)[70a] and neopulchellidine (58)[70b] have been established on the basis of extensive spectral data and chemical degradation. Additionally, the corresponding non-nitrogenous compounds pulchellin (59)[70a,c] and neopulchellin (60)[70b] were also isolated from the same species and it was found that they could be converted stereospecifically into their respective alkaloid counterparts simply by treatment with piperidine. An X-ray analysis of 11,13-dibromopulchellin fully confirmed these structures and allowed assignment of absolute configuration.[70d] Using a series of secondary amines, a variety of Michael addition products of this type were produced.[71] Finally, the reverse reaction, *e.g.* pulchellidine → pulchellin, was readily effected under mild Hofmann degradation conditions.

A synthesis (Scheme 3) of the perhydrocyclopenta[*c,d*]indoline derivative (66), which represents the skeleton of dendrobine (43; R = H), has been reported.[72] Condensation of carvotanacetone (61) with butadiene gave the adduct (62) which was converted into the ring-contracted product (63) using a well-known reaction sequence. The latter was readily transformed to a stereoisomeric mixture of

[69] S. Khakimdzhanov, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 142 (*Chem. Abs.*, 1970, **73**, 66 773*t*).

[70] *a* M. Yanagita, S. Inayama, and T. Kawamata, *Tetrahedron Letters*, 1970, 131; *b ibid.*, 1970, 3007; *c* K. Aota, C. N. Caughlan, M. T. Emerson, W. Herz, S. Inayama, and Mazhar-Ul-Haque, *J. Org. Chem.*, 1970, **35**, 1448: *d* T. Sekita, S. Inayama, and Y. Iitaka, *Tetrahedron Letters*, 1970, 135.

[71] T. Kawamata and S. Inayama, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 643.

[72] K. Yamamoto, I. Kawasaki, and T. Kaneko, *Tetrahedron Letters*, 1970, 4859.
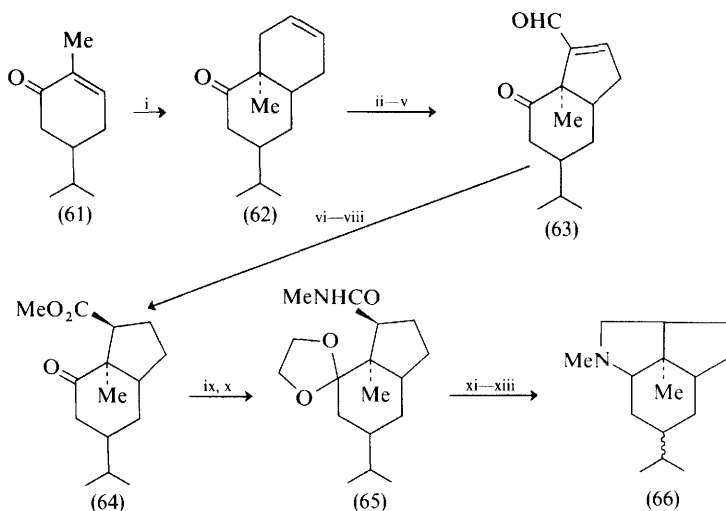
Reagents: i, CH_2=CHCH=CH_2, $AlCl_3$; ii, I_2, AgOAc, HOAc–H_2O; iii, OH⁻; iv, HIO_4, THF–H_2O; v, HOAc, $C_5H_{11}N$, C_6H_6, 60 °C; vi, H_2, PtO_2; vii, CrO_3, HOAc; viii, CH_2N_2; ix, $HOCH_2CH_2OH$, TsOH, $HC(OEt)_3$; x, 30 % $MeNH_2$, EtOH, 100 °C; xi, $LiAlH_4$; xii, HCl; xiii, H_2, PtO_2, 200 °C, 50 atm.

Scheme 3

keto-esters from which (64) was isolated by preparative g.c. and assigned the indicated stereochemistry by n.m.r. analysis. Consecutive ketalization and treatment with methylamine produced the amide (65) which was reduced, deketalized, and hydrogenated to give (66) as an isomeric mixture.
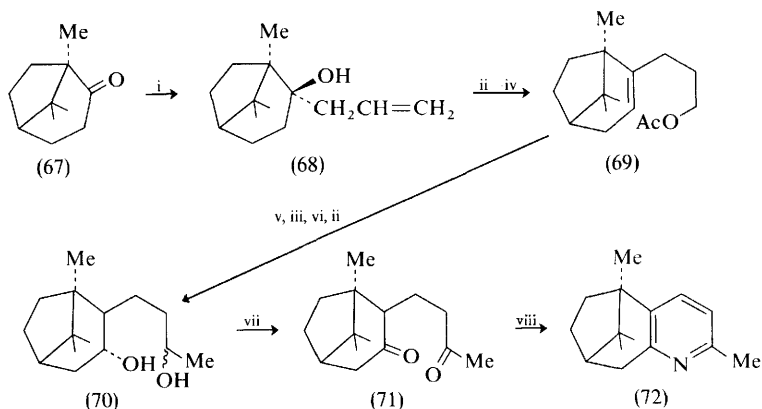
Reagents: i, CH_2=CHCH_2MgBr, Et_2O; ii, B_2H_6; iii, Ag_2CO_3, Celite, C_6H_6; iv, Ac_2O; v, 2N-NaOH, MeOH; vi, MeMgI; vii, CrO_3, pyridine; viii, NH_2OH,HCl, 150 °C.

Scheme 4

Patchoulipyridine (72), an interesting alkaloid from the essential oils of *Pogostemon patchouly*, has been synthesized (see Scheme 4).[73] The Grignard reaction of homocamphor (67) with allylmagnesium bromide gave the axially-oriented tertiary alcohol (68). The same reaction with $BrMgC\equiv CCO_2H$ gave poor results. Hydroboration of (68) followed by acetylation gave the dehydrated monoacetate (69) which was converted into the diol (70) without incident. Oxidation of (70) to the diketone (71) proved to be a delicate reaction. After unsuccessful trials with Jones' reagent and silver carbonate on Celite, the transformation was achieved utilizing Sarett's reagent. To complete the synthesis, the diketone (71) was treated with hydroxylamine to give patchoulipyridine (72).

[73] M. C. Cren, G. Defaye, and M. Fetizon, *Bull. Soc. chim. France*, 1970, 3020.

3
Tropane Alkaloids

BY J. E. SAXTON

In a field as thoroughly investigated as this one it is not surprising that very little new work has been reported during the last year. Several Solanaceous plants of the *Datura* and *Scopolia* genera have been examined for the first time or re-examined, but no new alkaloids have been isolated. The only new alkaloid in this group, bellendine, is also the first alkaloid to be isolated from the family Proteaceae, a large family of plants which occur widely in the Southern hemisphere. Bellendine (1) was isolated from the flowers of the monotypic shrub *Bellendena montana* R. Br., which flourishes on Tasmanian mountain plateaux; its novel γ-pyronotropane structure was established by *X*-ray crystal structure determination.[1] The absolute configuration of bellendine has not yet been elucidated, but it is written arbitrarily as (1) to correspond with the structurally-related *Coca* alkaloid, methyl ecgonidine (2).
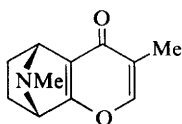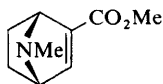
Bellendine (1)   (2)

Although the alkaloid content of the aerial parts and roots of *Datura sanguinea* has been examined by various workers the seeds of this species have not previously been investigated, with the exception of a paper chromatographic determination by Drey and Foster,[2] in which the presence of hyoscine was established. Leary[3] has now confirmed that the most abundant alkaloid present in the seeds is hyoscine, and that it is accompanied by hyoscyamine; apohyoscine, tropine, pseudotropine and two other, unidentified, alkaloids are also present. *Datura suaveolens* contains[4] meteloidine in addition to the

[1] W. D. S. Motherwell, N. W. Isaacs, O. Kennard, I. R. C. Bick, J. B. Bremner, and J. Gillard, *Chem. Comm.*, 1971, 133.
[2] R. E. A. Drey and G. E. Foster, *J. Pharm. Pharmacol.*, 1953, **5**, 839.
[3] J. D. Leary, *Lloydia*, 1970, **33**, 264.
[4] S. I. Balbaa, A. H. Saber, M. S. Karawya, and G. A. El-Hossary, *J. Pharm. Sci. U.A.R.*, 1969, **10**, 125 (*Chem. Abs.*, 1970, **73**, 127 727).

previously observed hyoscyamine and scopolamine. Hyoscyamine is also the major alkaloid of the roots of the Australian Solanaceous plant, *Duboisia hopwoodii* F. Muell; other constituents, identified chromatographically but not isolated, are hyoscine, nornicotine, hygrine, cuskhygrine, anabasine, and isopelletierine.[5] The leaves of this species, which are chewed by the aborigines as a narcotic and also used to poison water-holes in emu-hunting, were earlier shown[6] to contain nicotine and nornicotine, an observation which has now[5] been confirmed; apparently the tropane alkaloids are restricted to the roots. The much-investigated *Datura metel* has also been re-examined,[7] and the seasonal variation in alkaloid content in the various organs noted. Generally, the maximum alkaloid content was observed during the flowering and fruiting stages, and the elevation at which the plants were grown was also shown to influence the total alkaloid content. Plants grown at an elevation of over 2000 m exhibited a significantly higher alkaloid content than those grown at sea level. The same phenomenon has been observed by a group of Russian workers[8] in respect of Caucasian-grown *Scopolia carniolica*. The rhizomes of this plant contain 0.34—0.85 % alkaloids, of which the major constituents are hyoscyamine and scopolamine, as reported earlier. These two alkaloids also occur in *S. tangutica*, together with cuskhygrine.[9—11] The localization of alkaloids in the various organs and tissues of this plant has also been investigated, as well as the dependence of the alkaloid content on the age of the plants and their vegetative phase. The seeds of *S. stramonifolia*, apparently not previously examined, have been shown to contain atropine and scopolamine.[12]

The growth and alkaloid production of callus tissues of four *Datura* species, cultured in various media, have also been studied;[13] the species investigated include *D. stramonium*, *D. stramonium* var. *tatula* (L) Torrey, *D. stramonium* L. var. *godronii* Danert, and *D. innoxia* Mill. Generally, the alkaloids formed were similar regardless of species, or of substances added to the culture medium; atropine, scopolamine, tropine, apoatropine, and five unidentified alkaloids were detected by t.l.c.

In connection with the pharmaceutical applications of the tropane alkaloids several contributions deal with analytical and separation procedures. Thus, the various extraction procedures for atropine and scopolamine from *D. stramonium* powder have been critically evaluated,[14] and an improved separation of the

⁵ G. S. Kennedy, *Phytochemistry*, 1971, **10**, 1335.
⁶ W. Bottomley and D. E. White, *Austral. J. Sci. Res.*, 1951, **A4**, 107.
⁷ C. R. Karnick and M. D. Saxena, *Planta Med.*, 1970, **18**, 266 (*Chem. Abs.*, 1970, **73**, 63 213).
⁸ I. L. Krylova, L. N. Shakhnovskii, S. V. Rusakova, and E. F. Mikhailova, *Rast. Resur.*, 1971, **7**, 9 (*Chem. Abs.*, 1971, **74**, 108 128).
⁹ G. M. Ulicheva, *Rast. Resur.*, 1970, **6**, 528 (*Chem. Abs.*, 1971, **74**, 95 405).
¹⁰ G. M. Ulicheva, *Rast. Resur.*, 1971, **7**, 18 (*Chem. Abs.*, 1971, **74**, 108 126).
¹¹ I. Barene and S. A. Minina, *Rast. Resur.*, 1971, **7**, 124 (*Chem. Abs.*, 1971, **74**, 108 131).
¹² M. Gorunovic, N. Prum, and J. Raynaud, *Plant Med. Phytother.*, 1970, **4**, 286 (*Chem. Abs.*, 1971, **74**, 108 125).
¹³ M. Konoshima, M. Tabata, H. Yamamoto, and N. Hiraoka, *J. Pharm. Soc. Japan*, 1970, **90**, 370.
¹⁴ M. J. Solomon and F. A. Crane, *J. Pharm. Sci.*, 1970, **59**, 1680.

tropane alkaloids by t.l.c. has been reported.[15] A method for the quantitative assay of hyoscyamine and scopolamine by gas chromatography of their *O*-trimethylsilyl derivatives has been developed,[16] while a procedure for the estimation of scopolamine or atropine in pharmaceutical preparations involves t.l.c. followed by nitration, reduction, diazotization, and coupling with *N*-naphthylethylenediamine.[17]

A sensitive and reproducible colorimetric determination of the tropane alkaloids by the ferric hydroxamate method has been described,[18] and so has the nitration and dehydration of tropane alkaloids on the microgram scale on t.l.c. plates.[19]

Three tropic acid esters, ($\pm$)-tropoyltropan-3β-ol (3), ($\pm$)-tropoylgranatan-3-β-ol (4), and its C-3 epimer, have been synthesized and characterized for evaluation as mydriatics and spasmolytics.[20] Another group[21] has prepared 26 diarylacrylic esters of tropine for pharmacological evaluation; all are potent spasmolytics (in mice) but devoid of mydriatic activity. The activities of these esters have been correlated with their structures,[22] and a certain degree of success is claimed; in this very limited field it may therefore prove possible to predict approximately the activity of hitherto unprepared compounds, and therefore increase the effectiveness of this particular area of pharmaceutical research.

Three new methods for the preparation of nortropine (5) have been reported.[23] All three routes involve *N*-demethylation by means of ethyl chloroformate, *e.g.* from tropine acetate (6).

The conformations of 3α-chloro- and 3α-bromo-tropane have been studied by means of n.m.r. spectroscopy and dipole moment measurements.[24] The results
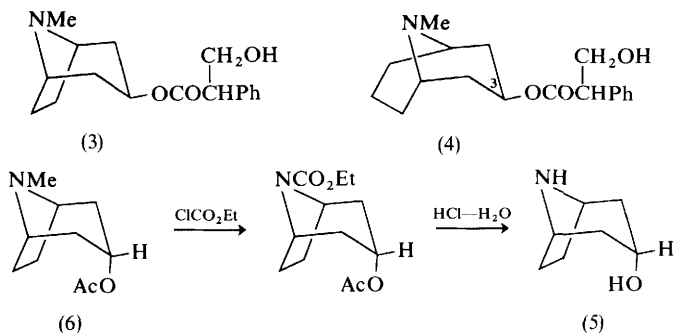
[15] J. Polesuk and T. S. Ma, *Mikrochimica Acta*, 1970, 670.
[16] T. Minamikawa, *J. Pharm. Soc. Japan*, 1970, **90**, 1457.
[17] T. Bićan-Fišter, *J. Chromatography*, 1971, **55**, 417.
[18] J. A. Feldman and B. J. Robb, *J. Pharm. Sci.*, 1970, **59**, 1646.
[19] J. Polesuk and T. S. Ma, *Mikrochimica Acta*, 1970, 677.
[20] R. J. Hunt and J. B. Robinson, *J. Pharm. Pharmacol.*, 1970, **22** Suppl., 29.
[21] H. C. Caldwell, J. A. Finkelstein, P. P. Goldman, A. J. Sivak, J. Schlosser, C. Pelikan, and W. G. Groves, *J. Med. Chem.*, 1970, **13**, 1076.
[22] P. N. Craig, H. C. Caldwell, and W. G. Groves, *J. Med. Chem.*, 1970, **13**, 1079.
[23] G. Kraiss and K. Nador, *Tetrahedron Letters*, 1971, 57.
[24] P. Scheiber, G. Kraiss, and K. Nador, *J. Chem. Soc.* (*B*), 1970, 1366.

indicate that an equilibrium exists between two piperidine chair conformations, (7a) ($\sim 90\%$) and (7b) ($\sim 10\%$), in which the methyl group is, respectively, equatorially and axially oriented. However, the calculated and observed dipole moments are not in exact agreement when the calculations are based on idealized piperidine chair conformations. It is therefore suggested that the 3α-substituent is responsible for significant distortion of the piperidine chair, the C-2, C-3, C-4 plane being altered by up to 30° from the normal angle, though probably somewhat less than this.

$$\text{(7a)} \qquad X = \text{Cl or Br} \qquad \text{(7b)}$$
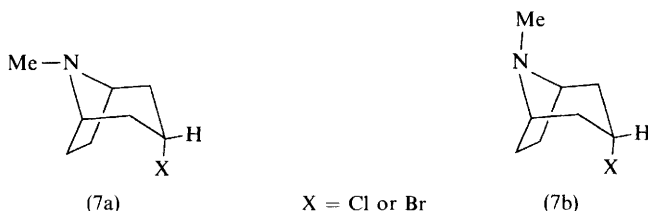
Following earlier controversy over Fodor's rule concerning the course of quaternization of tropane, tropine, and related compounds Fodor and his collaborators have themselves re-examined these reactions in detail.[25] As claimed earlier it has now been shown conclusively, with the aid of new correlations, that the major products in these quaternization reactions result from equatorial attack on nitrogen. Thus, the product (8) of *N*-alkoxycarbonyl-methylation of tropine was correlated with the lactone (9) of undisputed stereochemistry. The conversion of (8) into tropine ethobromide (10), and the comparison of intermediates in this transformation with other quaternization products, establishes also the preferred equatorial attack in ethylation, hydroxyethylation, and chloroethylation quaternization reactions.

The structure of *N*-ethylnortropine methobromide (11) had been established earlier,[26] but difficulties were encountered in the *X*-ray analysis of tropine ethobromide (10), owing to the rapid conversion of the orthorhombic crystals into a disordered cubic modification. However, this difficulty has now been overcome by cooling the crystals to $-150\,°\text{C}$, and although conversion still occurred it proved possible to obtain the appropriate intensity data, from which the structure (10) was unequivocally established.[27]

The exact geometrical shape of the tropane ring system clearly influences the course of these quaternization reactions. Thus, in pseudotropine (12) the ring angles at C-2 and C-4 are 141°, and those at C-1 and C-5 in the five-membered ring are 137°. Hence both rings are somewhat deformed, but the consequences are that axial interactions by 2β and 4β hydrogen atoms discourage axial attack on nitrogen to a greater extent than compression by hydrogen atoms at C-6 and

[25] G. Fodor, R. V. Chastain, D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Amer. Chem. Soc.*, 1971, **93**, 403.
[26] C. H. MacGillavry and G. Fodor, *J. Chem. Soc.*, 1964, 597.
[27] P. Benci, C. H. Stam, and C. H. MacGillavry, *Tetrahedron Letters*, 1971, 243.

(8)   (9)

(10)   (11)   (12)
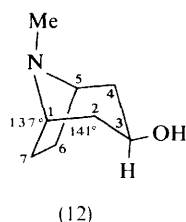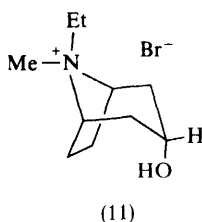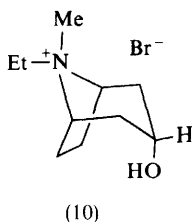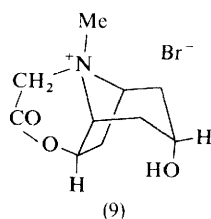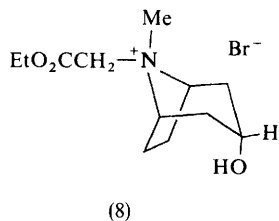
C-7 discourages attack at the equatorial side. It is also believed that the existing group attached to the nitrogen atom can accommodate diaxial interactions with 2β and 4β hydrogen atoms better than can an incoming group, but there would obviously be expected to be a retardation in quaternization reactions of derivatives already carrying a bulky group on nitrogen, as in fact is found experimentally.[25]

The preference for equatorial attack appears not to be observed in reactions leading to *N*-oxide formation.[28] Thus, the oxidation of tropine with 30% hydrogen peroxide at 75 °C affords only 2.8% of the equatorial *N*-oxide (13), m.p. 216 °C, the major product (65%) being the axial isomer (14), m.p. 253 °C.

(13)   (14)
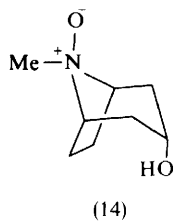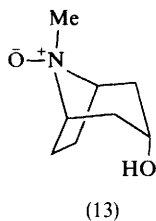
[28] G. Werner and R. Schickfluss, *Annalen*, 1971, **746**, 65.

4

The Pyrrolizidine Alkaloids

BY J. E. SAXTON

1 The Necine Bases and Simple Related Alkaloids

The first synthesis of the necine base, ($\pm$)-supinidine, has been recorded.[1] Addition of Δ^1-pyrroline N-oxide to methyl γ-hydroxycrotonate gave the hydroxy-substituted isoxazolidine (1), which was converted into the methanesulphonate and subjected to palladium-catalysed hydrogenolysis. The product, methyl 2-hydroxypyrrolizidine-1-carboxylate (2), is obviously obtained *via* hydrogenolysis of the nitrogen–oxygen bond followed by internal alkylation of the secondary amino-group by the primary methanesulphonate group. Dehydration of (2) with phosphorus oxychloride gave the conjugated unsaturated ester, which was converted into ($\pm$)-supinidine (3) by reduction with lithium aluminium hydride–aluminium chloride.[1]

(1) (2) Supinidine (3)
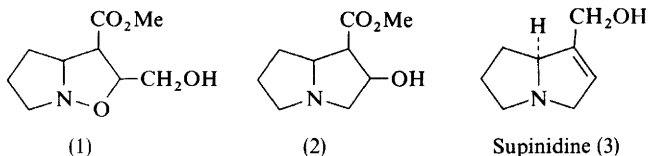
The total synthesis of ($\pm$)-dehydroheliotridine (4), a toxic metabolite of the pyrrolizidine alkaloids (*e.g.* lasiocarpine and heliotrine), has also been described.[2] The pyrrole ring was obtained by reaction of 1,6-dihydroxy-2,5-dicyanohexa-1,3,5-triene-1,6-dicarboxylic ester (5) with β-alanine, which afforded the N-substituted pyrrole ester (6), together with the appropriate amide of oxalic acid. Careful hydrolysis of (6) with dilute alkali afforded the related tricarboxylic acid, which was converted, by Dieckmann cyclization, hydrolysis and decarboxylation, into the keto-acid (7). Esterification of (7) with diazomethane, followed by reduction with lithium aluminium hydride, finally afforded ($\pm$)-dehydroheliotridine (4), identical, except in optical rotation, with dehydroheliotridine obtained earlier by Culvenor *et al.*[3]

[1] J. J. Tufariello and J. P. Tette, *Chem. Comm.*, 1971, 469.
[2] M. Viscontini and H. Gillhof-Schaufelberger, *Helv. Chim. Acta*, 1971, **54**, 449.
[3] C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Tetrahedron Letters*, 1969, 3599.

(5)   (6)   (7)

Dehydroheliotridine (4)   (8)   (9)
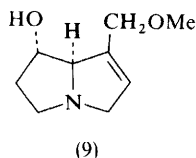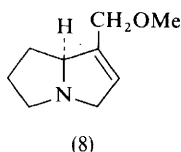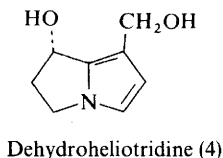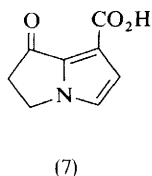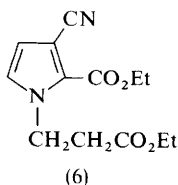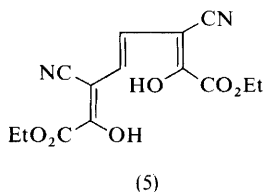
The seeds of *Crotalaria medicaginea* were earlier reported[4] to contain two liquid bases, A and B, the second of which was later isolated by other workers.[5] These two bases have now been identified as the methyl ethers (8) and (9), respectively, of supinidine and heliotridine.[6] This latter base (9) had previously been isolated[7] from *C. trifoliastrum* Willd., a species which is taxonomically closely related to *C. medicaginea*.

Decorticasine, a constituent of *Adenocarpus decorticans*, is formulated as (10).[8] It is of some interest to compare the structure and configuration of this compound with that of festucine (11); unfortunately, full details of the work on which the structure of (10) is based are not available at present, since the original reference is not readily available.

Decorticasine (10)   Festucine (11)

Alafine (12)
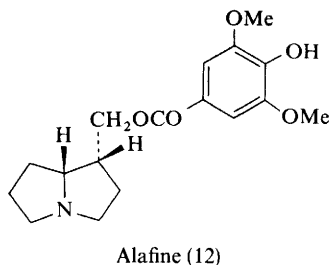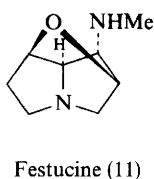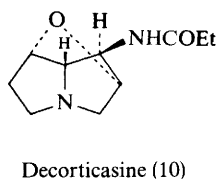
2 The Ester Alkaloids

The inaccessibility of exotic drugs during the aftermath of the second world war frequently resulted in the adulteration of drugs, or their substitution by foreign

[4] M. L. Sethi and C. K. Atal, *Indian J. Pharm.*, 1963, **25**, 159 (*Chem. Abs.*, 1963, **59**, 4206).
[5] R. N. Gandhi, T. R. Rajagopalan, and T. R. Seshadri, *Current Sci.*, 1966, **35**, 460.
[6] R. S. Sawhney and C. K. Atal, *J. Indian Chem. Soc.*, 1970, **47**, 741.
[7] C. C. J. Culvenor, G. M. O'Donovan, and L. W. Smith, *Austral. J. Chem.*, 1967, **20**, 757.
[8] J. P. Soto, *Acta Cient. Compostelana*, 1969, **6**, 37 (*Chem. Abs.*, 1970, **73**, 109 943).

matter of conveniently similar appearance. One such example was the fraudulent sale of 'white *Strophanthus*' in place of the seeds of *Strophanthus gratus* Franchet. Although the exact identity of the 'white *Strophanthus*' was unknown, it was suspected that it originated from another Apocynaceous plant, *Alafina multiflora* Stapf. That this is almost certainly true is shown by the isolation of the same alkaloid, alafine, from both genuine *Alafina multiflora* seeds and from a specimen of 'white *Strophanthus*'. The structure of alafine (12) follows from its hydrolysis to trachelanthamidine and syringic acid.[9]

Continuing their survey of orchidaceous plants, Brandänge *et al.* have isolated[10] another new trachelanthamidine derivative, cornucervine (13), from *Phalaenopsis cornu-cervi* Rchb. f. Methanolysis of cornucervine gives, in addition to trachelanthamidine, an optically active ester indistinguishable except in optical properties from racemic dimethyl 2-isobutylmalate. Since cornucervine gives a prominent peak at $M - 59$ in its mass spectrum owing to loss of the methoxycarbonyl group, but no peak at $M - 73$ owing to loss of CH_2CO_2Me, cornucervine is formulated as (13). The absolute configuration of the isobutylmalate component remains to be determined.

The major alkaloid of the bark of *Bhesa archboldiana* (Merr. and Perry) Ding Hou (*Kurrimia archboldiana* Merr. and Perry), a large rainforest tree indigenous to New Guinea, is 9-angeloylretronecine *N*-oxide (14),[11] a previously unrecorded alkaloid; the parent tertiary base also appears to be present.
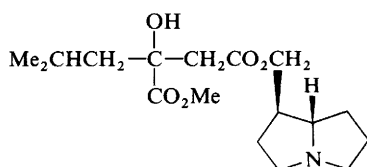
Cornucervine (13)
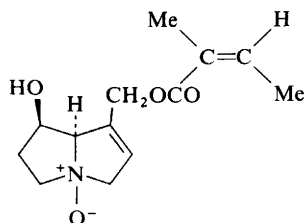
(14)
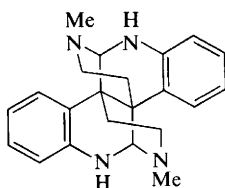
(15)

[9] M. Pais, F. X. Jarreau, P. Fouché, and R. Goutarel, *Ann. pharm. franc.*, 1971, **29**, 57.
[10] S. Brandänge, B. Lüning, C. Moberg, and E. Sjöstrand, *Acta Chem. Scand.*, 1971, **25**, 349.
[11] C. C. J. Culvenor, S. R. Johns, J. A. Lamberton, and L. W. Smith, *Austral. J. Chem.*, 1970, **23**, 1279.

Although pyrrolizidine alkaloids have been isolated from a number of plant families this is the first recorded occurrence of a member of this group in any species of the family Celastraceae. A second point worthy of note is the co-occurrence in *B. archboldiana* of calycanthine (15), which has previously only been obtained from the family Calycanthaceae.

Full details of the work[3] of Culvenor and his collaborators on the dihydro-pyrrolizine analogues of the pyrrolizidine alkaloids have now been published.[12,13] In particular, the ready oxidation of 1,2-dehydropyrrolizidine derivatives containing C(7)—OH or C(1)—CH$_2$OH groups with manganese dioxide is rationalized and explained mechanistically.

The mass spectra of nine pyrrolizidine alkaloids have been discussed, and their fragmentation patterns elucidated.[14] In general, the results are consistent with those obtained earlier,[15,16] and they are being used to identify the gross structure of pyrrolizidine alkaloids isolated from Danish rough-leaved plants.

Cynoglossum officinale (hound's tongue) has previously been shown to contain cynoglossophine, heliosupine *N*-oxide, and heliotridine viridiflorate *N*-oxide. A re-examination of this species[17] has shown that the minor alkaloids include acetylheliosupine (16) and 7-angeloylheliotridine (17). Another plant containing

(16)

(17)

Anacrotine (18)

Usuramine (19)
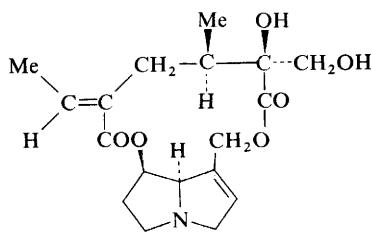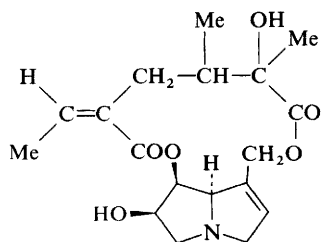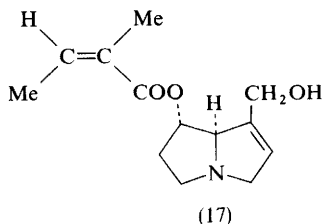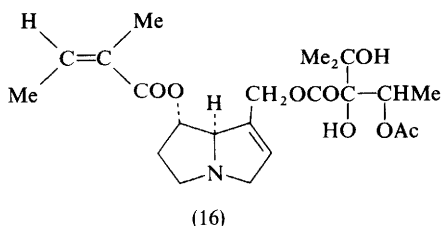
[12] C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Austral. J. Chem.*, 1970, **23**, 1853.
[13] C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Austral. J. Chem.*, 1970, **23**, 1869.
[14] E. Pedersen and E. Larsen, *Org. Mass Spectrometry*, 1970, **4** Suppl., 249.
[15] D. H. G. Crout, *J. Chem. Soc.* (*C*), 1969, 1379.
[16] N. Neuner-Jehle, H. Nesvadha, and G. Spiteller, *Monatsh.*, 1965, **96**, 321.
[17] E. Pedersen, *Dansk Tidsskr. Farm.*, 1970, **44**, 287 (*Chem. Abs.*, 1971, **74**, 72 780).

diester alkaloids which has been reinvestigated is *Crotalaria incana* L., which was already known to contain integerrimine[18] and anacrotine (18).[19] The presence of integerrimine has now been confirmed,[20] and usuramine (19), the geometrical isomer of retrorsine, has also been isolated. Usuramine is believed to be identical with mucronatinine, isolated earlier[21] from *C. mucronata* Desv.

Several *Senecio* species indigenous to New Zealand have been screened for their alkaloid content.[22] Most of these gave only a weakly positive response, but it was established that *S. bipinnatisectus* Belcher (*Erechtites atkinsoniae* F. Muell.) contains retrorsine, and *S. spathulatus* A. Rich. contains the geometrical isomers integerrimine and senecionine.

The level of alkaloids in *Symphytum officinale* (comfrey) at various stages of plant development has been investigated. The alkaloid content appears to be greatest in the aerial parts during flowering and in the roots at the end of fruit formation. The alkaloids identified include lasiocarpine and heliosupine *N*-oxide in the aerial parts, and viridiflorine, echinatine, and heliosupine *N*-oxide in the roots.[23]

A parallel investigation on rough comfrey (*S. asperum*) yielded similar results as far as the alkaloid concentration is concerned. Asperumine and heliosupine *N*-oxide were identified in the aerial parts, and heliosupine *N*-oxide and echinatine in the roots.[24] Asperumine, $C_{18}H_{25}NO_4$, was first isolated[25] from *S. asperum* in 1969, and since it hydrolyses to heliotridine and angelic acid, it must be 1,6-diangeloylheliotridine (20).[26] In addition to anadoline,[27] two further alkaloids, symphytine and echimidine, have been identified among the constituents of *S. orientale*.[28]

The stems and leaves of *Lappula intermedia* (*Echinospermum intermedium*), at the fruit-bearing stage of development, contain lasiocarpine (21) and two other alkaloids, which were not identified.[29] In general, the alkaloid content is stated to be similar to that of Caucasian comfrey.

Some specimens of S. African *Senecio othonniformis* Fourcade contain two alkaloids, bisline, $C_{18}H_{27}NO_6$, and its acetate, isoline.[30] Other specimens of this plant apparently contained small amounts of isoline only, while yet other

[18] R. Adams and B. L. Van Duuren, *J. Amer. Chem. Soc.*, 1953, **75**, 4631.
[19] A. R. Mattocks, *J. Chem. Soc. (C)*, 1968, 235.
[20] R. S. Sawhney and C. K. Atal, *J. Indian Chem. Soc.*, 1970, **47**, 667.
[21] N. S. Bhacca and R. K. Sharma, *Tetrahedron*, 1968, **24**, 6319.
[22] E. P. White, *New Zealand J. Sci.*, 1969, **12**, 165.
[23] I. V. Man'ko, B. K. Kotovskii, and Y. G. Denisov, *Rast. Resur.*, 1970, **6**, 409 (*Chem. Abs.*, 1971, **74**, 61 608).
[24] I. V. Man'ko, B. K. Kotovskii, and Y. G. Denisov, *Rast. Resur.*, 1970, **6**, 582 (*Chem. Abs.*, 1971, **74**, 84 023).
[25] I. V. Man'ko, M. P. Korotkova, and N. M. Shevtsova, *Rast. Resur.*, 1969, **5**, 508 (*Chem. Abs.*, 1970, **72**, 87 175).
[26] I. V. Man'ko and B. K. Kotovskii, *J. Gen. Chem. U.S.S.R.*, 1970, **40**, 2506 (*Zhur. obshchei Khim.*, 1970, **40**, 2579; *Chem. Abs.*, 1971, **75**, 1243).
[27] A. Ulubelen and S. Doganca, *Tetrahedron Letters*, 1970, 2583.
[28] A. Ulubelen and S. Doganca, *Phytochemistry*, 1971, **10**, 441.
[29] I. V. Man'ko and P. N. Vasil'kov, *Trudy Leningrad Khim. Farm. Inst.*, 1968, **26**, 166 (*Chem. Abs.*, 1970, **73**, 73 849).
[30] E. D. Coucourakis and C. G. Gordon-Gray, *J. Chem. Soc. (C)*, 1970, 2312.
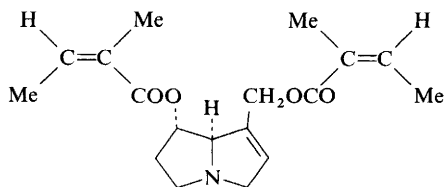
Asperumine (20)
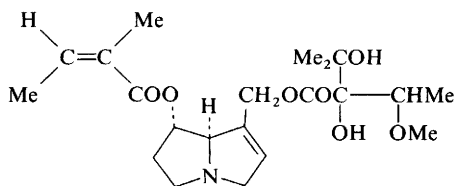
Lasiocarpine (21)

specimens contained only retrorsine. Hydrolysis of isoline affords acetic acid, retronecine, and a new acid, isolinecic acid, $C_{10}H_{18}O_6$, which gives both a mono-lactone and a dilactone. The dilactone, (v_{max} 1775 cm^{-1}) appears to contain two equivalent γ-lactone systems. Isoline contains an ethyl group, a secondary and a tertiary methyl group (n.m.r. spectrum), which must be present in isolinecic acid. This acid behaves as an α-hydroxy-acid (FeCl$_3$ test, and reaction with lead tetra-acetate), and must contain two such groupings, since isolinecic acid reacts with sodium bismuthate to give two moles of carbon dioxide. This evidence, together with the mass spectral data, is interpreted in terms of the structure (22) for isolinecic acid; isoline is then (23) and bisline is (24). At present, however, the
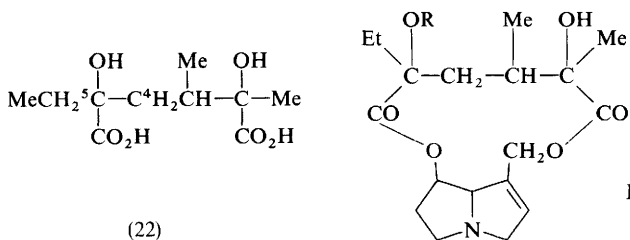
(22)

Isoline (23; R = Ac)
Bisline (24; R = H)

alternative structure for isoline in which the acetoxy-group is situated at position 4 cannot be rigorously excluded, although this possibility does not accord with the behaviour of isolinecic acid towards sodium bismuthate, nor does it explain the formation of a dilactone which exhibits a single carbonyl absorption band in the i.r. spectrum.[30] The stereochemistry of these alkaloids has not yet been elucidated.

3 Pharmacological Aspects

The well-established toxicity of the pyrrolizidine alkaloids has been studied intensively during the last few years, and the whole subject has been comprehensively reviewed.[31] More recent original contributions in this area have been concerned with the necrosis of liver cells induced by lasiocarpine,[32] and with the effect of fulvine (25) on the liver and kidney of the rat.[33] The formation of pancreatic tumours has also been observed in rats fed with a diet including *Heliotropium supinum*, and also in rats given a large single dose of intermedine and its diastereoisomer lycopsamine (26), the principal alkaloids of tarweed (*Amsinckia intermedia* Fisch and Mey), a plant which is known to cause liver damage to livestock in the United States.[34]

The proposal that pyrrole derivatives of the pyrrolizidine alkaloids are the toxic metabolites is now generally accepted, and efforts have recently been made to demonstrate this directly. However, difficulties are encountered owing to the comparative instability of the pyrrole derivatives, which readily suffer destruction by aqueous body fluids. This difficulty has been circumvented by injecting the test substance in DMF solution into the experimental animal intravenously as closely as possible to the target organ. In this way it was shown that monocrotaline pyrrole (27) and retrorsine pyrrole (28) cause lesions in the lung and liver similar to those produced by the pyrrolizidine alkaloids.[35] The formation of pyrrolic metabolites in biological systems has been amply demonstrated[31] using animal tissues *in vitro*, including human liver tissue.[36] The actual metabolite derived from heliotrine (29) and lasiocarpine following incubation *in vitro* with sheep rumen contents was shown to be 7α-hydroxy-1α-methyl-8α-pyrrolizidine (30);[37] this metabolite was also formed from sheep rumen contents after feeding with *Heliotropium europaeum*. *In vitro* metabolism of the same alkaloids by rat-liver microsomes afforded a chloroform-soluble pyrrolic derivative, which was shown to be dehydroheliotridine (4).[38] This demonstration that a simple pyrrole derivative is formed suggests that, if such a metabolite is the toxic agent, the esterifying acid in the initially administered ester alkaloid may play only a very minor role. Some evidence in support of this proposal comes from the demonstration that the pyrrole derivatives of the toxic alkaloids retrorsine and monocrotaline have very similar toxicities.[35,39]

The exact route by which the pyrrole metabolites are formed remains to be established. Although N-oxides are also formed from the alkaloids in biological

[31] E. K. McLean, *Pharmacol. Rev.*, 1970, **22**, 429.
[32] A. E. Rogers and P. M. Newborne, *Toxicol. Appl. Pharmacol.*, 1971, **18**, 356.
[33] T. V. N. Persaud, H. P. Putzke, D. Tessmann, and A. Bienengraber, *Acta Histochem.*, 1970, **37**, 369 (*Chem. Abs.*, 1971, **74**, 51 750).
[34] R. Schoental, M. E. Fowler, and A. Coady, *Cancer Res.*, 1970, **30**, 2127.
[35] W. H. Butler, A. R. Mattocks, and J. M. Barnes, *J. Pathol.*, 1970, **100**, 169.
[36] S. J. Armstrong and A. J. Zuckerman, *Nature*, 1970, **228**, 569.
[37] G. W. Lanigan and L. W. Smith, *Austral. J. Agr. Res.*, 1970, **21**, 493 (*Chem. Abs.*, 1970, **73**, 86 056).
[38] M. V. Jago, J. A. Edgar, L. W. Smith, and C. C. J. Culvenor, *Mol. Pharmacol.*, 1970, **6**, 402.
[39] A. R. Mattocks, *Nature*, 1970, **228**, 174.
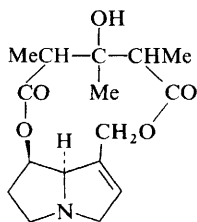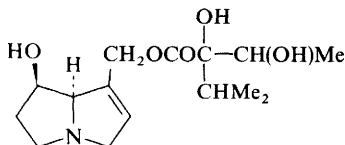
OH
|
MeCH—C—CHMe
/ | \
CO   Me   CO
| /
O   H   CH₂O
(pyrrolizidine ring structure)

Fulvine (25)

OH
|
HO   H   CH₂OCOC—CH(OH)Me
|
CHMe₂
(pyrrolizidine ring structure)

Lycopsamine (26)

Me   Me   Me
| | |
H—C——C——C—CO
| | | |
CO   OH   OH   O
| |
O   CH₂
(pyrrolizidine ring structure)

Monocrotaline pyrrole (27)

Me   CH₂OH
| |
H   CH₂—CH—C—OH
\   / |
C=C   CO
/   \   \
Me   COO   CH₂O
(pyrrolizidine ring structure)

Retrorsine pyrrole (28)

CHMe₂
|
HO   CH₂OCOC—CHMe
| |
HO   OMe
(pyrrolizidine ring structure)

Heliotrine (29)

HO   H   Me
(pyrrolizidine ring structure)
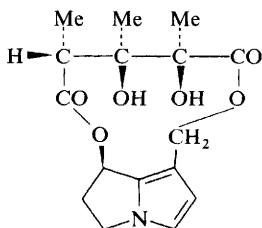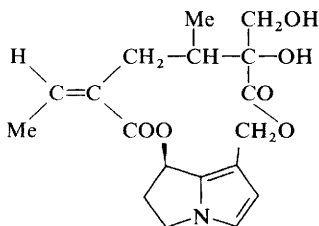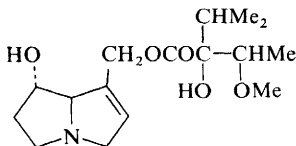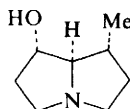
(30)

systems, they appear not to be intermediates in this conversion since, at best, only trace amounts of pyrrole derivatives are formed from the *N*-oxides.[38,40] Since the 1,2-double bond is known to be essential for hepatotoxicity, but not necessarily a formal pyrrolizidine ring [senkirkine (31) and hydroxysenkirkine (32) are toxic] Schoental[41] proposes that the proximal active forms of the alkaloids are the corresponding 1,2-epoxides. This view is rejected by Culvenor *et al.*[42] on the basis that neither the $1\alpha,2\alpha$- nor the $1\beta,2\beta$-epoxide of monocrotaline is hepatotoxic. In any event, the formation of pyrrole derivatives from otonecine esters [*e.g.* (31) and (32)] may be very simply conceived as the result of *N*-demethylation, followed by dehydration. This possibility was studied in the case of otosenine (33), another otonecine ester, which was shown to be metabolized by

[40] A. R. Mattocks and I. N. H. White, *Chem. Biol. Interactions*, 1971, **3**, 383.
[41] R. Schoental, *Nature*, 1970, **227**, 401.
[42] C. C. J. Culvenor, J. A. Edgar, L. W. Smith, M. V. Jago, and J. E. Peterson, *Nature New Biol.*, 1971, **229**, 255.

rat-liver microsomes to a pyrrole derivative strongly suspected to be dehydro-retronecine (34),[42] and therefore exactly analogous to the pyrrolic metabolites produced by the other hepatotoxic alkaloids. This same group of workers has also established that (34) and its enantiomer dehydroheliotridine (4) have very similar biological effects, and in particular the latter is a very potent hepatotoxic agent.[42,43]

Senkirkine (31; R = H)
Hydroxysenkirkine (32; R = OH)

Otosenine (33)

(34)

Rosmarinine (35)

(36)
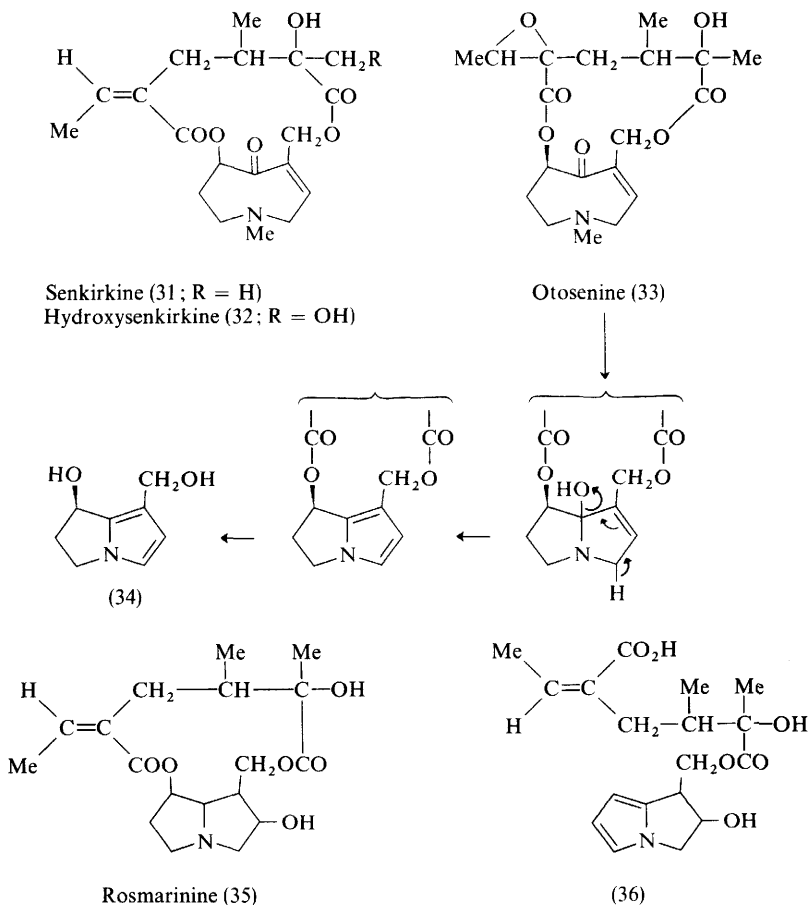
A further point of interest is that not all the pyrrolizidine alkaloids are toxic, even though they may be metabolized to pyrrole derivatives. Thus, rosmarinine (35) is not hepatotoxic, although it is metabolized to a pyrrolic substance, formulated as (36).[44] Thus it seems clear that the reason for the toxicity of the pyrrolic

[43] M. V. Jago, *Austral. J. Exp. Biol. Med. Sci.*, 1970, **48**, 93 (*Chem. Abs.*, 1970, **72**, 98 652).
[44] A. R. Mattocks and I. N. H. White, *Nature New Biol.*, 1971, **231**, 114.

metabolites is to be found in the nature of their ester groups. The pyrroles [*e.g.* (27) and (28)] from the toxic alkaloids have ester groups attached to the C(9) methylene group which are allylically situated with respect to the nitrogen atom. These esters are thus very effective alkylating agents and react readily with nucleophilic reagents, and they are so rapidly hydrolysed that in an aqueous medium only the related hydroxyderivatives can be isolated. In contrast, the non-toxic pyrrole derivatives [*e.g.* (36)] contain unactivated ester functions; these metabolites, therefore, do not behave as alkylating agents, and can be isolated without suffering hydrolysis.[44]

5
The Indolizidine Group

BY J. E. SAXTON

1 *Ipomoea* Alkaloids

The structure of ipalbidine (1) has been confirmed by two syntheses, the first of which[1] utilizes the route developed earlier by Govindachari *et al.*[2] for the synthesis of septicine. The ketone (2), prepared from 4-methoxyphenylacetic ester by the method used for the analogous septicine intermediate, was reacted with methyl-lithium to give the expected tertiary alcohol, which was dehydrated by sulphuric acid to *O*-methylipalbidine (3). Demethylation with aluminium chloride then afforded (±)-ipalbidine (1).
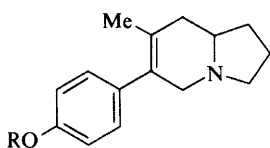
Ipalbidine (1; R = H)
O-Methylipalbidine (3; R = Me)

(2)
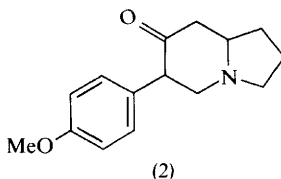
The second route to ipalbidine also provides the first synthesis of its β-D-glucoside ipalbine.[3] 2-Methoxypyrroline (4) was condensed with methyl acetoacetate at 85 °C in the absence of solvent to give the keto-ester (5). Acylation of the sodium salt of (5) was achieved with *p*-methoxyphenylacetyl chloride, but the expected acyl derivative could not be isolated. However, after the addition of a further equivalent of sodium hydride and heating at 80 °C the cyclization product (6) was obtained in moderately good yield. Some of the corresponding carboxylic acid was also isolated. Demethylation and decarboxylation of (6) by means of 48 % hydrobromic acid then gave the tetrasubstituted pyridone (7), which was

[1] T. R. Govindachari, A. R. Sidhaye, and N. Viswanathan, *Tetrahedron*, 1970, **26**, 3829.
[2] T. R. Govindachari and N. Viswanathan, *Tetrahedron*, 1970, **26**, 715.
[3] A. E. Wick, P. A. Bartlett, and D. Dolphin, *Helv. Chim. Acta*, 1971, **54**, 513.

reduced with an excess of aluminium chloride–lithium aluminium hydride to crystalline ($\pm$)-ipalbidine (1). Resolution was achieved by conversion into ($\pm$)-O-acetylipalbidine, and fractional crystallization of the salts with di-O-p-toluoyltartaric acid. The crystalline (+)-ipalbidine obtained by decomposition of the salt followed by hydrolysis still contained solvent, but pure (+)-ipalbidine was eventually isolated as a colourless glass. Glucoside formation was effected by reaction of (+)-ipalbidine with tetra-acetyl-α-D-bromoglucose in acetone in the presence of dilute aqueous sodium hydroxide, followed by deacetylation by means of a catalytic amount of sodium methoxide. The glucoside so obtained was identical with ipalbine (8), and was shown to be a β-D-glucoside by n.m.r. comparison with p-cresyl α- and β-D-glucosides and their tetra-acetyl derivatives.[3]
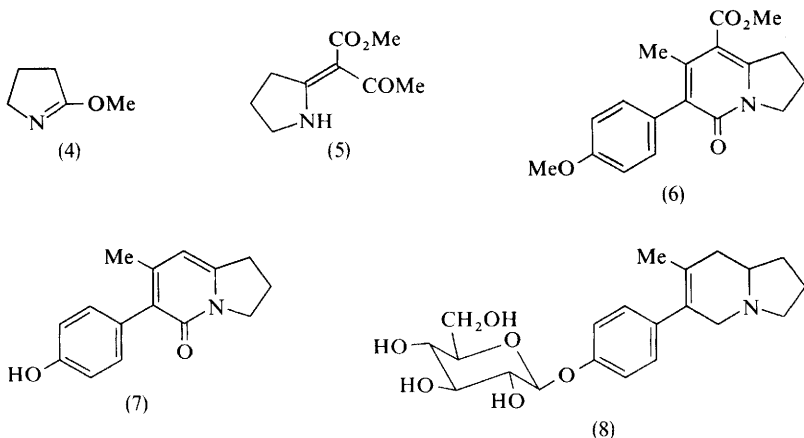
The melting points of synthetic ($\pm$)-ipalbidine and the two enantiomers reveal that, in all probability, natural ipalbidine is racemic (no rotation was recorded[4] for natural ipalbidine although a sample of the hydrochloride showed a very small optical rotation, thus revealing that it is essentially racemic). The rotation of synthetic ipalbine derived from (+)-ipalbidine differs from that recorded for natural ipalbine, although the value for the former is in better agreement with that calculated from the molecular rotations of (+)-ipalbidine and p-cresyl β-D-glucopyranoside. From these calculations, it is estimated that natural ipalbine is a diastereomeric mixture consisting of 85% of (+)-ipalbidine β-D-glucopyranoside and 15% of (−)-ipalbidine β-D-glucopyranoside. It is relevant to note that the diastereomeric mixture of β-D-glucosides derived from ($\pm$)-ipalbidine is crystalline but inseparable, and its spectral properties are identical with those of ipalbine.[3]

[4] J. M. Gourley, R. A. Heacock, A. G. McInnes, B. Nikolin, and D. G. Smith, *Chem. Comm.*, 1969, 709.

2 Slaframine

The structure (9) of slaframine,[5] a metabolite isolated[6] from the fungus *Rhizoctonia leguminicola* and responsible for producing excessive salivation in cattle, has now been confirmed by total synthesis.[7] 2-Bromo-5-nitropyridine was converted, by fusion with cuprous cyanide, into the corresponding nitrile, which was then transformed into 5-acetamido-2-ethoxycarbonylpyridine by conventional methods. Hydrogenation of the pyridine ring in this ester afforded the corresponding piperidine derivative, which condensed with ethyl acrylate to the amino-ester (10). Dieckmann cyclization of (10) gave the unstable bicyclic keto-ester, which was hydrolysed and decarboxylated to the amino-ketone (11).
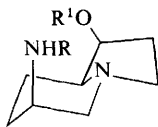
Slaframine (9; R = H, R^1 = Ac)
(13) R = R^1 = Ac
(14) R = R^1 = H
(15) R = Cbz, R^1 = H

(10)

(11)

(12)
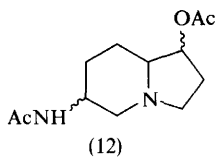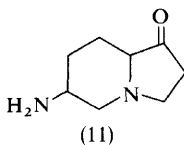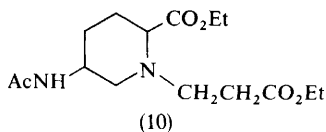
Sodium borohydride reduction of (11), followed by acetylation of the product, gave a mixture of four diastereomeric 1-acetoxy-6-acetamidoindolizidines (12), which were separated by careful chromatography on alumina. One of these isomers, *cis,cis*-1-acetoxy-6-acetamidoindolizidine, was identified as (±)-*N*-acetylslaframine (13). Deacetylation of (13) was achieved by prolonged boiling with hydrazine hydrate. The *ON*-deacetyl derivative (14) so produced was converted by means of benzyl chloroformate into *N*-carboxybenzylslaframine (15), which was acetylated and finally hydrolysed by hydrobromic acid in acetic acid to (±)-slaframine (9).[7]

[5] R. A. Gardiner, K. L. Rinehart, J. J. Snyder, and H. P. Broquist, *J. Amer. Chem. Soc.*, 1968, **90**, 5639.
[6] S. D. Aust, H. P. Broquist, and K. L. Rinehart, *J. Amer. Chem. Soc.*, 1966, **88**, 2879.
[7] D. Cartwright, R. A. Gardiner, and K. L. Rinehart, *J. Amer. Chem. Soc.*, 1970, **92**, 7615.

3 *Elaeocarpus* Alkaloids

A new series of indolizidine alkaloids has been isolated from the leaves of *Elaeocarpus kaniensis* Schltr., a rain-forest tree which flourishes in New Guinea.[8] The structures of six of these alkaloids have been assigned on the basis of detailed spectroscopic studies, consideration of their biosynthesis and their presumed structural relationships with other alkaloids of the *Elaeocarpus* genus.[9]

Elaeokanine A, $C_{12}H_{19}NO$, is a colourless oil which contains an $\alpha\beta$-unsaturated carbonyl group and a *trans*-indolizidine ring system (Bohlmann bands in its i.r. spectrum). Detailed examination of the n.m.r. spectrum reveals the presence of a butyryl group, one olefinic proton adjacent to a methylene group and a ring-junction hydrogen similarly adjacent to a methylene group. On the basis of these data and the similarity of the mass spectral fragmentation with those of related indolizidines, elaeokanine A is formulated as (16). Elaeokanine B is regarded as the structurally, but not necessarily stereochemically, related secondary alcohol (17).

Elaeokanine C is also a colourless gum, and is suspected to have the molecular formula $C_{12}H_{21}NO_2$, although it has not been subjected to elemental analysis. Its i.r. and n.m.r. spectra are consistent with the structure (18), in which the hydrogen atom at C-7 is equatorial and those at C-8 and C-9 are axially disposed.* This gross structure is supported by the reaction of elaeokanine C with ethanolic potassium hydroxide, which affords an $\alpha\beta$-unsaturated ketone having the same retention time on g.l.c. as elaeokanine A.[8]
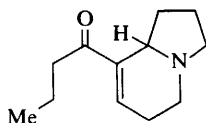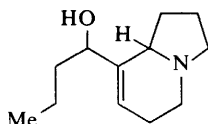
Elaeokanine A   (16)   Elaeokanine B   (17)   Elaeokanine C   (18)
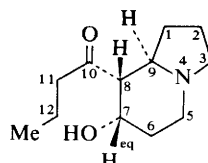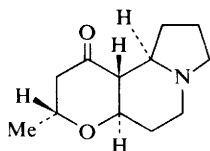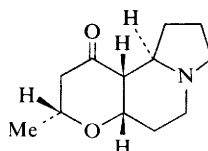
Elaeokanine D   (19)   Elaeokanine E   (20)

[8] N. K. Hart, S. R. Johns, and J. A. Lamberton, *Chem. Comm.*, 1971, 460.
[9] For a brief summary of this work see 'The Alkaloids,' (Specialist Periodical Report), ed. J. E. Saxton, The Chemical Society, London, 1971, Vol. 1, p. 76.

* In this and the following formulae only the *relative* stereochemistry is implied; the absolute configurations are unknown.
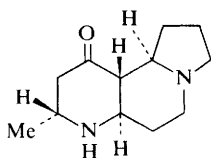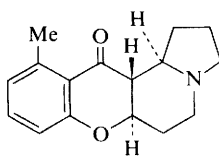
Elaeokanidine A (21)   (+)-Elaeocarpine (22)

Elaeokanine D and elaeokanine E, two crystalline alkaloids, are stereoisomers (i.r. and mass spectra) whose n.m.r. spectra are interpreted in terms of the structures (19) and (20) respectively. A sixth alkaloid, elaeokanidine A, contains two nitrogen atoms, but is regarded as a close relative of elaeokanine D in view of the similarity of their n.m.r. spectra. In consequence, elaeokanidine A is formulated as the tricyclic base (21). Finally, two further crystalline alkaloids, elaeokanidines B and C, have been isolated, but not yet extensively investigated. Preliminary data indicate that they are probably stereoisomers of elaeokanidine A.

The biosynthesis of the elaeocarpine (22) series of alkaloids has been discussed earlier, and it was suggested that they originated from ornithine and a C_{12} polyketide unit. By analogy it is suggested that the elaeokanine–elaeokanidine series arises by condensation of ornithine with a C_8 polyketide component.[8]

The synthesis of ($\pm$)-elaeocarpine and ($\pm$)-isoelaeocarpine[10] confirms the structures assigned to them by Johns *et al.*[9] 6-Methoxy-2-methylbenzoic acid was converted into the related diazoketone, which reacted with an excess of pyrrole in the presence of copper powder to give the 2-pyrrolylmethyl ketone (23). Hydrogenation of the pyrrole ring in (23), followed by condensation with ethyl acrylate, furnished a keto-ester (24) which was cyclized to the diketoindolizidine derivative (25). Dealkylation of the methyl ether group in (25) was achieved by means of boron tribromide at room temperature; the product cyclized spontaneously to give the chromanone (26), which was dehydrated to the corresponding chromone. Attempted hydrogenation of this chromone failed, so it was reduced
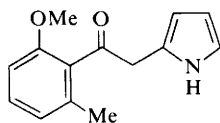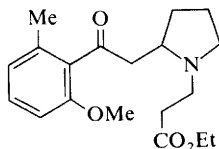
(23)   (24)
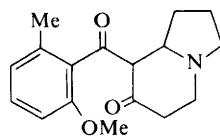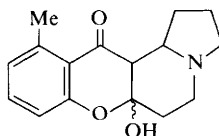
(25)   (26)

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[10] T. Tanaka and I. Iijima, *Tetrahedron Letters*, 1970, 3963.

(27)   (28)   (29)
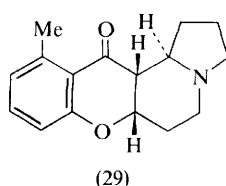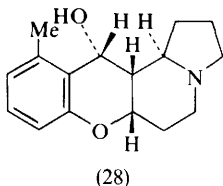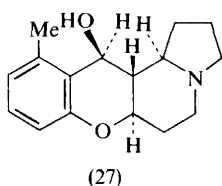
by sodium borohydride. The product proved to be a separable mixture of epimeric alcohols (27) and (28), which were identified with authentic samples. Finally, chromium trioxide–acetic acid oxidation of (27) and (28) afforded, respectively, ($\pm$)-elaeocarpine (22) and ($\pm$)-isoelaeocarpine (29).[10]

4 The Tylophorine Group

New extractions of *Cynanchum vincetoxicum* (L.) Pers. have resulted in the isolation[11] of a new base which is not separable on t.l.c. or by fractional crystallization from Alkaloid A (30), previously isolated[12] from the same source. Separation of the two alkaloids was achieved by acetylation, when the new alkaloid furnished an *O*-acetate, which was separated from Alkaloid A by preparative t.l.c. The new alkaloid is not phenolic, and since its hydroxy-group can be easily removed by hydrogenolysis it must be situated in a benzylic position. The product of hydrogenolysis is Alkaloid A (30). Since the new alkaloid is not a carbinolamine the hydroxy-group must be attached to C-14; the new alkaloid is therefore 14-hydroxy-2,3,6-trimethoxyphenanthroindolizidine (31), *i.e.* an isomer of tylophorinine, which bears the methoxy-groups in positions 3, 6 and 7.

The absolute configuration at C-13a in (30) follows from the identification of D-proline among the products of vigorous ozonolysis in acidic solution. D-Proline was identified by observing its degradation by D-amino-acid oxidase. In Wiegrebe's Alkaloid A (30), and consequently also in (31) and Wiegrebe's Alkaloid C [6-hydroxy analogue of (30)], C-13a has the *R*-configuration.[13]

The constituents of *Tylophora crebriflora* S. T. Blake have also been re-examined and, in addition to tylocrebrine (32) and tylophorine, a total of six alkaloids has been isolated.[14] Of these, Alkaloid F is septicine,[15] and the remainder (Alkaloids A—E) are new.

Rao's Alkaloid A (33), $C_{24}H_{27}NO_5$, contains four methoxy-groups and one benzylic hydroxy-group and furnishes on hydrogenolysis a tetramethoxy-phenanthroindolizidine isomeric with tylocrebrine (32). Alkaloid C is a phenolic demethyl derivative of A, since it can be converted into Alkaloid A by methylation.[15] Hydrogenolysis of Alkaloid C gives Alkaloid B, which can be methylated to the same isomer of tylocrebrine as is obtained by hydrogenolysis of

[11] W. Wiegrebe, H. Budzikiewicz, and L. Faber, *Arch. Pharm.*, 1970, **303**, 1009.
[12] W. Wiegrebe, L. Faber, H. Brockmann, H. Budzikiewicz, and U. Krüger, *Annalen*, 1969, **721**, 154.
[13] W. Wiegrebe, L. Faber, and T. Breyhan, *Arch. Pharm.*, 1971, **304**, 188.
[14] K. V. Rao, R. Wilson, and B. Cummings, *J. Pharm. Sci.*, 1970, **59**, 1501.
[15] K. V. Rao, *J. Pharm. Sci.*, 1970, **59**, 1608.

Alkaloid A. Since Alkaloids A and C are not carbinolamines the hydroxy-group in these alkaloids must be attached to C-14. The positions of the methoxy-substituents in these alkaloids were deduced from an examination of the n.m.r. spectra of these and related alkaloids (*e.g.* tylophorinine). In those compounds possessing a hydroxy-group at C-14, the signal due to the hydrogen at C-1 is shifted downfield as a result of deshielding by the C-14 hydroxy-group. This signal is one half of an ortho-coupled *AB* quartet in Alkaloids A and C, which therefore contain hydrogen atoms at positions 1 and 2. Since the signals due to the two remaining aromatic protons (in ring c) are singlets Alkaloid A must have the constitution (33).[15]
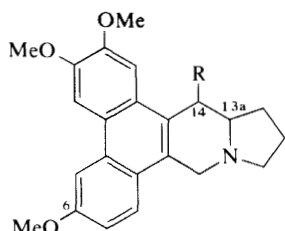
Wiegrebe's Alkaloid A ≡ Demethoxytylophorine
≡ Antofine (30; R = H)
(31; R = OH)
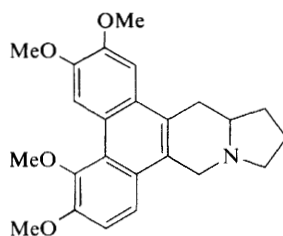
Tylocrebrine   (32)
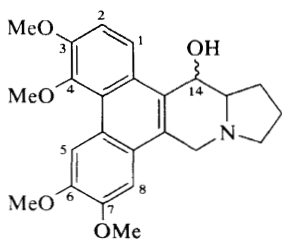
Rao's Alkaloid A   (33)
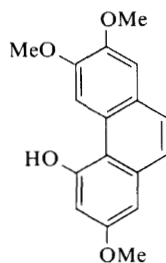
(34)
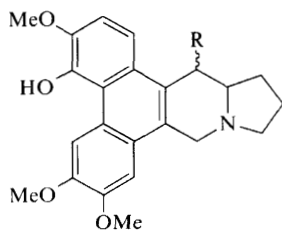
Alkaloid B (35; R = H)
Alkaloid C (36; R = OH)
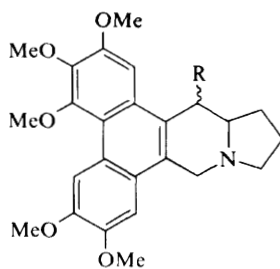
Alkaloid D (37; R = OH)
Alkaloid E (38; R = H)

The free phenolic hydroxy-group in Alkaloids B and C is almost certainly situated at C-4. This may be concluded from the exact position of the signal at lowest field in the n.m.r. spectra of Alkaloids A, B, and C, which is due to the proton at C-5. The chemical shift of this proton in the spectrum of Alkaloid A agrees well with values recorded by other workers[16,17] for 'bay' protons in phenanthrene systems, particularly those[16] in closely-related hydroxyphenan-threne derivatives [*e.g.* (34)]. In Alkaloids B and C this proton appears at slightly higher field; for example in the spectrum of Alkaloid C it appears 25 Hz higher, otherwise the spectrum is identical in the aromatic region with that of Alkaloid A. Hence the free hydroxy-group must be situated at either C-4 or C-6, and of these the former is considered the more likely, since methylation of phenolic groups normally has little effect on the absorptions of protons situated at the *ortho* positions. Hence Alkaloid B is (35) and Alkaloid C is (36). This deduction is consistent with a positive Gibbs test exhibited by both alkaloids, since position 4 is the only one in (35) and (36) with an unsubstituted *para* position.[15]

Alkaloids D and E constitute another related pair, Alkaloid D being the 14-hydroxy derivative of Alkaloid E. Both alkaloids contain five methoxy-groups and since the n.m.r. spectrum of Alkaloid D contains a downfield *singlet* not exhibited by Alkaloid E, it is regarded as containing methoxy substituents at positions 2, 3, and 4 in ring A. As in Alkaloids A—C, the remaining methoxy-groups are situated at positions 6 and 7. Alkaloid D therefore has the structure (37) and Alkaloid E is (38).[15]

Another phenolic alkaloid is tylophorinidine, $C_{22}H_{23}NO_4$, one of the minor constituents of *Tylophora asthmatica*, which occurs to the extent of 0.009 % in the roots of 3-year old plants.[18] The classification of tylophorinidine as a phenan-throindolizidine is confirmed by the presence of a strong peak at $M^+ - 69$ in its mass spectrum, owing to bis-benzylic fission with loss of the pyrrolidine ring [(39) $\rightarrow$ (39a)]. The mass spectrum also provides evidence for the presence of two methoxy- and two phenolic hydroxy-groups; this was confirmed by methyla-tion with diazomethane, which afforded a dimethyl ether devoid of hydroxy-groups. The aromatic region in the n.m.r. spectrum of diacetyltylophorinidine discloses the presence of two *para*-oriented and two *meta*-oriented protons; if this is accepted, tylophorinidine must be derived from one of four possible tetrahydroxyphenanthroindolizidines and of these the 2,3,5,7-tetrahydroxy-compound is preferred. The complete structure proposed for tylophorinidine is (39).[18]

Although full details of the work on tylophorinidine are not yet available, the structure (39) can not be regarded as having been firmly established, since it does not explain satisfactorily all the reported data. In particular, the structure (39) contains one 'bay' proton at position 4 and a hydroxy-group at position 5. The C-4 proton in this environment would be expected to resonate at very low field,

[16] J. Reisch, M. Bathory, K. Szendrei, E. Minker, and I. Novak, *Tetrahedron Letters*, 1969, 67.
[17] K. D. Bartle and J. A. S. Smith, *Spectrochimica Acta*, 1967, **23A**, 1689.
[18] N. B. Mulchandani, S. S. Iyer, and L. P. Badheka, *Chem. and Ind.*, 1971, 505.

(39)   (39a)
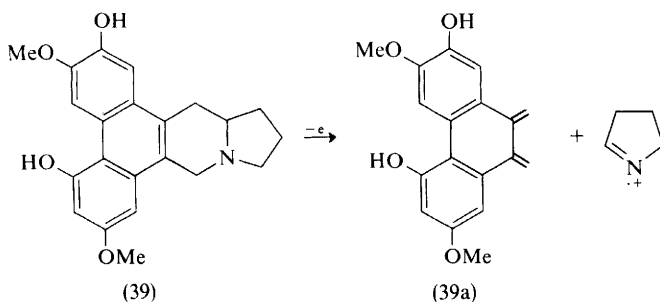
probably close to, or just below, τ 1.0; in the acetate it would be expected to resonate at even lower field. Yet the lowest-field signals quoted for the n.m.r. spectrum of diacetyltylophorinidine are at τ 1.67 and τ 2.0, and these are assigned to protons (at C-1 and C-6) which would be expected to absorb at higher fields than that at C-4, according to published data.[15—17] The conclusion is inescapable that tylophorinidine contains hydrogen atoms at both positions 4 and 5, or at neither. The latter possibility conflicts with the report that the alkaloid contains two *para*-oriented and two *meta*-oriented hydrogen atoms, and so the former must be preferred. This leads to the tentative formulation of tylophorinidine as a derivative of 2,3,6,8-tetrahydroxyphenanthroindolizidine. Such a formulation still leaves unexplained the absorption at 1724 cm^{-1} in the i.r. spectrum of diacetyltylophorinidine, which is characteristic of an alcoholic rather than a phenolic acetate; however, the presence of an alcoholic hydroxy-group cannot be reconciled with the report that tylophorinidine reacts with diazomethane to give a dimethyl ether devoid of hydroxy-groups. Nevertheless, it is relevant to note that the melting points of tylophorinidine and its derivatives are not very different from those of demethyltylophorinine [(*cf.* tylophorinine (40)], which has recently been isolated from the stems, leaves, and roots of *T. asthmatica* ($\equiv$ *T. indica*), and from *T. dalzellii*.[19] The stems and leaves of *T. asthmatica* also contain two new alkaloids of unknown structure, one of which also occurs in *T. dalzellii*.[19]

New syntheses of the biologically-active phenanthroindolizidine alkaloids, ($\pm$)-tylocrebrine, ($\pm$)-tylophorine, and ($\pm$)-antofine have been reported.[20] As an example, the route to ($\pm$)-tylocrebrine may be cited. The appropriate tetramethoxyphenanthrene carboxylic acid (41a), synthesised by a modified Pschorr procedure, was reduced (diborane) to the corresponding primary alcohol, which was converted into the chloride and condensed with benzyl L-prolinate in dimethylformamide to yield the amino-ester (42a). Since less drastic methods of closing the six-membered ring failed, the acid derived from (42a) by hydrogenolysis of the benzyl ester in the presence of Adams' catalyst in acidic solution was cyclized by polyphosphoric acid; unfortunately this reaction was accompanied by racemization of the single asymmetric centre. The resulting

[19] K. V. Rao, U.S.P. 3 497 593 (*Chem. Abs.*, 1970, **72**, 125 054).
[20] B. Chauncy and E. Gellert, *Austral. J. Chem.*, 1970, **23**, 2503.

ketone (43a) was finally converted into (±)-tylocrebrine (44a) by sodium
borohydride reduction of the corresponding tosyl hydrazide. The synthesis of
(±)-tylophorine (44b) and (±)-antofine (44c ≡ 30)[12] was accomplished in an
exactly analogous manner.[20]

Tylophorinine   (40)   (41)

(42)   (43; R = O)
                                               (44; R = H$_2$)
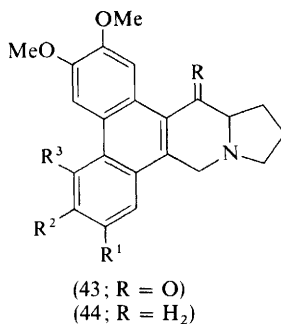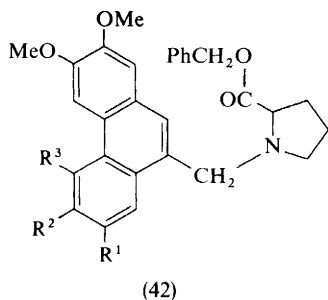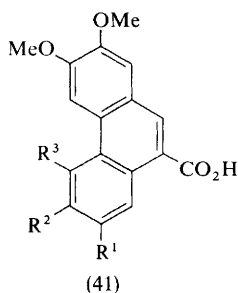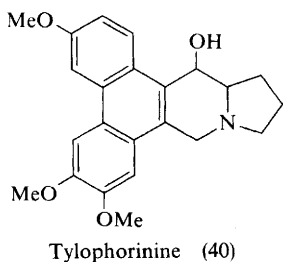
a; R^1 = H, R^2 = R^3 = OMe, Tylocrebrine series
b; R^1 = R^2 = OMe, R^3 = H, Tylophorine series
c; R^1 = R^3 = H, R^2 = OMe, Antofine series

6
The Quinolizidine Alkaloids

BY J. E. SAXTON

1 Lupine Group

Petaline and petaline methine, the only alkaloids hitherto isolated from *Leontice leontopetalum* L., belong to the benzylisoquinoline group.[1] In contrast, the alkaloids obtained from other species of the *Leontice* genus are almost all of the quinolizidine type. It is therefore of some interest to note that the aerial parts of *L. leontopetalum* contain (−)-stylopine (1), (+)-lupanine (2), and the new quinolizidine alkaloid leontiformine,[2] which has now been shown to have the constitution (3).[3] The structure and stereochemistry of (3) were established by hydrolysis to the deformyl compound (4), which was identified by comparison with its enantiomer ('Base V'), prepared by the method of Bohlmann[4] from (−)-17-oxosparteine.

(1)

(+)-Lupanine (2)

Leontiformine (3; R = CHO)
(4; R = H)

Ammodendrine (5)
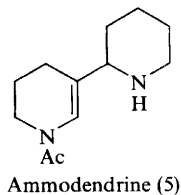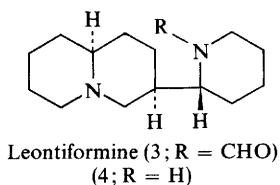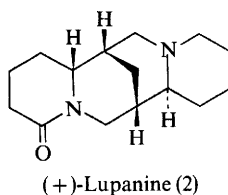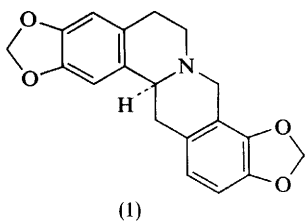
[1] J. McShefferty, P. F. Nelson, J. L. Paterson, J. B. Stenlake, and J. P. Todd, *J. Pharm. Pharmacol.*, 1956, **8**, 1117; N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron Letters*, 1964, 3841.
[2] P. P. Panov, N. M. Mollov, and L. Panova, *Compt. rend. Acad. bulg. Sci.*, in press, quoted in ref. 3.
[3] N. M. Mollov and I. C. Ivanov, *Tetrahedron*, 1970, **26**, 3805.
[4] F. Bohlmann, *Chem. Ber.*, 1959, **92**, 1798.

(−)-Lupanine occurs with (+)-sparteine and (+)-ammodendrine (5) in the leaves of *Liparia sphaerica* L. and *L. parva* Vog. ex Walp.; this is the first recorded occurrence of quinolizidine alkaloids in the sub-tribe Lipariinae of the Leguminosae.[5] Lupanine, of unknown absolute configuration, is stated to be the principal alkaloid of *Priestleya hirsuta* DC. and *P. vestita* DC, although it would appear not to have been rigorously identified as yet.[6]

Sparteine also occurs, in association with retamine, in Catalonian *Genista triflora*, *Cytisus purgans*, and *Anagyris foetida*.[7] The last two species also contain anagyrine (6), while *A. foetida* also contains cytisine.

Preliminary studies[8] on the alkaloid content of the seeds of Chilean *Sophora tetraptera sensu* Reiche have indicated the presence of cytisine, *N*-methylcytisine, and matrine. The amounts and proportions of these alkaloids estimated to be present differ considerably from those reported[9] for the morphologically similar New Zealand species, *S. tetraptera* J. Mill. and *S. microphylla* Ait. Although further work needs to be done, including a quantitative study of the seasonal and regional variations in the alkaloid content in these species, these results provisionally support the proposed segregation of the Chilean and New Zealand species of *Sophora*.

The pods of *Bolusanthus speciosus* Harms. (Leguminosae) constitute a further source of cytisine and *N*-methylcytisine;[10] the leaves of this species contain the same alkaloids, but in smaller amounts. In an earlier investigation[11] the presence of cytisine, *N*-methylcytisine, anagyrine, thermopsine, and rhombifoline in dried, flowering plants of *Thermopsis rhombifolia* (Nutt.) Richards was established. Recently,[12] very young (6 weeks old) plants have been shown to contain lupanine and 5,6-dehydrolupanine (7). The occurrence of lupanine in very young plants, followed by 5,6-dehydrolupanine and then anagyrine (6) lends support to the proposal that anagyrine is formed in the plant by dehydrogenation of lupanine, itself probably derived by oxidation of sparteine.

Sarothamnus catalaunicus Webb has already yielded several quinolizidine alkaloids, namely, (−)-sparteine, (+)-lupanine, angustifoline, 13-hydroxylupanine, cineverine, and catalauverine.[13] More recently, the branches of this species have been shown to contain sarodesmine (8), which was identified as the 3,4,5-trimethoxybenzoate of 13-hydroxylupanine.[14] Continuing their investigations

[5] E. Steinegger and E. Schlunegger, *Pharm. Acta Helv.*, 1970, **45**, 369.
[6] E. Steinegger, E. Schlunegger, F. Schnyder, and R. Frehner, *Pharm. Weekblad*, 1971, **106**, 245.
[7] T. Adzet, L. Batllori, and R. San Martin, *Plant Med. Phytother.*, 1970, **4**, 21 (*Chem. Abs.*, 1970, **73**, 84 641).
[8] A. Urzúa and B. K. Cassels, *Phytochemistry*, 1970, **9**, 2365.
[9] L. H. Briggs and J. Ricketts, *J. Chem. Soc.*, 1937, 1795; L. H. Briggs and W. S. Taylor, *J. Chem. Soc.*, 1938, 1206; L. H. Briggs and J. L. Mangan, *J. Chem. Soc.*, 1948, 1889.
[10] T. M. Smalberger, R. Vleggaar, and H. L. De Waal, *Tydskr. Natuurwetensk.*, 1970, **10**, 213 (*Chem. Abs.*, 1971, **74**, 95 432).
[11] R. H. F. Manske and L. Marion, *Canad. J. Research*, 1943, **21B**, 144.
[12] Y. D. Cho and R. O. Martin, *Canad. J. Chem.*, 1971, **49**, 265.
[13] G. Faugeras and M. Paris, *Ann. pharm. franc.*, 1968, **26**, 265.
[14] G. Faugeras and R. R. Paris, *Compt. rend.*, 1970, **271** *D*, 611.

on the constituents of *Genista cinerea* D.C., the same workers[15] have now isolated yet another ester alkaloid, which was shown to be *O*-formylcinegalleine (9).
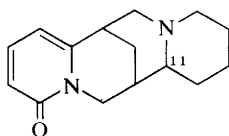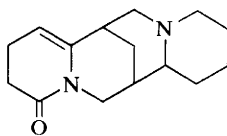
Anagyrine (6)   5,6-Dehydrolupanine (7)
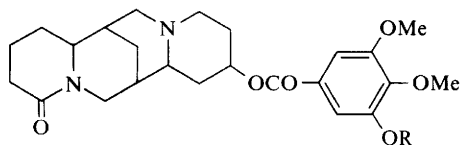
Sarodesmine (8; R = Me)
O-Formylcinegalleine (9; R = CHO)

The aerial parts of *Lupinus hispanicus* B. and R. (var. bicolor Merino) contain four alkaloids, of which three were identified as (+)-epilupinine, (−)-lupinine, and gramine. The fourth alkaloid (Alkaloid Y), an amorphous but apparently homogeneous base, was obtained in such small amounts that it has not yet proved possible to determine its structure.[15a]

A new quinolizidine alkaloid, tinctorine (10), $C_{15}H_{20}N_2O$, m.p. 112—113 °C, $[\alpha]_D^{25} - 49°$ (EtOH), has been isolated from flowering *Genista tinctoria* plants;[16] since it appears to be present in trace amounts only in plants harvested in Autumn it has not previously been detected. The spectroscopic characteristics of tinctorine disclose that it is an α-pyridone alkaloid containing a vinyl group, which features were also established by chemical methods, *viz.* the oxidative removal of the terminal methylene group as formaldehyde, and the hydrogenation of tinctorine to (−)-hexahydrotinctorine (11) and (+)-hexahydrodeoxotinctorine (12). These data, and the undoubted presence of an *N*-methyl group (mass spectral fragmentation) suggested that tinctorine may well be related to an *N*-methyl derivative of angustifoline (13). Conversion of angustifoline into (+)-*N*-methyldihydroangustifoline and comparison with (−)-hexahydrotinctorine (11) demonstrated that these compounds are enantiomers, from which it follows that the structure and absolute configuration of tinctorine are as given in (10).

The physical properties of tinctorine are reminiscent of those recorded recently for alteramine, an alkaloid of *Thermopsis alterniflora*, also isolated from plants

[15] G. Faugeras and R. R. Paris, *Compt. rend.*, 1970, **271** *D*, 1219.
[15a] I. Ribas-Marqués and M. Reguerio-García, *Anales de Quím.*, 1971, **67**, 93.
[16] D. Knöfel and H. R. Schütte, *J. prakt. Chem.*, 1971, **312**, 887.
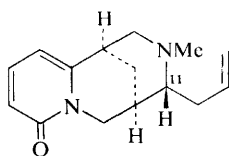
Tinctorine (10)
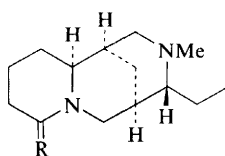
(11; R = O)
(12; R = H₂)
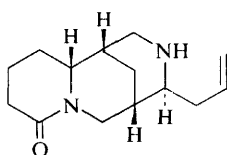
Angustifoline (13)
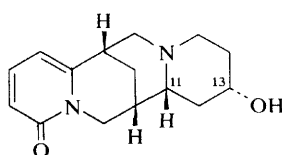
Argentamine (14)

collected in Spring.[17] The melting points of the salts (perchlorate and picrate) of the two bases are also very similar, the u.v. maxima are identical, and the mass spectra of both alkaloids exhibit important peaks at m/e 160 and 146. The authors' initial conclusion[17] was that alteramine had a tricyclic cytisine-like structure containing a C_3H_5 substituent; later[18] they derived the same gross structure as had been deduced earlier for tinctorine (10), mainly on the basis of the mass spectral fragmentation pattern. No comment was made on the stereochemistry of alteramine, but its identity with tinctorine seems very probable.

Argentamine, an alkaloid of *Ammodendron argenteum* O. Kuntze,[19] has been converted into α-isosparteine, and is formulated as ($-$)-13-hydroxythermopsine (14), *i.e.* the C-11 epimer of baptifoline.[20]

The latest synthesis[21] of ($\pm$)-epilupinine utilizes the Michael addition of acrylonitrile to 2-cyanomethylenepiperidine, which affords 1-cyano-4-oxo-1,10-dehydroquinolizidine (15). Diborane reduction of this lactam-nitrile gave an epimeric mixture of cyanoquinolizidines (16), which was converted into the equatorial isomer and simultaneously hydrolysed by heating with potassium hydroxide in aqueous diethylene glycol. The product (17) was esterified and reduced (LiAlH₄), with formation of ($\pm$)-epilupinine (18).[21]

Alternatively, the cyanoquinolizidine mixture may be epimerized to the equatorial isomer by treatment with sodium hydride in benzene. Reduction

[17] R. A. Shaimardanov, S. Iskandarov, and S. Y. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 276 (*Chem. Abs.*, 1970, **73**, 45 650).
[18] R. A. Shaimardanov, S. Iskandarov, and S. Y. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 169.
[19] Y. K. Kushmuradov, Pham Hoang Ngok, A. S. Sadykov, and K. A. Aslanov, *Nauch. Trudy Tashkent Gos. Univ.*, 1968, No. 341, 95.
[20] Pham Hoang Ngok, Y. K. Kushmuradov, K. A. Aslanov, A. S. Sadykov, Z. S. Ziyavit-dinova, V. G. Zaikin, and N. S. Vul'fson, *Khim. prirod. Soedinenii*, 1970, **6**, 111 (*Chem. Abs.*, 1970, **73**, 35 593).
[21] Y. Yamada, K. Hatano, and M. Matsui, *Agric. and Biol. Chem. (Japan)*, 1971, **35**, 285.

(15)

(16)

(17; R = CO$_2$H)
Epilupinine (18; R = CH$_2$OH)
(19; R = CH$_2$NH$_2$)
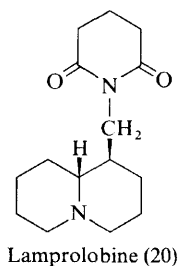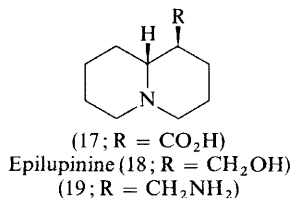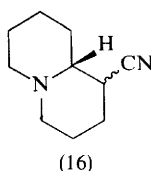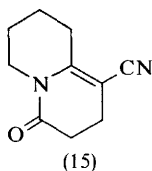
Lamprolobine (20)

(LiAlH$_4$) of the product afforded an aminomethylquinolizidine (19) which, on reaction with glutaric anhydride followed by acetic anhydride, afforded (±)-lamprolobine (20).[22]

The ability of sparteine to behave as a bidentate ligand has again been examined.[23] N.m.r. evidence indicates that it is an exceptionally good ligand for magnesium and forms, with magnesium dialkyls, complexes such as (21) that undergo inversion, carbon–magnesium bond exchange, and magnesium ligand exchange slowly on the n.m.r. time scale.

This ligand-forming ability for lithium and magnesium was previously noted, and was adduced to explain partial asymmetric induction in the synthesis of allenes from *gem*-dibromocyclopropanes and butyl-lithium,[24] and in the Grignard carbinol synthesis,[25] in the presence of (−)-sparteine. Details of these investigations have now been published.[26]

(21) R = 2-methylbutyl
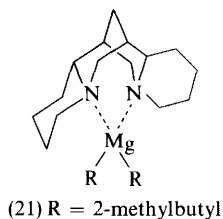
[22] Y. Yamada, K. Hatano, and M. Matsui, *Agric. and Biol. Chem. (Japan)*, 1970, **34**, 1536.
[23] G. Fraenkel, C. Cottrell, J. Ray, and J. Russell, *Chem. Comm.*, 1971, 273.
[24] H. Nozaki, T. Aratani, and R. Noyori, *Tetrahedron Letters*, 1968, 2087.
[25] H. Nozaki, T. Aratani, and T. Toraya, *Tetrahedron Letters*, 1968, 4097.
[26] H. Nozaki, T. Aratani, T. Toraya, and R. Noyori, *Tetrahedron*, 1971, **27**, 905.

Extracts of various *Sophora* species have earlier been reported to show anti-tumour activity, and it was therefore of interest to determine which, if any, of the alkaloidal constituents was responsible for this activity. Kojima *et al.*[27] have now shown that matrine exhibits anti-tumour activity against Ehrlich ascites tumour in mice, and both matrine and matrine *N*-oxide show activity against solid Sarcoma-180 in mice. In fact, the chemotherapeutic index of matrine *N*-oxide for Sarcoma-180 is estimated to be about 7.8 times that of mitomycin C.

2 *Ormosia* Alkaloids

The total synthesis of the *Ormosia* alkaloids from the intermediate (22)[28] has now been realized.[29] Wolff–Kishner reduction of the synthetic keto-dilactam (22) (earlier[28] assigned the incorrect configuration at C-6) gave the corresponding dilactam (α-H at C-16), which was hydrogenated to a mixture of C-18 epimers in which the desired epimer (23) strongly predominated. Diborane reduction of (23) gave ormosanine (24), identical with natural (racemic) ormosanine. The catalytic epimerization of (24) at C-6, as previously reported,[30] then gave (±)-piptanthine (24; β-H at C-6), while conversion of (24) into the hexacyclic base (±)-panamine (25) was achieved by reaction with *N*-chlorosuccinimide in methylene chloride.[29]

(22)   (23)

Ormosanine (24)   (−)-Panamine (25)
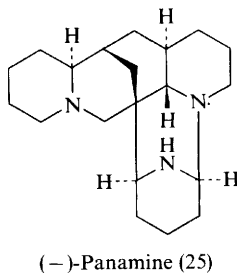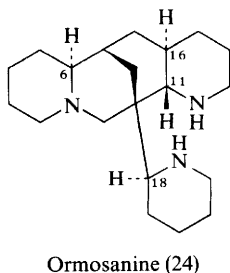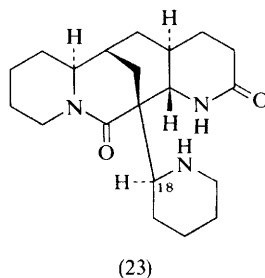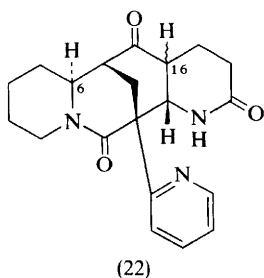
[27] R. Kojima, S. Fukushima, A. Ueno, and Y. Saiki, *Chem. Pharm. Bull.*, 1970, **18**, 2555.
[28] H. J. Liu, Z. Valenta, J. S. Wilson, and T. T. J. Yu, *Canad. J. Chem.*, 1969, **47**, 509.
[29] H. J. Liu, Z. Valenta, and T. T. J. Yu, *Chem. Comm.*, 1970, 1116.
[30] P. Deslongchamps, Z. Valenta, and J. S. Wilson, *Canad. J. Chem.*, 1966, **44**, 2539.
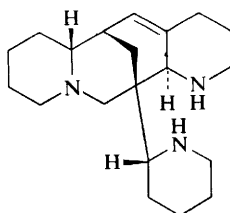
(26)

The genus *Ormosia* comprises approximately 100 species of woody legumes native to tropical America and S.E. Asia.[31] The geographical separation of these two regions and the absence of *Ormosia* species elsewhere suggests that genetic isolation may have been complete for up to fifty million years; a phytochemical comparison of species from the two regions is therefore of particular interest. The occidental *Ormosias* have been intensively studied in recent years,[32] but the oriental species have not hitherto been examined, with the exception of *O. emarginata* Benth. from Hong Kong, which was shown[33] to contain ormosanine (24) and panamine (25). McLean *et al.*[31] have recently examined five oriental species, and have shown that the alkaloidal constituents belong to the same group as do those of the American species. Thus, *O. semicastrata* Hance contains (±)-ormosanine (24), (±)-piptanthine [C-6 epimer of (24)], and 18-epiormosanine. Neither racemic piptanthine nor 18-epiormosanine has previously been obtained from natural sources. A fourth alkaloid, $C_{20}H_{33}N_3$, m.p. 263 °C (decomp.), of unknown constitution, was also isolated. This alkaloid is not identical with dihydro-ormojanine (26), but may be stereoisomeric with it, although the possibility that it may differ structurally, particularly with respect to the position of the double bond, has not yet been eliminated. The seeds of *O. sumatrana* Prain contain ormosanine, and the bark of *O. pachycarpa* Champ. contains (±)-piptanthine. The seeds of *O. emarginata* and *O. indurata* Chen contain, respectively, *N*-methylcytisine and *N*-methyltetrahydrocytisine.[31]

[31] S. McLean, P. K. Lau, S. K. Cheng, and D. G. Murray, *Canad. J. Chem.*, 1971, **49**, 1976.
[32] F. Bohlmann and D. Schumann in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1967, Vol. 9, pp. 213–217.
[33] H. R. Arthur and S. N. Loo, *Austral. J. Chem.*, 1967, **20**, 809.

7

Quinoline, Quinazoline, Acridone, and Related Alkaloids

BY V. A. SNIECKUS

1 Quinoline Alkaloids

An introductory chapter on the furoquinoline alkaloids with excellent coverage and leading references to the literature has been published as part of a general volume on alkaloids.[1] A detailed chromatographic analysis of quinoline alkaloids in liquid–liquid systems with buffered aqueous phase and a polarographic method for the determination of dubinidine from *Haplophyllum foliosum* have been reported.[2] From a pH–R_f relationship, the optimum conditions for extraction and chromatography were developed.[2a]

New isolation and structural elucidation studies are summarized in the Table.

Table *Isolation of quinoline alkaloids*

Species	Alkaloid (Structure)	Ref.
Esenbeckia febrifuga	Flindersiamine (1; $R^1 + R^2 = OCH_2O$, $R^3 = OMe$) Maculine (1; $R^1 + R^2 = OCH_2O$, $R^3 = H$) Skimmianine (1; $R^1 = H$, $R^2 = R^3 = OMe$)	3
Fagara macrophylla	Skimmianine*	4
Flindersia ifflaiana	Ifflaiamine* (14; $R^1 = H$, $R^2 = Me$) Unnamed (14; $R^1 = Me$, $R^2 = H$)	5
Haplophyllum foliosum	Foliosidine acetonide (2; $R^1 + R^2 = Me_2C$)	6
H. suaveolens	Dictamnine (1; $R^1 = R^2 = R^3 = H$) Skimmianine	7

[1] P. J. Scheuer in 'Chemistry of the Alkaloids,' ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, p. 355.
[2] *a* E. Soczewinski and B. Szabelska, *Diss. Pharm. Pharmacol.*, 1970, **22**, 243 (*Chem. Abs.*, 1971, **74**, 6406*m*); *b* D. A. Rakhimov, E. K. Dobronravova, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1970, **6**, 778 (*Chem. Abs.*, 1971, **74**, 112 271*y*).
[3] J. C. Vitagliano and J. Comin, *Anales Asoc. quim. argentina*, 1970, **58**, 59 (*Chem. Abs.*, 1971, **74**, 34 576*k*).
[4] F. Fish and P. G. Waterman, *J. Pharm. Pharmacol.*, 1971, **23**, 67.
[5] M. F. Grundon and T. R. Chamberlain, *J. Chem. Soc. (C)*, 1971, 910.
[6] V. A. Tel'nov, I. A. Bessopova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 724 (*Chem. Abs.*, 1971, **74**, 112 270*x*).
[7] M. Ionescu and I. Mester, *Phytochemistry*, 1970, **9**, 1137.

Table (continued)

Species	Alkaloid (Structure)	Ref.
Orixa japonica	Japonine (3) Kokusagine* (1; $R^1 = H$, $R^2 + R^3 = OCH_2O$)	} 8
Ptelea trifoliata	Ptelefoline (4)	9
Ruta graveolens	Graveoline*† [5; $R^1 = Me$, $R^2 = 3,4$-$(OCH_2O)C_6H_3$] Kokusaginine* (1; $R^1 = R^2 = OMe$, $R^3 = H$) 2-[4-(3,4-Methylenedioxyphenyl)butyl]quinoline*	}10
Vepris ampody	Kokusaginine Alkaloid [5; $R^1 = H$, $R^2 = (CH_2)_9COMe$] Alkaloid [5; $R^1 = H$, $R^2 = (CH_2)_8CH_2OH$] Alkaloid [5; $R^1 = H$, $R^2 =$ $(CH_2)_2CH=CHCH_2CH=CHEt$]	}11

* Known alkaloid, previously isolated from the same species, but may be from a different locality. *Cf.* (*a*) J. J. Willaman and H.-L. Li, *Lloydia*, 1970, **33**, No. 3A (Suppl.) and (*b*) R. A. Raffauf, 'A Handbook of Alkaloids and Alkaloid-Containing Plants,' Wiley–Interscience, New York, 1970.

† Structure incorrectly indicated in ref. (*b*), footnote (*) above.
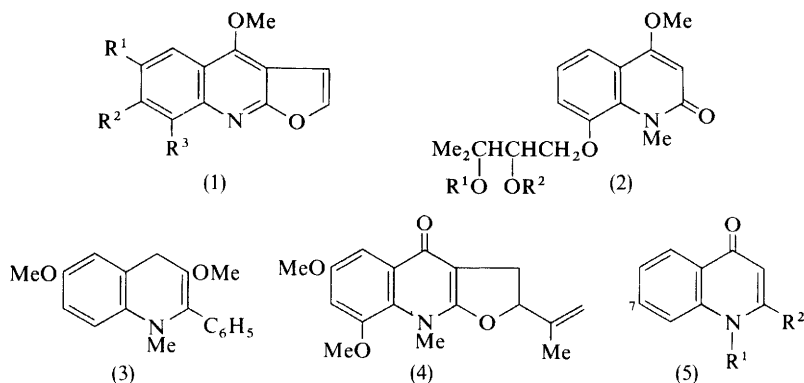
Foliosidine acetonide (2; $R^1 + R^2 = Me_2C$), isolated from *Haplophyllum foliosum*, may be an artifact.[6] It was hydrolysed to foliosidine (2; $R^1 = R^2 = H$) which has also been isolated from the same species. Treatment of an acetone solution of the latter with sulphuric acid afforded foliosidine acetonide. The isolation of dictamnine and skimmianine from *Haplophyllum suaveolens* is of chemotaxonomic interest.[7] Previously, kokusaginine (1; $R^1 = R^2 = OMe$, $R^3 = H$) and khaplofoline (6) had been obtained from this species.[12] The

[8] Ha-Hug-Ke, M. Luckner, and J. Reisch, *Phytochemistry*, 1970, **9**, 2199.

[9] J. Reisch, K. Szendrei, V. Papay, I. Novak, and E. Minker, *Tetrahedron Letters*, 1970, 3365.

[10] A. Z. Gulubov, Il. Z. Bozhkova, and T. O. Sunguryan, *Nauch. Tr. Vissh. Pedagog. Inst., Plovdiv, Mat., Fiz., Khim. Biol.*, 1970, **8**, 125 (*Chem. Abs.*, 1971, **74**, 61 600v).

[11] C. Kan-Fan, B. C. Das, P. Boiteau, and P. Potier, *Phytochemistry*, 1970, **9**, 1283.

[12] See 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, vol. 1, p. 96.

structure of the new alkaloid japonine (3) was deduced from chemical and spectral properties.[8] In particular, comparison with the spectral behaviour of synthetic 2- and 3-phenyl-4(1*H*)-quinolines was helpful.

In earlier reports, evidence for the structure of ptelefoline (authors' code number Pt/13) (7) and related *N*-methyl-2-quinolone alkaloids from *Ptelea trifoliata* had been presented.[13] A somewhat confusing situation has arisen as a result of ascribing the same name to another alkaloid isolated from the same species which, however, possesses the structure (4) and code number Pt/22.[9] The structure (4) of Pt/22 was established by spectral means; importantly, the mass spectrum of (4) showed a base peak at $M - 15$ which was attributed to the benzopyrylium ion (8). It is to be hoped that either Pt/13 or Pt/22 will be re-named in the near future.

(6)

(7)

(8)
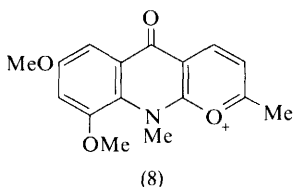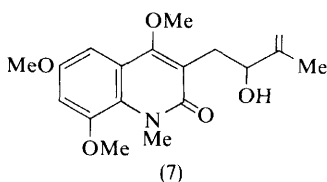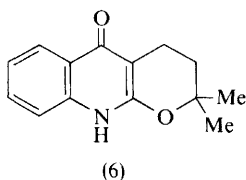
Details of the structural elucidation of bucharidine (9), isolated from *Haplophyllum bucharicum*, have appeared.[14] Aside from functional-group, i.r., n.m.r., and mass spectral analysis, it was reported that refluxing bucharaine (10), also previously isolated from the same species, in decalin solution afforded bucharidine (9). It should be noted that the structure of bucharine (bucharaine, bukharaine?) has been revised from that which was advanced earlier.[12] Furthermore, it has been reported that bucharaine undergoes a Claisen rearrangement in the mass spectrometer to give (11) at 60 °C and 40 eV and the 'abnormal' Claisen rearrangement product (12) at 110 °C.[15] These results invite further investigation of the rearrangement reactions of this alkaloid. The results of mass spectrometric studies of other furoquinoline alkaloids have been published.[16]

[13] Ref. 12, p. 97.
[14] Z. Sh. Faizutdinova, I. A. Bessonova, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 239 (*Chem. Abs.*, 1970, **73**, 131 179*v*).
[15] Ya. V. Rashkes, Z. Sh. Faizutdinova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 577 (*Chem. Abs.*, 1971, **74**, 54 044*p*).
[16] Ya. V. Rashkes, Z. Sh. Faizutdinova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 107 (*Chem. Abs.*, 1970, **73**, 35 581*z*).
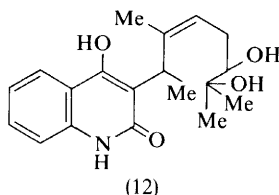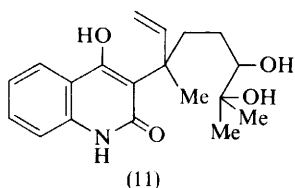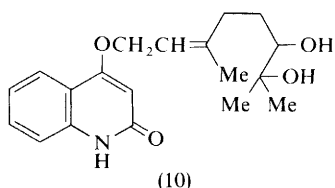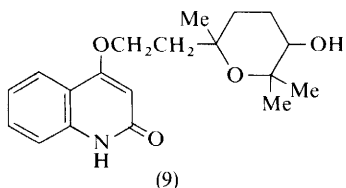
Details concerning the synthesis of ifflaiamine (14; R^1 = H, R^2 = Me) have appeared.[5] Treatment of the silver salt of 4-hydroxy-1-methyl-2-quinolone with 3,3-dimethylallyl bromide gave the *O*-dimethylallyl ether (13) in 16% yield together with *C*-alkylation products. Compound (13) was then subjected to Claisen rearrangement conditions to yield (14; R^1 = Me, R^2 = H; 36%), (15a; 20%) and (16a; 44%). Presumably, the 4-hydroxyquinoline (15a) arose by 'abnormal' Claisen rearrangement of (13) involving the intermediates (17) and (18). Variation of reaction conditions (time, temperature, solvent, addition of base) did not lead to the formation of ifflaiamine (14; R^1 = H, R^2 = Me). In one attempt, it was reasoned that addition of base to the reaction mixture would form the anion of intermediate (17), thus inhibiting the 'abnormal' Claisen rearrangement to (18). However, when this experiment was carried out, the 'normal' angular product (16b) was obtained in high yield. Therefore, a new approach was adopted which involved heating the ether (13) in *N*-methyl-piperidine containing acetic anhydride to trap the intermediate 'normal' product (15b). This reaction was accomplished in quantitative yield and the product (15b) was converted into the methyl ether (15c) by successive basic hydrolysis and treatment with diazomethane. When either the acetate (15b) or the ether (15c) was allowed to react with hydrogen bromide in acetic acid at room temperature, a good yield of ifflaiamine was obtained together with small amounts of other previously observed products. Apparently concurrently with this work,

(13) (14) (15a; R^1 = R^2 = H, R^3 = Me)
(15b; R^1 = Ac, R^2 = Me, R^3 = H)
(15c; R^1 = R^2 = Me, R^3 = H)

(16a; R^1 = Me, R^2 = H)   (17)   (18)
(16b; R^1 = H, R^2 = Me)
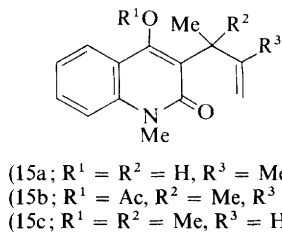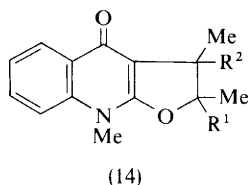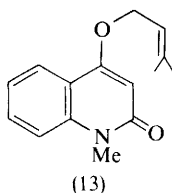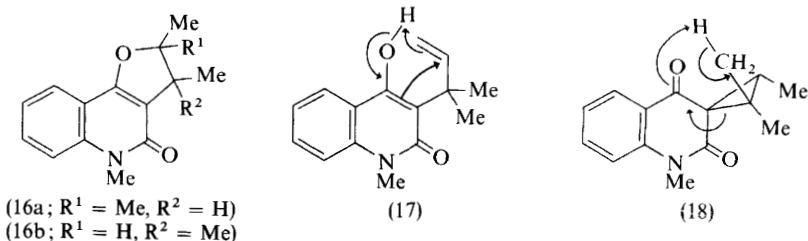
re-examination of *Flindersia ifflaiana* led to the isolation of both 'normal' (14; R^1 = H, R^2 = Me) and 'abnormal' (14; R^1 = Me, R^2 = H) Claisen rearrangement products. On the basis of biosynthetic experiments with related alkaloids, it is probable that these rearrangements operate in Nature.[5]

A simple synthesis of edulein [5; R^1 = Me, R^2 = Ph, C(7)-OMe] has been reported.[17] Syntheses of acronycidine (19; R^1 = R^2 = R^3 = OMe),[18] acro-phylline (20),[19] and 7-*O*-demethylevolitrine (19; R^1 = R^3 = H, R^2 = OH)[19] by essentially the same method have been described. For example, acid-catalysed cyclization of (21) gave the furoquinolone (22) which was converted into acrony-cidine (19; R^1 = R^2 = R^3 = OMe) by successive sodium borohydride reduction and methylation with diazomethane.[18] Routes for the preparation of cinchoninic acid and its derivatives have been improved.[20] The conditions required for the transformation of the 3-hydroxyquinoline derivative (23; R = H) to either the furoquinoline (24) (acetic anhydride, acetic acid) or the open-chain acetate (23; R = Ac), may be of general interest.[21]

(19)   (20)   (21)

(22)   (23)   (24)
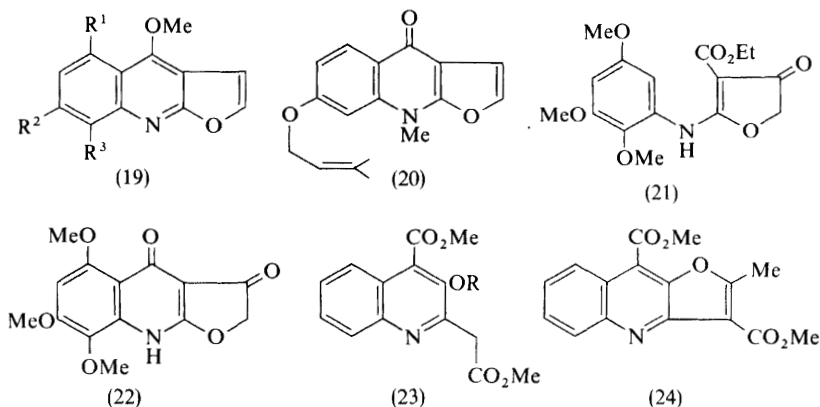
[17] P. Venturella, A. Bellino, M. L. Marino, and F. Piozzi, *Gazzetta*, 1970, **100**, 678.
[18] S. Prabhakar, B. R. Pai, and V. N. Ramachandran, *Indian J. Chem.*, 1971, **9**, 191.
[19] S. Prabhakar, B. R. Pai, and V. N. Ramachandran, *Indian J. Chem.*, 1970, **8**, 857.
[20] O. E. Schultz and U. Amschler, *Annalen*, 1970, **740**, 192.
[21] E. Winterfeldt, *Chem. Ber.*, 1971, **104**, 677.

An interesting sequence of reactions used in the preparation of the quinolone derivative (25) has been presented.[22] The isatin (26) was treated with base to afford the Pfitzinger rearrangement product (27). Although treatment of (27) with polyphosphoric acid gave the γ-lactone (28), reaction in refluxing dimethylaniline produced the δ-lactone (29). Successive treatment of the latter with phosphorus oxychloride and potassium hydroxide gave the furoquinoline (25).

(25) (26) (27)

(28) (29)
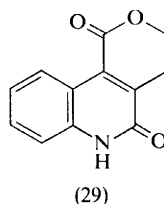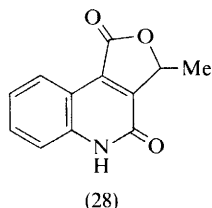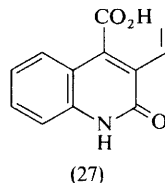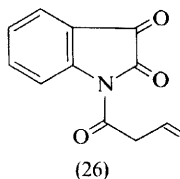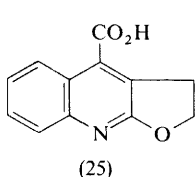
2 Quinazoline Alkaloids

Peganine (33; R = H) has been isolated from *Galena officinalis*.[22a]

The identification of deoxyvasicinone (30) as a minor alkaloid of *Mackinlaya macrosciadea* is of biogenetic interest.[23] Another alkaloid, $C_{12}H_{16}N_2O$, isolated from the same species, was obtained in insufficient amount for structural study. Two new alkaloids, pegamine (31)[24] and peganidine (32),[25] have been obtained from *Peganum harmala*. Since the latter closely resembles peganine (vasicine) (33; R = H) in behaviour, it should undoubtedly be represented by (33; R = CH₂COMe).

(30) (31)
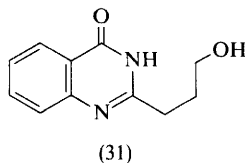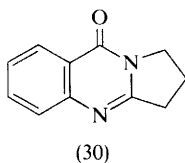
[22] P. Lakshminarayana, P. Shanmugam, and K. K. Balasubramanian, *Tetrahedron Letters*, 1970, 4947.

[22a] J. Schaefer and M. Stein, *Biol. Zentralblatte*, 1969, **88**, 755 (*Chem. Abs.*, 1970, **73**, 22 112x).

[23] N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1971, **24**, 223.

[24] Kh. N. Khashimov, M. V. Telezhenetskaya, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 453 (*Chem. Abs.*, 1971, **74**, 10 342e).

[29] Kh. N. Khashimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 599 (*Chem. Abs.*, 1970, **73**, 32296z).

CH$_2$COMe

(32)

R

(33)
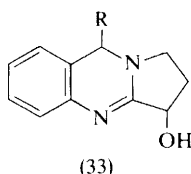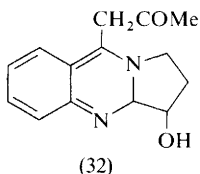
The high-resolution mass spectra of cyclopenin (34) and viridicatin (35) have been analyzed with the aid of deuteriated derivatives.[26] In the case of cyclopenin, two independent fragmentation pathways have been shown to account for virtually all of the major peaks. In both of these, certain important differences from those proposed previously[27] on the basis of low-resolution spectral analysis were observed. For example (Scheme 1) although the initial steps [(36) → (37) and (38)] were the same, exact mass measurements and observations of metastable transitions required that the fragment (38) decay by successive losses of H (39) and HCN (40) rather than by direct expulsion of CO to produce ion (41), as earlier formulated.[27] The second major pathway (Scheme 2) for cyclopenin (34) was found to proceed by methyl isocyanate loss to ions (42a) and (42b) rather than to the molecular ion of viridicatin (35). Fragmentation by the latter route had been advanced earlier[27] on the basis of the knowledge that various conditions (including pyrolytic) readily effect this transformation [(34) → (35)].[28] Thus it was found that the most intense peak, formulated as being due to (43) and supported by the presence of the appropriate metastable peak, was totally absent in the spectrum of (35). Additionally, the presence of a metastable peak correlating a C_6H_5CO fragment with an ion at m/e 237 may be explained readily by structure (42b) but cannot be envisaged to arise from (35). The major fragmentation pathways (Scheme 3) of viridicatin (35) were confirmed to be strikingly dissimilar to those of other carbostyril derivatives. The latter class of compounds usually show molecular ions of low stability and strong $M - 28$ peaks due to ring decarbonylation. Comparison of the spectrum of (34) with that of the benzylidene derivative (44) showed distinct differences in fragmentation modes. In the latter case (Scheme 4), transannular scission of the heterocyclic ring was found to be the main pathway leading to the ions (45) and (46). A separate scheme [(44) → (50) and (51)] involving a McLafferty rearrangement was required to account for peaks at m/e 146 and 132. A parallel mode of fragmentation [(44) → (49)] to that observed with cyclopenin and the successive losses of CHO (47) and H (48) accounted for the other major peaks in the spectrum of (44).

A facile synthesis of d,l-vasicine (33; R = H) has been reported.[29] Condensation of o-nitrobenzyl chloride with 3-hydroxypyrrolidine gave compound (52). Reduction of the nitro-function (conditions not given) followed by treatment with mercuric acetate–edta gave vasicine (33; R = H) and not the other possible cyclization product (53).

[26] M. McCamish and J. D. White, *Org. Mass Spectrometry*, 1970, **4**, (Suppl.), 241.
[27] M. Luckner, K. Winter, L. Nover, and J. Reisch, *Tetrahedron*, 1969, **25**, 2575.
[28] Ref. 12, p. 100.
[29] H. Moehrle and P. Gundlach, *Tetrahedron Letters*, 1970, 3249.

(34)   (35)

$(34)^{+\cdot}$ ⟶

(36)

$C_6H_5C≡\overset{+}{O}$
m/e 105
(37)

m/e 161
(40)

− HCN

m/e 188
(39)

− H·

m/e 189
(38)

− CO

(41)

Scheme 1

$(34)^{+\cdot}$ − MeNCO ⟶

m/e 237
(42a)

+

m/e 237
(42b)

⫽ − MeNCO

$(35)^{+\cdot}$

m/e 119
(43)

Scheme 2

m/e 209

m/e 165

m/e 236

Scheme 3

m/e 131
(45)

m/e 147
(46)

m/e 146
(50)

m/e 132
(51)

m/e 249
(47)

m/e 221
(49)

m/e 248
(48)
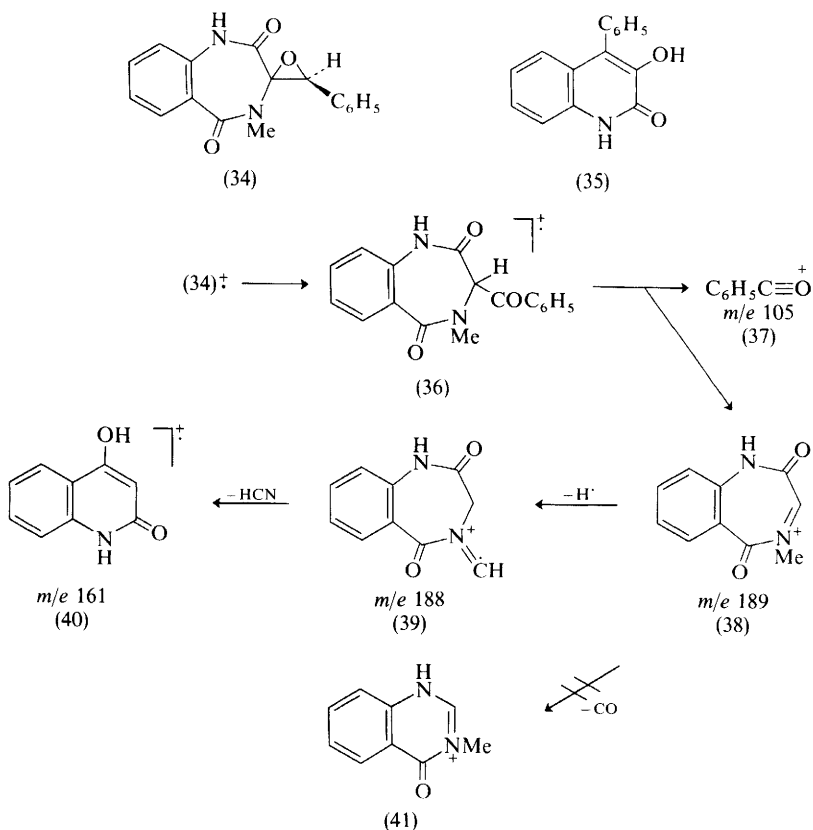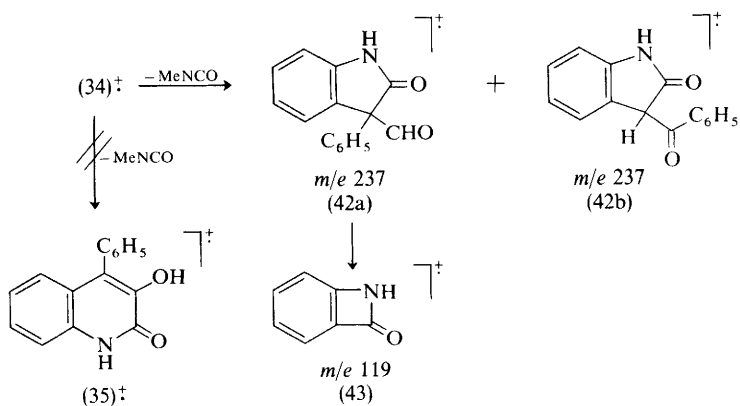
Scheme 4

A febrifugine analogue (54) has been prepared and shown to have lower toxicity against *Plasmodium berghei* than febrifugine.[30]

(52)

(53)

(54)

(55)

(56)

(57)

(58)
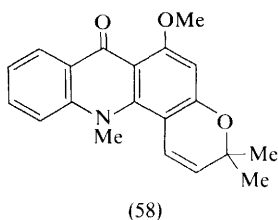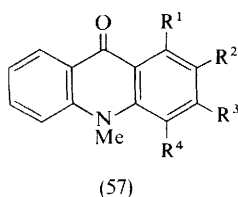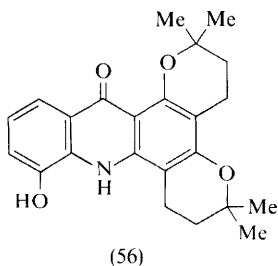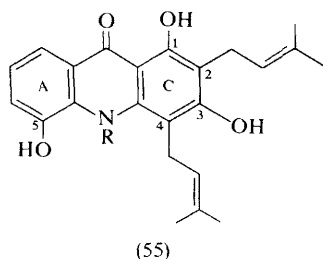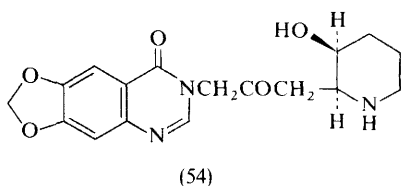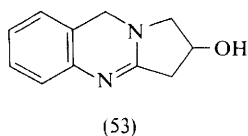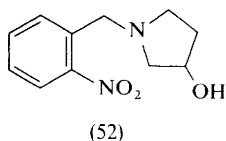
3 Acridone Alkaloids

Two new alkaloids, atalaphylline (55; R = H) and *N*-methylatalaphylline (55; R = Me) have been isolated from *Atalantia monophylla*.[31] The structure of (55; R = H) was suggested by comparison of its i.r., n.m.r., and mass spectra with those of related acridone alkaloids. In particular, the aromatic proton

[30] P.-L. Chien and C.-C. Cheng, *J. Medicin. Chem.*, 1970, **13**, 867.

[31] T. R. Govindachari, N. Viswanathan, B. R. Pai, V. N. Ramachandran, and P. S. Subramanian, *Tetrahedron*, 1970, **26**, 2905.

region of (55; R = H) was similar to other $C(5)$-oxygenated alkaloids. Methyla-
tion of atalaphylline with diazomethane gave the 3,5-dimethoxy-compound
showing the expected inertness of the *peri* $C(1)$-hydroxy-group. Treatment
of atalaphylline with formic acid produced bicycloatalaphylline (56), thus
confirming the location of the other hydroxy-group at $C(5)$. Since ring C
must have a $C(1)$-OH and a prenyl group at $C(2)$, the second hydroxy-group and
prenyl group must be at $C(3)$ or $C(4)$ or *vice versa*. In conformation with accepted
biogenetic considerations, the former arrangement was adopted. *N*-Methylatala-
phylline (55; R = Me) was correlated with the $N,C(1),C(3)$-trimethyl ether ob-
tained from the reaction of atalaphylline with methyl iodide and potassium
carbonate. Compounds (55; R = H) and (55; R = Me) are only the second and
third acridone alkaloids found in nature with ring-A oxygenation. Two other
acridones, (57; $R^1 = R^3 = H$, $R^2 = R^4 = OMe$) and evoxanthine (57; $R^1 =$
OMe, $R^2 + R^3 = OCH_2O$, $R^4 = H$), have been isolated from *Vepris ampody*.[11]

Details of the previously outlined[32] synthesis of acronycine (58), an alkaloid
isolated from *Acronychia baueri* which showed anti-tumour activity, have now
appeared.[33] In this paper, it is shown that unequivocal confirmation of structure
(58) for acronycine may also be obtained from n.m.r. and nuclear Overhauser
effect studies.

[32] Ref. 12, p. 101.
[33] J. R. Hlubucek, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1970, **23**, 1881.

8

β-Phenethylamines and the Isoquinoline Alkaloids

BY H. O. BERNHARD AND V. A. SNIECKUS

1 β-Phenethylamines

An introduction to this group appears in a book which provides a survey of the chemistry of the most important classes of alkaloids.[1]

A new n.m.r. shift reagent, tris-[3-(t-butylhydroxymethylene)-*d*-camphorato]-europium(III), should prove to be useful for the determination of enantiomeric purity of chiral β-phenethylamines.[2] For example, it was found that the $CHNH_2$ resonances of (*R*)- and (*S*)-amphetamines were separated by 0.7 p.p.m. in a carbon tetrachloride solution of the europium reagent (~ 0.15 mol l^{-1}). In comparison to the use of optically active solvents for the same purpose, this technique has the advantage of showing very large shifts between resonances of enantiomers. Mass spectrometry has been used in the detection of mescaline and tetrahydro-isoquinoline precursors as biochemical intermediates.[3] Spectral differences of 4-chloro-2-nitrobenzenesulphonyl derivatives of ephedrine and related compounds have been used for identification purposes.[4]

No doubt as a result of the continuing widespread use of alkaloid-containing drugs, new and sensitive analytical methods for their identification have been developed. For example, amphetamines and phenethylamines in blood and urine have been determined by gas chromatography as their corresponding acetamide derivatives[5] or directly by combination of fluorometry, gas–liquid and thin-layer chromatographies.[6] The latter technique may also be used independently for this purpose.[7,8]

As part of an extensive chemical investigation of the *Croton* genus (see Section 3D), *Croton humilis* has been examined and shown to contain *N*-methyltyramine

[1] A. Brossi and B. Pecherer in 'Chemistry of the Alkaloids,' ed. S. W. Pelletier, Van Nostrand Reinhold, New York, 1970, p. 11.
[2] G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, 1970, **92**, 6979.
[3] J. E. Lindgren, S. Agurell, J. Lundstrom, and U. Svenson, *Fed. Bur. Biochem. Soc. Lett.*, 1971, **13**, 21 (*Chem. Abs.*, 1971, **74**, 121 116*d*).
[4] J. Halmekoski, K. Lappi, and K. Ristola, *Farm. Aikak.*, 1970, **79**, 202; (*Chem. Abs.*, 1971, **74**, 115 933*b*).
[5] P. Lebish, B. S. Finkle, and J. W. Brackett, jun., *Clinical Chem.*, 1970, **16**, 195.
[6] S. J. Mule, *J. Chromatog.*, 1971, **55**, 255.
[7] G. H. Jolliffe and E. J. Shellard, *J. Chromatog.*, 1970, **48**, 125.
[8] J. G. Montalvo, E. Klein, D. Eyer, and B. Harper, *J. Chromatog.*, 1970, **47**, 542.

and *N*-methylhomotyramine.[9] The latter compound appears not to have been previously isolated from plants. The folkloric medicinal use of various cacti in the genus *Ariocarpus* continues to stimulate phytochemical investigations of new as well as previously examined species of this genus. As a result, *A. trigonus* yielded hordenine, *N*-methyltyramine, and *N*-methyl-3,4-dimethoxy-β-phenethylamine, whose identity was confirmed by synthesis.[10] The latter compound was also isolated from *A. fissuratus* var. *fissuratus* and had previously been reported to occur in three other cactus species.[11] It was also isolated, along with *N*-methyl-4-methoxy-β-phenethylamine, during the re-examination of non-phenolic extracts of *A. retusus*.[12] An alkaloid which may possess a β-phenethylamine structure has been found in the cactus *Coryphantha palmeri* Britton–Rose.[13] A new alkaloid isolated from *Swinglea glutinosa* has been shown to be *N*-benzoyl-4-(4'-acetoxygeranyloxy)phenethylamine by n.m.r. spin decoupling and degradative studies.[13a] Synthetic work indicated that previously isolated alkaloids of this structural type possess nerol rather than geraniol stereochemistry.

Cathine (*d*-norpseudoephedrine), cathinine, and ephedrine have been isolated from the leaves of *Catha edulis*.[14] Examination of *Erica lusitanica* yielded *p*-methoxy-β-phenethylamine, which had previously been shown to be absent in 16 other *Erica* species and 28 other Ericaceous plants.[15] Phenylacetamide has been isolated from *Vepris ampody*.[15a]

2-Amino-1-(3-hydroxyphenyl)ethanol has been prepared by an improved and possibly general method for this class of compounds.[16] An interesting report on the partial asymmetric induction in the reduction of acetophenone-*N*-benzylimine at the mercury cathode with chiral supporting electrolytes may have potential for the chiral synthesis of alkaloids.[17] For example, using (−)-(*R, S*)-*N*-methylephedrine methiodide as the electrolyte resulted in the formation of (−)-(*R*)-*N*-benzyl-α-phenethylamine of 7.3% optical purity. Of interest for biosynthetic studies are the reports of the preparation of specifically labelled substituted β-phenethylamines[18] and of (+)-*N*-(*o*-chlorobenzyl)-α-methylphenethylamine hydrochloride ^{14}C-labelled at the β-carbon.[19]

A full report on the unusual photochemical rearrangement of *N*-chloroacetylmescaline (1) has now appeared.[20] Irradiation of (1) in aqueous solution

[9] K. L. Stuart and D. Y. Byfield, *Phytochemistry*, 1971, **10**, 460.
[10] W. W. Speir, V. Mihranium, and J. L. McLaughlin, *Lloydia*, 1970, **33**, 15.
[11] D. G. Norquist and J. L. McLaughlin, *J. Pharm. Sci.*, 1970, **59**, 1840.
[12] J. M. Neal and J. L. McLaughlin, *Lloydia*, 1970, **33**, 395.
[13] X. A. Dominguez, S. Escarria, and C. Perez E., *Planta Med.*, 1970, **18**, 315.
[13a] D. L. Dreyer, *Tetrahedron*, 1970, **26**, 5745.
[14] M. S. Karawya, M. A. Elkiey, and M. G. Ghourab, *J. Pharm. Sci. U.A.R.*, 1968, **9**, 147 (*Chem. Abs.*, 1970, **73**, 117 169k).
[15] E. P. White, *New Zealand J. Sci.*, 1970, **13**, 359 (*Chem. Abs.*, 1970, **73**, 127 747m).
[15a] C. Kan-Fan, B. C. Das, P. Boiteau, and P. Potier, *Phytochemistry*, 1970, **9**, 1283.
[16] T. Kametani, F. Satoh, H. Agui, K. Ueki, K. Kigasawa, M. Hiiragi, H. Ishimaru, and S. Horie, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1161.
[17] L. Horner and D. H. Skaletz, *Tetrahedron Letters*, 1970, 3679.
[18] J. Lundstrom and S. Agurell, *Acta. Pharm. Suecica*, 1970, **7**, 247.
[19] J. Lintermans, A. Benakis, and R. Ratouis, *J. Labelled Compounds*, 1970, **6**, 289.
[20] O. Yonemitsu, H. Nakai, Y. Kanaoka, I. L. Karle, and B. Witkop, *J. Amer. Chem. Soc.*, 1970, **92**, 5691.

gave the benzazepine derivative (2) and the novel bicyclic compound (3; R = H), in addition to small amounts of *N*-acetylmescaline. On the other hand, photolysis in anhydrous methanol yielded (3; R = Me) and the medium-sized ring lactam (4). Photoproduct (3; R = H) was racemic and its structure was elucidated by *X*-ray analysis. It underwent an interesting fragmentation reaction in refluxing glacial acetic acid to yield compounds (5) and (6) whereas in methanolic hydrochloric acid at 20 °C it was converted to (7), whose structure was also determined by *X*-ray analysis. Compound (7) may result from an initial transannular aldol condensation, as indicated by carrying out the rearrangement in ethanol and in CD$_3$OD.

(1)

(2)

(3)

(4)

(5)

(6)

(7)
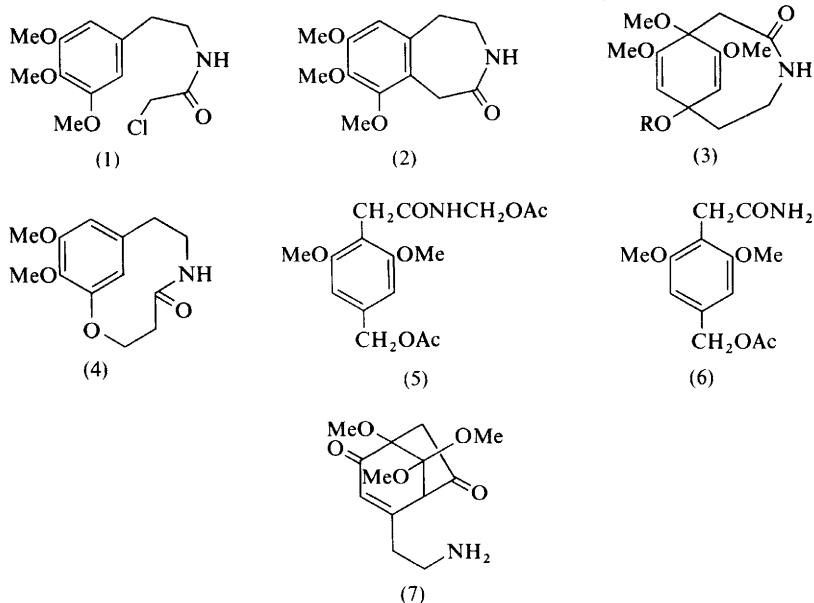
2 Simple Isoquinoline Alkaloids

The only significant report in the area of analytical methods deals with the mass spectrometric behaviour of cotarnine (8; R = OMe) and hydrastinine (8; R = H).[21] For example, the carbinolamine (8; R = H) undergoes disproportionation to yield oxyhydrastinine (9) and hydrohydrastinine (10), thus explaining the formation of a $M - 14$ peak in the mass spectrum. Some 1-phenethyl-1,2,3,4-tetrahydroisoquinoline derivatives have been synthesized[22] and their n.m.r. spectra have been examined.[23]

[21] G. Habermehl, J. Schunck, and G. Schaden, *Annalen*, 1970, **742**, 138.
[22] K. Ito, H. Furukawa, H. Tanaka, and S. Kato, *J. Pharm. Soc. Japan*, 1970, **90**, 1169 (*Chem. Abs.*, 1970, **73**, 135 750*x*).
[23] K. Ito, H. Tanaka, T. Ito, and H. Furukawa, *J. Pharm. Soc. Japan*, 1970, **90**, 1144 (*Chem. Abs.*, 1970, **73**, 3491*z*).

A review on *Thalictrum* alkaloids includes a section on the simple isoquinoline derivatives isolated from this genus.[24] During the past year, the following new sources of alkaloids have been uncovered: *Acacia concinna*, from which calycoto-mine (11; R^1 = H, R^2 = CH_2OH, R^3 = R^4 = Me) has been isolated;[25] *Ancistro-cladus heyneanus*, the first species of the *Ancistrocladus* genus to be examined chemically, which yielded ancistrocladine (12; R^1 = R^2 = H);[26] *Corydalis gortschakovii*, which gave corgoine (11; R^1 = $CH_2 \cdot C_6H_4$-*p*-OH, R^2 = R^4 = H, R^3 = Me;[27] *Haloxylon articulatum*, which yielded carnegine (11; R^1 = R^2 = R^3 = R^4 = Me) and a new alkaloid, *N*-methylisosalsoline (11; R^1 = R^2 = R^3 = Me, R^4 = H);[28] *Nelumbo nucifera* embryo, from which methylcorypalline (11; R^1 = R^3 = R^4 = Me, R^2 = H) has been obtained;[29] *Thalictrum fendleri*, which gave *N*-methylthalidaldine (13; R^1 = OMe, R^2 = R^3 = Me) and *N*-methylcorydaldine (13; R^1 = H, R^2 = R^3 = Me);[30] *T. flavum* which produced thalflavine (13; R^1 = OMe, R^2 + R^3 = CH_2);[31] and *T. minus* f. *elatum*, which yielded hydroxy-*N*-norhydrastinine (8; R = OH; NH for NMe).[31a] Most of these structures were elucidated by a combination of spectral and degradative methods and some were confirmed by synthesis. For example, spectral data alone were insufficient in order to distinguish between (13; R^1 = OMe, R^2 = R^3 = Me) and the alternative structure with the OMe function at C(8) rather than C(5)

R   OH
(8)

O
(9)

(10)

(11)
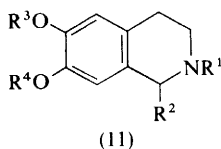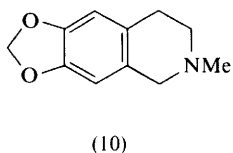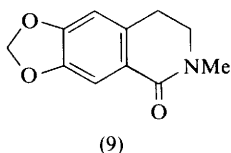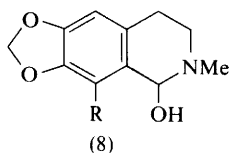
[24] P. L. Schiff, jun., and R. W. Doskotch, *Lloydia*, 1970, **33**, 403.
[25] G. L. Gupta and S. S. Nigam, *Planta Med.*, 1971, **19**, 55.
[26] *a* R. Govindachari and P. C. Parthasarathy, *Indian J. Chem.*, 1970, **8**, 567; *b* R. Govinda-chari and P. C. Parthasarathy, *Tetrahedron*, 1971, **27**, 1013.
[27] M. U. Ibragimova, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 638 (*Chem. Abs.*, 1971, **74**, 54 046r).
[28] C. Carling and F. Sandberg, *Acta. Pharm. Suecica*, 1970, **7**, 285 (*Chem. Abs.*, 1970, **73**, 63 154f).
[29] *a* T.-H. Yang and C.-M. Chen, *J. Chinese Chem. Soc.* (*Taiwan*), 1970, **17**, 54 (*Chem. Abs.*, 1970, **73**, 99 072s); *b* T.-H. Yang and C.-M. Chen, *ibid.*, p. 235 (*Chem. Abs.*, 1971, **74**, 100 254g).
[30] M. Shamma and Sr. M. A. Podczasy, *Tetrahedron*, 1971, **27**, 727.
[31] Kh. S. Umarov, Z. F. Ismailov, and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1970, **6**, 444 (*Chem. Abs.*, 1971, **74**, 1042e).
[31] *a* N. M. Mollov, P. P. Panov, T. Le Nhat, and L. Panova, *Doklady Bolgar. Akad. Nauk*, 1970, **23**, 1243 (*Chem. Abs.*, 1971, **74**, 61 584t).

(12)

(13)

(14)

(15)

(16)
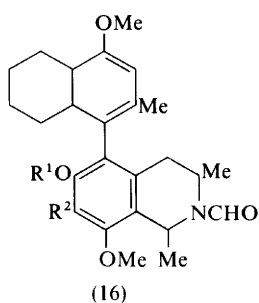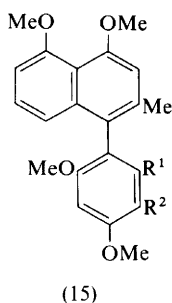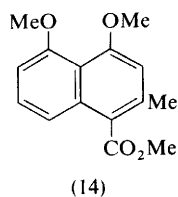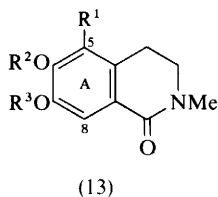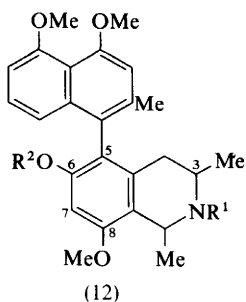
for the alkaloid *N*-methylthalidaldine. Confirmation of the correct structure as the former was achieved by comparison with a sample obtained by careful potassium permanganate oxidation of a benzylisoquinoline alkaloid bearing the identical methoxy-substitution pattern in ring A as *N*-methylthalidaldine.[30]

The basis[26b] of the structural assignment (12; $R^1 = R^2 = H$) for the unusual alkaloid ancistrocladine deserves special mention. I.r. spectral data and the formation of a diacetyl derivative indicated the presence of OH and NH groups and the n.m.r. spectrum of its crystalline hydrochloride exhibited absorptions due to two secondary methyls, three *O*-methyls, and one aromatic methyl group. Evidence for the presence of a 1-substituted 4,5-dimethoxy-2-methylnaphthalene system was obtained by oxidation of ancistrocladine hydrochloride with potassium permanganate followed by esterification with diazomethane. This sequence of reactions yielded the naphthalene derivative (14), which was synthesized by two unambiguous routes. *ON*-Dimethylancistrocladine (12; $R^1 = R^2 = Me$), prepared in four steps from the alkaloid, showed a 100 MHz n.m.r. spectrum fully compatible with the proposed structure, and this compound was now used in a stepwise Hofmann degradation which furnished evidence for the linkage of the naphthalene system at C(5) and the presence of a 1,3-dimethyltetrahydroisoquinoline ring. The first Hofmann reaction yielded the methine [15; $R^1 = -CH:CHMe$, $R^2 = -CH(Me)NMe_2$] whose n.m.r. spectrum showed, among the other required absorptions, a quartet at δ 1.28 due to the olefinic methyl function. The shielded nature of this function necessitated the placement of the

naphthalene ring at C(5) as indicated in structure (12; $R^1 = R^2 = H$). The second Hofmann elimination yielded an *optically active*, nitrogen-free bismethine (15; $R^1 = -CH:CHMe$, $R^2 = CH:CH_2$) and a small amount of the alcohol [15; $R^1 = -CH:CHMe$, $R^2 = -CH(OH)Me$]. The latter compound was ozonized to give an aldehyde, which on oxidation followed by acid treatment gave a five-membered-ring lactone derivative. This observation is only compatible with a compound having the propenyl and α-hydroxyethyl side-chains *ortho* to each other as in [15; $R^1 = -CH:CHMe$, $R^2 = -CH(OH)Me$] and thus proves the presence of a 1,3-dimethyltetrahydroisoquinoline ring in ancistrocladine. Finally, the placement of the phenolic OH at C(6) was based on n.m.r. evidence, while the position of the third methoxy-group was determined to be at C(8) rather than at C(7) by effecting a Claisen rearrangement on another degradation product (16; $R^1 = -CH_2CH:CH_2$, $R^2 = H$) which yielded the expected product (16; $R^1 = H$, $R^2 = -CH_2CH:CH_2$). Ancistrocladine (12; $R^1 = R^2 = H$) is thus the first isoquinoline alkaloid which possesses a C(3)-methyl group, a structural feature which may be biogenetically indicative of a polyketide origin.

Two synthetic reviews, one dealing generally with isoquinolines[32] and the other with phenethylisoquinoline alkaloids,[33] have been published in the Japanese language. The major new developments in the synthesis of simple isoquinoline alkaloids deal not so much with structural confirmation of natural products but rather with subtle modification of aromatic-ring substituents. Tepenine (19), an example of a relatively rare 7,8-dioxygenated alkaloid, has been synthesized by application of Bobbitt's modification of the Pomeranz–Fritsch reaction (see Scheme 1).[34] Thus the Schiff base (17) was converted into (18) by treatment with methyl Grignard reagent; cyclization of (18) with hydrochloric acid, followed by hydrogenolysis and reductive N-methylation
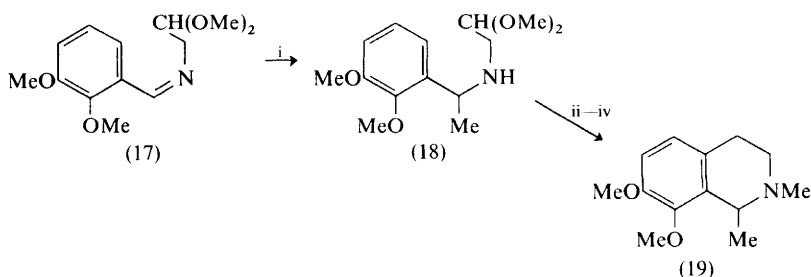
Reagents: i, MeMgX; ii, HCl; iii, H_2, Pd–C; iv, CH_2O, $NaBH_4$.

Scheme 1

[32] Y. Ogata and S. Suyama, *J. Japanese Chem.*, 1970, **24**, 433 (*Chem. Abs.*, 1970, **73**, 66 344*d*).

[33] T. Kametani and H. Yagi, *J. Japanese Chem.*, *Suppl.*, 1969, **87**, 99 (*Chem. Abs.*, 1970, **73**, 35 562*u*).

[34] J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, 1965, **30**, 2247.

(20)   (21)   (22)

(23)

(22) ←vii—ix   → ←i, vi   (24)
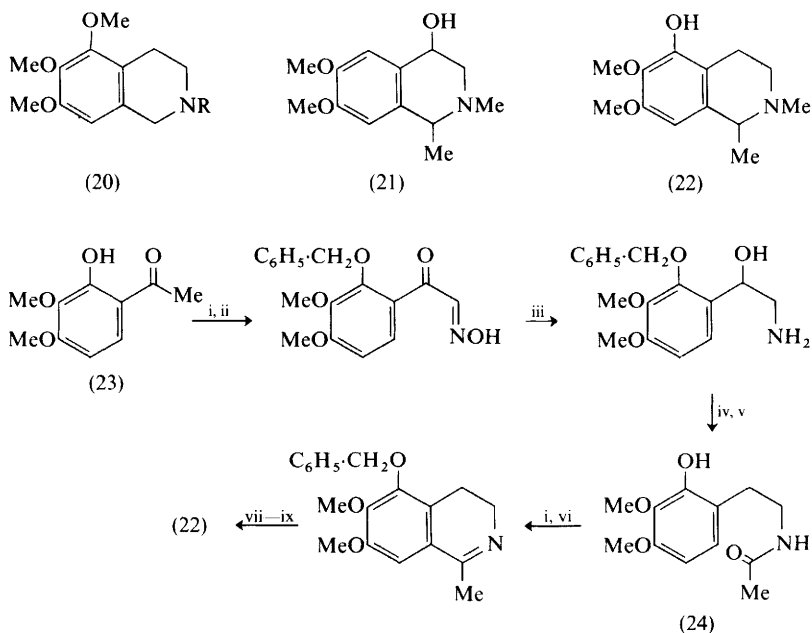
Reagents: i, $C_6H_5CH_2Br$, K_2CO_3; ii, isoamyl nitrite, NaOEt; iii, $LiAlH_4$; iv, Ac_2O, pyridine; v, H_2, Pd–C; vi, $POCl_3$, $C_6H_5\cdot Me$; vii, MeI; viii, $NaBH_4$; ix, H_2, Pd–C.

Scheme 2

afforded racemic tepenine (24 % overall yield).[35] Tehaunine (20; R = Me) was prepared by *N*-methylation of (20; R = H) which in turn had been previously synthesized by a similar sequence of reactions.

Gigantine, previously assigned structure (21), has now been shown to be (22).[35,36] The alkaloid gave a positive Gibb's test, characteristic of phenols with a free *para*-position, and the n.m.r. spectrum showed absorption at δ 6.29 (s, 1H) which was shifted upfield by 0.41 p.p.m. upon base treatment, characteristic of an aromatic proton *para* to a phenolic hydroxy-group.[35] Final confirmation of structure (22) for gigantine was obtained by total synthesis by two routes involving a common intermediate (24). The more unusual route is described by the sequence in Scheme 2.[36]

Conditions have been developed which favour certain preferential *O*-demethylation of aromatic ring dimethoxy-substituted 3,4-dihydroisoquinolines[37] and

[35] G. J. Kapadia, M. B. E. Fayez, M. L. Sethi, and G. S. Rao, *Chem. Comm.*, 1970, 856.
[36] G. J. Kapadia, G. S. Rao, B. E. Fayez, B. K. Chowdhury, and M. L. Sethi, *Chem. and Ind.*, 1970, 1593.
[37] A. Brossi and S. Teitel, *Helv. Chim. Acta.*, 1970, **53**, 1779.

trimethoxy-1,2,3,4-tetrahydroisoquinoline alkaloids.[38] Thus, controlled acid hydrolysis leads to cleavage at the 5-methoxy-group with the 5,6- and 5,8-isomers (25; $R^1 = R^2 = OMe$, $R^3 = R^4 = H$ and $R^1 = R^4 = OMe$, $R^2 = R^3 = H$) respectively, at the 6-methoxy-group with the 6,8-isomer (25; $R^1 = R^3 = H$, $R^2 = R^4 = OMe$), at the 7-methoxy-group with the 5,7-isomer (25; $R^1 = R^3 = OMe$, $R^2 = R^4 = H$), and at the 8-methoxy-group with the 7,8-isomer (25; $R^1 = R^2 = H, R^3 = R^4 = OMe$).[37] Two other reactions reported in this work may be of general interest: a modified Birch reduction [(26; $R^1 = H, R^2 = R^3 = R^4 = OMe) \rightarrow (26; R^1 = R^2 = H, R^3 = R^4 = OMe)$] and the reductive removal of a phenolic hydroxy-group *via* the tetrazole derivative (27). On the other hand, treatment of the trimethoxy-substituted alkaloids, *O*-methylanhalidine (26; $R^1 = Me$, $R^2 = R^3 = R^4 = OMe$) and ($\pm$)-*O*-methylpellotine (28; $R^1 = Me$, $R^2 = R^3 = R^4 = OMe$) with 20% hydrochloric acid at reflux temperature gave (26; $R^1 = Me, R^2 = R^4 = OMe, R^3 = OH$; 81%) and (28; $R^1 = Me, R^2 = R^4 = OMe, R^3 = OH$; 72%) respectively.[38] Application of these conditions to anhalinine (26; $R^1 = H$, $R^2 = R^3 = R^4 = OMe$) and ($\pm$)-*O*-methylanhalonidine (28; $R^1 = H$, $R^2 = R^3 = R^4 = OMe$) gave the corresponding phenols (26; $R^1 = H$, $R^2 = R^3 = OMe$, $R^4 = OH$) and (28; $R^1 = H$, $R^2 = R^3 = OMe$, $R^4 = OH + 28; R^1 = H, R^2 = R^4 = OMe, R^3 = OH$). However, in these last cases, yields of monophenols were poor and similar amounts of diphenolic compounds in addition to starting material were obtained. Selective *O*-demethylation reactions have also been used in the synthesis of 7-methoxy-1,2,3,4-tetrahydro-5-isoquinolinol[39] and corypalline (11; $R^1 = R^3 = Me$, $R^2 = R^4 = H$).[40]

As noted previously, 7,8-dioxygenated tetrahydroisoquinoline alkaloids may be synthesized by a modified Pomeranz–Fritsch reaction. Application of the Bischler–Napieralski or Pictet–Spengler reactions usually leads to cyclization in an undesired sense, *e.g.*, in (29; X = H) to the 2- rather than to the 6-position. This can be avoided by blocking the 2-position with a bromine function. Thus homopetaline (30; $R = CH_2CH_2 \cdot C_6H_4 \text{-} p \text{-OMe}$) has been synthesized from (29; $R = CH_2CH_2 \cdot C_6H_4 \text{-} p \text{-OMe}$) in four steps, the bromo-substituent being removed by catalytic hydrogenation over Raney nickel in the final step.[41]

(25)   (26)   (27)
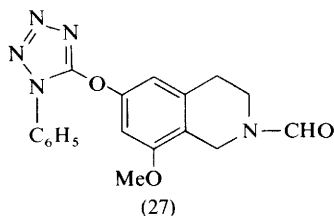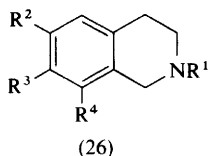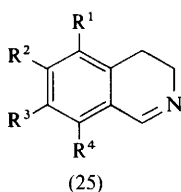
[38] A. Brossi and S. Teitel, *Chem. Comm.*, 1970, 1296.
[39] S. Teitel and A. Brossi, *J. Heterocyclic Chem.*, 1970, **7**, 1401.
[40] A. Brossi, J. P. O'Brien, and S. Teitel, *Org. Prep. Procedures*, 1970, **2**, 281.
[41] T. Kametani, K. Fukumoto, and M. Fujihara, *J. Org. Chem.*, 1971, **36**, 1293.
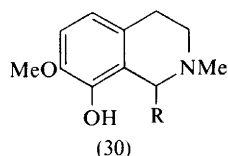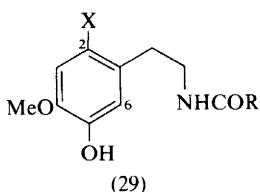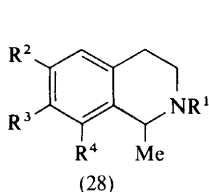
The absolute configurations of (1*R*, 4*R*)-1,2,3,4-tetrahydro-4-hydroxy-6-methoxy-2-methyl-1-phenylisoquinoline (31) and its epimer (1*S*, 4*R*), synthesised from D-(+)-2-amino-1-(3-hydroxyphenyl)ethanol, have been determined with the aid of n.m.r. spectral and o.r.d. and c.d. measurements.[42] These results may prove to be useful in the determination of the absolute configuration of 1-phenylisoquinoline alkaloids. In this regard, another report on the conformation and configuration of differently substituted tetrahydroisoquinolines may be consulted.[43]

Increasing interest has been expressed in electrolytic oxidative coupling reactions of phenolic tetrahydroisoquinolines.[44,45] The series (32; R = H, Me, Et, Bu^s) has been oxidized on a platinum anode and the results have been compared with those observed for catalytic (O_2, Pt) and chemical oxidations.[44] For example, electrolytic oxidation of compound (32; R = H) gave the dimers (33; R = H) and (34; R = H, *n* = 0) while (32; R = Bu^s) produced (34; R = Bu^s, *n* = 0) and the trimer (34; R = Bu^s, *n* = 1). In many cases, theoretically predicted enantiomeric pairs were obtained and separated but stereochemical assignments could not be made. Both C—C (33; R = H and R = Me) and C—O—C (34; R = H and Me, *n* = 0) dimers were also formed in the catalytic oxidation of (32; R = H) and (32; R = Me), and both methods appear to be superior to chemical oxidation for the formation of these types of compounds. A further favourable aspect of the electrolytic method which may be useful for the synthesis of complex alkaloids is the absence of products resulting from oxidation of the nitrogen ring system. Finally, the proportion of C—O—C to C—C dimers formed in either the electrolytic or catalytic oxidations is strongly dependent on the nature of the *C*(1)-substituent, increasing markedly in the order (32; R = H > R = Me > R = Et > R = Bu^s). The results of the chemical oxidation of (32; R = Me) quoted in the above work[44] should be viewed in the light of a thorough re-examination of this reaction.[45] It was found that potassium ferricyanide in aqueous sodium carbonate was the most favourable condition for the formation of the C—O—C dimer (34; R = Me, *n* = 0). Pertinent to this discussion is the

[42] T. Kametani, H. Sugi, H. Yagi, K. Fukumoto, and S. Shibuya, *J. Chem. Soc. (C)*, 1970, 2213.

[43] M. A. Khaimova, M. D. Palamareva, B. I. Kurtev, S. Novkova, and S. Spasov, *Chem. Ber.*, 1970, **103**, 1347.

[44] J. M. Bobbitt, K. H. Weisgraber, A. S. Steinfeld, and S. G. Weiss, *J. Org. Chem.*, 1970, **35**, 2884.

[45] O. Hoshino, H. Hara, M. Wada, and B. Umezawa, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 637.

report on the electrode deactivation in the anodic voltammetry of corypalline
(32; R = H).[46]

(31)   (32)   (33)

(34)

(35)
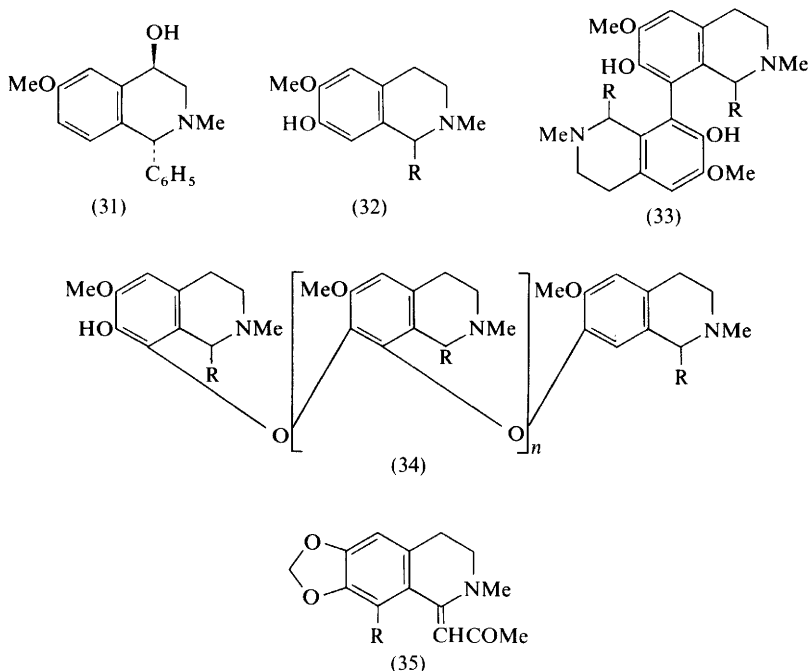
Cotarnine (8; R = OMe) and hydrastinine (8; R = H) undergo interesting
reactions with diazoacetone to produce compounds (35; R = OMe) and (35;
R = H) respectively.[47]

3 Benzylisoquinoline Alkaloids

A general introduction and survey of this group has appeared.[48] Two reviews,
one concerning the synthesis of morphinandienone, cularine, and ochotensimine
alkaloids[33] and the other dealing with classification of Papaveraceae alkaloids,[49]
are not readily accessible. A comprehensive review on the *Thalictrum* alkaloids
offers discussions on benzylisoquinoline, pavine, aporphine, protoberberine,
protopine, phenanthrene, and bis-benzylisoquinoline alkaloids which are found
in this genus.[24] A brief but illuminating account of the distribution and relative

[46] J. T. Stock, *Microchem. J.*, 1970, 15, 564.
[47] B. Goeber, G. Bauer, and S. Pfeifer, *Pharmazie*, 1971, 26, 51.
[48] M. Shamma in 'Chemistry of the Alkaloids,' ed. S. W. Pelletier, Van Nostrand Reinhold
New York, 1970, p. 31.
[49] R. K. Puri, *Pharmacos*, 1968, 13, 83 (*Chem. Abs.*, 1971, 74, 91 099*j*).

incidence of alkaloids in plants, which incorporates information on most benzyl-isoquinoline-alkaloid-producing families, has appeared.[50]

The use of u.v. spectroscopy to determine the nature and position of methoxy- and methylenedioxy-substituted aromatic rings has been systematically applied to protoberberine, protopine, benzophenanthridine, and proto-ochotensimine alkaloids.[51] I.r. spectra of examples of almost all subgroups of benzylisoquinoline alkaloids, including emetine, have been recorded and characteristic bands in the 1800—1480 cm^{-1} region have been used to identify a particular subgroup.[52]

A general method for the identification of alkaloid-containing drugs, including those commonly named ipecacuanha, hydrastis, and opium, has been published.[7] In this connection, an older review should be noted.[53]

Of general importance in the area of benzylisoquinoline alkaloids is a recent controversy which has arisen as a result of the proposal that alcohol addiction may involve specific biochemical events which lead to morphine-type alkaloids.[54]

A. Simple Benzylisoquinolines.—Advances in the analytical chemistry of this group have mainly dealt with spectrophotometric[55—57] and thin-layer chromatographic[58—61] methods. For example, papaverine can be determined in lower than microgram amounts in a mixture of opium alkaloids using a fluorometric method.[57] A novel reverse-phase thin-layer chromatographic technique has been applied to the separation of papaverine in a drug mixture.[60] Use of paper electrophoresis[62] and gravimetric[63] methods for the determination of papaverine have also been reported. Finally, reports on the anodic voltammetry[46] and kinetics of autoxidation in the presence of metal ions[64] of benzylisoquinoline alkaloids have appeared.

The following new sources of alkaloids have been reported: *Anona muricata*, which yielded reticuline;[65] *Cinnamomum* species, from which cinnamolaurine $(36; R^1 = Me, R^2 + R^3 = CH_2, R^4 = H), (+)$-reticuline $(37; R = H)$, and a new

[50] R. F. Raffauf, *Econ. Botany*, 1970, **24**, 34 (*Chem. Abs.*, 1970, **73**, 84 589s).
[51] L. Hruban, F. Santavy, and S. Hegerova, *Coll. Czech. Chem. Comm.*, 1970, **35**, 3420; F. Santavy, L. Hruban, V. Simanek, and D. Walterova, *ibid.*, p. 2418.
[52] M. E. Perel'son, Kh. Sh. Baisheva, B. K. Rostotskii, and A. A. Kir'yanov, *Lek. Rast.* 1969, **15**, 382; From *Ref. Zhur., Khim.*, 1970, Abs. 9Zh657 (*Chem. Abs.*, 1971, **74**, 148 540z).
[53] L. Fishbein and H. L. Falk, *Chromatog. Rev.*, 1969, **11**, 1.
[54] T. L. Sourkes, *Nature*, 1971, **229**, 413; V. E. Davis and M. J. Walsh, *Science*, 1970, **170**, 1114; M. H. Seevers, *ibid.*, p. 1113.
[55] Z. Blagojevic and M. Skrlj, *Arhiv Farm.* (*Belgrade*), 1970, **20**, 109 (*Chem. Abs.*, 1970, **73**, 112 999w).
[56] G. I. Oleshko and G. I. Kudymov, *Khim. Farm. Zhur.*, 1970, **4**, 41 (*Chem. Abs.*, 1971, **74**, 134 008z).
[57] R. A. Chalmers and G. A. Wadds, *Analyst*, 1970, **95**, 234.
[58] F. Reimers, *Arch. Pharm. Chemi*, 1971, **78**, 201 (*Chem. Abs.*, 1971, **74**, 146 432s).
[59] K. Jensen, *Arch. Pharm. Chemi*, 1971, **78**, 249 (*Chem. Abs.*, 1971, **75**, 9901a).
[60] K. Groningsson, *Acta Pharm. Suecica*, 1970, **7**, 635 (*Chem. Abs.* 1971, **74**, 115 966q).
[61] E. Roeder, *Mitt. deut. pharm. Ges.*, 1970, **40**, 176 (*Chem. Abs.*, 1970, **73**, 84 469c).
[62] L. V. Pesakhovich, *Farm. Zhur.* (*Kiev*), 1970, **25**, 10 (*Chem. Abs.*, 1971, **74**, 125 880w).
[63] Gh. Morait, *Farmacia* (*Bucharest*), 1970, **18**, 257 (*Chem. Abs.*, 1970, **73**, 69 888v).
[64] E. Pawelczyk, T. Hermann, and K. Jurkiewicz, *Diss. Pharm. Pharmacol.* 1970, **22**, 153.
[65] G. Aguilar-Santos, J. R. Librea, and A. C. Santos, *Philippine J. Sci.*, 1967, **96**, 399 (*Chem. Abs.*, 1971, **74**, 1066r).

alkaloid, norcinnamolaurine (36; $R^1 = R^4 = H$, $R^2 + R^3 = CH_2$), were iso-lated;[66] *Hernandia papuana*, which produced L-(+)-laudanidine [37; R = H; C(7)-OMe for OH];[66a] *Nelumbo nucifera* embryo, which gave ($\pm$)-armepavine (36; $R^1 = R^2 = R^3 = Me$, $R^4 = H$) and the new alkaloid demethylcoclaurine (36; $R^1 = R^2 = R^3 = R^4 = H$);[67,68] *Papaver fugax* and *P. triniaefolium*, both of which yielded (−)-armepavine (36; $R^1 = R^2 = R^3 = Me$, $R^4 = H$);[69] *Thalictrum fendleri*, which gave the known veronamine (38);[30] and *T. minus* f. *elatum*, which was shown to contain 1-(4-hydroxybenzyl)-2-methyl-5-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.[31a]

The report on the investigation of the *Papaver* species[69] is exhaustive (see also Sections 3C, G, H, and I) and has chemotaxonomic interest.

(36)   (37)   (38)
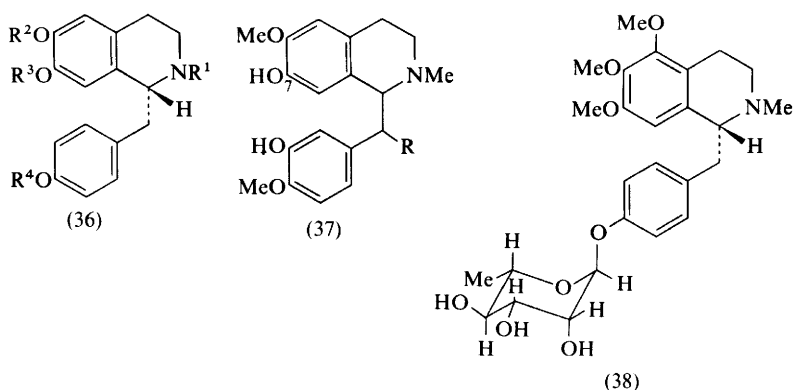
Papaverine and other benzylisoquinoline alkaloids have been isolated from Russian Kirghiz opium.[70] Examination of opium samples from various localities in Korea has revealed that papaverine content does not vary from area to area.[71] Four species of Papaveraceae have been examined for relative amounts of papa-verine and other alkaloids in different segments of plant tissue.[72] A study of the variation with time of papaverine content in the germinating seedling of *Papaver somniferum* has been reported.[73]

[66] E. Gellert and R. E. Summons, *Austral. J. Chem.*, 1970, **23**, 2095.

[66a] F. N. Lahey and K. F. Mak, *Austral. J. Chem.*, 1971, **24**, 671.

[67] H. Koshiyama, H. Ohkuma, H. Kawaguchi, H.-Y. Hsu, and Y.-P. Chen, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2564.

[68] J. Kunitomo, Y. Nagai, Y. Okamoto, and H. Furukawa, *J. Pharm. Soc. Japan*, 1970, **90**, 1165 (*Chem. Abs.*, 1971, **74**, 1110a).

[69] V. Preininger and F. Santavy, *Pharmazie*, 1970, **25**, 356.

[70] I. A Bessonova, Z. Sh. Faizutdinova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 711 (*Chem. Abs.*, 1971, **74**, 84 055u).

[71] C. K. Lee and H. K. Kim, *Bull. Narcotics*, 1970, **22**, 41.

[72] D. Vagujfalvi, *Bot. Kozlem.*, 1970, **57**, 113 (*Chem. Abs.*, 1971, **74**, 993d).

[73] F. A. Crane and J. W. Rairbairn, *Trans. Illinois State Acad. Sci.*, 1970, **63**, 86.

In the realm of synthesis, two groups[74,75] have reported a facile preparation of the 3-isoquinolone derivative (40) by the same method, and one of these has used this compound as an intermediate for entries into tetrahydropapaverine (41; R = H) and (±)-laudanosine (41; R = Me) as shown in Scheme 3.[75] Intermolecular acylation of 3,4-dimethoxyphenylacetic acid with polyphosphoric acid gave (39) in 60%[75] or 95%[74] yield. The latter compound was readily converted into tetrahydropapaverine (41; R = H) in three steps. On the other hand, treatment of (42), prepared by dehydration of (39) in refluxing decalin, with methylamine followed by identical steps to those used in the synthesis of (41; R = H) gave (±)-laudanosine (41; R = Me).

Bischler–Napieralski and Pictet–Spengler reactions continue to serve well for benzylisoquinoline syntheses.[76,77] In the latter reaction, use of α-formylphenylacetic esters for the non-nitrogen-containing component appears to be advantageous.[77] An interesting sequence of reactions (43) → → (44) (Scheme 4) has apparently been applied to the synthesis of papaverine [44; R = 3,4-(MeO)$_2$-C$_6$H$_3$CH$_2$·] and related alkaloids.[78] An attempt to convert (±)-reticuline (37; R = H) into a morphinandienone-type alkaloid by enzymic oxidation with
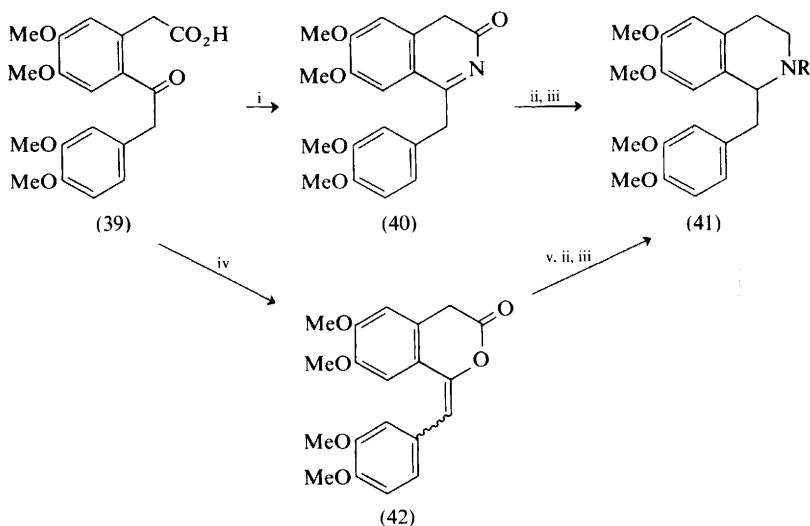
Reagents: i, NH$_4$OAc, AcOH; ii, H$_2$, PtO$_2$; iii, B$_2$H$_6$, THF; iv, 190 °C, decalin; v, MeNH$_2$.

Scheme 3

[74] G. N. Dorofeenko and V. G. Korobkova, *Zhur. obshchei Khim.*, 1970, **40**, 249.

[75] I. W. Elliott, *J. Heterocyclic Chem.*, 1970, **7**, 1229.

[76] D. G. Farber and A. Giacomazzi, *Anales Asoc. quim. argentina*, 1970, **58**, 133 (*Chem. Abs.*, 1970, **73**, 131 173*p*).

[77] E. Yamato, *Chem. and Pharm. Bull.* (*Japan*), 1971, **18**, 2038.

[78] S. V. Krivun, G. N. Dorofeenko, and E. Z. Sadekova, *Zhur. obshchei Khim.*, 1970, **40**, 1429.
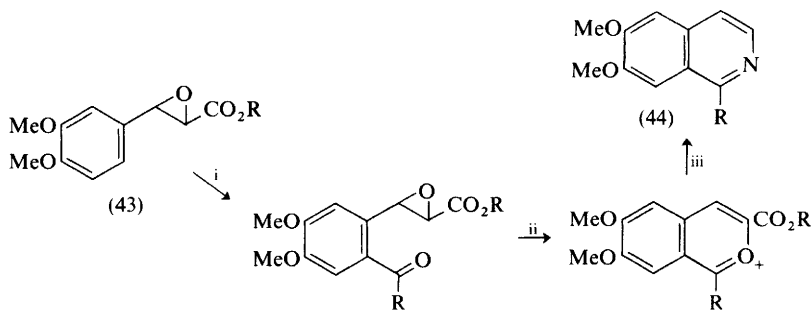
Reagents: i, AcCl or Ac_2O; ii, HCl; iii, NH_4OH.

Scheme 4

Papaver rhoeas and hydrogen peroxide only gave a low yield of the hydroxy-derivative (37; R = OH)[79] (see also Sections 3D and 3I).

An unusual synthesis of petaline (47) which takes advantage of a Stevens rearrangement has been reported.[80] Treatment of the quaternary salt (45) with phenyl-lithium gave compound (46) which was selectively demethylated to the C(8)-phenol. The latter was resolved with *OO*-dibenzoyl-L-tartaric acid and converted into petaline (47). That the demethylation reaction occurs by a mechanism involving cleavage of the heterocyclic ring (48) was supported by the fact that optically active (46) upon treatment with hydrobromic acid gave racemic base [46; C(8)-OH].

Preferential demethylation reactions by mineral acids have been extended to papaverine (49; $R^1 = R^2 = R^3 = R^4 = Me$) which yielded a 1:1 mixture of compounds (49; $R^1 = R^2 = R^3 = Me, R^4 = H$) and (49; $R^1 = R^2 = R^4 = Me, R^3 = H$)[81] and to the trimethoxytetrahydroisoquinoline (50; $R^1 = R^2 = Me$) which gave (50; $R^1 = Me, R^2 = H$).[38] Aniline hydriodide has also been used as a selective demethylation reagent in the synthesis of (50; $R^1 = H, R^2 = Me$).[82] (See also Sections 3A and 3C.)

For almost 40 years it had been known that 3,4-dihydropapaveraldine (51; R = H) gives an intense green colour upon heating with acetic anhydride. A similar observation has now been made with (51; R = Me), and the compound (52; R = Me) responsible for the colour has been isolated and characterized by spectral and degradative methods.[83] Repetition of the reaction on (51; R = H) did not lead to the corresponding derivative (52; R = H) but gave (53) as the major product among four that were isolated and at least twenty (!) other compounds that were detected by thin-layer chromatography. Another

[79] T. Kametani, S. Takano, and T. Kobari, *J. Chem. Soc. (C)*, 1971, 1030.

[80] G. Grethe, H. L. Lee, M. R. Uskokovic, and A. Brossi, *Helv. Chim. Acta*, 1970, **53**, 874.

[81] A. Brossi and S. Teitel, *J. Org. Chem.*, 1970, **35**, 1684.

[82] V. St. Georgiev and N. M. Mollov, *Izvest. Otdel. Khim. Nauki, Bulg. Akad. Nauk*, 1970, **3**, 775 (*Chem. Abs.*, 1971, **74**, 125 373*h*).

[83] H. Budzikiewicz, U. Krueger, W. D. Sasse, and W. Wiegrebe, *Annalen*, 1970, **737**, 119.

(45) (46) (47)

(48) (49) (50)

(51) (52) (53)
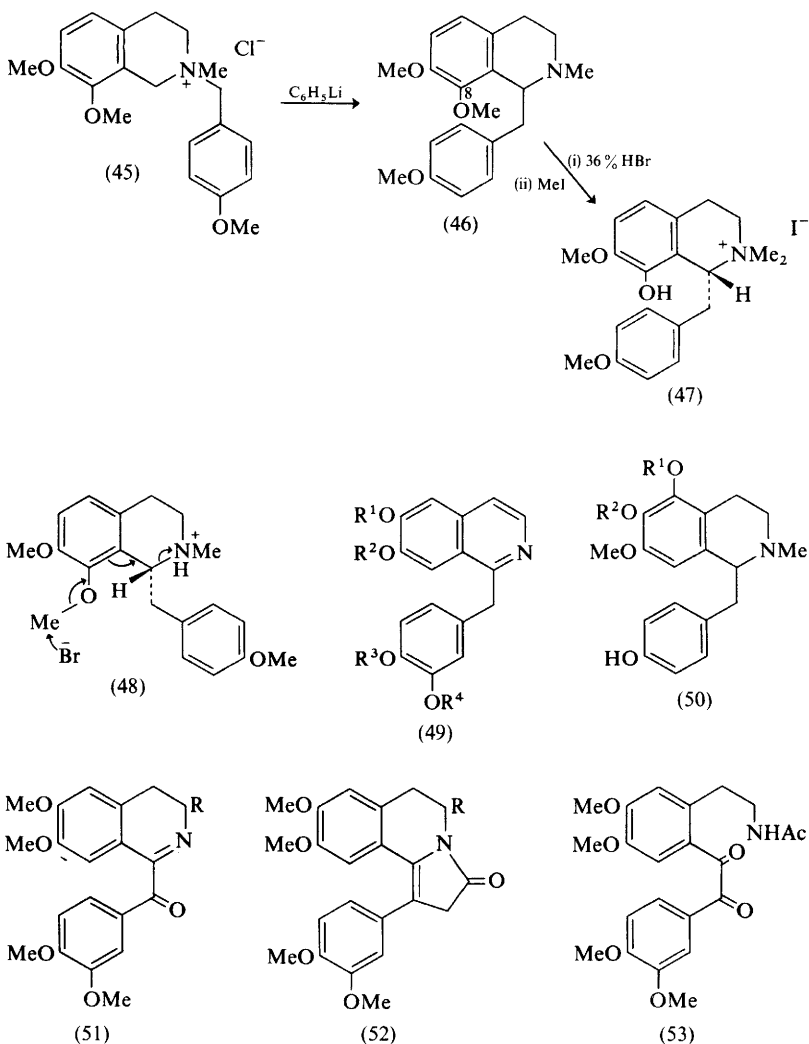
unusual reaction (54) → (55) has been discovered during an attempt to effect dehydrogenation of the heterocyclic ring of (54).[84] The bright red dihydro-azaberbinone (55) was converted into the totally unsaturated yellow azaberbinone (56). The latter has been shown to be identical with the product from the reaction of 6′-nitropapaverine (54; 3,4-double bond) with triethyl phosphite, which had been previously assigned the indolobenzazepine structure (57) by other workers.

[84] M. P. Cava, M. J. Mitchell, and D. T. Hill, *Chem. Comm.*, 1970, 1601.

Continuation of a comprehensive study on the acid-catalysed dihydroisoquino-
line rearrangement (58) → (59) has shown that the isoquinolinium salt (60) is a
significant by-product of the reaction.[85] The highest amount of elimination
and rearrangement was observed with (58; $R^1 = CH_2 \cdot C_6H_4\text{-}p\text{-}NO_2$, $R^2 = H$)
and (58; $R^1 = CH_2 \cdot C_6H_5$, $R^2 = OMe$) respectively. When a 3-substituted
dihydroisoquinoline [61; $R^1 = 3,4\text{-}(\cdot OCH_2O\cdot)C_6H_3 \cdot CH_2\cdot$, $R^2 + R^2 = OCH_2O$,
$R^3 = Me$) was subjected to the rearrangement conditions, only 5% of elimina-
tion to (60; $R^2 + R^2 = OCH_2O$, 3-Me) occurred and starting material was
recovered in 95% yield. Other papers in this series stress the facility of the re-
arrangement with compounds exhibiting 6,7-dialkoxy-substitution[86] and hin-
drance to it by large *N*-substituents.[87] For example, whereas rearrangement of
[58; $R^1 = 3,4\text{-}(OMe)_2C_6H_3 \cdot CH_2\cdot$, $R^2 = OMe$] to [59; $R^1 = 3,4\text{-}(OMe)_2C_6H_3 \cdot$
$CH_2\cdot$, $R^2 = OMe$] took place quantitatively at reflux in 2M-HCl during one
hour, compound [62; $R = 3,4\text{-}(OMe)_2C_6H_3 \cdot CH_2\cdot$] was stable for five hours under
these conditions. In these and other cases, aside from the elimination described
above, disproportionation side-reactions [*e.g.*, (62) → (63) + (64); $R = 3,4\text{-}$
$(OMe)_2C_6H_3 \cdot CH_2\cdot$] which were independent of the *N*-substituent were ob-
served.[87] Similar reactions have been reported for allyl (58; $R^1 = CH_2CH$: CH_2,
$R^2 = OMe$)[88,89] and styryl (58; $R^1 = CH$: $CH \cdot C_6H_5$, $R^2 = OMe$)[88] dihydro-
isoquinolines. Whereas the styryl compound exclusively gave disproportiona-
tion products, the allyl derivative gave the rearranged salt (59; $R^1 = CH_2CH$:
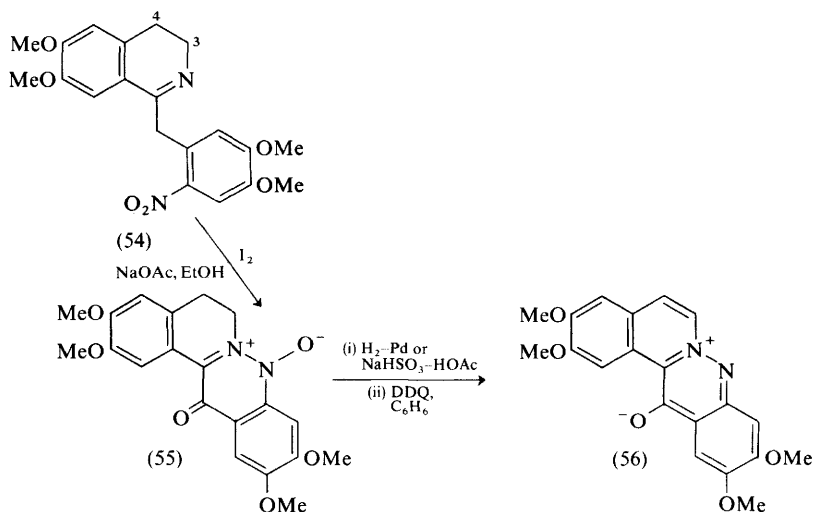
[85] J. Knabe, W. Krause, and K. Sierocks, *Arch. Pharm.*, 1970, **303**, 255.
[86] J. Knabe, W. Krause, H. Powilleit, and K. Sierocks, *Pharmazie*, 1970, **25**, 313.
[87] J. Knabe and H. Powilleit, *Arch. Pharm.*, 1971, **304**, 52.
[88] J. Knabe and H. D. Hoeltje, *Arch. Pharm.*, 1970, **303**, 404.
[89] M. Sainsbury, S. F. Dyke, D. W. Brown, and R. G. Kinsman, *Tetrahedron*, 1970, **26**, 5265.

(57)   OMe   OMe

R^2 R^2 NMe   R^1 (58)

R^2 R^2 R^1 NMe   X$^-$ (59)

R^2 R^2 3   NMe   X$^-$ (60)

R^2 R^2 R^3 NMe   R^1 (61)

MeO   MeO   NPr^i R   (62)

MeO   MeO   NPr^i R   X$^-$ (63)

MeO   MeO   NPr^i R   (64)

MeO   MeO   CH(OMe)$_2$ NR^1 R^2 (65)

MeO   MeO   CHO   NMe   H   (66)

MeO   MeO   H   NMe   (67)

H   Me   NMe   (68)
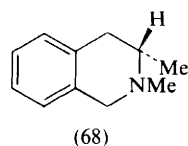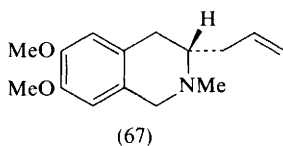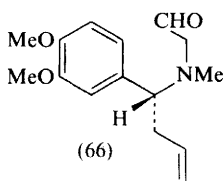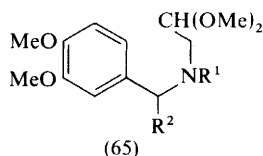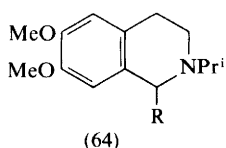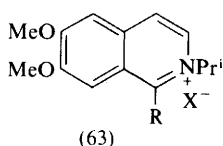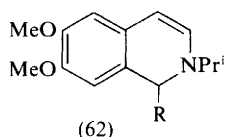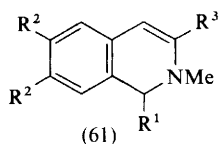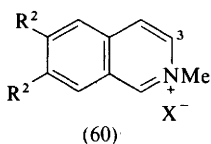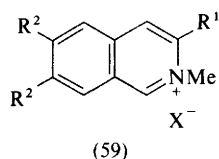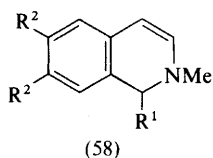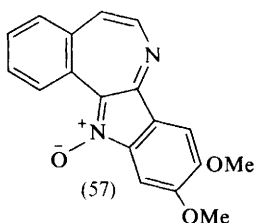
CH_2, $R^2 = OMe$) in high yield. Furthermore, it was conclusively established that the allyl migration occurs by an intramolecular process.[89] Rearrangement of [65; $R^1 = Me$, $R^2 = CH(Me)CH:CH_2$] either as a diastereomeric mixture or as a single diastereomer led to the 3-crotyl product (59; $R^2 = OMe$, $R^1 = CH_2CH:CHMe$) with no detectable amount of the 3-methallyl-3,4-dihydroiso-quinolinium salt being formed. An attempted cross-over experiment of an equi-molar mixture of (65; $R^1 = Me$, $R^2 = CH_2CH:CH_2$) and [65; $R^1 = H$, $R^2 = CH(Me)CH:CH_2$] gave only two products, (59; $R^1 = CH_2CH:CH_2, R^2 = OMe$), and (59; $R^1 = CH_2CH:CHMe$, $R^2 = OMe$; NH for NMe). Finally, in an unambiguous experiment, rearrangement of the optically active aldehyde (66) of R-configuration gave S-(67) with essentially 100 % retention of optical activity, as required for an intramolecular rearrangement. The S-configuration of (67) was established by comparison of its o.r.d. curve with that of S-(68). This re-arrangement may thus be classified as a suprafacial sigmatropic [3,3] reaction analogous to the Cope rearrangement.

B. Pavine Alkaloids.—Eschscholtzine (70; R = Me) has been isolated from *Eschscholtzia californica*.[89a] The structure of (±)-bis-norargemonine (70; R = H) has been confirmed by synthesis.[90] The key intermediate (69), prepared by two unexceptional methods, was converted into (70; R = H) in three steps. Interestingly, 1,2-dihydroisoquinoline derivatives do not give this type of product but rather undergo a variety of other reactions if excess acid is avoided [see reactions of compound (58)].
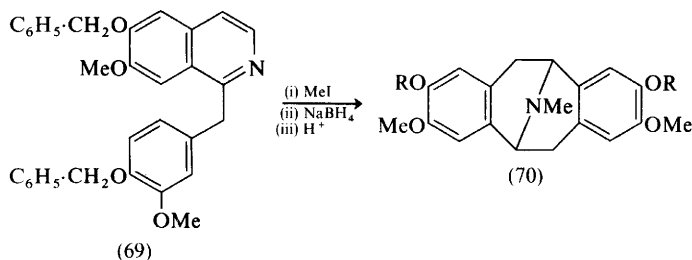
C. Proaporphine, Aporphine, and Homoproaporphine Alkaloids.—Thin-layer and gas chromatographic methods have been developed for qualitative and quantitative analysis of a series of N-alkylated nornuciferine derivatives (71; $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = R^6 = R^7 = H$).[91] Surprisingly, g.c. analysis of the phenolic compounds (71; $R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = R^6 = R^7 = H$) offered no difficulties, presumably as a result of their decreased polarity due to hydrogen-bonding of the phenolic hydroxy-group with the oxygen of the adjacent methoxy-group.

A large number of studies dealing with isolation and structural elucidation of alkaloids have been reported and these are summarized in Table 1. Certain important structures and significant structural elucidation results will be discussed.

The structure of imenine (72; $R^1 = R^2 = OMe$, $R^3 = R^4 = Me$, $R^5 = H$), the first ketoaporphine alkaloid to have a substituent in the heterocyclic ring, was elucidated mainly by X-ray analysis.[92] The absolute configuration of S-(+)-isoboldine isolated from *Corydalis pallida* var. *tenuis* was assigned on the basis of o.r.d. and c.d. studies; interestingly, all alkaloids isolated from this species belong to the S-series.[97] The structure of the reduced proaporphine jaculadine

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$(74; R^1 = R^2 = H, R^3 = Me, R^4, R^5 = H, OH)$ was deduced by acetylation and hydrogenation to $(77; R^1 = R^2 = H)$ which, in turn, had been prepared by Wolff–Kishner reduction of the ketone $(77; R^1 + R^2 = O).$[99] The configuration of $C(6a)$-$β$-H in jaculadine was assigned on the basis of the rotation of $(77; R^1 + R^2 = O)$ which was the same as that of the hydrogenation product $(77; R^1 = R^2 = H)$. The usual application of n.m.r. spectroscopy was insufficient and did not lead to conclusive assignment of the $C(10)$-hydroxy-group configuration of jaculadine. It appears that the configuration of the $C(7a)$ centre must be determined by X-ray studies. In the same study,[99] the structure of discolorine $(74; R^1 = R^2 \text{ or } R^3 = Me, R^3 \text{ or } R^2 = H, R^4 = OH, R^5 = H)$ was defined except for the methoxy–hydroxy-group arrangement of ring A. Although previous workers considered that a $M - 83$ fragment (78) is characteristic of reduced proaporphines containing a cyclohexenol system, such a peak was not observed for discolorine. It appears that jacularine $[74; R^1 = R^3 = H, R^2 = Me, R^4 + R^5 = O, C(6a)$-$β$-H], isolated originally from *Croton linearis*, is identical with crotsparinine, which was found in *C. sparsiflorus*.[100] The absolute configuration of duguentine $(71; R^1 = R^2 = R^3 = Me, R^4 = R^7 = H, R^5 = R^6 = OMe)$ has been determined to be $6aS,7S$ by o.r.d. studies.[101] The structure of hernandonine $[75; R^1 + R^2 = CH_2, R^3 + R^4 = OCH_2O, R^5 = H, C(7)$-oxo] was established by spectral evidence and by synthesis from *N*-methylhernovine $(71; R^1 = Me, R^2 + R^3 = CH_2, R^4 + R^5 = OCH_2O, R^6 = R^7 = H)$ by chromium trioxide–pyridine oxidation.[103] The presence of laurolitsine $(71; R^1 = R^2 = R^4 = R^7 = H, R^3 = Me, R^5 = OMe, R^6 = OH)$ in *Palmeria* NGF 24998 was detected only by thin-layer chromatography.[104] Laurotetanine $(71; R^1 = R^4 = R^7 = H, R^2 = R^3 = Me, R^5 = OMe, R^6 = OH)$ and *N*-methyl-laurotetanine $(71; R^1 = R^2 = R^3 = Me, R^4 = R^7 = H, R^5 = OMe, R^6 = OH)$ had been previously isolated from *P. gracilis*, earlier wrongly identified as *P. fengeriana*.[104]

The distinction between structures $(72; R^1 = R^2 = H, R^3 + R^4 = CH_2, R^5 = OMe)$ and $[75; R^1 + R^2 = CH_2, R^3 = R^5 = H, R^4 = OMe, C(7)$-oxo] for oxoxylopine could not be made on the basis of its n.m.r. spectrum alone (both would show 1,2,4-proton pattern for ring D).[105] However, it is known that the correspondingly substituted aporphines with reduced heterocyclic rings and lacking the $C(7)$-oxo function show different u.v. spectra. Therefore, oxoxylopine was reduced with zinc and hydrochloric acid to give a compound whose u.v.

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Table 1 *Isolation of proaporphine and aporphine alkaloids*

Plant species	Alkaloid (Structure)	Ref.
Abuta imene	Imenine (72; $R^1 = R^2 = $ OMe, $R^3 = R^4 = $ Me, $R^5 = $ H)	92
Anona muricata	Atherosperminine (72; $R^1 = R^5 = $ H, $R^2 = $ OMe, $R^3 + R^4 = CH_2$)	65
Aristolochiaceae sp. (crude drug Batore)	Asimilobine (71; $R^1 = R^2 = R^4 = R^5 = R^6 = R^7 = $ H, $R^3 = $ Me)	93
Berberis vulgaris	Magnoflorine* (71; N^+Me_2 for NR^1, $R^2 = $ Me, $R^3 = R^6 = R^7 = $ H, $R^4 = $ OH, $R^5 = $ OMe)	94
Cinnamomum sp.	(+)-Corydine (71; $R^1 = R^2 = $ Me, $R^4 = R^5 = $ OMe, $R^3 = R^6 = R^7 = $ H)	66
Coptis japonica	Magnoflorine*	95
C. quinquefolia	Magnoflorine	95
Corydalis gortschakovii	Isocorydine* (71; $R^1 = R^2 = R^3 = $ Me, $R^4 = $ OH, $R^5 = $ OMe, $R^6 = R^7 = $ H)	96
C. pallida var. *tenuis*	(+)-Isoboldine (71; $R^1 = R^2 = $ Me, $R^3 = R^4 = R^7 = $ H, $R^5 = $ OMe, $R^6 = $ OH)	97
Croton discolor, *C. plumieri*	Crotonosine (73; $R^1 = R^2 = $ H, $R^3 = $ Me, $R^4 + R^5 = $ O)	
	Discolorine (74; $R^1 = R^2$ or $R^3 = $ Me, R^3 or $R^2 = $ H, $R^4 = $ OH, $R^5 = $ H)	
	Jaculadine (74; $R^1 = R^2 = $ H, $R^3 = $ Me, $R^4, R^5 = $ H, OH)	
	Jacularine [74; $R^1 = R^3 = $ H, $R^2 = $ Me, $R^4 + R^5 = $ O, C(6a)-β-H]	98, 99
	Linearisine (74; $R^1 = R^3 = $ Me, $R^2 = $ H, $R^4 + R^5 = $ O)	
	L-*N*-Methylcrotonosine (73; $R^1 = R^3 = $ Me, $R^2 = $ H, $R^4 + R^5 = $ O)	
	Pronuciferine (73; $R^1 = R^2 = R^3 = $ Me, $R^4 + R^5 = $ O)	
C. linearis	Jaculadine	99
C. sparsiflorus	Crotsparine (Crotoflorine?) (73; $R^1 = R^3 = $ H, $R^2 = $ Me, $R^4 + R^5 = $ O)	
	Crotsparinine (Jacularine?) [74; $R^1 = R^3 = $ H, $R^2 = $ Me, $R^4 + R^5 = $ O, C(6a)-β-H]	
	NO-Dimethylcrotsparine (73; $R^1 = R^2 = R^3 = $ Me, $R^4 + R^5 = $ O)	100
	N-Methylcrotsparine (73; $R^1 = R^2 = $ Me, $R^3 = $ H, $R^4 + R^5 = $ O)	
	N-Methylcrotsparinine (74; $R^1 = R^2 = $ Me, $R^3 = $ H, $R^4 + R^5 = $ O)	
	Sparsiflorine* (71; $R^1 = R^3 = R^4 = R^6 = R^7 = $ H, $R^2 = $ Me, $R^5 = $ OH)	
C. wilsonii	Hernovine* (71; $R^1 = R^6 = R^7 = $ H, $R^2 + R^3 = CH_2$, $R^4 + R^5 = OCH_2O$)	
	N-Methylhernovine* (71; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 + R^5 = OCH_2O$, $R^6 = R^7 = $ H)	
	O(10)-Methylhernovine* (71; $R^1 = R^6 = R^7 = $ H, $R^2 + R^3 = CH_2$, $R^4 = $ OH, $R^5 = $ OMe)	98
	N-Methyl-*O*(10)-Methylhernovine* (71; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 = $ OH, $R^5 = $ OMe, $R^6 = R^7 = $ H)	
	Wilsonirine* (71; $R^1 = R^3 = R^4 = R^7 = $ H, $R^2 = $ Me, $R^5 = R^6 = $ OMe)	

(71)

(72)

(73)

(74)

(75)

(76)

Table 1 (continued)

Plant species	Alkaloid (Structure)	Ref.
Duguentia sp.	$(-)$-Dicentrine (71; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 = R^7 = $ H, $R^5 = R^6 = $ OMe)	
	Duguentine (71; $R^1 = R^2 = R^3 = $ Me, $R^4 = R^7 = $ H, $R^5 = R^6 = $ OMe)	101
	Norglaucine [71; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 = R^7 = $ H, $R^5 = R^6 = $ OMe, $C(7)$-OH]	
Eschscholtzia californica	Lauroscholtzine* (71; $R^1 = R^2 = R^3 = $ Me, $R^4 = R^7 = $ H, $R^5 = $ OMe, $R^6 = $ OH)	89a
Glaucium corniculatum	d-Corydine* (71; $R^1 = R^2 = $ Me, $R^3 = R^6 = R^7 = $ H, $R^4 = R^5 = $ OMe)	102
Hernandia ovigera	Hernandonine [75; $R^1 + R^2 = CH_2$, $R^3 + R^4 = OCH_2O$, $R^5 = $ H, $C(7)$-oxo]	
	Hernangerine* (Nandigerine) (71; $R^1 = R^6 = R^7 = $ H, $R^2 + R^3 = CH_2$, $R^4 = $ OMe, $R^5 = $ OH)	
	N-Methylhernangerine (71; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 = $ OMe, $R^5 = $ OH, $R^6 = R^7 = $ H)	103
	Hernovine* (Ovigerine)	
	N-Methylhernovine	
H. papuana	Hernandonine	
	Hernangerine	66a
Menispermum dauricum	Magnoflorine	
	Menispermine (71; $N^+ Me_2$ for NR^1, $R^2 = R^3 = $ Me, $R^4 = $ OH, $R^5 = $ OMe, $R^6 = R^7 = $ H)	
	Stepharine (73; $R^1 = $ H, $R^2 = R^3 = $ Me, $R^4 + R^5 = $ O)	103a

Table 1 (continued)

Plant species	*Alkaloid (Structure)*	*Ref.*
Nelumbo nucifera	Anonaine (71; $R^1 = R^4 = R^5 = R^6 = R^7 = $ H, $R^2 + R^3 = CH_2$)	
	Liriodenine (75; $R^1 + R^2 = CH_2$, $R^3 = R^4 = R^5 = $ H)	
	O-Nornuciferine (71; $R^1 = R^3 = $ Me, $R^2 = R^4 = R^5 = R^6 = R^7 = $ H)	
	N-Nornuciferine* (71; $R^1 = R^4 = R^5 = R^6 = R^7 = $ H, $R^2 = R^3 = $ Me)	68
	Nuciferine* (71; $R^1 = R^2 = R^3 = $ Me, $R^4 = R^5 = R^6 = R^7 = $ H)	
	Pronuciferine*	
	Remerine* (71; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 = R^5 = R^6 = R^7 = $ H)	
Palmeria arfakiana and *Palmeria* NGF 24998	Laurolitsine (?) (71; $R^1 = R^2 = R^4 = R^7 = $ H, $R^3 = $ Me, $R^5 = $ OMe, $R^6 = $ OH)	
	Laurotetanine (71; $R^1 = R^4 = R^7 = $ H, $R^2 = R^3 = $ Me, $R^5 = $ OMe, $R^6 = $ OH)	104
	N-Methyl-laurotetanine (71; $R^1 = R^2 = R^3 = $ Me, $R^4 = R^7 = $ H, $R^5 = $ OMe, $R^6 = $ OH)	
Papaver bracteatum	Isothebaine* (71; $R^1 = R^2 = $ Me, $R^3 = R^5 = R^6 = R^7 = $ H, $R^4 = $ OMe)	69
	(+)-Nuciferine	
P. fugax	(−)-Mecambrine (73; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 + R^5 = $ O)	69
P. triniaefolium	Aporheine (*d*-Remerine)*	
	(−)-Mecambrine*	69
	(+)-Remerine*	
Stephania abyssinica	Oxoxylopine (72; $R^1 = R^2 = $ H, $R^3 + R^4 = CH_2$, $R^5 = $ OMe)	105
S. sasakii	Crebanine* (71; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 = R^5 = $ H, $R^6 = R^7 = $ OMe)	
	Nuciferine	
	Phanostenine (71; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 = R^7 = $ H, $R^5 = $ OH, $R^6 = $ OMe)	106
	Pronuciferine	
	Remerine	
	Tuduranine (71; $R^1 = R^4 = R^6 = R^7 = $ H, $R^2 = R^3 = $ Me, $R^5 = $ OH)	
Thalictrum aquilegifolium	Isocorydine	107
T. simplex	Magnoflorine*	
	Thalicmine [71; $R^1 = $ Me, $R^2 + R^3 = CH_2$, $R^4 = R^7 = $ H, $R^5 = R^6 = $ OMe, C(3)-OMe]	
	Thalicminine [75; $R^1 + R^2 = CH_2$, $R^3 = $ H, $R^4 = R^5 = $ OMe, C(3)-OMe]	108
	Thalicsimidine [71; $R^1 = R^2 = R^3 = $ Me, $R^4 = R^7 = $ H, $R^5 = R^6 = $ OMe, C(3)-OMe]	
Uvariopsis solheidii	Uvariopsine (76)	109

Table 1 (continued)

Plant species	*Alkaloid (Structure)*	*Ref.*
Xylopia brasiliensis	Anonaine	
	Liriodenine (72; $R^1 = R^2 = R^5 = H$,	
	$R^3 + R^4 = CH_2$)	
	9-Methoxyliriodenine (72; $R^1 = R^2 = H$,	110
	$R^3 + R^4 = CH_2, R^5 = OMe$)	
	Xylopine (71; $R^1 = R^4 = R^5 = R^7 = H$,	
	$R^2 + R^3 = CH_2, R^6 = OMe$)	

* Known alkaloid, previously isolated from the same plant species but usually from a different locality. The absence of an asterisk after a name does not imply that the alkaloid is unknown but simply that it has not been heretofore isolated from a particular species. *Cf.* J. J. Willaman and H.-L. Li, *Lloydia*, 1970, 33, No. 3A (Suppl.) and R. A. Raffauf, 'A Handbook of Alkaloids and Alkaloid-Containing Plants,' Wiley–Interscience, New York, 1970.

spectrum was identical with that of the known alkaloid xylopine (71; $R^1 = R^4 = R^5 = R^7 = H, R^2 + R^3 = CH_2, R^6 = OMe$). Final confirmation was obtained by comparison with an authentic sample of *N*-acetylxylopine (71; $R^1 = Ac$, $R^2 + R^3 = CH_2, R^4 = R^5 = R^7 = H, R^6 = OMe$). Lanuginosine, previously isolated from *Michelia lanuginosa* Wall. (Magnoliaceae) and assigned the same structure as oxoxylopine, shows distinctly different physical and spectral properties and was tentatively assigned structure [75; $R^1 + R^2 = CH_2, R^3 = R^5 = H$, $R^4 = OMe, C(7)$-oxo].[105]

From the point of view of synthesis, this class of alkaloids has received a great deal of attention throughout the world and a number of total syntheses have been reported: (±)-bracteoline (71; $R^1 = R^2 = Me, R^3 = R^4 = R^7 = H, R^5 = OH$, $R^6 = OMe$);[111] cassameridine (82);[112](±)-domesticine (71; $R^1 = R^2 = Me$, $R^3 = R^4 = R^7 = H, R^5 + R^6 = OCH_2O$);[113] (±)-homolinearisine (73; $R^1 = R^3 = Me, R^2 = H, R^4 + R^5 = O$);[114] isoboldine (71; $R^1 = R^2 = Me, R^3 = R^4 = R^7 = H, R^5 = OMe, R^6 = OH$);[115] kreysiginone (105);[116] lanuginosine [75; $R^1 + R^2 = CH_2, R^3 = R^4 = H, R^5 = OMe, C(7)$-oxo];[117] laureline (71; $R^1 = Me, R^2 + R^3 = CH_2, R^4 = R^6 = R^7 = H, R^5 = OMe$);[118] (±)-glaucine

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[108] Kh. S. Umarov, M. V. Telezhenetskayo, Z. F. Ismailov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 224 (*Chem. Abs.*, 1970, **73**, 63 193t).
[109] A. Bouquet, A. Cave, A. Cave, and R. R. Paris, *Compt. rend.*, 1970, **271**, C, 1100.
[110] C. Casagrande and G. Merotti, *Farmaco, Ed. Sci.*, 1970, **25**, 799 (*Chem. Abs.*, 1971, **74**, 23 047n).
[111] P. Kerekes, K. Delenk-Heydenreich, and S. Pfeifer, *Tetrahedron Letters*, 1970, 2483.
[112] F. N. Lahey and K. F. Mak, *Tetrahedron Letters*, 1970, 4511.
[113] S. V. Kessar, S. Batra, and S. S. Gandhi, *Indian J. Chem.*, 1970, **8**, 468.
[114] S. Ishiwata and K. Itakura, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1841.
[115] T. Kametani, A. Kozuka, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 1021.
[116] R. E. Harmon and B. L. Jensen, *J. Heterocyclic Chem.*, 1970, **7**, 1077.
[117] T. R. Govindachari, N. Viswanathan, S. Narayanaswami, and B. R. Pai, *Indian J. Chem.*, 1970, **8**, 475.
[118] M. S. Gibson, G. W. Prenton, and J. M. Walthew, *J. Chem. Soc. (C)*, 1970, 2234.

(77)   (78)
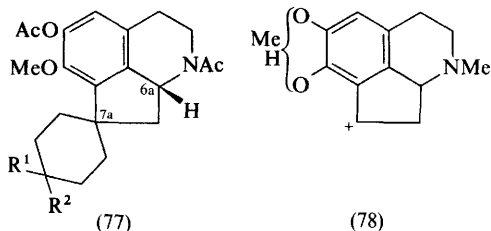
(71; $R^1 = R^2 = R^3 = Me$, $R^4 = R^7 = H$, $R^5 = R^6 = OMe$), O-methylorient-alinone, and O-methyliso-orientalinone [73; $R^1 = R^2 = R^3 = Me$, $R^4 + R^5 = O$, $C(11)$-OMe];[119] N-methylovigerine (71; $R^1 = Me$, $R^2 + R^3 = CH_2$, $R^4 + R^5 = OCH_2O$, $R^6 = R^7 = H$);[120] oconovine (88);[121] ($\pm$)-pronuciferine (73; $R^1 = R^2 = R^3 = Me$, $R^4 + R^5 = O$);[122] and thalicsimidine [71; $R^1 = R^2 = R^3 = Me$, $R^4 = R^7 = H$, $R^5 = R^6 = OMe$, $C(3)$-OMe].[123] Almost invariably, the synthetic methodology involves two distinct stages: (*a*) the formation of an

(79)   (82)

(80)   (81)
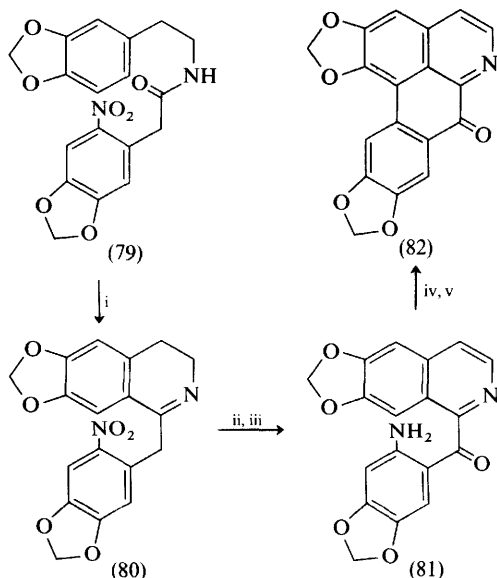
Reagents: i, PPE; ii, CrO_3, HOAc; iii, KOH, EtOH; iv, H_2, Raney Ni; v, $NaNO_2$, H_2SO_4.

Scheme 5

[119] S. Ishiwata and K. Itakura, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 1224.
[120] M. P. Cava and M. Srinivasan, *Tetrahedron*, 1970, **26**, 4649.
[121] M. P. Cava and M. V. Lakshmikantham, *J. Org. Chem.*, 1970, **35**, 1867.
[122] S. Ishiwata, K. Itakura, and K. Misawa, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 1219.
[123] T. Kametani, K. Takahashi, T. Sugahara, M. Koizumi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1971, 1032.

(83)
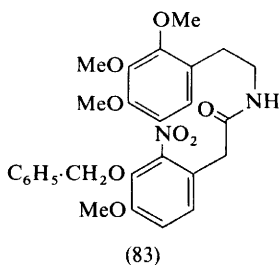
appropriately substituted benzylisoquinoline derivative by a Bischler–Napier-alski reaction, and (*b*) a Pschorr cyclization reaction. A variation on stage (*a*) has been to use Reissert compounds.[120,121]

Typically, the synthesis (Scheme 5) of cassameridine (82) began with Bischler–
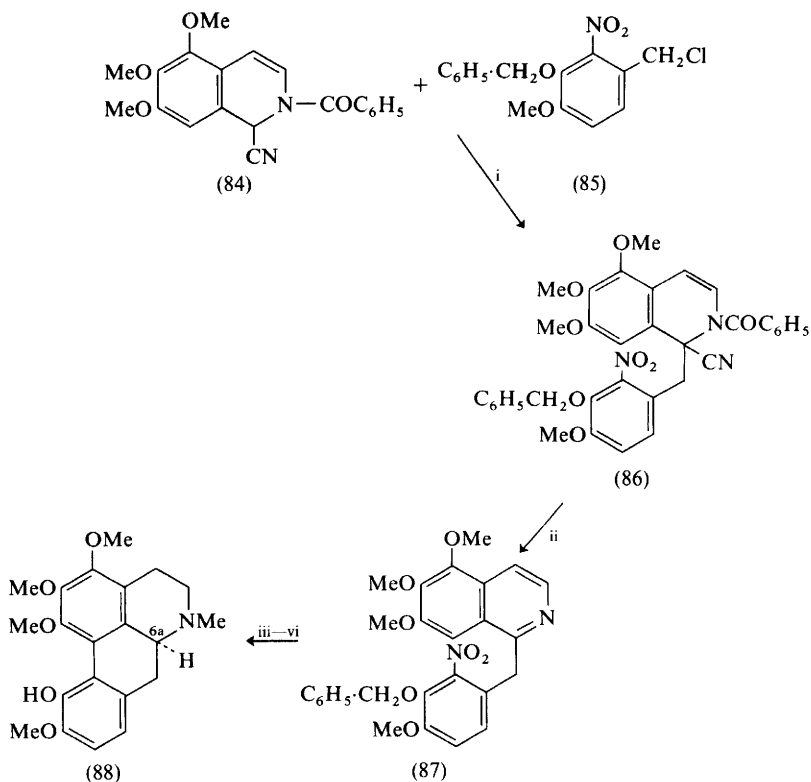
Reagents: i, NaH, DMF; ii, Triton B, DMF; iii, MeI; iv, NaBH$_4$; v, Zn, HOAc; vi, NaNO$_2$, HCl.

Scheme 6

Napieralski cyclization of (79) in the presence of the very effective reagent poly-phosphate ester, to yield the dihydroisoquinoline derivative (80). Two successive oxidation stages led to the fully aromatic system (81) which, upon reduction and Pschorr cyclization, gave cassameridine (82).[112]

In the synthesis of oconovine (88), difficulty was encountered in effecting the Bischler–Napieralski reaction on (83).[121] This problem was circumvented by using an alternative approach (Scheme 6) *via* the alkylation of the Reissert com-pound (84) with the benzyl chloride derivative (85), which gave (86). The product (86) was smoothly hydrolysed to (87) using a new reagent for this purpose, Triton B in dimethylformamide. The remaining steps to oconovine (88) were unexcep-tional. The alkaloid was assigned the stereochemistry indicated, in agreement with the general observation that all dextrorotatory aporphines show this configuration at $C(6a)$. It would appear that an approach to aporphine alkaloids using Reissert intermediates may be of general utility.[120,121] A somewhat related method involving a base-catalyzed condensation between hydrastinium iodide (89) and 5-methoxy-2-nitrotoluene to give compound (90) was used for the synthesis of lanuginosine [75; $R^1 + R^2 = CH_2$, $R^3 = R^4 = H$, $R^5 = OMe$, $C(7)$-oxo].[117]

The required intermediate for a Pschorr reaction may also be obtained by nitration of a substituted isoquinoline derivative.[123] For example, (91; X = H) was converted into (91; X = NO$_2$) with the intent of using the latter for the synthesis of morphinandienone and hasubanan alkaloids. (See Section 3D). Instead, Pschorr reaction on the diazonium salt corresponding to (91; X = NO$_2$) gave thalicsimidine [71; $R^1 = R^2 = R^3 = Me$, $R^4 = R^7 = H$, $R^5 = R^6 = OMe$, $C(3)$-OMe] and a variety of oxidation and degradation products. ($\pm$)-Predicent-rine (71; $R^1 = R^3 = Me$, $R^2 = R^4 = R^7 = H$, $R^5 = R^6 = OMe$) was also obtained by a similar approach.[123]

There is a preliminary indication that the photolytic Pschorr reaction may be a better synthetic method for aporphine alkaloids than the conventional route.[124] Irradiation of the diazonium salt (92; X = N$_2^+$) gave (71; $R^1 = R^3 = Me$, $R^2 = CH_2 \cdot C_6H_5$, $R^4 = R^5 = OMe$, $R^6 = R^7 = H$) in 11.5% yield in addition to reduced product (92; X = H) and a morphinandienone derivative (see Section 3D). Two other reports on the use of the conventional Pschorr cyclization for the synthesis of model aporphine substances have appeared.[125,126] One of these (Scheme 7) offers the first potential entry into the 7-hydroxyaporphine system.[126] Reduction of (93), prepared by oxidation of 1-(2-nitrobenzyl)isoquinoline with sodium dichromate in glacial acetic acid, followed by treatment with phosgene, produced the oxazolidone (94). Two consecutive catalytic reductions gave (95) which afforded (96) under standard Pschorr ring-closure conditions. The latter was transformed by simple metal hydride reduction into the 7-hydroxyaporphine (97; R = H). Alternatively, treatment of (96) with methyl-lithium gave the tertiary amine (97; R = Me).

[124] T. Kametani, K. Fukumoto, and K. Shishido, *Chem. and Ind.*, 1970, 1566.

[125] J. G. Cannon and M. A. Aleem, *J. Heterocyclic Chem.*, 1971, **8**, 305.

[126] J. L. Neumeyer and F. E. Granchelli, *Tetrahedron Letters*, 1970, 5261.

(89)

(90)

(91)

(92)
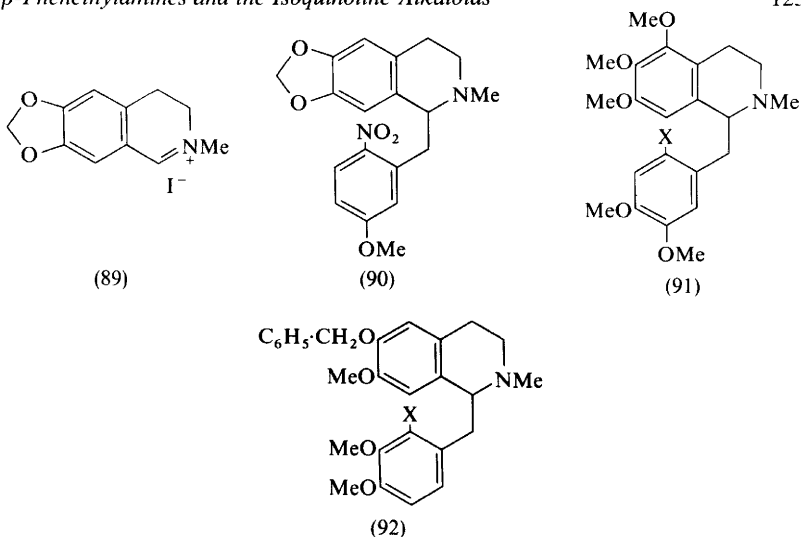
Alternative approaches to aporphine alkaloids using benzyne intermediates have been reported.[113,118] For example, treatment of the readily available bromo-benzylisoquinoline derivative (98; X = Br, Y = H) with potassium amide gave the corresponding amino-compound (98; X = H, Y = NH$_2$), which upon

(93)

(94)

(95)

(96)

(97)
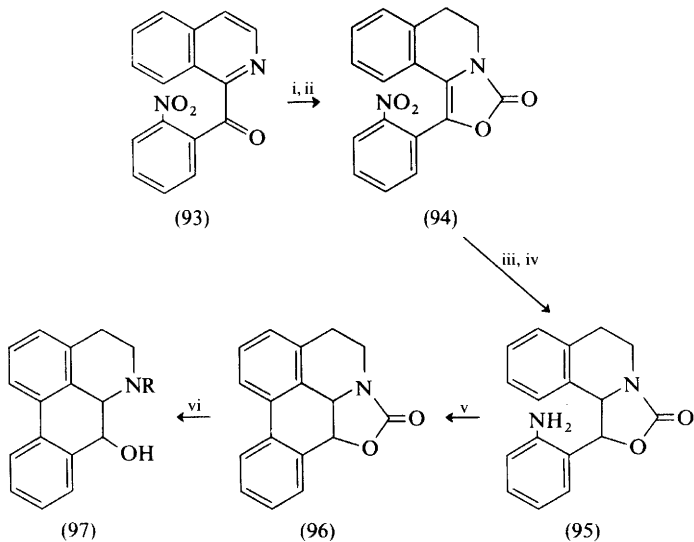
Reagents: i, NABH$_4$, ii, COCl$_2$, Et$_3$N, CH$_2$Cl$_2$, 0—5 °C; iii, H$_2$, Pd–C; iv, H$_2$, Pt, HOAc–THF; v, HNO$_2$, CuO; vi, LiAlH$_4$.

Scheme 7

(98)
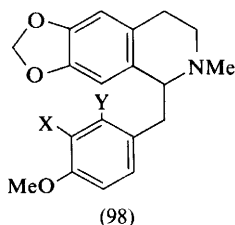
diazotization followed by Pschorr reaction gave laureline (71; $R^1 = Me$, $R^2 +$ $R^3 = CH_2$, $R^4 = R^6 = R^7 = H$, $R^5 = OMe$).[118] This report also contains information on precautions which must be taken in order to avoid polymerization in amine-catalysed condensations of aromatic aldehydes with nitromethane.

When Pschorr cyclization was carried out on the diazonium salt corresponding to the amine (101), both proaporphine (73; $R^1 = R^2 = R^3 = Me$, $R^4 + R^5 = O$) and aporphine (102) compounds were formed.[114,119,122] In an example of this approach (Scheme 8), by applying the Bischler–Napieralski reaction, the amide (99) was converted into a mixture of the required dihydroisoquinoline (100) and (103), the product of the alternative cyclization mode.[122] For the purpose of the synthesis, the undesired isomer was removed at a late stage by chromatography and cyclization was effected on (101) to give 20% of ($\pm$)-pronuciferine (73; $R^1 =$ $R^2 = R^3 = Me$, $R^4 + R^5 = O$) and a small amount of the aporphine derivative (102). As expected, dienone–phenol rearrangement of pronuciferine gave (102). Homolinearisine (73; $R^1 = R^3 = Me$, $R^2 = H$, $R^4 + R^5 = O$), whose synthesis by the phenolic oxidative coupling reaction had been previously unsuccessful, was obtained in a similar manner.[114] However, the phenolic oxidative coupling may be used for proaporphine synthesis if the hydroxy-groups are appropriately arranged in the precursor to give activation to the required C—C bond formation. Thus, kreysiginone (105) was obtained from reticuline (104) hydrochloride in 12% yield.[116] In contrast, use of potassium ferricyanide or the relatively new reagents vanadyl trichloride and silver carbonate on Celite for the oxidative coupling reaction of (104) led to low yields of isoboldine (71; $R^1 = R^2 = Me$, $R^3 = R^4 =$ $R^7 = H$, $R^5 = OMe$, $R^6 = OH$) and a morphinandienone derivative[115] (see Section 3D).

Related work not directly dealing with total synthesis of proaporphine, aporphine, or homoproaporphine alkaloids has appeared. A series of homopro-aporphine-type compounds (110) have been prepared, as shown in Scheme 9.[127] Compound (106), readily prepared from 3,4-dimethoxy-β-phenethylamine and the appropriate keto-acid derivative, was transformed by reduction and acetylation to (107). Acetylation effectively blocked any complications from the cyclohexane oxygen function during the subsequent Bischler–Napieralski cyclization. Consecutive reduction, alkylation, and hydrolysis gave the key intermediate (109) which was transformed into the tetracyclic spiro-system (110) by reaction with polyphosphate ester under strictly defined conditions. Other conditions and

[127] F. Schneider and K. Bernauer, *Helv. Chim. Acta*, 1970, **53**, 938.

(99) → (100)

(102) (73, $R^1 = R^2 = R^3 = Me$, $R^4 + R^5 = O$) (101)
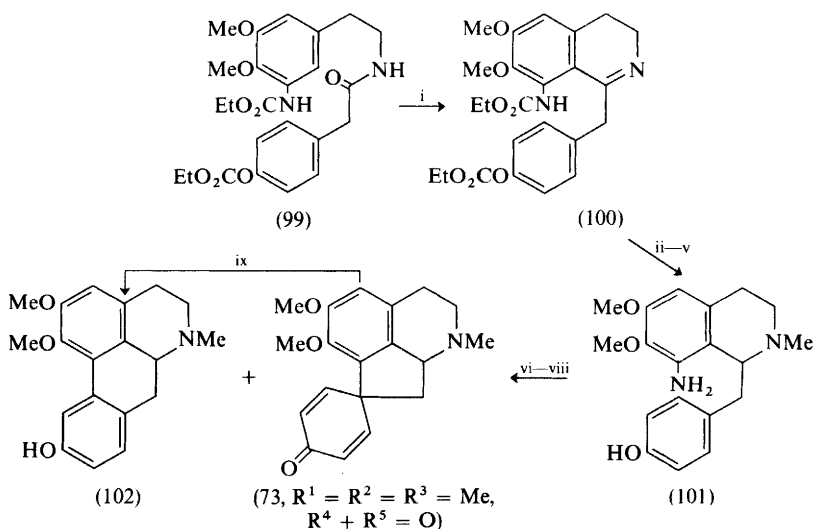
Reagents: i, $POCl_3$; ii, $NaBH_4$; iii, 36% CH_2O; iv, $NaBH_4$; v, KOH, EtOH, N_2; vi, $NaNO_2$, H_2SO_4; vii, NaOAc; viii, NaOH; ix, conc. HCl, HOAc.

Scheme 8

(103)

(104) $\xrightarrow[\text{(ii) NH}_4\text{OH}]{\text{(i) FeCl}_3}$ (105)
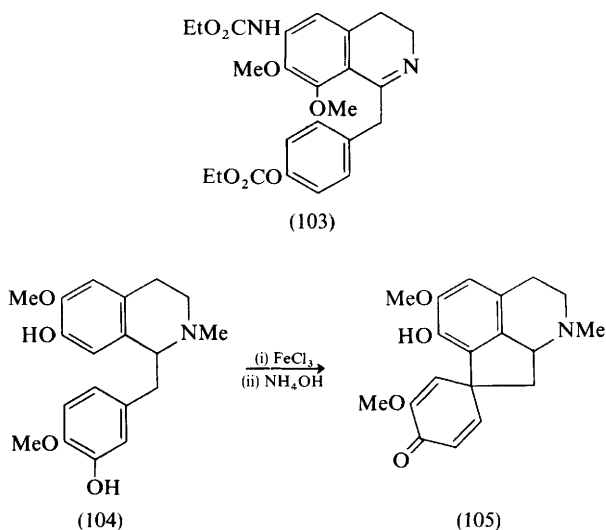
acidic reagents gave products of partial or complete demethylation. In an alternative series, compound (108) was first formylated and hydrolysed to the amide (111) which, upon successive acid and base treatment, gave (110).
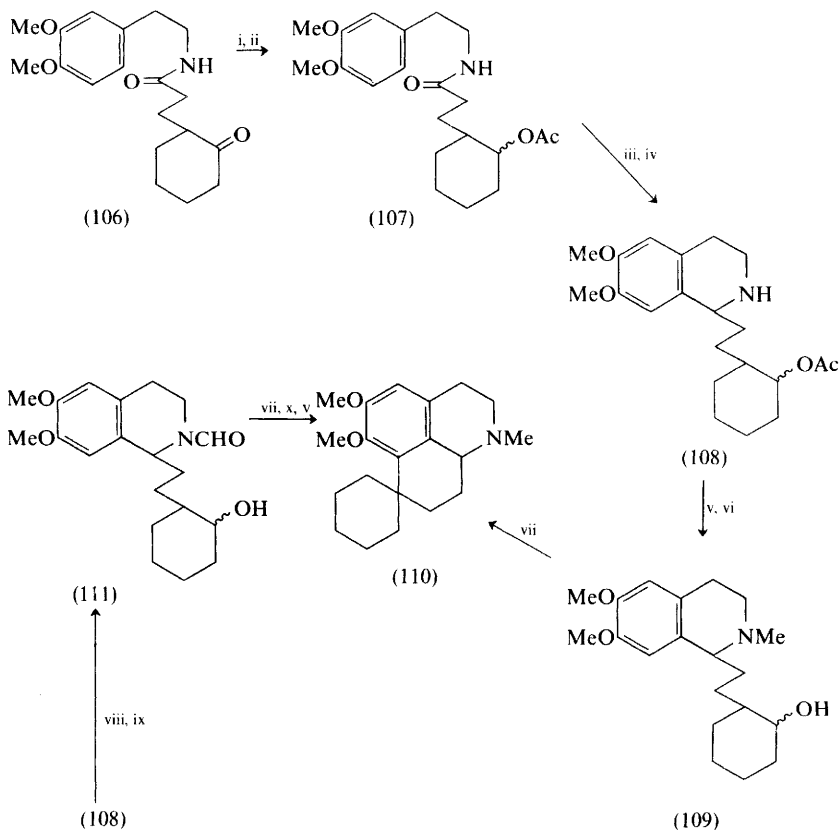
Reagents: i, NaBH$_4$; ii, Ac$_2$O; iii, POCl$_3$; iv, NaBH$_4$; v, CH$_2$O, HCO$_2$H; vi, NaOH, EtOH; vii, PPA; viii, HCO$_2$Me; ix, 1M-HCl; x, KOH, EtOH.

Scheme 9

A surprising yield (60%) of the more highly functionalized homoproaporphine derivative (112) has been obtained by the phenolic oxidative coupling reaction.[128] On the other hand, application of the Pschorr sequence on (113) gave (114) as a mixture of diastereomers as well as anisaldehyde. Treatment of the diazonium salt corresponding to (113) with hypophosphorous acid also gave the diastereomeric mixture (114) and, in addition, the deamination product and 4-methoxy-styrene.[129]

The synthesis of (±)-hexahydropronuciferine (119) (Scheme 10) has been reported utilizing Bobbitt's modification of the Pomeranz–Fritsch reaction as

[128] T. Kametani and M. Mizushima, *J. Pharm. Soc. Japan*, 1970, **90**, 696 (*Chem. Abs.*, 1970, **73**, 55 945z).

[129] T. Kametani, K. Fukumoto, M. Kawatsu, and M. Fujihara, *J. Chem. Soc.* (*C*), 1970, 2209.

(112)   (113)   (114)
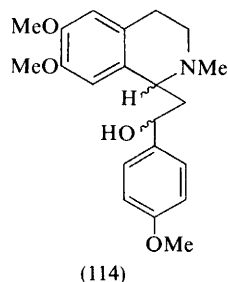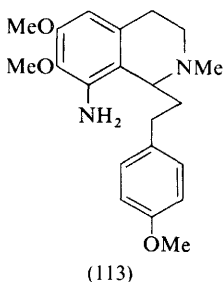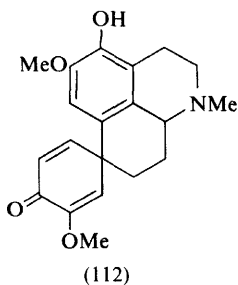
the key step in the construction of the tetracyclic spiro-skeleton.[130] Reduction of the keto-nitrile (115) gave the aldehyde (116) which by successive Wittig homologation, hydrolysis, and oxidation reactions was transformed into the substituted phenylpropionic acid (117). Polyphosphoric acid cyclization of (117) gave the ketone (118) and the six-step, one-pot conversion of the latter into ($\pm$)-hexahydropronuciferine (119) completed the synthesis.

(115)   (116)   (117)

(119)   (118)
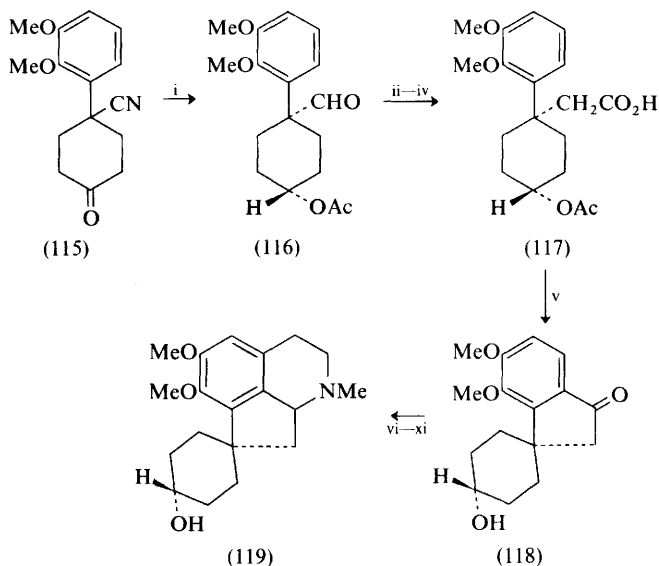
Reagents: i, LiAlH$_4$, then Ac$_2$O, py; ii, (C$_6$H$_5$)$_3$PCHOMe, Bu^{n}Li; iii, HClO$_4$, Et$_2$O; iv, Jones reagent; v, PPA; vi, H$_2$NCH$_2$CH(OR)$_2$, C$_6$H$_5$Me; vii, H$_2$, PtO$_2$; viii, 6M-HCl; ix, H$_2$, Pd–C; x, ClCO$_2$Et, pyridine, 0 °C; xi, LiAlH$_4$.

Scheme 10

[130] J. W. Huffman and C. E. Opliger, *J. Org. Chem.*, 1971, **36**, 111.

(120)
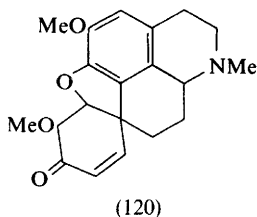
Among the miscellaneous reports, those describing the use of hydriodic acid in acetic anhydride for the selective $C(1)$-demethylation of nornuciferine-type (71) derivatives,[91] the photolysis of kreysiginone (105) to (120),[116] and the configurational relationships of the chemical and catalytic reduction products of $(-)$-mecambrine (73; $R^1 = Me$, $R^2 + R^3 = CH_2$, $R^4 + R^5 = O$)[131] may be noted. $(-)$-Glaziovine (73; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 + R^5 = O$) has been assigned the L-configuration on the basis of c.d. measurements.[132]

D. Morphine Alkaloids*.—A masterly introduction to this group, suitable for advanced study, has appeared.[133] The morphinandienone subgroup has been thoroughly reviewed.[134] Short reviews on the opium alkaloids[135] and on mass spectroscopy of morphinan, morphine, and hasubananine systems[136] have been published.

In view of the increasing involvement of modern society with various forms of drugs, it is not surprising that a great deal of effort is being expended in the advancement of methods for morphine drug analysis. Table 2 summarizes relevant studies carried out during the past year. The partition chromatographic method for opium analysis has been recommended as official first action and the combined fluorometry, t.l.c., and g.l.c. analysis of human urine appears to offer potential for routine identification of drugs. The use of isobaric solvent systems[61] and graphic t.l.c. methods[137] for morphine alkaloid analysis has been described. A short review describing the susceptibility of morphine to enzymic oxidation in opium samples has appeared.[138]

The rate of change of morphine, codeine, and thebaine content with time in *Papaver somniferum*[73] and the localization of these alkaloids in different segments of plant tissue[72] have been studied. Examination of Korean opium from various

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* Including the homomorphinandienone (androcymbine) alkaloids.

[131] J. Slavik, P. Sedmera, and K. Blaha, *Coll. Czech. Chem. Comm.*, 1970, **35**, 1558.
[132] G. Ferrari and C. Casagrande, *Farmaco, Ed. Sci.*, 1970, **25**, 449 (*Chem. Abs.*, 1970, **73**, 35 569b).
[133] K. W. Bentley in 'Chemistry of the Alkaloids,' ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, p. 117.
[134] K. L. Stuart, *Chem. Rev.*, 1971, **71**, 47.
[135] O. Gasic and M. Pergal, *Tehnika (Belgrade)*, 1971, **26**, 140 (*Chem. Abs.*, 1971, **74**, 125 879c).
[136] D. A. Fesenko, *Farmatsiya (Moscow)*, 1970, **19**, 64 (*Chem. Abs.*, 1970, **73**, 77 399b).
[137] J. A. Gisbert Calabuig and E. Villanueva, *Zacchia*, 1970, **6**, 180 (*Chem. Abs.*, 1970, **73**, 102 098n).
[138] G. Schenck, *Asian Med. J.*, 1970, **13**, 149 (*Chem. Abs.*, 1970, **73**, 123 448s).

Table 2 *Analysis of morphine alkaloids*

Source	Substance analysed†	Methods	Ref.
Opium	—	t.l.c.	7, a, b, c
Opium	M	spectrophotometry	57, d, e
Opium	M	partition chromatography	f
Opium, *Tinctura opii simplex*	M	t.l.c., colorimetry	g
Omnopon	M, C, T	spectrophotometry	h
Tetrapon	M, C	t.l.c.	59
Marihuana	M	t.l.c.	i
Human Urine	M, C	t.l.c.	8
Human Urine	—	t.l.c., fluorometry, g.l.c.	6
Synthetic	M, C	t.l.c.	55, 58
Synthetic	M, C	t.l.c., counter-current partition	j
Synthetic (?)	—	g.c. of trimethylsilyl derivatives	k
Synthetic	—	i.r.	l
Synthetic	C	paper electrophoresis	62
Synthetic	C	dye complexes, spectrophotometry	m
Synthetic	C	$B(C_6H_5)_4^-$ salts, anhydrous media	63
Commerical tablets	M	spectrophotometry	n
Codeine phosphate (tablets)	C	colorimetry	o
Synthetic	ethyl-M, C	t.l.c., spectrophotometry	p
Synthetic	ethyl-M, diethyl-M	t.l.c., n.m.r., mass spectroscopy	q

† M = morphine, C = codeine, T = thebaine

a P. Bose, *J. Inst. Chemists (India)*, 1970, **42**, 113 (*Chem. Abs.*, 1971, **74**, 2767g).

b S. Janicki, *Herba Pol.*, 1969, **15**, 247 (*Chem. Abs.*, 1970, **73**, 28 994h); 1969, **15**, 239 (*Chem. Abs.*, 1970, **73**, 28 993g).

c A. Z. Gulubov and At. Venkov, *Nauch. Tr. Vissh. Pedagog. Inst., Plovdiv, Mat., Fiz., Khim., Biol.*, 1969, **7**, 133 (*Chem. Abs.*, 1970, **73**, 7133m).

d H. Fukamauchi, R. Ideno, and N. Sanbongi, *J. Pharm. Soc. Japan*, 1970, **90**, 1039 (*Chem. Abs.*, 1970, **73**, 11 300a).

e S. J. Mule and P. J. Hushin, *Analyt. Chem.*, 1971, **43**, 708.

f E. Smith, *J. Assoc. Offic. Analyt. Chemists*, 1970, **53**, 603.

g M. Sobiczewska and B. Borkowsi, *Farm. Pol.* 1970, **26**, 539 (*Chem. Abs.*, 1971, **74**, 67 742q).

h F. E. Kagan and G. A. Vaisman, *Farm. Zhur. (Kiev)*, 1971, **26**, 80 (*Chem. Abs.*, 1971, **75**, 9902b).

i H. C. Honecker and H. Coper, *Deut. Med. Woch.*, 1970, **95**, 2129 (*Chem. Abs.*, 1971, **74**, 51 719b).

j V. E. Chichiro, *Farmatsiya (Moscow)*, 1970, **19**, 44 (*Chem. Abs.*, 1971, **74**, 45 633c).

k A. Baerheim Svendsen, *Praep. Pharm.*, 1970, **6**, 121 (*Chem. Abs.*, 1970, **73**, 112 860u).

l M. Sarsunova, B. Kakac, and L. Krasnec, *J. Chromatog.*, 1970, **48**, 353.

m G. L. Starobinets and D. E. Peshko, *Doklady Akad. Nauk Beloruss. S.S.R.*, 1970, **14**, 340 (*Chem. Abs.*, 1970, **73**, 69 886t).

n A. M. Wahbi and A. M. Farghaly, *J. Pharm. Pharmacol.*, 1970, **22**, 848;

o M. Sobiczewska, *Acta Pol. Pharm.*, 1971, **28**, 31 (*Chem. Abs.*, 1971, **74**, 130 412z).

p E. Lang, *Pharmazie*, 1970, **25**, 493.

q S. Pfeifer, G. Behnsen, and L. Kuehn, *Pharmazie*, 1970, **25**, 529.

localities showed that it was invariably high in morphine and codeine content compared to samples of foreign origin.[71] A review on breeding programmes of poppies and the yields of alkaloids obtained therefrom may be of general interest.[139]

139 H. Boehm, *Planta Med.*, 1970, **19**, 93.

Table 3 summarizes reports concerning new sources of alkaloids. All new alkaloids exhibit the increasingly important morphinandienone or the complex and as yet rare hasubanan skeletons.

Table 3 *Isolation of morphine alkaloids*

Plant Species	Alkaloid (Structure)	Ref.
Corydalis pallida	Pallidine (121; R^1 = Me, R^2 = OH, R^3 = OMe, R^4 = H)	140
C. pallida var. *tenuis*	Pallidine	97
Croton discolor	8,14-Dihydrosalutaridine (122; R^1 = Me, R^2 = H, R^3 = OMe, R^4 = OH; 8,14-dihydro)	99
C. balsamifera, *C. flavens*, *C. linearis*	Flavinine* (122; R^1 = R^4 = H, R^2 = OMe, R^3 = OH)	
	Flavinantine (122; R^1 = Me, R^2 = OMe, R^3 = OH, R^4 = H)	
	Norsinoacutine* (121; R^1 = R^2 = H, R^3 = OMe, R^4 = OH)	98, 134
	Salutaridine† (122; R^1 = Me, R^2 = H, R^3 = OMe, R^4 = OH)	
	Sinoacutine (121; R^1 = Me, R^2 = H, R^3 = OMe, R^4 = OH)	
Menispermum dauricum	Acutumidine*	
	Acutumine*	103a, 140a
	Sinomenine (123; R^1 + R^2 = O)	
Papaver bracteatum	Salutaridine*	69
Stephania abyssinica	Stephavanine (124)	141
S. delavayi	Delavaine (121 or 122; R^1 = Me, R^2 + R^3 = OCH_2O, R^4 = OMe or R^2 = OMe, R^3 + R^4 = OCH_2O)	142
S. hernandifolia	Hernandoline* (133; R = Me)	143
	Hernandolinol [133; R = Me, C(6)-OH]	144
	Stephisoferuline (130)	145

* See footnote (*), Table 1.
† Isolated only from *C. balsamifera*.

The structural elucidation of pallidine (121; R^1 = Me, R^2 = OH, R^3 = OMe, R^4 = H) was relatively simple since its racemate, ($\pm$)-isosalutaridine, had been previously synthesized.[97] The absolute configuration of pallidine was established

[140] L. I. Stekol'nikov, *Priroda* (*Moscow*), 1970, 107 (*Chem. Abs.*, 1971, **74**, 1075t).
[140a] M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, and K. Goto, *Tetrahedron Letters*, 1967, 2421.
[141] S. M. Kupchan, M. I. Suffness, R. J. McClure, and G. A. Sim, *J. Amer. Chem. Soc.*, 1970, **92**, 5756.
[142] I. I. Fadeeva, T. N. Il'inskaya, M. E. Perel'son, and A. D. Kuzovkov, *Khim. prirod. Soedinenii*, 1970, **6**, 140 (*Chem. Abs.*, 1970, **73**, 45 639p).
[143] I. I. Fadeeva, M. E. Perel'son, T. N. Il'inskaya, and A. D. Kuzovkov, *Farmatsiya* (*Moscow*), 1970, **19**, 28 (*Chem. Abs.*, 1970, **73**, 25 717j).
[144] I. I. Fadeeva, T. N. Il'inskaya, M. E. Perel'son, and A. D. Kuzovkov, *Khim. prirod. Soedinenii*, 1970, **6**, 492 (*Chem. Abs.*, 1971, **74**, 10 357p).
[145] S. M. Kupchan and M. I. Suffness, *Tetrahedron Letters*, 1970, 4975.

(121)   (122)   (123)
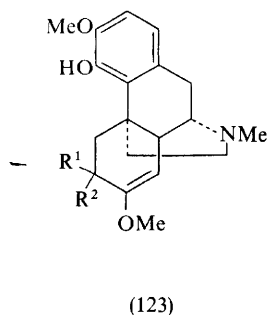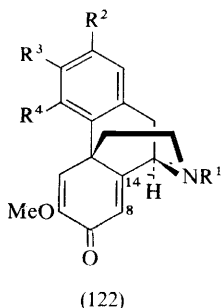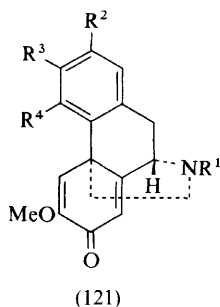
by comparison of its o.r.d. and c.d. spectra with those of sinoacutine (121; R^1 = Me, R^2 = H, R^3 = OMe, R^4 = OH) of known configuration. The continued extensive work on the *Croton*[98] and *Papaver*[69] genera may be of chemotaxonomic interest.

Stephavanine (124) is the most highly oxygenated hasubanan alkaloid yet found and the first to exhibit ketal and ester functions.[141] Alkaline hydrolysis of stephavanine gave vanillic acid and stephine (125). The latter upon oxidation with Jones reagent gave 6-dehydrostephine (126) which was converted by base into iso-6-dehydrostephine (127). Whereas the mass spectrum of (126) showed its base peak at m/e 214 (128), that of (127) exhibited a peak at m/e 301 (129) resulting from the loss of the D ring, a process characteristic of C-ring-enone hasubanan alkaloids. Reduction of (126) with sodium borohydride gave stephine (125) stereospecifically. The cage ring system of the alkaloid allowed the assignment of four [C(8), C(10), C(13), and C(14)] of the six asymmetric centres. That the C(6)-vanillate ester was axially (β) oriented was indicated by the high-field signals and line separation for the methylene protons (τ 4.28 and 4.78, d, J = 1.5 Hz) in the 6,7-bistrimethylsilyl derivative of (125). Molecular models showed that close proximity of the aromatic ring of the vanillate ester to the methylenedioxy-protons is only possible in the 6β-axial ester. This assignment was in agreement

(124)   (125)

(126)

(127)

(128)

(129)
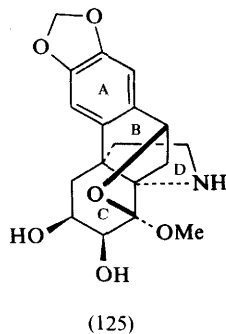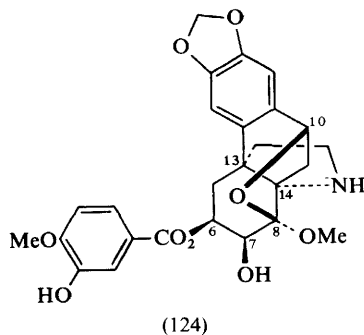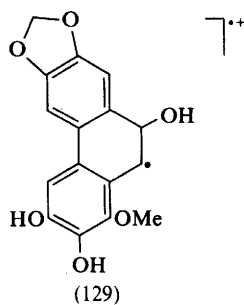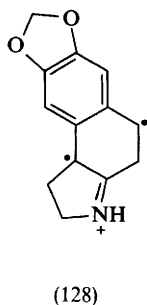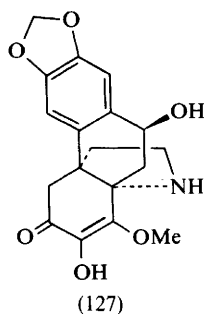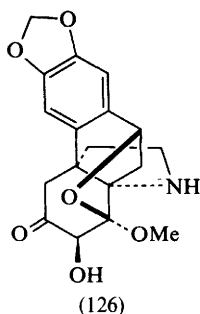
with the stereospecific sodium borohydride reduction of (126) to give the β-axial alcohol (125). Tentative assignment of the 7β-equatorial alcohol configuration was made on the basis of the selective Jones oxidation of the diol (125) to the monoketone (126). Since proof of structure by chemical interrelationship with known hasubanan alkaloids could not be attempted owing to the unique ring A substitution pattern, the final assignment of structure and absolute configuration (124) was achieved by X-ray analysis of stephavanine hydrobromide.

The oxygenation pattern in stephisoferuline (130) was, on the other hand, the same as that of c-ring-enone hasubanan alkaloids and its interrelation with 4-demethylnorhasubanonine (133) was achieved.[145] Successive basic hydrolysis, acetylation, and acid treatment gave the triacetyl derivative (131). Hydrogenation to remove the C(9)—C(10) double bond and treatment with acetone dimethylacetal and toluene-p-sulphonic acid gave the rearranged triacetyl derivative (132). Compound (132) was also obtained by successive sodium borohydride reduction and acetylation of 4-methylnorhasubanonine (133; R = H). Since (133; R = H) had been interrelated with (133; R = Me), whose structure and absolute stereochemistry had been unequivocally defined by X-ray analysis, this correlation established complete structure (130) for stephisoferuline.

The structures of delavaine (121 or 122; R^1 = Me, R^2 + R^3 = OCH_2O, R^4 = OMe or R^2 = OMe, R^3 + R^4 = OCH_2O)[142] and hernandoline (133; R = Me)[143] were determined by n.m.r. spectroscopy and exhaustive Hofmann degradation.

(130)

(131)

(132)

(133)
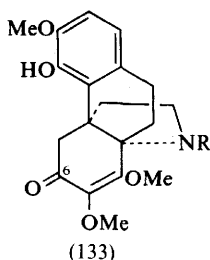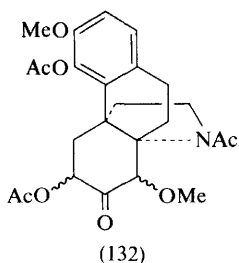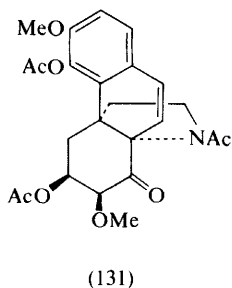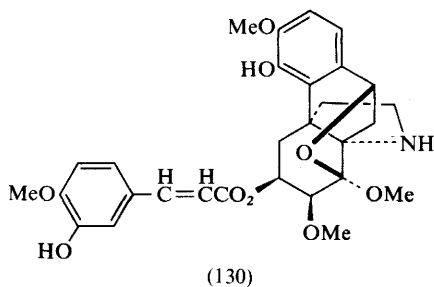
Little work directly related to the synthesis of morphine alkaloids has appeared. Pallidine (121; R^1 = Me, R^2 = OH, R^3 = OMe, R^4 = H) was obtained, together with an aporphine alkaloid (see Section 3C), by a phenolic coupling reaction of reticuline in very low yield using silver carbonate on Celite, $K_3Fe(CN)_6$ and sodium bicarbonate, or vanadyl trichloride as the oxidizing agents.[115] A similar attempt to synthesize salutaridine (122; R^1 = Me, R^2 = H, R^3 = OMe, R^4 = OH) by oxidation of (±)-reticuline with homogenized *Papaver rhoeas* in the presence of hydrogen peroxide failed.[79] However, Pschorr cyclization of the diazotized benzylisoquinoline corresponding to (134; R^1 = R^3 = R^6 = Me, R^2 = R^5 = OMe, R^4 = H) gave the morphinandienone system (135; R^1 = R^3 = R^6 = Me, R^2 = R^5 = OMe, R^4 = H), an aporphine alkaloid, and other degradation products.[123] An aporphine-type compound and the deamination product were also obtained as major products together with 0.5% of (135; R^1 = R^3 = Me, R^2 = R^5 = H, R^4 = OMe, R^6 = $CH_2 \cdot C_6H_5$) when the Pschorr reaction of the diazonium salt corresponding to (134; R^1 = R^3 = Me, R^2 = R^5 = H, R^4 = OMe, R^6 = $CH_2 \cdot C_6H_5$) was carried out under photolytic conditions. (With regard to the last three reactions, see also Section 3C). A compound (136) of the type which has been proposed as a biogenetic precursor to the hasubanan and *Erythrina* alkaloids has been prepared by phenolic oxidative coupling.[146] (See Chapter 10). Details concerning the formal synthesis of a hasubanan alkaloid

[146] T. Kametani, R. Charubala, M. Ihara, M. Koizumi, and K. Fukumoto, *Chem. Comm.*, 1971, 289.
[146a] S. L. Keeley, jun., A. J. Martinez, and F. C. Tahk, *Tetrahedron*, 1970, 26, 4729.

(Scheme 11)[146a] and several successful approaches to the unsubstituted hasubanan carbocyclic system (Scheme 12)[146a,146b] have appeared. These outstanding reports further emphasize the applicability of enamine annelation reactions in alkaloid synthesis.

(134)   (135)   (136)
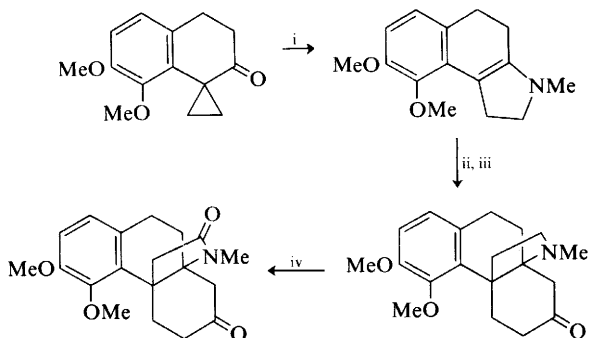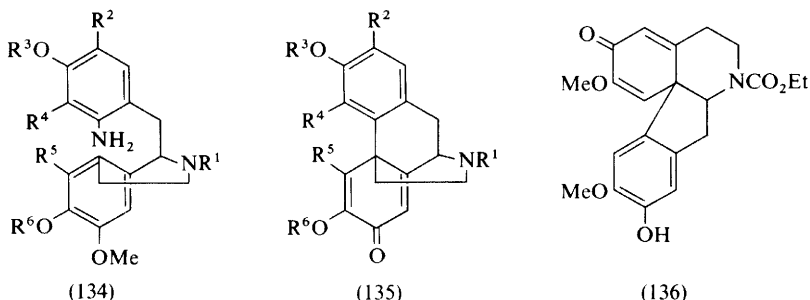
Reagents: i, MeNH$_2$, C$_6$H$_6$, 110 °C; ii, CH$_2$=CHCOMe, r.t. →40 °C; iii, HOAc, 40 °C; iv, KMnO$_4$.

Scheme 11

Whereas total syntheses of alkaloids have been few, a great deal of attention has been given to the modification of alkaloid skeletons and to the synthesis of alkaloid analogues in an effort to prepare new pharmacologically active compounds. To begin, the bromination product of thebaine (137), 14-bromocodeinone (138; R^1 + R^2 = O), has been the subject of a number of reports.[147—154]

[146b] D. A. Evans, C. A. Bryan, and G. M. Wahl, *J. Org. Chem.*, 1970, **35**, 4122.
[147] D. E. Rearick and M. Gates, *Tetrahedron Letters*, 1970, 507.
[148] W. Fleischhacker, F. Vieboeck, and F. Zeidler, *Monatsh.*, 1970, **101**, 1215.
[149] W. Fleischhacker, *Monatsh*, 1971, **102**, 558.
[150] G. Heinisch and F. Vieboeck, *Monatsh.*, 1970, **101**, 1253.
[151] G. Heinisch, V. Klintz, and F. Vieboeck, *Monatsh.*, 1971, **102**, 530.
[152] W. Fleischhacker and H. Markut, *Monatsh.*, 1971, **102**, 569.
[153] G. Heinisch and F. Vieboeck, *Monatsh.*, 1970, **101**, 1759.
[154] W. Fleischhacker and H. Markut, *Monatsh.*, 1971, **102**, 587.
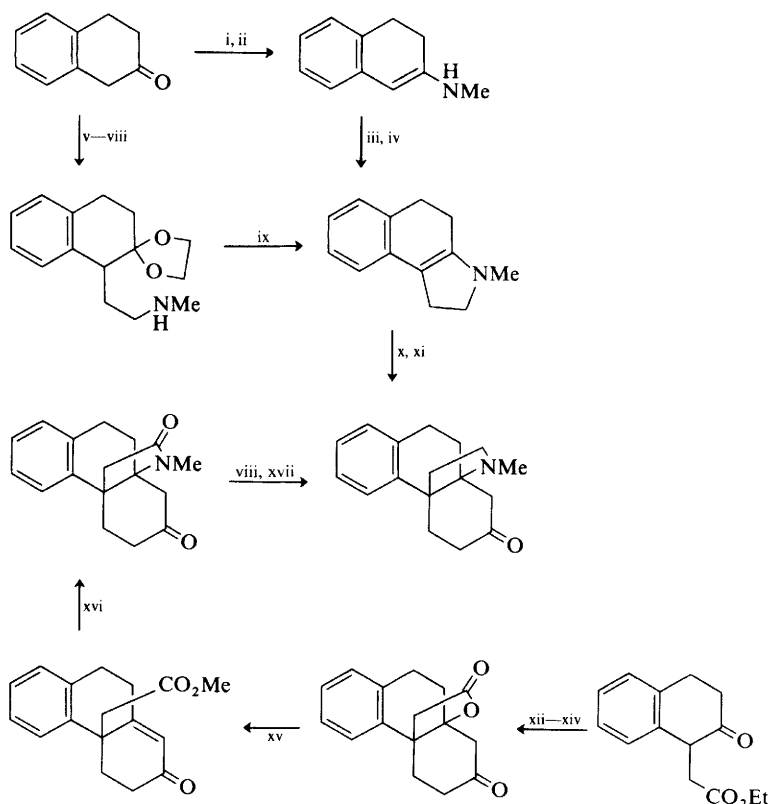
Reagents: i, MeNH$_2$; ii, TiCl$_4$; iii, Pr^{i}MgCl, THF; iv, BrCH$_2$·CH$_2$Cl; v, pyrrolidine, C$_6$H$_6$, BrCH$_2$CO$_2$Et; vi, HOCH$_2$·CH$_2$OH, TsOH; vii, LiAlH$_4$–MeNH$_2$; viii, LiAlH$_4$, THF; ix, 3M-H$_2$SO$_4$, EtOH; x, CH$_2$=CHCOMe, MeCN, r.t.; xi, HOAc, 80 °C; xii, KOH, MeOH–H$_2$O, CH$_2$=CHCOMe, –10 °C; xiii, Δ; xiv, HCl; xv, K$_2$CO$_3$, MeI; xvi, LiAlH$_4$–MeNH$_2$; xvii, Jones reagent.

Scheme 12

This compound undergoes rearrangement to 6-*O*-demethylsalutaridine (139) in the presence of Claisen's alkali.[147] The product has been correlated with salutaridine and a mechanism involving S_N2' attack by base on the allylic bromide function to form the intermediate (140; X = OH) has been proposed. Compound (139) has also been obtained independently by treatment of 7-bromoneopinone (140; X = Br) perchlorate with sodium acetate–acetic acid and several pertinent mechanistic observations on this reaction have been presented.[149] Attempts to prepare the proposed intermediate (140; X = OH) from (140; X = Br) perchlorate by treatment with aqueous silver nitrate at room temperature gave no reaction, while under reflux a quantitative yield of (139) perchlorate was obtained. Compound (140; X = Br) perchlorate was stable to base in the cold while at reflux temperature a Hofmann degradation product was obtained.[150] It is interesting to

compare the reaction $(138; R^1 + R^2 = O) \rightarrow (139)$ with the mild base-catalysed re-
arrangement of 14-bromocodeinone dimethylacetal $(138; R^1 = R^2 = OMe)$ to
compounds $[141; R^1 = H, R^2 = OMe, C(7)\text{-}OMe$ configuration undetermined$]$
and (142).[151] In extensions of this work, a catalytic hydrogenation[152] and a
catalytic oxidation[149] of $(138; R^1 = R^2 = OMe)$ have been reported. Hydro-
genation in the presence of palladium yielded $(141; R^1 = OH, R^2 = H)$, $(141;$
$R^1 = R^2 = H)$, and $(141; R^1 = R^2 = H, 8,14\text{-dihydro})$ and the new dimeric
compounds (143), (144), and (145). The dimeric structures were deduced on the
basis of their n.m.r. and mass spectra and those of their corresponding diketone
derivatives.[152] On the other hand, aerial oxidation of $(138; R^1 = R^2 = OMe)$ in
alcoholic sodium hydroxide in the presence of a specially prepared palladium
catalyst gave $(141; R^1 = OH, R^2 = H)$ in up to 75% yield together with minor
amounts of $(141; R^1 = H, R^2 = OH)$, $(141; R^1 + R^2 = O)$, and the dimers (143),
$(143; N_a\text{-demethyl})$, and (144).[149] In analogy with the general behaviour of
morphine alkaloids, treatment of $(141; R^1 = OH, R^2 = H)$ with concentrated
mineral acid gave the aporphine derivative (146). In view of the accessibility of
the 7-hydroxy-neopinone dimethylacetal $(141; R^1 = OH, R^2 = H)$ and its
potential importance in the mechanism of the rearrangement $(138; R^1 + R^2 =$
$O) \rightarrow (139)$, it is somewhat disappointing that milder acid or possibly direct
vigorous base-catalysed reactions of this compound were not explored. A
further paper in this series has recently appeared.[153] The reduction of $(138;$
$R^1 + R^2 = O)$ with sodium bis-(2-methoxyethoxy)aluminium hydride or with
chromous sulphate to thebaine[154] and its microbial transformation by *Trametes
sanguinea* into $(138; R^1 = H, R^2 = OH)$[155] have been reported.
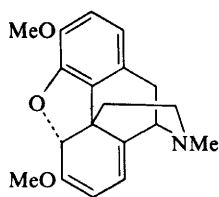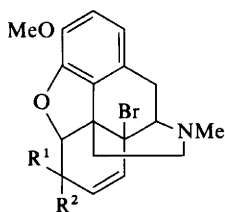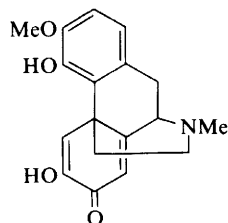
(137)   (138)   (139)
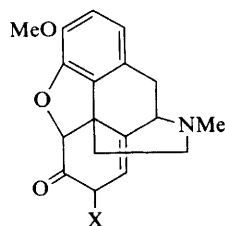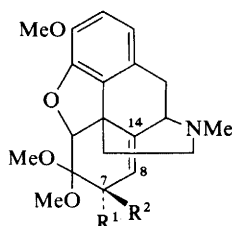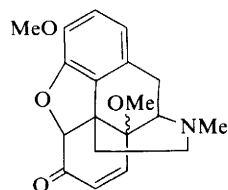
(140)   (141)   (142)

[155] K. Abe, M. Onda, H. Isaka, and S. Okuda, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2070.

(143)

(144)

(145)

(146)

(147)
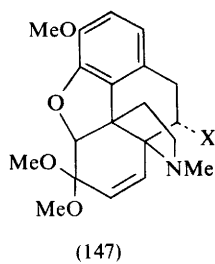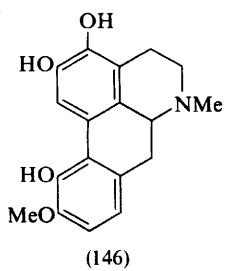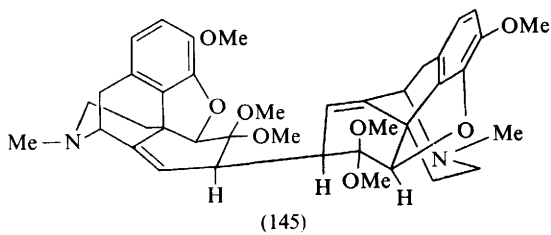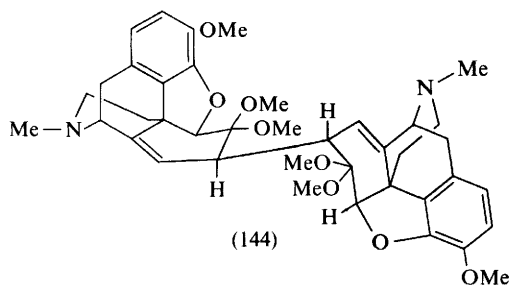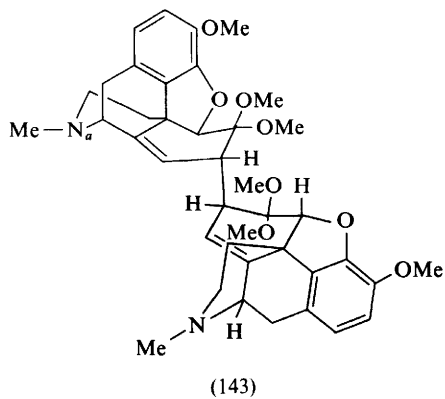
In contrast to bromination of thebaine (137), which gave 14-bromocodeinone (138; $R^1 + R^2 = O$), iodination in methanol–chloroform solution produced the 7-iodo-derivative (141; $R^1 = H, R^2 = I$).[156] The latter was transformed into the indolinocodeine (147; $X = OAc$) by treatment with silver acetate in acetic acid, thus offering an alternative route to those derivatives which had been previously prepared by solvolysis of 14-bromocodeine (138; $R^1 = OH, R^2 = H$). Similarly, treatment of (141; $R^1 = H, R^2 = I$) with silver cyanide and sodium azide afforded compounds (147; $X = NC$) and (147; $X = N_3$) respectively. This report should stimulate further investigation of the factors involved in yielding predominantly $C(14)$- or $C(7)$-substituted products in electrophilic reactions on thebaine.[156]

Bentley's original discovery that certain Diels–Alder derivatives of thebaine are analgesics about 10 000 times more potent than morphine itself[133] no doubt is

(148)   (149)

(150)

(151)   (152)
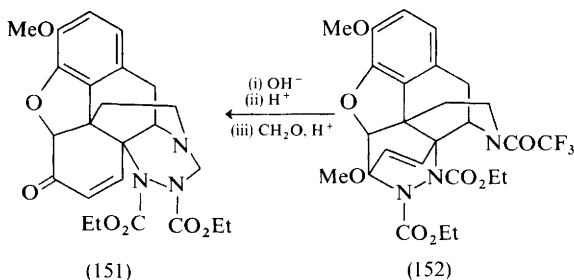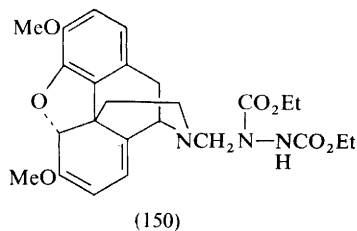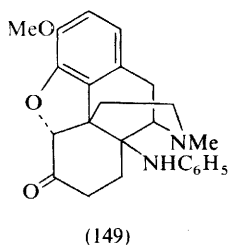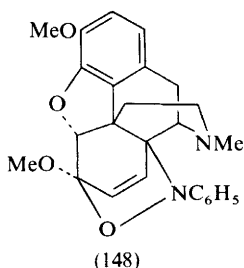
[156] R. M. Allen and G. W. Kirby, *Chem. Comm.*, 1970, 1346.

$(137) \rightarrow (150) \rightarrow$

(153)
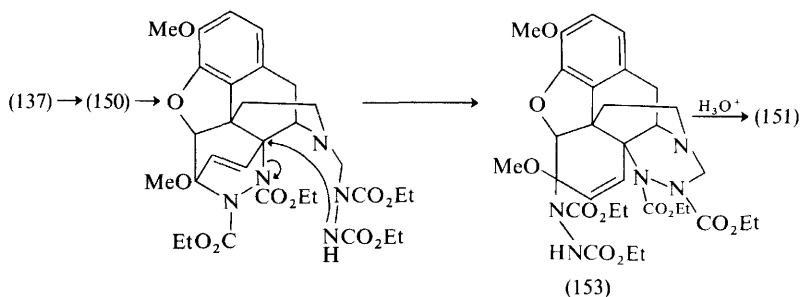
responsible for continued activity in this area. The reaction of thebaine (137) with nitrosobenzene has been shown to yield the adduct (148) which was converted into the previously unknown 14-aminocodeinone (149) by successive hydrolysis with hydrochloric acid and catalytic hydrogenation.[157] Interesting results were obtained from the reaction of thebaine with ethyl azodicarboxylate.[158] When the reaction was carried out with one equivalent of azodicarboxylic ester, the known insertion product (150) was isolated. However, when thebaine was treated with two moles of ethyl azodicarboxylate and the reaction mixture was hydrolysed with acid, the hexacyclic derivative (151) was obtained. Compound (151), which incidentally is a very strong base ($pK_a = 11.3$; compare thebaine $pK_a = 6.8$) was stable to vigorous acidic conditions in contrast to (150) which was readily hydrolysed to northebaine (137; NH for NMe). This stability was attributed to the part 1,3,5-triaza-adamantane-like structure of (151) whose resistance to acid hydrolysis had been noted previously. The mechanism of the formation of (151) was partially deduced from the reaction of N-trifluoroacetyl-northebaine (137; NCOCF$_3$ for NMe) with ethyl azodicarboxylate, which yielded the normal Diels–Alder adduct (152). This compound was transformed into (151) by a three-step sequence. On this basis the mechanism $(137) \rightarrow (153)$ was proposed for the reaction of thebaine with excess ethyl azodicarboxylate. The formation of (151) may then be readily explained by hydrolysis of (153) during the subsequent acid treatment.[158] A series of Diels–Alder adducts of thebaine with 1,1-disubstituted ethylenes has been synthesized[159] and the reaction of one of these (154) with phenylmagnesium bromide has been investigated.[160] In the presence of excess Grignard reagent, compound (154) gave a mixture of the imine (155) and the rearranged product (156). Compound (155) was converted into (156) by further treatment with phenylmagnesium bromide, or more efficiently, with lithium aluminium hydride, which indicates that the driving force for the formation of (156) may be base-catalysed abstraction of the imine hydrogen in (155).

[157] P. Horsewood and G. W. Kirby, *Loughborough Univ. Technol., Dept. Chem., Sum. Final Year Stud. Proj. Theses*, 1969, **10**, 147 (*Chem. Abs.*, 1970, **73**, 15 045z).

[158] H. Merz and K. H. Pook, *Tetrahedron*, 1970, **26**, 1727.

[159] J. W. Lewis, M. J. Readhead, I. A. Selby, A. C. B. Smith, and C. A. Young, *J. Chem. Soc. (C)*, 1971, 1158.

[160] J. W. Lewis and M. J. Readhead, *J. Chem. Soc. (C)*, 1971, 1161.
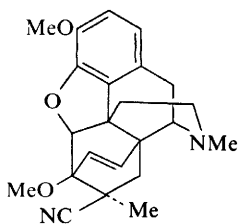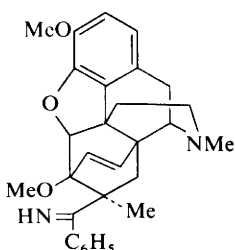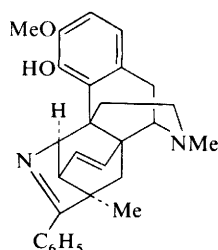
| (154) | (155) | (156) |

An efficient synthesis of the thebaine analogue (158), as outlined in Scheme 13, in which the nitrogen atom is translocated from C(17) to the 16-position has been reported.[161] It was converted into the 'Bentley adduct' (159) by successive Diels–Alder and Grignard reactions. Further work on the Diels–Alder reactions of morphine alkaloids is expected; for example, the enamine (160) has been prepared specifically for this purpose.[162]

Various other reports on miscellaneous reactions of morphine alkaloids and their derivatives have appeared. Aside from the classical example of the abnormal Beckmann rearrangement of dihydrocodeinone oxime which was the basis for distinguishing between the Robinson and Wieland formulations for the morphine skeleton,[133] this reaction has not been extensively studied. Now a series of oximes of the dihydrothebainone type (161) has been shown to rearrange to lactams (162) in the presence of polyphosphoric acid.[163] Oximes of Hofmann degradation products of dihydrothebainones also yielded corresponding Beckmann rearrangement products. Bisthiocodide, a product originally obtained by Pschorr from the reaction of bromocodide (163) with potassium mercaptide in ethanol, has been shown to possess the biochemically interesting structure (164).[164] Products from the reaction of codeine with benzaldehyde have not been fully characterized.[165] Various reactions of tosyl and mesyl derivatives of morphine alkaloids have been reported.[166—168] For example, the product from

[161] K. Wiesner, J. G. McCluskey, J. K. Chang, and V. Smula, *Canad. J. Chem.*, 1971, **49**, 1092.
[162] I. Seki, *Chem. and Pharm. Bull.*, (*Japan*), 1970, **18**, 671.
[163] I. Seki, *Chem. and Pharm. Bull.*, (*Japan*), 1970, **18**, 1269.
[164] S. Makleit, R. Bognar, T. Mile, and L. Radics, *Magyar Kém. Folyóirat*, 1970, **76**, 464 (*Chem. Abs.*, 1970, **73**, 131 175r); S. Makleit, R. Bognar, T. Mile, and L. Radics, *Acta Chim. Acad. Sci. Hung.*, 1970, **66**, 455 (*Chem. Abs.*, 1971, **74**, 100 247g).
[165] S. Brightwell and G. W. Kirby, *Loughborough Univ. Technol., Dept. Chem., Sum. Final Year Stud. Proj. Theses*, 1969, **10**, 131 (*Chem. Abs.*, 1970, **73**, 15 046a).
[166] S. Makleit and R. Bognar, *Acta Chim. Acad. Sci. Hung.*, 1970, **64**, 281 (*Chem. Abs.*, 1970, **73**, 35 587f).
[167] R. Bognar, S. Makleit, T. Mile, and L. Radics, *Acta Chim. Acad. Sci. Hung.*, 1970, **64**, 273 (*Chem. Abs.*, 1970, **73**, 35 582a).
[168] R. Bognar, S. Makleit, and L. Radics, *Acta Chim. Acad. Sci. Hung.*, 1971, **67**, 63 (*Chem. Abs.*, 1971, **74**, 142 106r); R. Bognar, S. Makleit, and L. Radics, *Magyar Kém. Folyóirat*, 1970, **76**, 461 (*Chem. Abs.*, 1970, **73**, 131 174q).
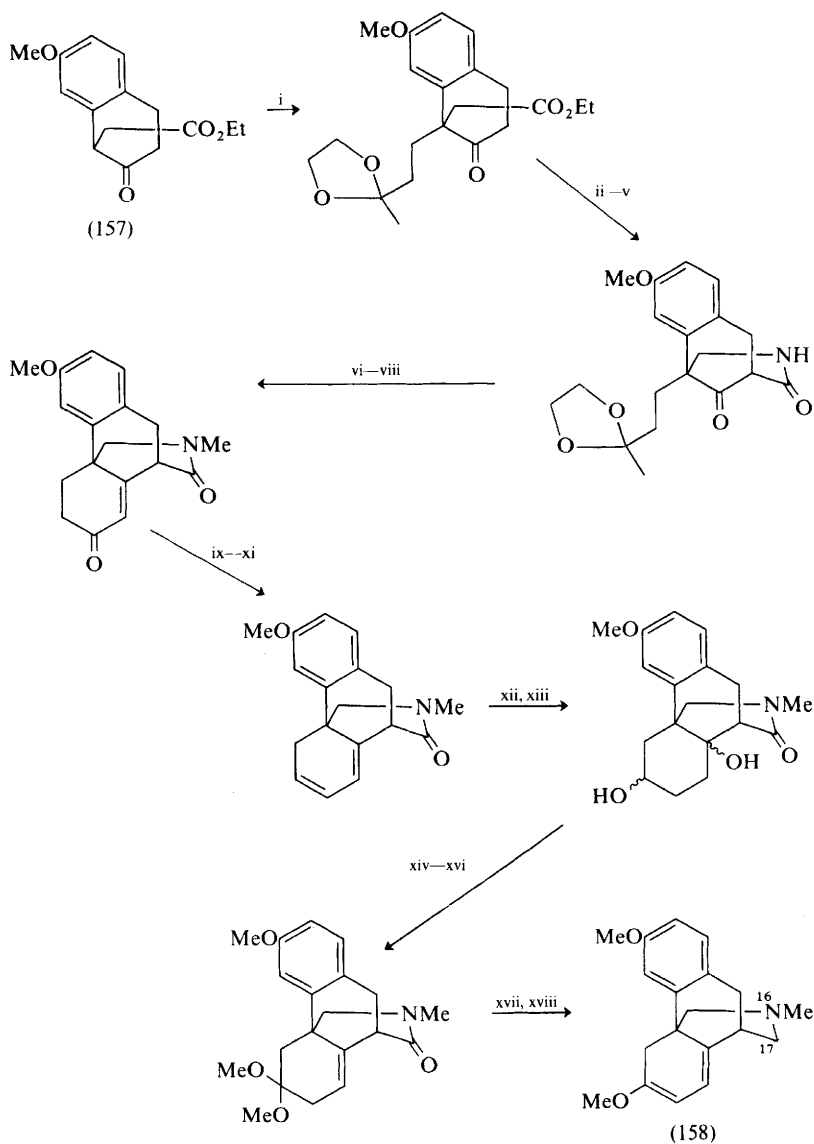
Reagents: i, NaH, C_6H_6; MeC(OCH$_2$CH$_2$O)CH$_2$CH$_2$OTs; ii, 5 % NaOH; iii, Et$_3$N, ClCO$_2$Et, NaN$_3$; iv, 80 °C, C$_6$H$_5$Me; v, NaH; vi, NaH, MeI, C$_6$H$_6$; vii, TsOH, MeCOMe, viii, TsOH, C$_6$H$_6$; ix, NaBH$_4$; x, C$_6$H$_5$·COCl, pyridine; xi, 200 °C; xii, *hv*, O$_2$, eosin; xiii, H$_2$, PtO$_2$; xiv, CrO$_3$, HOAc; xv, SOCl$_2$, pyridine; xvi, TsOH, HC(OMe)$_3$, C$_6$H$_6$; xvii, Δ, xylene; xviii, LiAlH$_4$.

Scheme 13

(159)
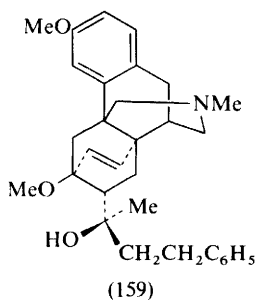
the reaction of 6-*O*-tosylcodeine with tetrabutylammonium fluoride in acetonitrile has been shown to possess the 6-deoxy-6-fluorocodeine structure (165).[168] The *N*-oxides of codeine and morphine have been prepared by an improved procedure.[169] Thus the *N*-oxide of morphine can be obtained directly without prior protection of the phenolic hydroxy-function.

(160)

(161)

(162)

(163)

(164)

(165)
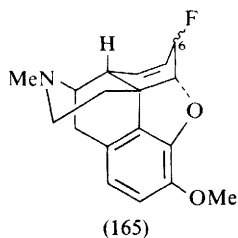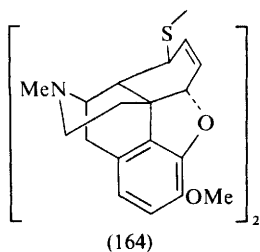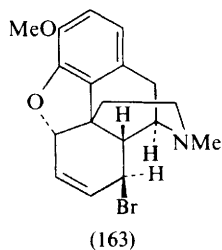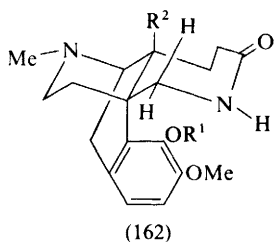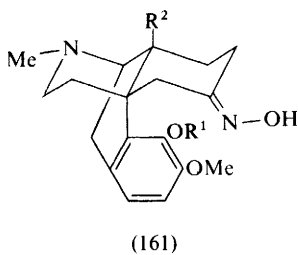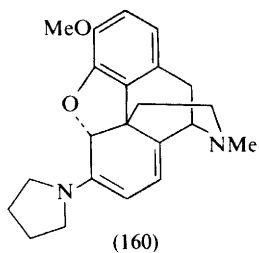
[169] C. J. Cymerman and K. K. Purushothaman, *J. Org. Chem.*, 1970, **35**, 1721.

Further derivatives of the B/C-ring *trans*-fused morphine system have been synthesized.[170,171] The intermediate (167) obtained by hydroboration of (166) was acetylated to give the alcohol-acetate (168). Other work dealing with the preparation of morphine-type compounds for the purpose of pharmacological evaluation has been published.[172]

The use of ^1H and ^{13}C n.m.r. and mass spectroscopy has allowed the reliable differentiation of the epimeric 10-oxo-des-N-morphinan structures (169 and 170; X = H_2 or O).[173] In the mass spectrum of (169; X = O), a very intense peak appears at m/e 198 assignable to (171) whereas it is of negligible intensity in the spectrum of (170; X = O). As expected from van der Waals interaction considerations, the axial protons on C(6), C(8), C(15), and C(17) are deshielded and the corresponding carbon atoms are shielded in the ^1H and ^{13}C n.m.r. spectra of (169; X = O).

(166)   (167)   (168)

(169)   (170)   (171)
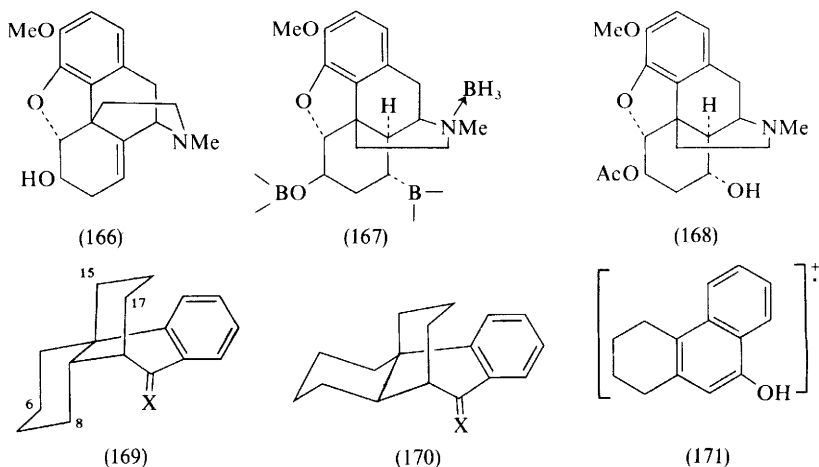
Homomorphinandienone (*Androcymbine*) *Alkaloids.* Photolytic Pschorr reaction of the diazonium salt corresponding to (172) gave O-methylandrocymbine (173) whose structure was conclusively established by comparison with material synthesized from the natural product (androcymbine).[174] On the other hand, thermal decomposition of the diazonium salt gave the spiroquinoline (174) whose structure was determined by spectral means and by Hofmann degradation to an

[170] H. Kugita, M. Takeda, and H. Inoue, *J. Medicin. Chem.*, 1970, **13**, 973.
[171] H. Inoue, M. Takeda, and H. Kugita, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 1569.
[172] I. Seki and H. Takagi, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 1; 1970, **18**, 1104; K. Oguri, H. Yoshimura, and H. Tsukamoto, *ibid.*, 1970, **18**, 209; T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, K. Wakisaka, F. Satoh, and S. Saito, *J. Medicin. Chem.*, 1970, **13**, 1064; J. L. Sargent and E. L. May, *ibid.*, p. 1061.
[173] R. E. Moore, U. R. Ghatak, J. Chakravarty, R. Dasgupta, and L. F. Johnson, *Chem. Comm.*, 1970, 1136.
[174] T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Comm.*, 1970, 1157.

indene derivative. Products of the type (174) were also obtained with differently substituted phenethylisoquinoline derivatives (172).[123] An additional report concerning the formation of degradation and unusual rearrangement products from the Pschorr reactions of phenethylisoquinoline systems has appeared.[175]

(172)

(173)

(174)
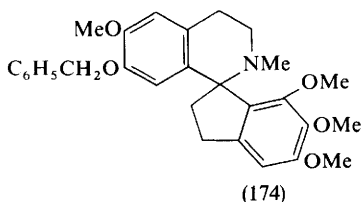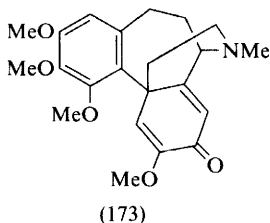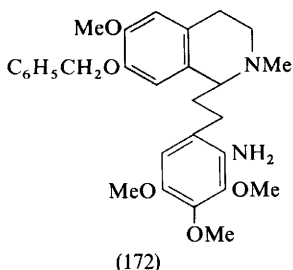
E. Colchicine Alkaloids.—A summary of the chemistry and photochemistry of colchicine has appeared as part of an advanced introductory text on alkaloids.[176] A survey of plant drugs with cytostatic activity includes a discussion on colchicine.[177]

A survey of Yugoslavian *Colchicum* species revealed the presence of colchicine in *C. arenarium, C. autumnale, C. bartolini, C. doerfleri, C. kochii, C. latifolium, C. macedonicum,* and *C. visianii.*[178] Unripe seeds of *Colchicum* plants were found to contain 40% less colchicine than fully ripe ones.

(175)

(176)
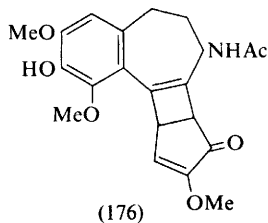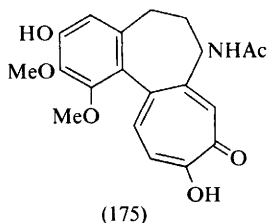
[175] T. Kametani, M. Koizumi, and K. Fukumoto, *J. Pharm. Soc. Japan*, 1970, **90**, 1331 (*Chem. Abs.*, 1971, **74**, 54 049u).
[176] W. C. Wildman in 'Chemistry of the Alkaloids,' Van Nostrand Reinhold Co., New York, 1970, p. 199.
[177] P. Lukic, *Arhiv Farm.* (*Belgrade*), 1969, **19**, 323 (*Chem. Abs.*, 1971, **74**, 24 946s).
[178] J. Tucakov and M. Mihajlov, *Lek. Sirovine*, 1968, **6**, 65 (*Chem. Abs.*, 1971, **74**, 146 289a).

A detailed re-examination of *C. autumnale* has led to assignment of structures to several previously unnamed colchicine alkaloids.[179] Known alkaloids have been isolated from *C. kesselringii*.[180] Two new alkaloids, L-5 and L-6, have been isolated from *C. luteum* and shown to possess structures (175) and (176) respectively, by correlation with known alkaloids.[181,182] Several known alkaloids and a compound $C_{21}H_{23}O_6N$ of unknown structure were also isolated.[181] Colchicine has been shown to be present in the previously unexamined *C. chalcedonicum*, *C. micranthum*, *C. szovitsii*, and *C. turcicum* species by t.l.c.[183] With the exception of *C. micranthum*, all species also contained demecolcine. *C. szovitsii* of another locality has been examined.[184] Colchicine has been identified as the chief alkaloid in *Gloriosa superba* growing in Ceylon.[185] In comparison with *G. superba* of European and African origin, the colchicine content of the Ceylonese variety was low.

F. Cularine.—New syntheses of ($\pm$)-cularine (180) and its derivatives using intramolecular Ullmann[186] and phenolic oxidative coupling[187,188] reactions as key steps have been reported. It is well known that 7,8-disubstituted isoquinolines cannot be prepared by the Bischler–Napieralski reaction. This problem was circumvented (Scheme 14) by using an ethoxycarbonylamino-*β*-phenethyl-amide (177) in order to activate the *para*-position and thus to effect the required cyclization reaction (177) $\rightarrow$ (178).[186] Conventional steps then led to the phenol (179) which under Ullmann reaction conditions gave ($\pm$)-cularine (180).

In an alternative synthetic attack,[187] preparation of a 7,8-dioxygenated isoquinoline (181; $R^1 = R^3 = CH_2 \cdot C_6H_5$, $R^2 = Me$, $R^4 = H$, $X = Br$) by the Pictet–Spengler reaction was made feasible by blocking the alternative mode of cyclization by the bromo-substituent. Unexceptional steps then gave the diphenol (181; $R^1 = R^3 = H$, $R^2 = R^4 = Me$, $X = H$) which, when subjected to the phenol coupling reaction with potassium ferricyanide followed by treatment with diazomethane, gave cularine (180) and the cancentrine-type compound (182). On the other hand, treatment of (181; $R^1 = R^2 = H$, $R^3 = R^4 = Me$, $X = H$) under the same conditions yielded two dienones (183) differing in configuration

[179] F. Santavy, *Coll. Czech. Chem. Comm.*, 1970, **35**, 2857.
[180] M. K. Yusupov and A. S. Sadykov, *Rast. Resur.* 1970, **6**, 104 (*Chem. Abs.*, 1970, **73**, 32 337*p*).
[181] B. Chommadov, M. K. Yusupov, and A. S. Sadykov, *Khim. prirod. Soedinenii.*, 1970, **6**, 82 (*Chem. Abs.*, 1970, **73**, 45 635*j*).
[182] B. Chommadov, M. K. Yusupov, F. G. Kamaev, and A. S. Sadykov, *Izvest. Akad. Nauk Turkm. S.S.R.*, *Ser. Fiz.-Tekh.*, *Khim.*, *Geol. Nauk.*, 1970, 111 (*Chem. Abs.*, 1971, **74**, 64 336*z*); B. Chommadov, M. K. Yusupov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1970, **6**, 275 (*Chem. Abs.*, 1970, **73**, 45 636*k*).
[183] T. Baytop and G. Ozcobek, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1970, **6**, 21 (*Chem. Abs.*, 1971, **74**, 1029*f*).
[184] S. Ya. Zolotnitskaya, I. S. Melkumyan, and G. O. Akopyan, *Biol. Zhur. Arm.*, 1969, **22**, 84 (*Chem. Abs.*, 1970, **73**, 32 276*t*).
[185] R. Dunwille, K. Balasubramaniam, and S. W. Bibile, *Ceylon J. Med. Sci.*, 1968, **17**, 1 (*Chem. Abs.*, 1970, **73**, 117 136*x*).
[186] S. Ishiwata, T. Fujii, N. Miyaji, Y. Satoh, and K. Itakura, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1850.
[187] T. Kametani, K. Fukumoto, and M. Fujihara, *Chem. Comm.*, 1971, 352.
[188] A. H. Jackson and G. W. Stewart, *Chem. Comm.*, 1971, 149.

(177)

(178)

(180)

(179)
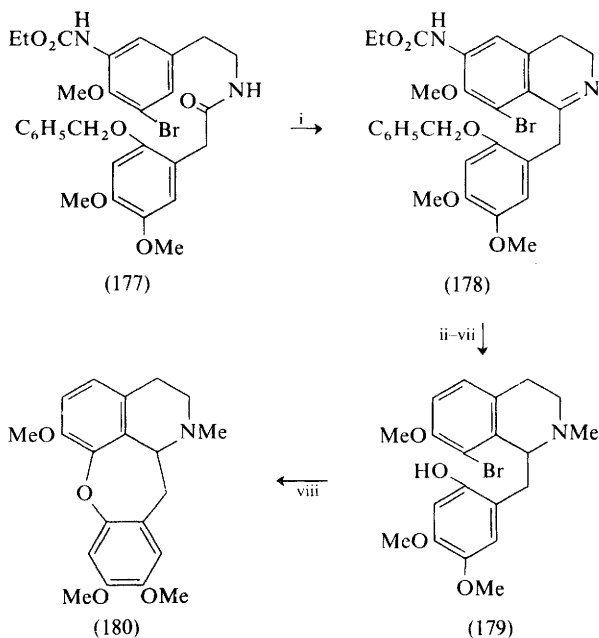
Reagents: i, POCl$_3$; ii, MeI; iii, NaBH$_4$; iv, KOH; v, HCl, NaNO$_2$; vi, H$_3$PO$_2$; vii, HCl; viii, CuO, pyridine, K$_2$CO$_3$, 160 °C.

Scheme 14

(181)

(182)

(183)
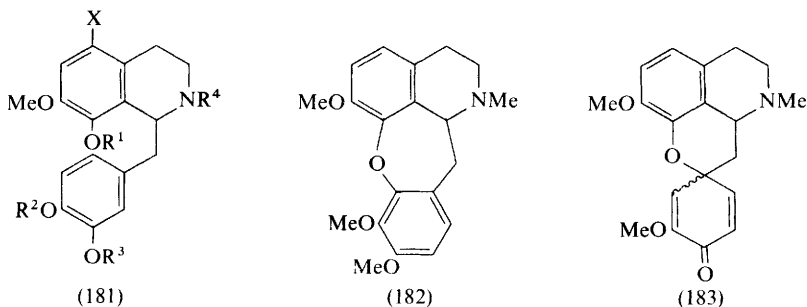
at the spiro centre. Interestingly, attempts to effect acid-catalysed rearrangement of (183) to cularine-type systems were not successful.

A synthesis of the required diphenol (181; R^1 = R^3 = X = H, R^2 = R^4 = Me) for phenolic oxidative coupling to cularine avoiding all blocking or activation operations has been developed (see Scheme 15).[188] The route involved the formation of the isoquinoline (186) *via* a variation [(184) → (185) → (186)] of the Pomeranz–Fritsch–Bobbitt method and its conversion into (181; R^1 = R^3 =
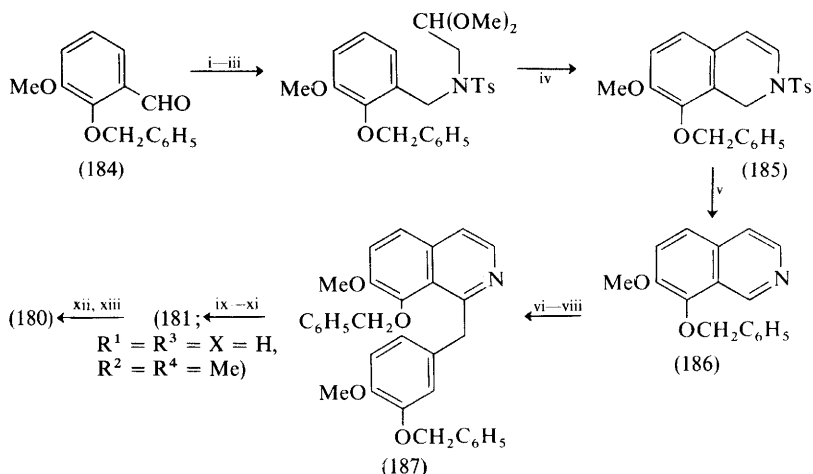
Reagents: i, $NH_2CH_2CH(OMe)_2$; ii, H_2, Pt; iii, TsCl, pyridine; iv, HCl, dioxan–H_2O; v, KOBu^t, Bu^{t}OH; vi, KCN, C_6H_5COCl; vii, NaH, DMF, 3-methoxy-4-benzyloxybenzyl chloride; viii, NaOH, EtOH, Δ; ix, MeI or MeSO$_3$F; x, NaBH$_4$; xi, HCl, EtOH; xii, $K_3Fe(CN)_6$, 8% NH_4OAc, CHCl$_3$; xiii, CH$_2N_2$.

Scheme 15
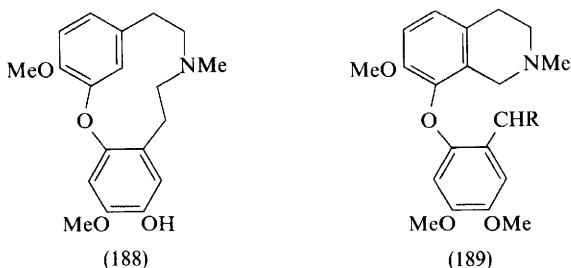
$X = H$, $R^2 = R^4 = Me$) by extension of the Reissert procedure [(186) → (187)] similar to the one used for the synthesis of some aporphine alkaloids (see Section 3C). An alternative biogenetic precursor (188) for cularine to the previously proposed diphenol (181; $R^1 = R^3 = H$, $R^2 = R^4 = Me$) was advanced.[188] An interesting attempt to prepare cularine by decomposition of the toluene-*p*-sulphonylhydrazone (189; $R = p$-Me·C_6H_4·SO$_2$NHN :) gave instead the insertion product [189; $R = (HO)Me$].[189]

G. Protoberberbine Alkaloids.—Alkaloids from *Fumaria officinalis* which were difficult to separate by partition chromatography and counter-current distribution were separated by the dependable method of column chromatography.[190]

[189] S. Ishiwata, T. Takada, and T. Nagasaka, *J. Pharm. Soc. Japan.*, 1970, **90**, 1461 (*Chem. Abs.*, 1971, **74**, 54 052q).

[190] W. Golkiewicz and T. Wawrzynowicz, *Chromatographia*, 1970, **3**, 356.

The appearance of a $M - 14$ peak rather than the expected molecular ion in the mass spectrum of berberine (190) has been shown to be due to its thermal disproportionation into dihydroberberine (191) and oxyberberine (192).[21]
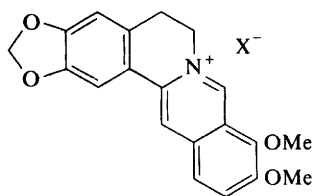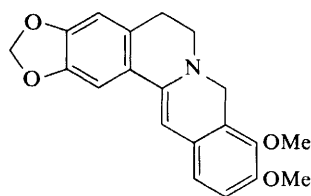
(190)   (191)
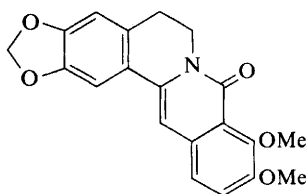
(192)

A considerable number of new plant species have been found to contain protoberberine alkaloids (Table 4). For the most part, however, little new structural variation has been encountered. The isolation of columbamine (194; $R^1 = R^4 = R^5 = Me$, $R^2 = R^3 = H$) from *Coptis quinquefolia* marked the first time that this alkaloid has been found in the *Coptis* genus.[95] Caseanadine (198; $R = H$), isolated from *Corydalis caseana*, has a ring-A substitution pattern not previously found in this group of alkaloids.[197] Its structure was deduced mainly on the basis of its n.m.r. spectrum and that of its O-acetyl derivative (198; $R = Ac$). Comparison of the n.m.r. spectra showed that two aromatic protons in (198; $R = Ac$) had shifted downfield relative to those in (198; $R = H$), indicating that they must be part of the ring carrying the O-acetyl function. From the spectra, it was clear that the lowest-field proton of (198; $R = Ac$) was the highest-field proton of (198; $R = H$) and the magnitude of the shift was in agreement with that generally observed for a proton *para* to a phenolic group which has been acetylated. The broadness of both the high-field signal of (198; $R = H$) and the low-field signal of (198; $R = Ac$) in comparison to the protons to which they were coupled suggested that the former were coupled to *ortho*-benzylic protons and led to the formulation (198; $R = H$) for caseanadine. This formulation was supported by double irradiation experiments which also eliminated from consideration the alternative, biogenetically less likely, structure which bears a 3-methoxy-4-hydroxy substitution pattern. The absolute configuration as written was suggested by the large negative optical rotation of the alkaloid.

Table 4 *Isolation of protoberberine alkaloids*

Plant species or source	Alkaloid (Structure)	Ref.
Arcangelisia loureirii	Berberine (190)	
	Jatrorrhizine (193; $R^1 = H$, $R^2 = R^3 = R^4 = Me$)	191
	Palmatine (193; $R^1 = R^2 = R^3 = R^4 = Me$)	
Berberis petiolaris	Berberine	
	Palmatine	192
B. vulgaris	(Berberine, Jatrorrhizine, Columbamine,	94, 193,
	Palmatine)*	194
Bocconia microcarpa	(Berberine, Coptisine)*	195
Coptis groenlandica	Berberine*	
	Coptisine (methoxy-hydroxy-derivative ?)	196
	Isocoptisine (196)	
C. japonica	(Berberine, Coptisine, Jatrorrhizine)*	95
C. quinquefolia	(Berberine, Coptisine, Jatrorrhizine)*	
	Columbamine (194; $R^1 = R^4 = R^5 = Me$,	95
	$R^2 = R^3 = H$)	
C. teeta	(Berberine, Coptisine, Jatrorrhizine)*	95
Corydalis caseana	Caseanadine (198; $R = H$)	197
C. pallida	Cycemanine (= kikemanine ?)	
	(194; $R^1 = R^2 = R^4 = Me$, $R^3 = R^5 = H$)	140
C. pallida var. *tenuis*	Capaurine (194; $R^1 = R^2 = R^4 = R^5 = Me$,	
	$R^3 = OH$)	
	Capauridine	
	Capaurimine (194; $R^1 = R^2 = R^4 = Me$,	
	$R^3 = OH$, $R^5 = H$)	
	Coptisine (193; $R^1 + R^2 = R^3 + R^4 = CH_2$)	
	Corydaline (195; $R^1 = R^2 = Me$, $R^3 = H$,	
	$R^4 = R^5 = OMe$)	97, 198,
	Corysamine (197; $R^1 + R^2 = CH_2$,	199, 200
	$R^3 + R^4 = OCH_2O$, $R^5 = H$)	
	Dehydrocorydaline (197; $R^1 = R^2 = Me$,	
	$R^3 = H$, $R^4 = R^5 = OMe$)	
	Kikemanine (*l*-Corydalmine) (194;	
	$R^1 = R^2 = R^4 = Me$, $R^3 = R^5 = H$)	
	l-Scoulerine (194; $R^1 = R^5 = Me$,	
	$R^2 = R^3 = R^4 = H$)	

[191] L. M. Garcia, K. Jewers, A. H. Manchanda, H. Ashok, P. Martinod, J. Nabney, and F. V. Robinson, *Phytochemistry*, 1970, **9**, 663.

[192] G. A. Miana and M. Ikram, *Pakistan J. Sci. Ind. Res.*, 1970, **13**, 49 (*Chem. Abs.*, 1970, **73**, 117 192*n*).

[193] L. P. Naidovich, B. K. Rostotskii, and P. N. Kibal'chich, *Farmatsiya* (*Moscow*), 1970, **19**, 47 (*Chem. Abs.*, 1971, **74**, 1009*z*).

[194] P. Petcu and T. Goina, *Planta Med.*, 1970, **18**, 372.

[195] H. Grabarczyk and H. Gertig, *Ann. Pharm.* (*Poznan*), 1970, **8**, 75 (*Chem. Abs.*, 1971, **74**, 95 419*h*).

[196] S. F. Cooper, J. A. Mockle, and J. Beliveau, *Planta Med.*, 1971, **19**, 23.

[197] C. K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Canad. J. Chem.*, 1971, **49**, 124.

[198] H. Kaneko and S. Naruto, *J. Pharm. Soc. Japan*, 1971, **91**, 101 (*Chem. Abs.*, 1971, **74**, 142 108*t*).

[199] T. Kametani, M. Ihara, and T. Honda, *J. Chem. Soc.* (*C*), 1970, 2342.

[200] T. Kametani, M. Ihara, Y. Kitahara, C. Kabuto, H. Shimanouchi, and Y. Sasada, *Chem. Comm.*, 1970, 1241.

Table 4 (continued)

Plant species or source	Alkaloid (Structure)	Ref.
C. pallida var. *tenuis* (continued)	*d*-Tetrahydrocorysamine (195; $R^1 + R^2 = CH_2$, $R^3 + R^4 = OCH_2O$, $R^5 = H$) *l*-Tetrahydropalmatine (194; $R^1 = R^2 = R^4 = R^5 = Me$, $R^3 = H$)	97, 198, 199, 200
C. platycarpa	*l*-Capaurine Cheilanthifoline (194; $R^1 = Me$, $R^2 = R^3 = H$, $R^4 + R^5 = CH_2$) *d*-Corybulbine* (195; $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = R^5 = OMe$) Corystamine† Dehydrocorybulbine† (197; $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = R^5 = OMe$) Jatrorrhizine† Palmatine†	201, 202
C. pseudoadunca	Coramine (Corexomine ?)¶ *l*-Skularine (Scoulerine ?) (194; $R^1 = R^5 = Me$, $R^2 = R^3 = R^4 = H$)	96
C. thalictrifolia	Cavidine (195; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 + R^5 = OCH_2O$)	203
C. tuberosa	Apocavidine (195; $R^1 = Me$, $R^2 = R^3 = H$, $R^4 + R^5 = OCH_2O$)	203
Coscinium wallichianum	Berberine Jatrorrhizine Palmatine	191
Eschscholtzia californica	(Californidine, Esholine)* α-Canadine methohydroxide (194; $R^1 + R^2 = CH_2$, $R^3 = H$, $R^4 = R^5 = Me$, NMe) Escholidine (194; $R^1 + R^2 = CH_2$, $R^3 = R^5 = H$, $R^4 = Me$, NMe)	204
E. douglasii, *E. glauca*	Californidine α-Canadine methohydroxide Escholidine Esholine‡	204
Kirghiz opium	*l*-Canadine	70
Mahonia aquifolium	Berberine *d,l*-Canadine (194; $R^1 + R^2 = CH_2$, $R^3 = H$, $R^4 = R^5 = Me$) *d,l*-Corypalmine (194; $R^1 = R^3 = H$, $R^2 = R^4 = R^5 = Me$)	193, 205
Papaver atlanticum	Coptisine*	69
P. bracteatum	Coptisine Mecambridine (199; $R^1 = CH_2OH$, $R^2 = OMe$) Orientalidine (199; $R^1 + R^2 = CH_2OCH_2O$)	69

[201] C. Tani, I. Imanishi, and J. Nishijo, *J. Pharm. Soc. Japan*, 1970, **90**, 1028 (*Chem. Abs.*, 1971, **74**, 20 389q).
[202] C. Tani, I. Imanishi, and J. Nishijo, *J. Pharm. Soc. Japan*, 1970, **90**, 407 (*Chem. Abs.*, 1970, **73**, 25 719m).
[203] C. K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Canad. J. Chem.*, 1970, **48**, 3673.
[204] J. Slavik, L. Dolejs, and P. Sedmera, *Coll. Czech. Chem. Comm.*, 1970 **35**, 2597.
[205] L. P. Naidovich, D. A. Fesenko, and B. K. Rostotskii, *Khim. prirod. Soedinenii*, 1970, **6**, 775 (*Chem. Abs.*, 1971, **74**, 95 418g).

Table 4 (continued)

P. fugax	Palmatine	
P. pilosum	Coptisine*	
P. rhoeas var. flore pleno	Coptisine	69
	Stylopine (HCl salt) (194; $R^1 + R^2 = R^4 + R^5 = CH_2, R^3 = H$)	
P. triniaefolium	Coptisine*	
Thalictrum fendleri	Tetrahydrothalifendine (194; $R^1 + R^2 = CH_2$, $R^3 = R^5 = H, R^4 = Me$)	30

* See footnote (*), Table 1.

† The structure is inferred on the basis of the isolation of a tetrahydro-derivative by sodium borohydride reduction of the crude quaternary alkaloid mixture.

‡ Absent in *E. glauca*.

¶ *Cf.* F. Santavy in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1970, Vol. XII, pp. 384, 424.

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(201)
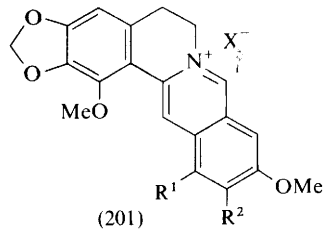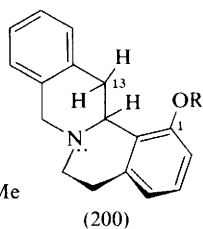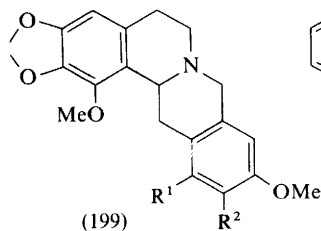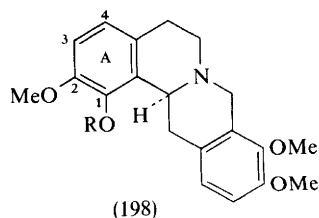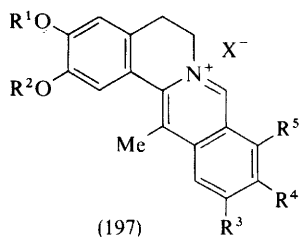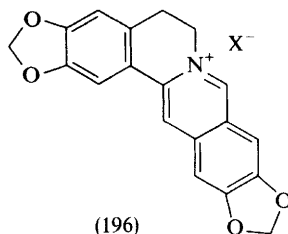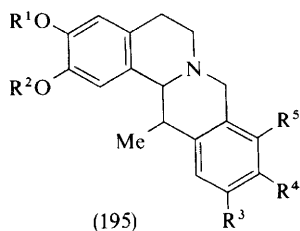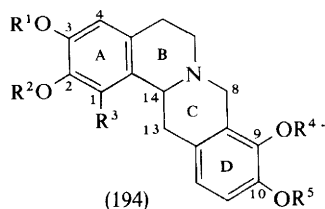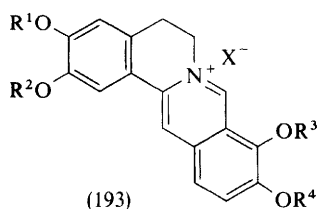
On the basis of its mass spectrum, kikemanine could be assigned structure (194; $R^1 = R^2 = R^4 = Me$, $R^3 = R^5 = H$) or (194; $R^1 = R^2 = R^5 = Me$, $R^3 = R^4 = H$).[97] The latter was synthesized and shown to be different from the isolated alkaloid.

In 1942, Manske assigned structure (194; $R^1 = R^2 = R^5 = Me$, $R^3 = OH$, $R^4 = H$) to capaurimine isolated from *Corydalis pallida* and *C. montana*. Recent spectral, degradative, and *X*-ray crystallographic evidence forcefully established that capaurimine must be assigned the isomeric structure (194; $R^1 = R^2 = R^4 = Me$, $R^3 = OH$, $R^5 = H$).[199,200] Both mass and n.m.r. spectral data of capaurimine and deuteriated capaurimine (in which protons *ortho* and *para* to the phenolic hydroxy-functions had been exchanged) led to inconclusive results and i.r. spectral information was based on an empirical correlation and could only be used for a tentative assignment of the $C(1)$-OH.[199] However, repetition of the potassium permanganate oxidation of *OO*-diethylcapaurimine showed that one of the products was 3-methoxy-4-ethoxyphthalic acid and not 3-ethoxy-4-methoxyphthalic acid as originally assigned. Final confirmation of structure (194; $R^1 = R^2 = R^4 = Me$, $R^3 = OH$, $R^5 = H$) for capaurimine was obtained by *X*-ray crystallographic analysis of the $C(10)$-*p*-bromobenzoate derivative.[200] A study of the i.r. spectra of a series of protoberberine alkaloids led to the generalization that the appearance of Bohlmann bands may be taken as an indication of a $C(1)$-OH *cis*-quinolizidine-type conformation (200).[199]

The structural assignments of the two new 13-methyltetrahydroprotoberberine alkaloids, cavidine (195; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 + R^5 = OCH_2O$) and apocavidine (195; $R^1 = Me$, $R^2 = R^3 = H$, $R^4 + R^5 = OCH_2O$), were based mainly on spectroscopic evidence.[203] Cavidine may be identical to 'Base II', a previously described synthetic compound, and its relationship to apocavidine was confirmed by conversion of the latter into the former. Double-irradiation experiments and nuclear Overhauser effect (n.o.e) studies permitted the assignment of the position of the hydroxy-group in apocavidine. Examination of the n.m.r. spectra of a series of 13-methyltetrahydroprotoberberine alkaloids of known structure and stereochemistry showed that this spectroscopic technique may be used to assign the relative stereochemistry of these compounds and thus serve as a complement to i.r. spectral and conformational studies. All compounds with hydrogens at $C(13)$ and $C(14)$ *cis* to one another exhibit spectra in which the protons at $C(8)$ appear as an AB quartet ($J = 16$ Hz) with a large chemical shift difference (0.6—0.7 p.p.m.) while those with hydrogens at $C(13)$ and $C(14)$ *trans* to one another show a chemical shift difference between them which is much smaller (0.1—0.2 p.p.m.).[203] A similar n.m.r. study on two 13-methylprotoberberine alkaloids, one of which was examined in the above work, has been reported.[206]

The definitive chemical investigation of the *Papaver* genus also has broad chemotaxonomic significance.[69]

[206] T. R. Govindachari, K. Nagarajan, R. Charubala, B. R. Pai, and P. S. Subramanian, *Indian J. Chem.*, 1970, **8**, 769.

The structure of tetrahydrothalifendine (194; $R^1 + R^2 = CH_2$, $R^3 = R^5 = H$, $R^4 = Me$), from *Thalictrum fendleri*, was elucidated by spectral interpretation and chemical correlation with thalifendine (193; $R^1 + R^2 = CH_2$, $R^3 = Me$, $R^4 = H$) which had been isolated from the same plant species.[30] It appears that the isolation of a quaternary protoberberine alkaloid from a particular plant forecasts the discovery of the corresponding tetrahydro-alkaloid therein.

A full report on the isolation and structural elucidation of the unusual proto-berberine alkaloids PO-4 (201; $R^1 + R^2 = CH_2OCH_2O$), PO-5 (alborine) (201; $R^1 = CH_2OH$, $R^2 = OMe$), orientalidine (199; $R^1 + R^2 = CH_2OCH_2O$), and mecambridine (199; $R^1 = CH_2OH$, $R^2 = OMe$) has appeared.[207]

Berbericine iodide has been identified as palmatine iodide on the basis of spectral data.[208] The localization of berberine (190) in various segments of plant tissue of four Papaveraceae species has been studied.[72]

Total syntheses of ($\pm$)-capaurine (194; $R^1 = R^2 = R^4 = R^5 = Me$, $R^3 = OH$),[209] ($\pm$)-isocorybulbine (195; $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = R^5 = OMe$),[202] ($\pm$)-kikemanine (194; $R^1 = R^2 = R^4 = Me$, $R^3 = R^5 = H$),[210] and ($\pm$)-*O*-methylcaseadine (202)[211] have been reported. In all cases, conventional routes involving Bischler–Napieralski cyclization to form benzylisoquinoline deriva-tives and subsequent insertion of the C(8)-carbon by reaction with formaldehyde were adopted. A further example of *para*-activation by an ethoxycarbonyl-amino-function for the Bischler–Napieralski reaction may be noted.[211] In the synthesis of capaurine, the presence of the bromo-function in compound (203) forced the Mannich reaction with formaldehyde to produce the tetracyclic derivative (204) rather than the normally more favourable mode of cyclization *para* to the hydroxy-group. Debromination was effected at a later stage with zinc powder in 50 % acetic acid solution.[209]

A number of papers not related directly to the synthesis of specific alkaloids have appeared. An approach to 9,10-disubstituted and 9,10,11-trisubstituted tetrahydroprotoberberines *via* the aminobenzylisoquinoline (205) has been developed.[212] Treatment of (205) with formaldehyde gave the two isomeric tetracyclic systems (206; $R^1 = NH_2$, $R^2 = OMe$ and $R^1 = OMe$, $R^2 = NH_2$) either of which could be further transformed to deaminated or hydroxy-dimethoxy derivatives. For example, diazotization of (206; $R^1 = NH_2$, $R^2 = OMe$) followed by hypophosphorous acid deamination gave (206; $R^1 = H$, $R^2 = OMe$); on the other hand, treatment of the diazotized solution with copper sulphate gave (206; $R^1 = OH$, $R^2 = OMe$) albeit in only 3—7 % yield. A short four-step synthesis [(207) → (210)] of the berberine skeleton has been developed.[213]

[207] V. Simanek, V. Preininger, P. Sedmera, and F. Santavy, *Coll. Czech. Chem. Comm.*, 1970, **35**, 1440.
[208] G. A. Miana, M. Ikram, and J. Holubek, *Pakistan J. Sci. Ind. Res.*, 1970, **12**, 309 (*Chem. Abs.*, 1970, **73**, 15 057e).
[209] T. Kametani, H. Iida, T. Kikuchi, T. Honda, and M. Ihara, *J. Heterocyclic Chem.*, 1970, **7**, 491.
[210] T. Kametani, T. Honda, and M. Ihara, *Chem. Comm.*, 1970, 1253.
[211] S. Ishiwata and K. Itakura, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1846.
[212] S. Ishiwata and K. Itakura, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 896.
[213] W. Meise and F. Zymalkowski, *Arch. Pharm.*, 1971, **304**, 182, 175.

Condensation of 3,4-dimethoxy-β-phenethylamine with isochroman-3-one gave the amide (207) which under Bischler–Napieralski reaction conditions yielded (208). Basic treatment of (208) led to cyclization and aromatization of the heterocyclic ring to give (209) which was readily reduced to (210). Further work on this sequence led to the isolation of several side-products. It was found that these could be avoided by treatment of (208) with sodium borohydride, which led directly to the final product (210) in high yield.[213]

(202)

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(210)
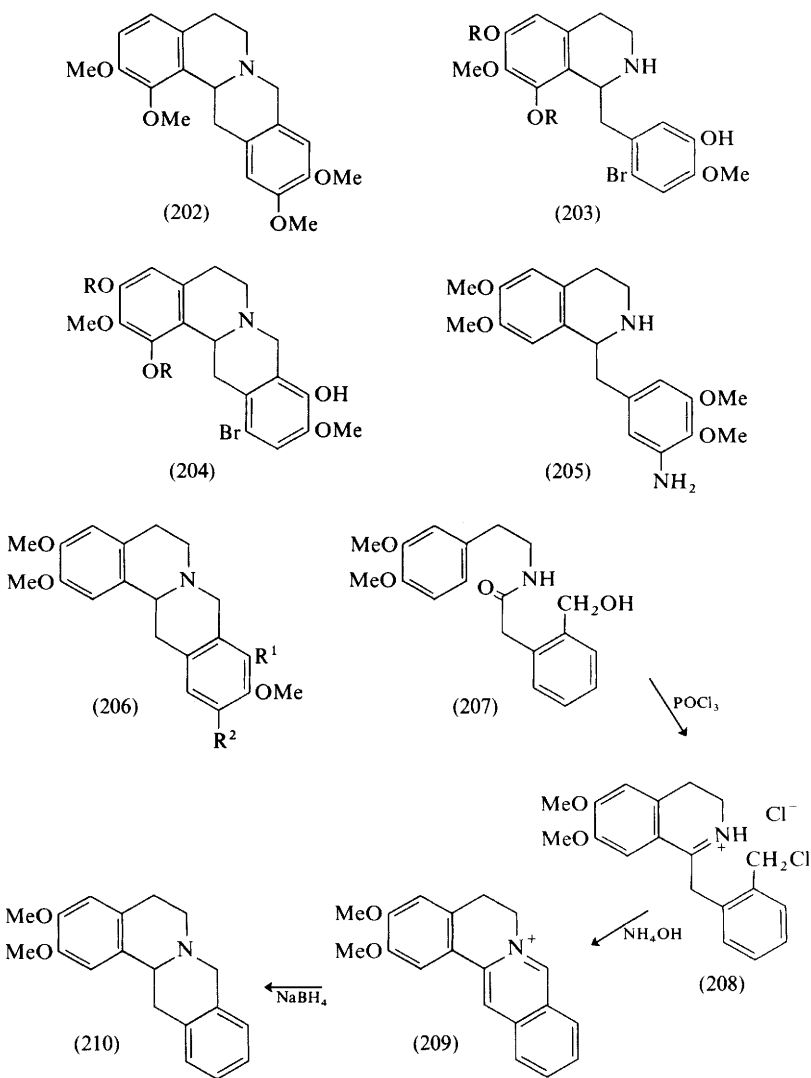
In view of the rapid advances in synthetic organic methodology and in bio-synthesis of alkaloids, it may be envisaged that complicated structures will be purposefully synthesized *prior* to their isolation from plant sources. Such an example has been reported recently. The synthesis of the homoprotoberberine skeleton (213) has been achieved by three different routes.[214] The most highly functionalized derivative was obtained by the sequence (211) → (212) → (213), the starting material (211) being prepared by condensation of 3,4-dimethoxy-*β*-phenethylamine with the acid chloride of phthalide-3-acetic acid. Two diastereo-isomeric lactam alcohols of structure (213) were formed and each could be reduced individually with lithium aluminium hydride to the homoprotoberberine alcohols (214) and (215) respectively. That these compounds possessed conformations and configurations as written was based on the following evidence: (i) the rates of methiodide formation for both compounds were fast and comparable to the quaternization rate of *cis*-B/C-fused protoberberines; (ii) both compounds lacked Bohlmann bands in their i.r. spectra; and (iii) in the n.m.r. spectra, the C(8)-equatorial hydrogen of (215) was more deshielded than the corresponding hydrogen in (214).

(211)   (212)   (213)

(i) H$_2$, PtO$_2$ then
(ii) KOH, MeOH
or NaBH$_4$

(214)   (215)   (216)
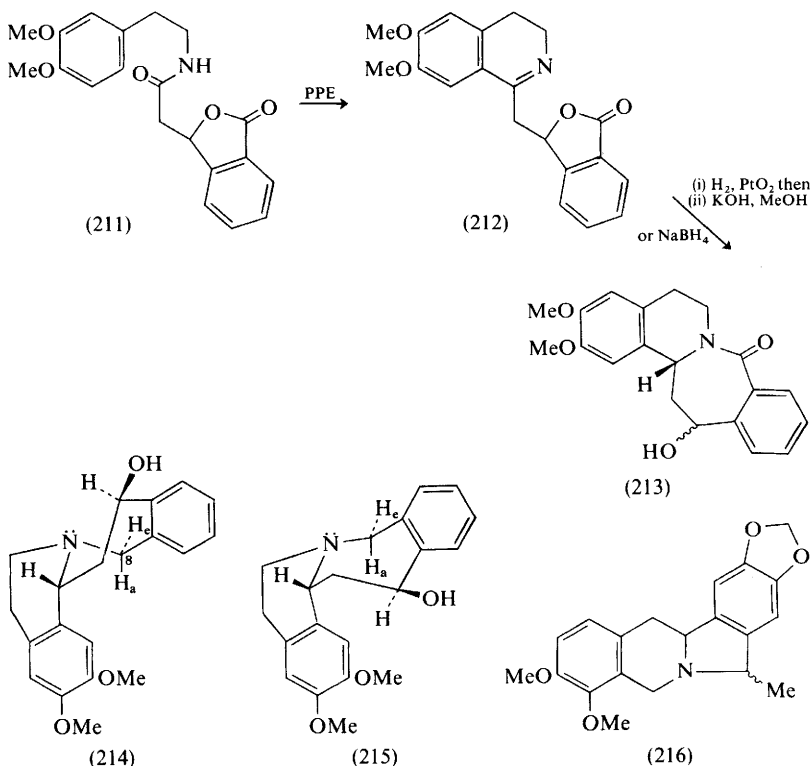
[214] M. Shamma and M. J. Hillman. *Tetrahedron*, 1971, **27**, 1363.

The thermal decomposition of tetrahydroberberine methine base hydrochloride has been shown to yield an epimeric mixture of the rearranged product (216).[215] An interesting transformation of a protoberberine into a benzophenanthridine alkaloid is discussed in Section 3J. Other work dealing with the synthesis of proto-berberine-type structures has been reported.[216—218] A procedure for the preparation of radioiodinated (^{131}I) berberine has appeared.[219]

An important rule concerning the determination of the absolute configuration of tetrahydroberberine alkaloids has been formulated.[220] Empirical correlations of o.r.d. and c.d. data observed for alkaloids and for simple model systems in the past have led fortuitously to the assignment of the correct known absolute configuration. Now a rule has been proposed which takes into account the chirality of the second sphere (the non-aromatic ring condensed to the benzene ring) and a sector rule for the third (fourth...) sphere contributions. It is believed that this rule, using six upper and six lower sectors, is more appropriate for the benzene chromophore than the quadrant rule previously proposed for correlation of the c.d. curves with the stereochemistry of Amaryllidaceae alkaloids. The application of the sector rule requires knowledge of the conformation of the second sphere. On the basis of this rule, the absolute stereochemistries of the protoberberine alkaloids mecambridine and orientalidine were determined.

H. Protopine Alkaloids.—Alkaloids of *Fumaria officinalis* which were difficult to separate by partition chromatography and counter-current distribution were separated by column chromatography.[190]

(217)   (218)

(219)
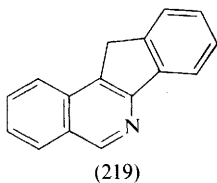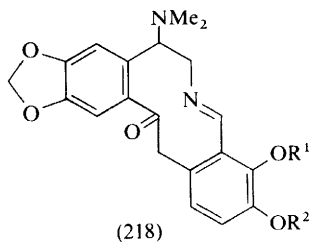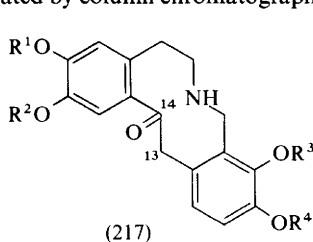
[215] C. Tani, S. Takao, and M. Sugiura, *J. Pharm. Soc. Japan*, 1970, **90**, 1012 (*Chem. Abs.*, 1970, **73**, 109 941r).
[216] W. Wiegrebe, D. Sasse, H. Reinhart, and L. Faber, *Z. Naturforsch.*, 1970, **25b**, 1408.
[217] T. R. Govindachari, K. Nagarajan, R. Charubala, and B. R. Pai, *Indian J. Chem.*, 1970, **8**, 766.
[218] T. R. Govindachari, K. Nagarajan, R. Charubala, and B. R. Pai, *Indian J. Chem.*, 1970, **8**, 763.
[219] R. S. Mani and O. P. D. Noronha, *Radiochem. Radioanalyt. Letters*, 1970, **5**, 119.
[220] G. Snatzke, J. Hrbek, jun., L. Hruben, A. Horeau, and F. Santavy, *Tetrahedron*, 1970, **26**, 5013.

Table 5 summarizes results of protopine alkaloid isolation studies. The structures assigned to the two alkaloids isolated from both *Fumaria parviflora* and *F. vaillantii* are of immediate interest and concern.[221] The detailed study of the *Papaver* genus is of general chemotaxonomic interest.[69]

Table 5 *Isolation of protopine alkaloids*

Plant species or source	Alkaloid (Structure)	Ref.
Corydalis pallida var. *tenuis*	Protopine (217; $R^1 + R^2 = R^3 + R^4 = CH_2$)	97, 198
C. platycarpa	Protopine*	201
C. pseudoadunca	Protopine*	96
Eschscholtzia californica	(Allocryptopine, Protopine)*	89a
Fumaria parviflora, *F. vaillantii*	Fumaramine (218; $R^1 + R^2 = CH_2$) Fumaridine (218; $R^1 = R^2 = Me$)	} 221
Glaucium corniculatum	Protopine* α-Allocryptonine	} 102
Kirghiz opium	Cryptopine (217; $R^1 = R^2 = Me$, $R^3 + R^4 = CH_2$) Protopine	} 70
Opium	Salutaridine (217; $R^1 = R^2 = Me$, $R^3 + R^4 = CH_2$; 13-oxo)	222
Papaver atlanticum	Muramine (217; $R^1 = R^2 = R^3 = R^4 = Me$) 13-Oxocryptopine (Salutaridine) Protopine* (and HCl salt)	} 69
P. bracteatum	Protopine Salutaridine*	} 69
P. californicum	Muramine	223
P. fugax	Protopine	69
P. monanthum	Protopine HCl salt*	69
P. triniaefolium	Protopine*	69
Thalictrum simplex	β-Allocryptopine* (Thalictrimine) (217; $R^1 + R^2 = CH_2$, $R^3 = R^4 = Me$; NMe for NH) Thalictricine (217; $R^1 + R^2 = CH_2$, $R^3 = Me$, $R^4 = H$; NMe for NH)	} 108

* See footnote (*), Table 1.

The synthesis of the parent ring-system of the protopine alkaloids using Perkin's method has been described.[224] The preparation of examples of the indeno[1,2-c]isoquinoline ring system (219), exhibited by a rearrangement product of cryptopine, has been described.[225] The transformation of protopine to benzophenanthridine alkaloids will be described in Section 3J.

[221] I. A. Israilov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 588 (*Chem. Abs.*, 1971, **74**, 42 528*m*).

[222] E. Brochmann-Hanssen, A. Y. Leung, Z. Kentaro, and G. Zanati, *Planta Med.*, 1970, **18**, 366.

[223] A. Nemeckova, F. Santavy, and D. Walterova, *Coll. Czech. Chem. Comm.*, 1970, **35**, 1733.

[224] V. Deulofeu, A. L. Margni, and D. Giacopello, *J. Chem. Soc. (C)*, 1970, 2578.

[225] S. F. Dyke, M. Sainsbury, D. W. Brown, M. N. Palfreyman, and D. W. Wiggins, *Tetrahedron*, 1971, **27**, 281.

I. Phthalideisoquinoline and Rhoeadine Alkaloids.—Spectrophotometric,[55,57] precipitation,[63] and thin-layer chromatographic (with isobaric solvent systems)[61] methods have been reported for the determination of narcotine.

The following plant species have been examined: *Corydalis gortschakovii*, which has been shown to contain *l*-adlumine (220; $R^1 = R^2 = Me$, $R^3 + R^4 = CH_2$; 1S, 9S) and *d*-bicuculline (220; $R^1 + R^2 = R^3 + R^4 = CH_2$; 1S, 9R);[96] *C. pseudoadunca*, which yielded *l*-adlumidine (220; $R^1 + R^2 = R^3 + R^4 = CH_2$), bicuculline, and hydrastine (220; $R^1 + R^2 = CH_2$, $R^3 = R^4 = Me$);[96] and Khirghiz opium has been examined, from which narcotine (220; $R^1 + R^2 = CH_2$, $R^3 = R^4 = Me$) and porphyroxine (papaverrubine D, 221; $R^1 = R^3 = H$, $R^2 = R^4 = Me$) have been isolated.[76] Continuations of detailed investigations and reinvestigations of alkaloids from the *Papaver* genus have been reported by the Czech school.[69,223] Papaverrubines B (221; $R^1 = H$, $R^2 = R^3 = R^4 = Me$), D (221; $R^1 = R^3 = H$, $R^2 = R^4 = Me$), and E (223; $R^1 = H$, $R^2 + R^3 = CH_2$, $R^4 = Me$) have been detected in *Papaver bracteatum*, *P. fugax*, and *P. triniae-folium*; papaverrubine A has been isolated from *P. rhoeas* var. *flore pleno*.[69] Re-examination of Papaveraceae species in the Section Orthorhoeades yielded the following alkaloids: *P. rhoeas* [isorhoeagenine (222; $R^1 = Me$, $R^2 + R^3 = CH_2$, $R^4 = H$), papaverrubine C (222; $R^1 = R^3 = H$, $R^2 = R^4 = Me$), papaverrubine F (only by t.l.c.) (223; $R^1 = H$, $R^2 = R^3 = R^4 = Me$), and the new alkaloids *N*-demethylisorhoeadine (alkaloid R-S, 221; $R^1 = H$, $R^2 + R^3 = CH_2$, $R^4 = Me$) and isorhoeagenine α-glucoside (alkaloid R-C, 222; $R^1 = Me$, $R^2 + R^3 = CH_2$, $R^4 = $ α-glucose)]; *P. commutatum* [isorhoeadine (221; $R^1 = R^4 = Me$, $R^2 + R^3 = CH_2$), isorhoeagenine, isorhoeagenine glucoside, and papaverrubines A, B, D, and E (by t.l.c. only)].[223] The rate of change of phthalide-isoquinoline alkaloid content with time in the germinating seedling of *P. somni-ferum* has been studied.[73]

(220)   (221)   (222)   (223)
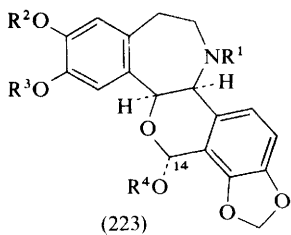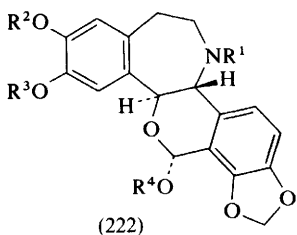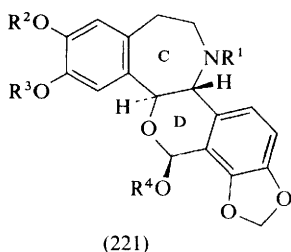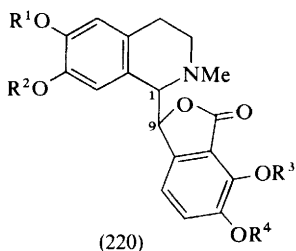
The first total synthesis of rhoeadine (223; $R^1 = R^4 = Me$, $R^2 + R^3 = CH_2$) has been reported.[226] Compound (224), available from previous studies dealing with the synthesis of spirobenzylisoquinoline alkaloids, was readily transformed (Scheme 16) into the urethane (225). Reduction of (225) gave only the diastereomer (226), as shown by lack of hydrogen-bonded OH in its i.r. spectrum. Wagner–Meerwein rearrangement gave a mixture of amines (227) and (229) in a 1:1 ratio notwithstanding the expected much greater thermodynamic stability of (229). This result made it possible to execute the ring-opening sequence to rhoeagenine diol [(227) → (228)]. Since the latter had been previously converted into rhoeadine, the total synthesis had been formally completed.

(224)   (225)   (226)

(228)   (227)
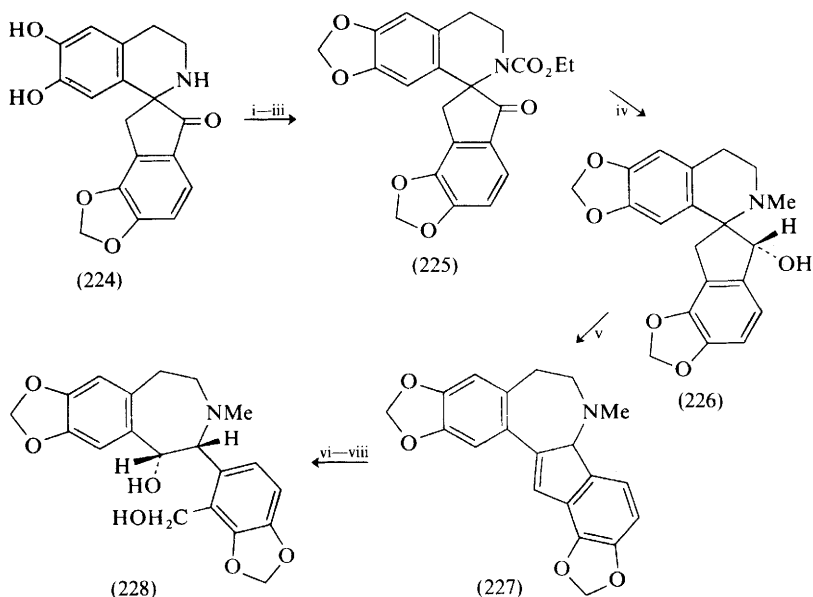
Reagents: i, $ClCO_2Et$, Et_3N; ii, OH^-; iii, CH_2I_2, K_2CO_3, DMSO; iv, $LiAlH_4$; v, $MeSO_2Cl$, Et_3N, THF; vi, OsO_4; vii, $NaIO_4$; viii, $NaBH_4$.

Scheme 16

(229)
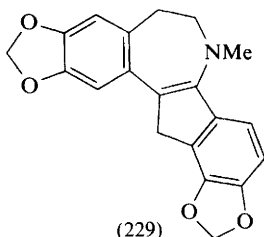
[226] H. Irie, S. Tani, and H. Yamane, *Chem. Comm.*, 1970, 1713.

Rhoeagenine diol (228) has also served to confirm the structure of the alkaloid 14-demethoxyrhoeadine (230).[227] Treatment of (228) with 2M-HCl for 2 hours on the steam bath gave a quantitative yield of (230). Further evidence for structure (230) was obtained by exhaustive Hofmann methylation and spectroscopic studies. On the basis of comparison of optical rotations for rhoeadine (223; $R^1 = R^4 = Me$, $R^2 + R^3 = CH_2$) and 14-demethoxyrhoeadine (230), the contribution of the optically active centre at C(14) in the former was determined to be $[\alpha]_D^{22} +396°$ (chloroform).[227]

It is pertinent to note that a convenient Hofmann degradation in the rhoeadine alkaloid series which may be useful in biosynthetic studies was effected by Ronsch.[228] Alpinigenine (231) was treated with hydroxylamine in pyridine solution to yield the oxime (232; $R^1 = H$, $R^2 = CH=NOH$) which with acetic anhydride at reflux gave the nitrile (232; $R^1 = Ac$, $R^2 = CN$). Hofmann degradation of (232; $R^1 = Ac$, $R^2 = CN$) methiodide gave the phthalimide derivative (233) presumably *via* the mechanism (234). Oxidative cleavage (OsO_4, $NaIO_4$) of (233) furnished the two known compounds (235) and (236).

(230)

(231)

(232)

(233)

(234)

(235)

(236)
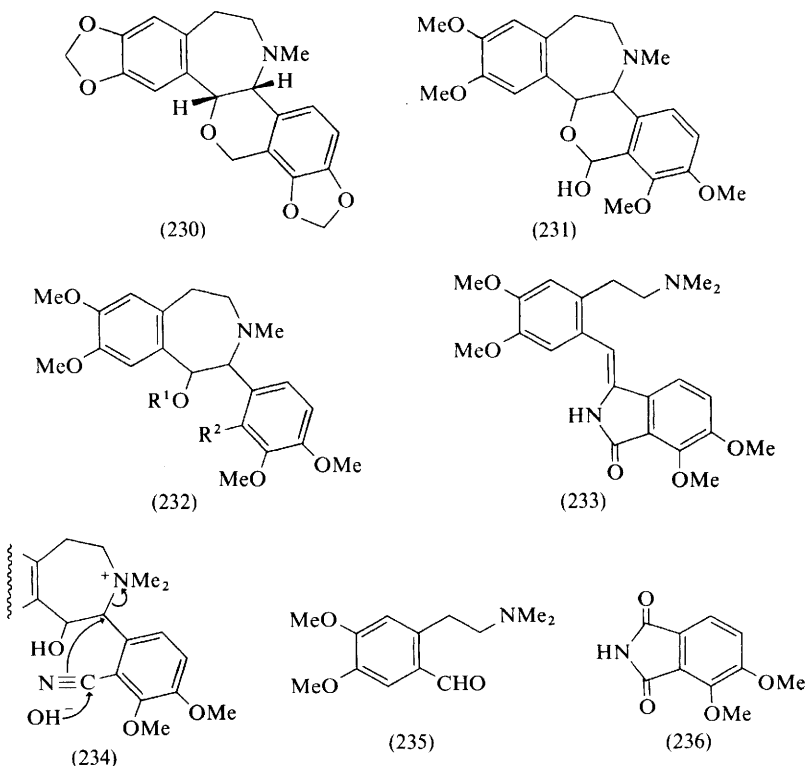
[227] J. Hrbek, jun., F. Santavy, and L. Dolejs, *Coll. Czech. Chem. Comm.*, 1970, **35**, 3712.
[228] H. Rönsch, *Tetrahedron Letters*, 1969, 5124.

The formation of $(\pm)$-β-hydroxyreticuline by treatment of $(\pm)$-reticuline with homogenized *Papaver rhoeas* and hydrogen peroxide may offer an initial clue to the biosynthesis of the rhoeadine alkaloids[79] (see also Section 3A).

Several derivatives of phthalideisoquinoline alkaloids have been prepared for pharmacological evaluation.[229]

J. Benzophenanthridine Alkaloids.—The lysosomal character of sanguinarine (237; $R^1 = H$, $R^2 + R^3 = OCH_2O$), added to the latex of *Chelidonium majus*, has been described.[230]

Table 6 summarizes the results of alkaloid isolation studies. The structure of the new alkaloid bocconine (239) from *Bocconia cordata* was deduced mainly on the basis of n.m.r. studies.[231] The C/D-ring substitution pattern was indicated by comparison of its n.m.r. spectrum with those of sanguinarine and chelerythrine. The downfield shift of the $C(11)$-H by 0.67 p.p.m. in 5,6-dihydrobocconine

Table 6 *Isolation of benzophenanthridine alkaloids*

Plant species	Alkaloid (Structure)	Ref.
Bocconia cordata	Bocconine (239)	231
B. microcarpa	Chelerythrine* (237; $R^1 = H$, $R^2 = R^3 = OMe$) Sanguinarine (237; $R^1 = H$, $R^2 + R^3 = OCH_2O$)	195
Corydalis incisa	Corynoloxine (242)	232, 233
C. pallida var. tenuis	Dihydrosanguinarine (237; $R^1 = H$, $R^2 + R^3 = OCH_2O$; 5,6-dihydro) Oxysanguinarine (238)	198
C. platycarpa	Sanguinarine	201
Fagara capensis	Chelerythrine Nitidine (237; $R^1 = R^2 = OMe$, $R^3 = H$)	234
F. macrophylla	Chelerythrine Nitidine	235, 236
Glaucium corniculatum	Sanguinarine*	102
Papaver bracteatum, P. dubium, P. gracile, P. pilosum, P. triniaefolium	Oxysanguinarine	69, 223
P. rhoeas L.	(Chelerythrine, Sanguinarine)*	223
Sanguinaria canadensis	Sanguinarine* $C_{43}H_{32}N_2O_9$	237

* See footnote (*), Table 1.

[229] P. Gorecki, *Ann. Pharm.* (*Poznan*), 1970, **8**, 35 (*Chem. Abs.*, 1971, **74**, 125 882*y*), *ibid.*, p. 43 (*Chem. Abs.*, 1971, **74**, 125 883*z*).

[230] P. Matile, B. Jans, and R. Rickenbacher, *Biochem. Physiol. Pflanz.*, 1970, **161**, 447 (*Chem. Abs.*, 1971, **74**, 72 773*e*).

[231] M. Onda, K. Abe, K. Yonezawa, N. Esumi, and T. Suzuki, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 1435.

[232] N. Takao, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 247.

[233] N. Takao, H. W. Bersch, and S. Takao, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 259.

[234] J. M. Calderwood, N. Finkelstein, and F. Fish, *Phytochemistry*, 1970, **9**, 675.

[235] F. Fish and P. G. Waterman, *J. Pharm. Pharmacol.*, 1971, **23**, 67.

[236] F. G. Torto and I. A. Mensah, *Phytochemistry*, 1970, **9**, 911.

[237] M. Tin-Wa, N. R. Farnsworth, H. H. Fong, and J. Trojanek, *Lloydia*, 1970, **33**, 267; M. Onda, K. Yonezawa, and K. Abe, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 31.

suggested the presence of a $C(10)$-oxygen substituent, and the relatively small dif-
ference in chemical shift (0.35 p.p.m.) of the ring-A proton between dihydro-
bocconine and 6-oxybocconine suggested oxygen functionalization at $C(7)$.
This information led to two possible structures (240) and (241) for dihydro-
bocconine, and conclusive evidence in favour of the former was obtained by
n.o.e. measurements. Irradiation of the methoxy-group signal (6.19 τ) in
dihydrobocconine gave a 47% increase in the 3.41 τ peak associated with the
ring-A aromatic proton. If structure (241) were correct, an n.o.e. between the
signal due to the methoxy-group and that of the $C(11)$-H would have been
expected. Thus, by inference, the structure (239) for the alkaloid bocconine was
established.

(237)   (238)   (239)   (240)   (241)   (242)
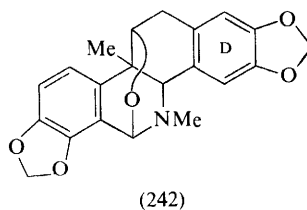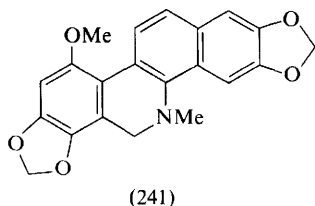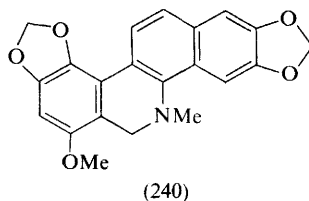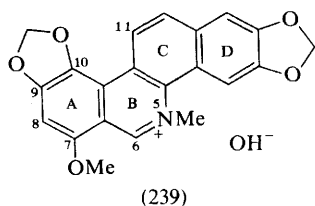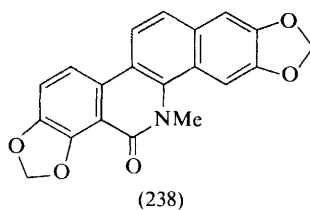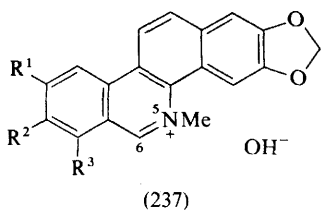
The structure of corynoloxine (242), from *Corydalis incisa*, is a further example
of the rare and interesting 13-methylbenzophenanthridine alkaloids.[232,233]
Emde degradation of corynoloxine methiodide gave both theoretically possible
products (243) and (244). Catalytic reduction of either base gave the same neutral
derivative (245).[232] Lithium aluminium hydride reduction of (242) gave coryno-
line (246), an alkaloid previously isolated from the same plant species. The same
tetracyclic compound (245) was obtained by a three-reaction sequence [quater-
nization with methyl iodide, Emde degradation to (247), and basic hydrolysis]

on corynoline (246).[233] That the acetoxy-function in (247) is in an axial orientation was suggested by its stability to basic hydrolysis. On the basis of this fact and the degradation sequences, the structure and configuration of corynoloxine as (248, ring D omitted) was advanced. Stereochemical assignments for (245) and other degradation products were not established.

(243)

(244)

(245)

(246)

(247)

(248)
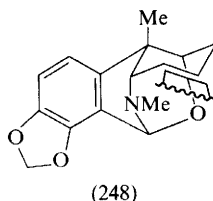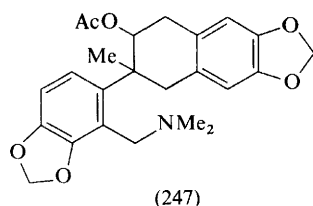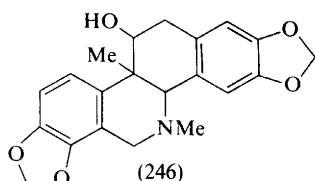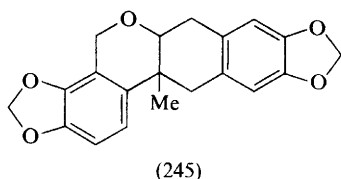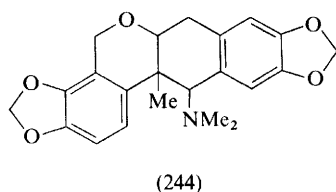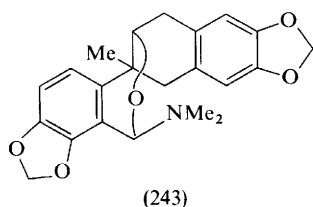
Details of a very interesting report concerning the transformation of protopine and protoberberine alkaloids into benzophenanthridine alkaloids have now appeared.[237] Previous attempts to effect acid-catalysed cyclization of (251), prepared in two steps from protopine alkaloids (249), to benzophenanthridine derivatives gave the spiro-alcohol (252) and its dehydration product. However, it was found (as shown in Scheme 17) that irradiation of (251; $R^1 + R^2 = OCH_2O$) gave (254; $R^1 + R^2 = OCH_2O$). Two consecutive dehydrogenation steps (Pd–C and DDQ) on (251; $R^1 + R^2 = OCH_2O$) and (251; $R^1 = R^2 = OMe$) led directly to the alkaloids sanguinarine (237; $R^1 = H, R^2 + R^3 = OCH_2O$) and chelerythrine (237; $R^1 = H, R^2 = R^3 = OMe$). The intermediate (251; $R^1 = R^2 = OMe$) required for the synthesis of chelerythrine could also be readily obtained from berberine chloride. The mechanism of the photocyclization

[238] M. Onda, K. Yonezawa, K. Abe, H. Toyama, and T. Suzuki, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 317.

[(251) → (254)] was shown by a trapping experiment[238] to proceed *via* the intermediate (255), formed by an electrocyclic reaction. When the irradiation was carried out in the presence of dimethyl acetylenedicarboxylate, the adduct (256) was obtained. A detailed analysis of the structure of this adduct by n.m.r. spectroscopic and n.o.e. measurements was carried out.[238]
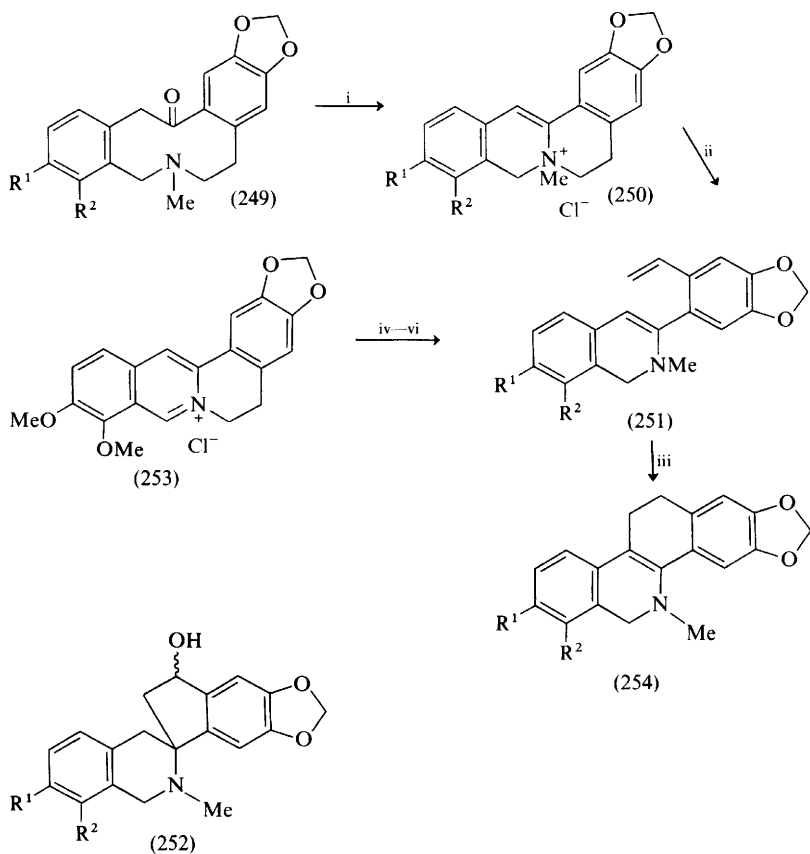
Reagents: i, PCl$_3$; ii, KOH, MeOH; iii, hv, C$_6$H$_6$, N$_2$; iv, NaBH$_4$; v, Me$_2$SO$_4$; vi, KOH, MeOH.

Scheme 17

A photocyclization which may involve a similar electrocyclic reaction and which may be useful for benzophenanthridine alkaloid synthesis has been described in preliminary form.[239] For example, irradiation of the enamide (257) gave an approximately 1:1 mixture of the octahydrophenanthridines (258; R^1 = H, R^2 + R^3 = OCH_2O) and (258; R^1 + R^2 = OCH_2O, R^3 = H). In this connection, an alternative synthesis of phenanthridines (260) by the reaction of diazonium salts (259) with sodium iodide in acetone may be noted.[240] A series of compounds, *e.g.* (261), temptingly related to benzophenanthridine alkaloids, have been synthesized.[241]

An important rule concerning the determination of the absolute configuration of benzophenanthridine alkaloids has been proposed.[220] (For a brief discussion of this rule, see Section 3G.) On the basis of this rule, the absolute configuration of chelidonine (262) has been determined.

(257)

(258)

(259)

(260)

(261)

(262)
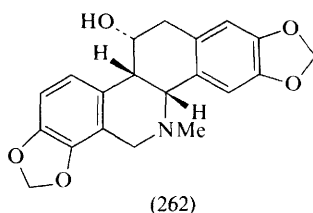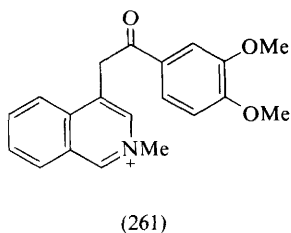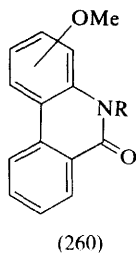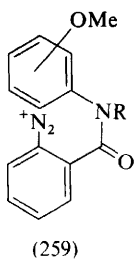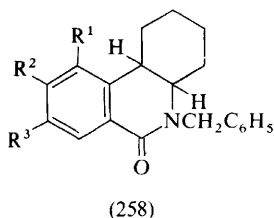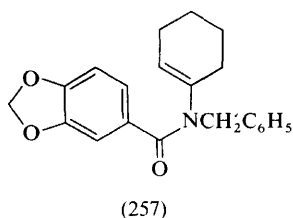
[239] I. Ninomiya, T. Naito, and T. Kiguchi, *Tetrahedron Letters*, 1970, 4451.

[240] D. H. Hey, G. H. Jones, and M. J. Perkins, *Chem. Comm.*, 1970, 1438.

[241] M. Sainsbury, D. W. Brown, S. F. Dyke, R. D. J. Clipperton, and W. R. Tonkyn, *Tetrahedron*, 1970, **26**, 2239.

K. Spirobenzylisoquinoline Alkaloids.—Since the report by McLean, Lin, and Manske in 1964 describing the structural elucidation of the first spirobenzyl-isoquinoline alkaloid, a number of alkaloids bearing this novel skeleton have been isolated. During the past year, the structures of the following new alkaloids have been elucidated: corpaine (263; $R^1 = Me$, $R^2 = H$, $R^3 = OH)^{242}$ and corydaine (263; $R^1 + R^2 = CH_2$, $R^3 = OH$ or stereoisomer at spiro junction)^{243} from *Corydalis paczoskii*; fumarophycine (264; $R^1 = Ac$, $R^2 = H$) from *Fumaria officinalis*;^{244} and parfumine (263; $R^1 = R^3 = H$, $R^2 = Me$) from *F. parvi-flora*.^{245} As in the elucidation of other alkaloids possessing this ring system, the structure and stereochemistry of fumarophycine rely heavily on the utiliza-tion of n.m.r. and n.o.e. measurements. Final structural confirmation was ob-tained by its correlation with fumaritine (264; $R^1 = R^2 = H$), whose structure had been previously established by synthesis.^{244}

(263)

(264)

(265)
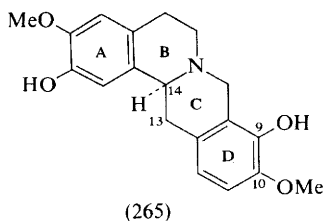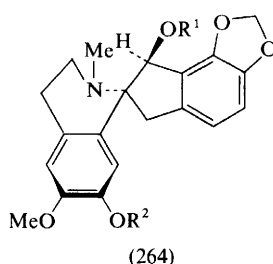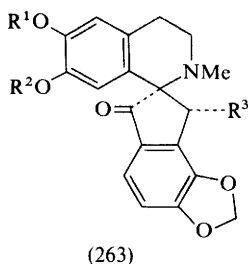
Two intriguing models for the biogenesis of spirobenzylisoquinoline alkaloids have been proposed.^{246,247} Knowledge that aurotensine (265) and other proto-berberine-derived alkaloids co-occur with ochotensine, a spirobenzylisoquinoline

242 Kh. Sh. Baisheva, D. A. Fesenko, M. E. Perel'son, and B. K. Rostotskii, *Khim. prirod. Soedinenii*, 1970, **6**, 574 (*Chem. Abs.*, 1971, **74**, 50 522v).
243 Kh. Sh. Baisheva, D. A. Fesenko, B. K. Rostotskii, and M. E. Perel'son, *Khim. prirod. Soedinenii*, 1970, **6**, 456 (*Chem. Abs.*, 1971, **74**, 10 343f).
244 M. Castillo, J. K. Saunders, D. B. MacLean, N. M. Mollov, and G. I. Yakimov, *Canad. J. Chem.*, 1971, **49**, 139.
245 I. A. Israilov, M. S. Yunusov, and S. Yu. Yunusov, *Doklady Akad. Nauk S.S.S.R.*, 1969, **189**, 1262 (*Chem. Abs.*, 1970, **73**, 66 767u).
246 M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, 1970, **92**, 4943.
247 M. Shamma and J. F. Nugent, *Tetrahedron Letters*, 1970, 2625.

(266)

(267)

(268)

(269)

(270)

(271)
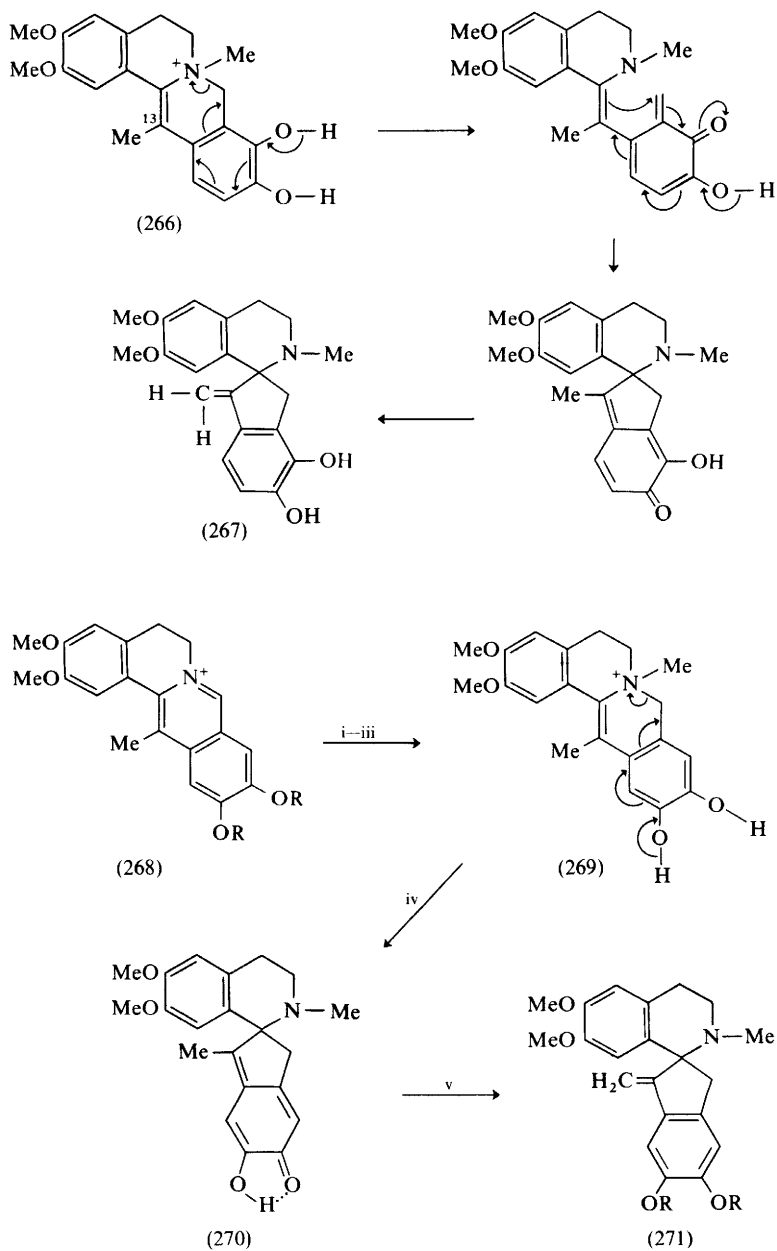
Reagents: i, LiAlH$_4$; ii, MeI, MeCN; iii, HBr, EtOH; iv, 1 equiv. NaOH, reflux, N$_2$;
v, DMSO.

Scheme 18

(272)   (273)
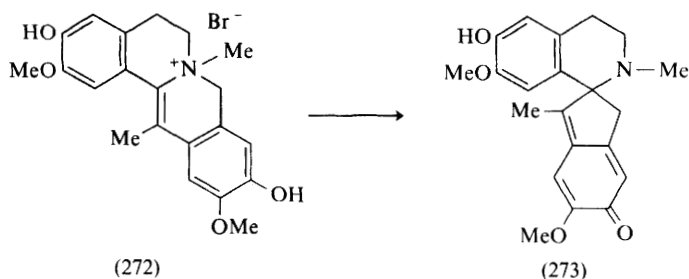
alkaloid, gave rise to the speculation that the latter type may be derived *in vivo* from the former by the prototype rearrangement (266) → (267), the requirement being the presence of the $C(13)$-methyl function and a $C(13)—C(14)$ double bond.[246] In order to test this hypothesis, the diphenol (269), which was more readily available than the desired isomeric $C(9)$, $C(10)$-diphenol analogue, was synthesized (Scheme 18) by a route which involved three critical terminal steps [(268; R = $CH_2\cdot C_6H_5$) → (269)]. Treatment of (269) with base did not effect the expected rearrangment to (271; R = H) but produced the quinone methide (270). However, when the latter was dissolved in dimethylsulphoxide, quantitative conversion into the diphenolic spirobenzylisoquinoline (271; R = H) occurred. When the *OO*-dibenzylated salt of (269) was treated under the basic conditions, no rearrangement products were obtained, thus showing that a diphenolic functionality is required for the rearrangement process to occur. An alternative biogenetic model in which the phenolic groups are in different rings gave directly the spirobenzylisoquinoline by prolonged treatment with ethanolic sodium hydroxide[(272) → (273)].[247] In this case, the quinone methide intermediate could not be isolated, undoubtedly due to lack of the intramolecular hydrogen-bonding which was present in (270). Possibly careful examination of spiroben-zylisoquinoline-alkaloid-producing plants for 13-methylprotoberberines is now warranted. In any case, the above study should stimulate *in vivo* studies with labelled precursors.

(274)   (275)   (276)

(277)

(278)
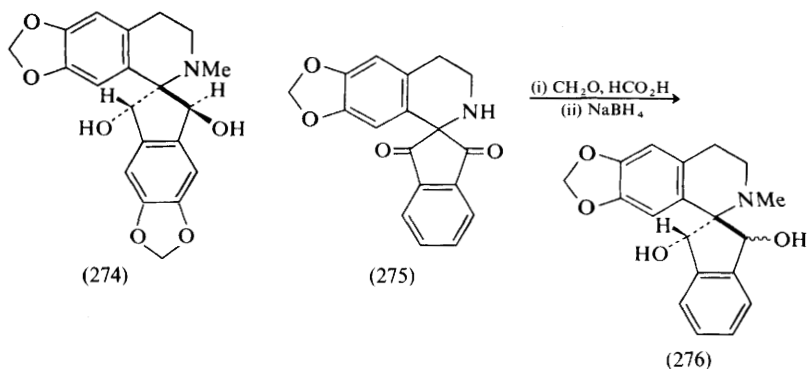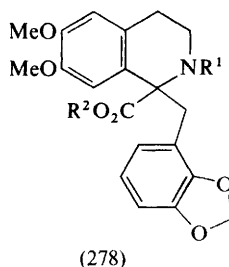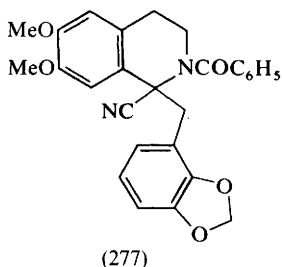
A model (276) of ochrobirine (274) has been prepared.[248] Condensation of 3,4-methylenedioxy-β-phenethylamine with ninhydrin under conditions which may be difficult to reproduce (abs. EtOH, 0 °C, 25 minutes, dry HCl gas passed *over the surface* at −78 °C until a clear solution was obtained) gave (275), which in two steps yielded (276) as an inseparable mixture of stereoisomers. A different attempt to prepare a spirobenzylisoquinoline skeleton by intramolecular Friedel–Crafts acylation of (277) and derivatives of (278) failed.[249] Compound (278) was prepared from the dihydro Reissert intermediate (277) by modification of the N-benzoyl and the cyano-functions, showing that the stability of such systems may be greater than intuitively expected.

L. Ipecacuanha Alkaloids.—An authoritative introduction to this class of alkaloids has been published as part of a general volume on alkaloids.[250]

Methods for the determination of cephaeline[251] and emetine[251b,252] in ipecacuanha extracts have been reported.

(279)

(280)
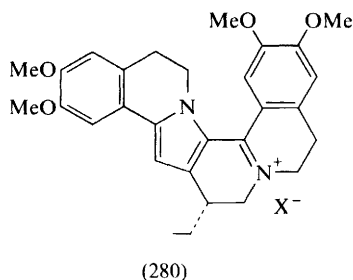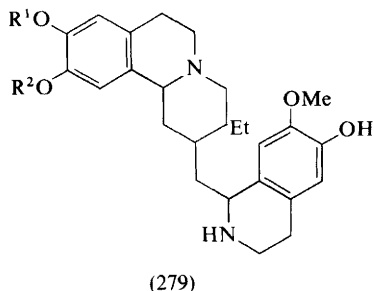
[248] R. H. F. Manske and Q. A. Ahmed, *Canad. J. Chem.*, 1970, **48**, 1280.
[249] M. Shamma and C. D. Jones, *J. Org. Chem.*, 1970, **35**, 3119.
[250] H. T. Openshaw in 'Chemistry of the Alkaloids,' ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, p. 85.
[251] *a* E. Graf and W. Roensberg, *Arch. Pharm.*, 1970, **303**, 209; *b* M. S. Habib and K. J. Harkiss, *Planta Med.*, 1970, **18**, 270; *c* M. Sobiczewska and B. Borkowski, *Acta Polon. Pharm.*, 1970, **27**, 469 (*Chem. Abs.*, 1971, **74**, 79 226a); *d* S. Janicki, *Herba Pol.*, 1969, **15**, 239 (*Chem. Abs.*, 1970, **73**, 28 993g).
[252] A. De Marco and E. Mecarelli, *Boll. chim. farm.*, 1970, **109**, 516 (*Chem. Abs.*, 1971, **74**, 130 415c).
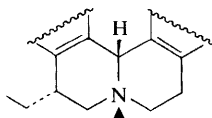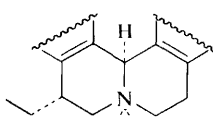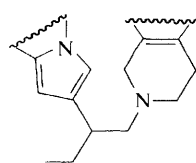
(281)   (282)   (283)

Aside from the known alkaloids psychotrine and tubulosine, a new alkaloid demethylcephaeline (279; R^1 = Me, R^2 = H or R^1 = H, R^2 = Me) has been isolated from *Alangium lamarckii*.[253]

Synthetic work related to these alkaloids[254] and to their derivatives possessing pharmacological activity[255] has been reported. Hydrogenation of the structurally related rubremetinium salt (280) under several sets of catalytic and chemical conditions gave in varying amounts the products (281), (282), and (283).[256]

4 Dimeric Benzylisoquinoline Alkaloids

The bisbenzylisoquinoline alkaloids occurring in species of the *Thalictrum* genus have been reviewed in detail.[24]

The structure of fetidine (284) has been confirmed by mass spectroscopy.[257] Examination of the mass spectra of the isomeric alkaloids thalicarpine and thalmelatine, dehydrothalicarpine and dehydrothalmelatine, and thalmetine and thalcimine (thalsimine) gave conclusive structural assignments on the basis of measurements of peak intensity for fragments containing the C=N function.[258] O.r.d. studies of a series of bisbenzylisoquinoline alkaloids isolated from *Thalictrum* species have been recorded.[259]
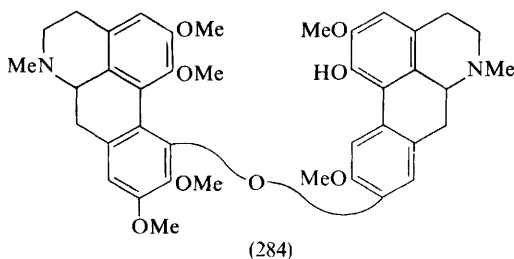
(284)

[253] S. C. Pakrashi and B. Achari, *Experientia*, 1970, **26**, 933.
[254] S. Gerszberg, *Anales Asoc. quim. argentina*, 1970, **58**, 63 (*Chem. Abs.*, 1971, **74**, 76 577s).
[255] A. Pedrazzoli, B. Gradnik, and L. Dell'Asta, *J. Medicin. Chem.*, 1971, **14**, 255.
[256] K. A. Kovar, *Arch. Pharm.*, 1970, **303**, 579.
[257] Z. F. Ismailov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 142 (*Chem. Abs.*, 1971, **74**, 35 590b).
[258] N. M. Mollov, V. St. Georgiev, and Kh. B. Duchevska, *Doklady Bolg. Akad. Nauk*, 1970, **23**, 383 (*Chem. Abs.*, 1970, **73**, 45 649s).
[259] G. P. Moiseeva, Z. F. Ismailov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 705 (*Chem. Abs.*, 1971, **74**, 112 278f).

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(294)

(295)
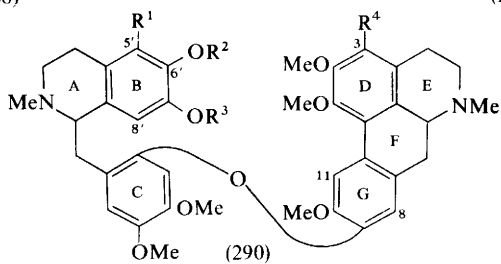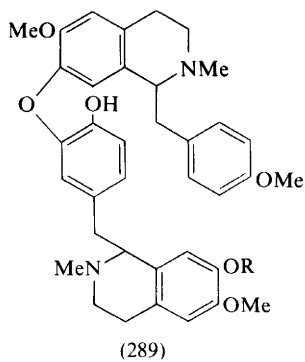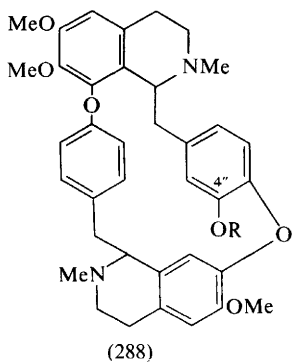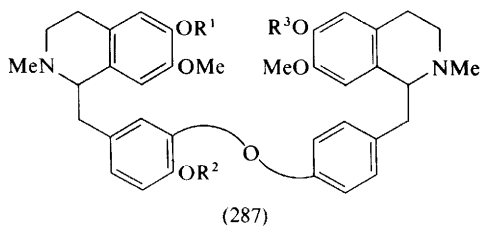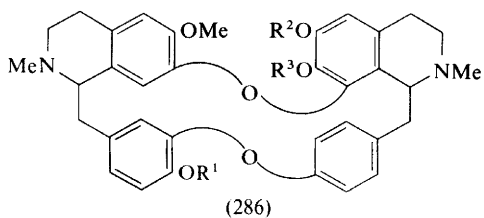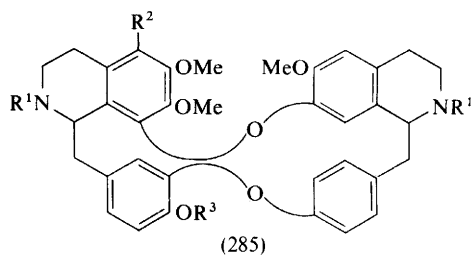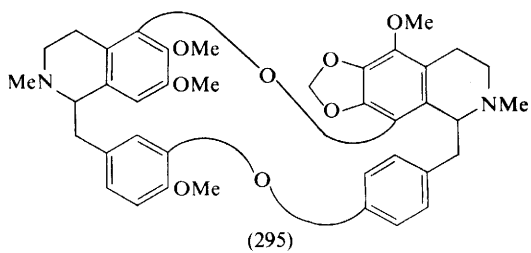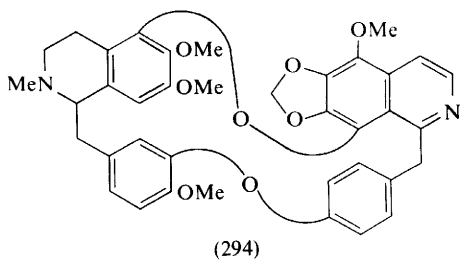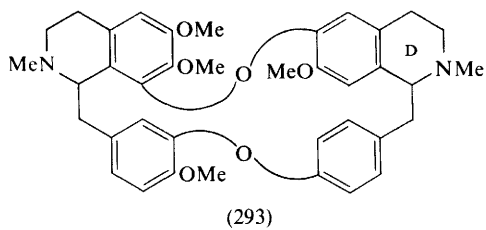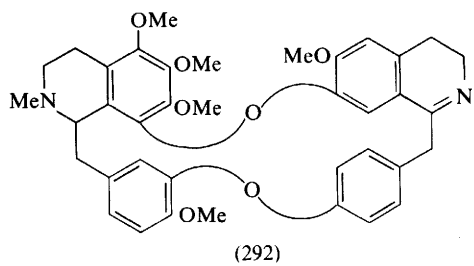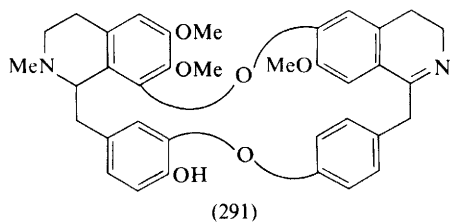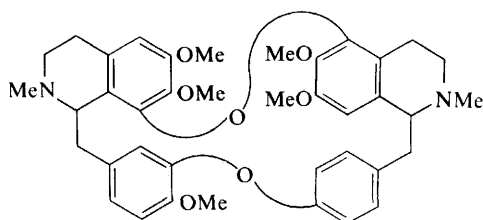
(296)

Table 7 *Isolation of dimeric benzylisoquinoline alkaloids*

Plant species	Alkaloid (Structure)	Ref.
Berberis petiolaris	Berbamine (285; R^1 = Me, R^2 = R^3 = H)	192
B. vulgaris	Berbamine, Oxyacanthine (286; R^1 = H, R^2 = R^3 = Me)*	193, 194
Chondrodendron platyphyllum	Chondrofoline (288; R = H)	260
Cissampelos ovalifolia	Dihydrowarifteine (297; $>$CH—NH— for C=N— in ring E; R^1 = R^3 = H, R^2 = R^4 = Me or *vice versa*) Dimethyldihydrowarifteine (305) Dimethylwarifteine (297; R^1 = R^2 = R^3 = R^4 = Me) Methyldihydrowarifteine (297; $>$CH—NH— for C=N— in ring E; R^1 = R^2 = Me, R^3 = H or Me, R^4 = Me or H). Methylwarifteine (297; R^1 = R^2 = Me, R^3 = H or Me, R^4 = Me or H) Warifteine (297; R^1 = R^3 = H, R^2 = R^4 = Me or *vice versa*)	261
Colubrina asiatica	O-Methyldauricine (287; R^1 = R^2 = R^3 = Me)	262
Dicentra canadensis	Cancentrine (316; R = H)	263
Mahonia aquifolium	Berbamine	193
Menispermum dauricum	Dauricine (287; R^1 = R^3 = Me, R^2 = H) Dauricinoline (287; R^1 = R^2 = H, R^3 = Me) Dauricoline (287; R^1 = R^2 = R^3 = H) Daurinoline (287; R^1 = Me, R^2 = R^3 = H)	103a, 264
Nelumbo nucifera	Isoliensinine (289; R = H) Neferine (289; R = Me)	29b
Stephania sasakii	Berbamine, Cepharanthine (286; R^1 = Me, R^2 + R^3 = CH_2)*	106
Thalictrum flavum	Thalicarpine (290; R^1 = R^4 = H, R^2 = R^3 = Me)	31
T. foetidum	Thalphine (294) Thalphinine (295)	265

[260] I. R. C. Bick, J. Baldas, Q. N. Porter, and M. J. Vernengo, *Chem. Comm.*, 1971, 132.

[261] W. Snedden, R. Parker, and C. Gorinsky, *Org. Mass Spectrometry*, 1970, **4**, (Suppl.), 607.

[262] R. Tschesche, R. Geipel, and H. W. Fehlhaber, *Phytochemistry*, 1970, **9**, 1683.

[263] G. R. Clarke, R. H. F. Manske, G. J. Palenki, R. Rodrigo, D. B. MacLean, L., Baczyn-skyi, D. E. F. Gracey, and J. K. Saunders, *J. Amer. Chem. Soc.*, 1970, **92**, 4998.

[264] M. Tomita, Y. Okamoto, Y. Nagai, K. Kitayama, and H. Yanagawa, *J. Pharm. Soc. Japan*, 1970, **90**, 1178 (*Chem. Abs.*, 1970, **73**, 131 187w).

[265] S. Abdizhabarova, Z. F. Ismailov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 279 (*Chem. Abs.*, 1970, **73**, 45 651m).

Table 7 (continued)

Plant species	Alkaloid (Structure)	Ref.
T. minus	O-Methylthalicberine (293)	
	Thalidazine (Thalidasine) (296)	107, 266
	Thalmethine* (291)	
T. minus L., var.	Thalmineline (290; R^1 = OH, R^2 = R^3 = Me,	
elatum Koch	R^4 = OMe)	267
T. minus f. elatum	Adiantifoline (290; R^1 = H, R^2 = R^3 = Me,	
	R^4 = OMe)	
	O-Demethyladiantifoline (290; R^1 = R^3 = H,	
	R^2 = Me, R^4 = OMe)	31a
	Thalmelatidine†	
	Thalmeline†	
	Unnamed (290; R^1 = R^4 = OMe, R^2 + R^3 = CH_2)	
T. rugosum	Thalcimine (Thalsimine) (292)	
	Thalidazine	107, 268
	Thaliglucine†	
T. simplex	Thalicsimine (Hernandezine)* (285;	
	R^1 = R^3 = Me, R^2 = OMe)	108
Tiliacora racemosa	Tiliacoridine‡	269
Triclisia dictyophylla,	NN'-Dimethylphaeanthine (285; N^+Me_2 for	
T. patens	NR^1, R^2 = H, R^3 = Me)	270
	Phaeanthine (Tetrandrine) (285; R^1 = R^3 = Me,	
	R^2 = H)	

* See footnote (*), Table 1.
† Structure unknown or original literature source not readily accessible.
‡ Structure unknown: $C_{39}H_{40}O_8N_2$, 3 OMe, 8 aromatic H, no NMe by n.m.r.

As seen from Table 7, there has been intense activity in the area of alkaloid isolation and structural elucidation. All alkaloids isolated from *Cissampelos ovalifolia* possess the relatively rare curine-type structure (297).[261] One of these, dimethylwarifteine, was shown to be identical with *O*-methylcissampereine (297; R^1 = R^2 = R^3 = R^4 = Me) whose structure was known. The mass spectral fragmentation pathways of this compound, although speculative, provided some insight into the structures of the other alkaloids. The predominant mode of cleavage in dimethylwarifteine occurred at *a* and *b* to yield the ion (299) (Scheme 19) which readily fragmented by successive losses of Me·, CO, CH_4, and a further CO by two alternative pathways to give the ion *m/e* 429 (302). Methylwarifteine and warifteine were both converted by treatment with diazomethane into dimethylwarifteine, and consequently all three alkaloids appear to possess the same skeleton and differ only in the number of methyl substituents in rings A and F. In agreement with this proposal, methylwarifteine and warifteine showed molecular

[266] V. G. Khodzhaev and Kh. Allayarov, *Khim. prirod. Soedinenii*, 1970, **6**, 496 (*Chem. Abs.*, 1971, **74**, 1060j).
[267] J. Reisch, H. Alfes, T. Kaniewska, and B. Borkowski, *Tetrahedron Letters*, 1970, 2113.
[268] N. M. Mollov, I. C. Ivanov, V. St. Georgiev, P. P. Panov, and N. Kotsev, *Planta Med.*, 1971, **19**, 10.
[269] A. K. Barua, P. Chakrabarti, and A. S. Dutta Gupta, *J. Indian Chem. Soc.*, 1970, **47**, 920.
[270] A. Kronlund, K. Kristiansson, and F. Sandberg, *Acta Pharm. Suecica*, 1970, **7**, 279 (*Chem. Abs.*, 1970, **73**, 75 273g).

ions at 14 and 28 mass units lower compared to (297; $R^1 = R^2 = R^3 = R^4 = $ Me). Additionally, in both compounds ready elimination of C_8H_8 took place followed by stepwise loss of Me· and CO, presumably by processes analogous to those observed with dimethylwarifteine [(299), (300), (301)] except that the ions were shifted by 14 and 28 mass units to lower mass respectively. However, instead of the subsequent loss of CH_4 and CO from (301), only CHO· elimination was observed for both compounds. This may be rationalized by (303) → (304) and suggests that ring F originally possessed only one OMe group and that the second OMe was replaced by an OH function. Methylwarifteine gave rise to an ion at *m/e* 311 (298) while warifteine showed a corresponding ion at *m/e* 297, implying that the former, like dimethylwarifteine, had two OMe groups in ring A while the latter had one of the OMe groups replaced by OH. This result confirmed that the second phenolic OH group of warifteine must be located in ring F. On the basis of these results, structures (297; $R^1 = R^3 = $ H, $R^2 = R^4 = $ Me or *vice versa*) and (297; $R^1 = R^2 = $ Me, $R^3 = $ H or Me, $R^4 = $ Me or H) were proposed for warifteine and methylwarifteine respectively, although the relative positions of the OH and OMe functions could not be determined with certainty.

(297)
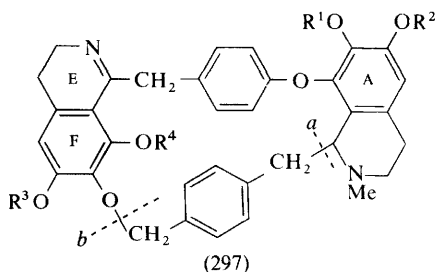
Sodium borohydride reduction of dimethylwarifteine, methylwarifteine, and warifteine cleanly gave the corresponding dihydro-derivatives (297; CH—NH— for C=N— in ring E). In the mass spectrum of dimethyldihydrowarifteine (305) (Scheme 20), the predominant cleavage now occurred at *a* and *c* (307) with a less significant fragmentation arising by loss of C_8H_8 (*a* and *b* cleavage, 308). No doubt this pathway is facilitated by the fully saturated nature of ring E. Also in contrast to the behaviour of the unsaturated alkaloid, dimethyldihydrowarifteine showed an intense ion at *m/e* 206 (306), presumably resulting by *b, c* cleavage with hydrogen transfer from (305) or *c* cleavage with hydrogen transfer from (308). Methyldihydrowarifteine and dihydrowarifteine showed analogous fragmentation patterns. Methylwarifteine is isomeric with the known alkaloid cissampereine (297; $R^1 = R^2 = R^3 = $ Me, $R^4 = $ H) but a comparison was not possible at this time.[261]

The structures of all alkaloids from *Menispermum dauricum* were elucidated by the usual two key reactions, sodium in liquid ammonia reduction and Hofmann degradation.[103a,264] The alkaloids isolated from *Thalictrum foetidum*

$(297, R^1 = R^2 = R^3 = R^4 = Me)^+$

a, b

MeO   OMe

CH_2

c

OMe

MeO

(299)

c, H
transfer

$- Me\cdot$

$- Me\cdot$

MeO   OMe

Me

(298)

Me

$CH_2—\}^+$

OMe

$CH_2—\}^+$

MeO

(300)

$CH_2—\}^+$

OH

(303)

$-CO$

$-CO$

H

$CH_2—\}^+$

O—Me

H

$CH_2—\}^+$

O—Me

$-\dot{C}HO$

(301)

$CH_2—\}^+$

(304)

$-CH_4$

$-CH_4$

H

$CH_2—\}^+$

H_2C

$CH_2—\}^+$

O

$-CO$

$C=O$

(302)
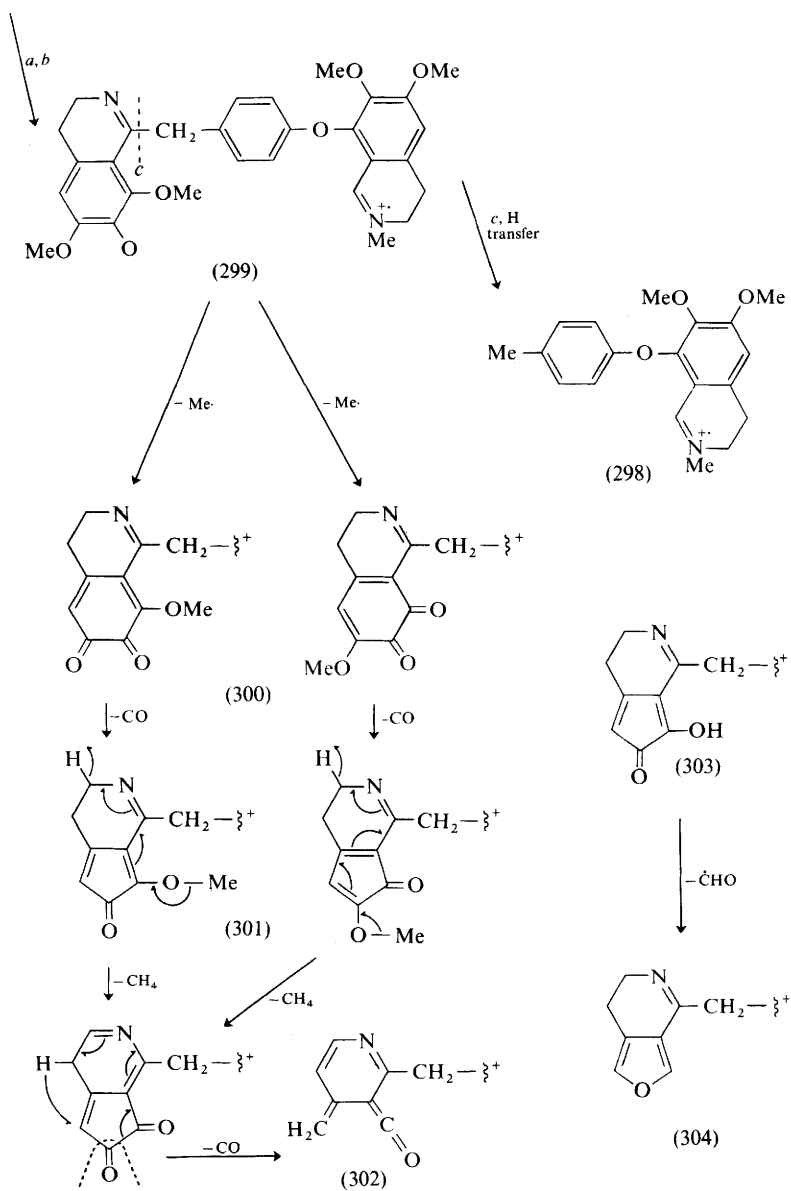
Scheme 19

represent a new structural type.[265] Not unlike a number of bisbenzylisoquino-
line alkaloids, those isolated from *Triclisia dictyophylla* and *T. patens* have been
shown to exhibit muscle relaxant effects.[270]
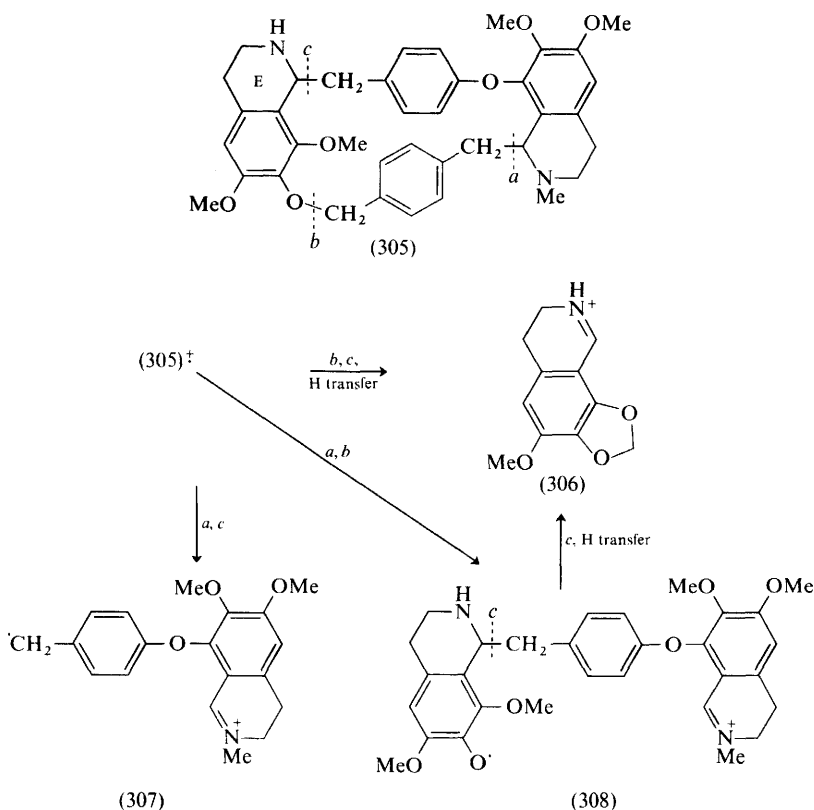
Scheme 20

In the determination of the structure of thalmineline (290; $R^1 = $ OH, $R^2 = $
$R^3 = $ Me, $R^4 = $ OMe) from *Thalictrum minus* L., var. *elatum* Koch, a great deal
of information was obtained from the comparison of its mass spectrum with those
of thalicarpine (290; $R^1 = R^4 = $ H, $R^2 = R^3 = $ Me) and adiantifoline (290;
$R^1 = $ H, $R^2 = R^3 = $ Me, $R^4 = $ OMe).[267] The parent molecular ion for thal-
mineline appeared at M^+ 742, indicating the presence of additional methoxy-
and hydroxy-groups in comparison to thalicarpine (M^+ 696). In agreement
with its dimeric benzylisoquinoline-aporphine structure, thalmineline showed
an intense peak at m/e 222 due to the immonium ion (309; R = OH). This
fragment appeared at 16 mass units higher (m/e 206) than in thalicarpine and
adiantifoline, suggesting that the phenolic hydroxy-group must be associated

with the benzylisoquinoline portion of the molecule. Thalmineline showed several other peaks (m/e 519, 520, 521) which were also found in the mass spectrum of adiantifoline, indicating the common dimeric constitution of the two alkaloids. In comparison with thalicarpine, thalmineline showed (n.m.r.) the presence of an additional methoxy-group and the absence of an aromatic proton. The ring-C protons were assigned on the basis of their similar chemical shift and lineshape to those in thalicarpine, and the C(8)- and C(11)-protons were assigned on the basis of previous n.m.r. information on similar structures. This therefore defined the position of the methoxy-group in thalmineline at C(3) of the aporphine unit and the substitution in rings C, D, E, F, and G as in adiantifoline. The position of the aromatic proton in ring B was assigned at C(8′) rather than C(5′) on the basis of its typical high-field absorption (δ 5.71) which is also found in other alkaloids possessing this structural feature. The assignment of the phenolic group at C(5′) rather than C(6′) is tentative.

Dequaternization of (+)-tubocurarine (310; $R^1 = Me, R^2 = R^3 = H, X = Cl$) with sodium thiophenoxide had been reported to give the corresponding tertiary base, (+)-tubocurine.[271] It has come to light recently that the structure of (+)-tubocurarine as well as those of (+)-chondrocurine (311; $R^1 = R^3 = H, R^2 = Me$) and (+)-chondrocurarine (310; $R^1 = R^3 = H, R^2 = Me, X = Cl$) has been incorrectly assigned.[272] Requaternization of the tertiary base prepared by the previous method[271] did not give (+)-tubocurarine but rather a compound whose physical constants agreed with those reported for (+)-chondrocurarine iodide. Methylation of the tertiary base with methyl iodide and sodium methoxide

(309)

(310)

(311)
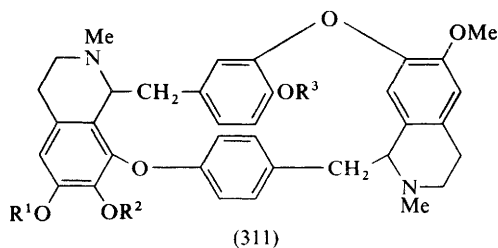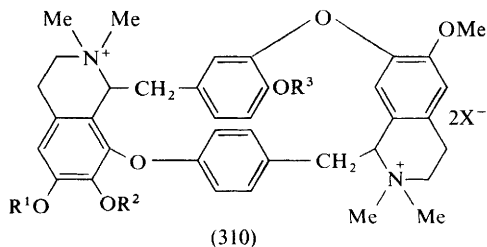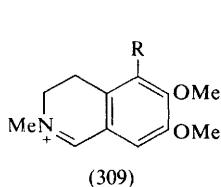
[271] M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Letters*, 1966, 1375.
[272] A. J. Everett, L. A. Lowe, and S. Wilkinson, *Chem. Comm.*, 1970, 1020.

gave the known *OO*-dimethyl-(+)-tubocurine dimethiodide (310; $R^1 = R^2 = R^3 = $ Me, X = I), showing that no skeletal rearrangement or optical configurational changes had occurred. Furthermore, it was found that the physical data of the tertiary base corresponded to those of (+)-chondrocurine and that its reaction with methyl iodide in methanol gave a compound identical with (+)-chondrocurine dimethiodide, prepared from an authentic sample of natural (+)-chondrocurine. To explain the conversion of (+)-tubocurarine chloride into (+)-chondrocurine on the basis of the previously derived structures, the transposition of the methyl group (R^1 in 310) and hydrogen (R^2 in 310) had to be postulated. This explanation could not be satisfied by further chemical observations and finally the structures of (+)-tubocurarine chloride and (+)-chondrocurarine chloride were clarified by spectroscopic analysis. The n.m.r. spectrum of (+)-tubocurarine chloride showed the presence of only three NMe functions, and one of these was shifted to high field upon addition of sodium deuteroxide, showing conclusively that one basic centre was not quaternary. Confirmatory evidence for the presence of a tertiary nitrogen atom was obtained from i.r. (2300—2700 cm^{-1}, N^+—H, shifted to 1800 cm^{-1} in compound recrystallized from D_2O) and mass spectra. Clearly, the structure of (+)-tubocurarine chloride possesses both a tertiary and a quaternary basic function. Additionally, it was converted by dequaternization into the tertiary base (+)-tubocurine (311; $R^1 = $ Me, $R^2 = R^3 = $ H) identical with (+)-chondrocurine, and therefore these two bases do not differ in the relative positions of methoxy- and phenolic groups as previously described. Finally, (+)-chondrocurarine chloride must be the dimethochloride of the tertiary base (+)-tubocurine (311; $R^1 = $ Me, $R^2 = R^3 = $ H), differing from (+)-tubocurarine only in the degree of quaternization and not in the location of the methyl ether function (271; $R^1 = $ Me, $R^2 = R^3 = $ H, X = Cl and 271; $R^1 = R^3 = $ H, $R^2 = $ Me, X = Cl) as originally assigned. The locations of the tertiary and quaternary basic sites in (+)-tubocurarine were established by sodium in liquid ammonia reduction of its *OO*-dimethyl ether acetate (312) (prepared with diazomethane) which gave compounds (313) and (314). Of necessity, the non-phenolic optically inactive fragment (313) must be derived from the quaternary half of the molecule, and therefore the correct structure of (+)-tubocurarine chloride, including the configuration which had been previously established, must be represented by (315).

With the aid of the above structural revision of chondrocurine and mass and n.m.r. spectral analysis, the structure of the curine-type alkaloid chondrofoline (288; R = H) from *Chondrodendron platyphyllum* has been established.[260] A simple method for the preparation of the C(4″)-trideuteriomethoxy-compound (288; R = CD$_3$) was also described.

The structure of a most unusual dimeric benzylisoquinoline alkaloid, cancentrine (316; R = H), has been elucidated almost forty years after it was originally isolated from *Dicentra canadensis*.[263] The n.m.r. spectrum of cancentrine showed signals corresponding to three aromatic methoxy-groups and one *N*-methyl group. Analysis of its hydrochloride and paper electrophoresis studies indicated the presence of one basic and one non-basic nitrogen. Hofmann degradation

(313)

(312)

(314)

(315)
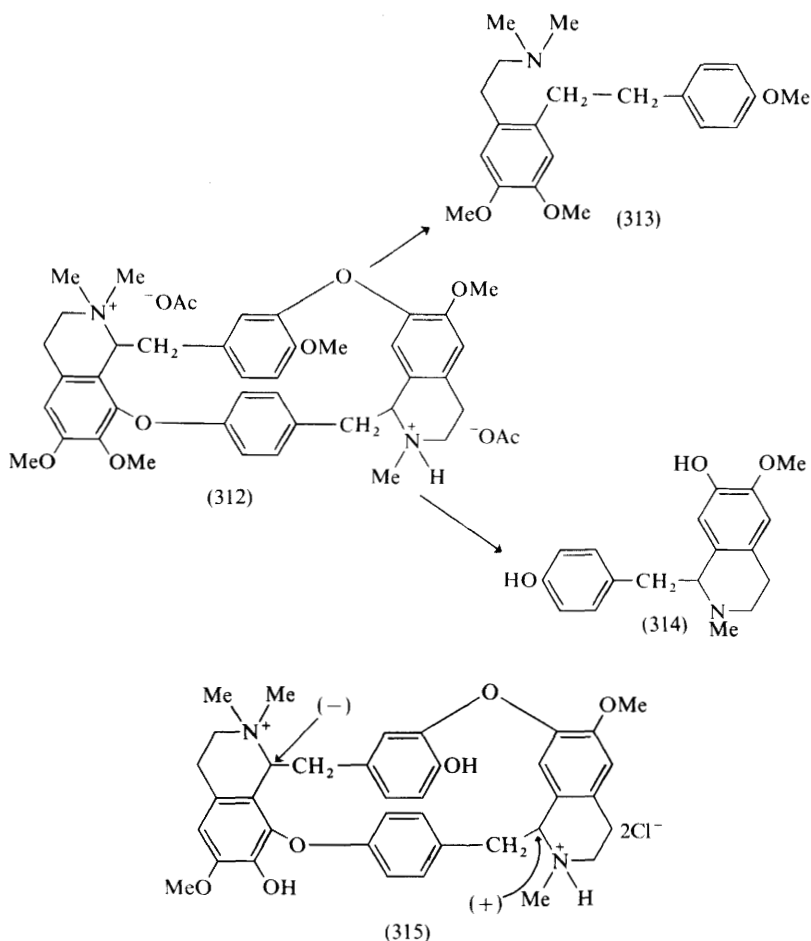
of cancentrine methiodide gave a methine (317; R = H) whose structure was deduced by an X-ray crystallographic analysis of its dihydromethine-O-methyl ether hydrobromide (318). That the conversion (316) → (317; R = H) involved only the opening of the nitrogen-containing bridge was shown by examination of the n.m.r. spectra of starting material and product. Both compounds showed the presence of a sharp singlet at δ 5.0 (1H) assignable to C(5)-H and three AB quartets due to the six aromatic protons. In addition, (317; R = H) showed an AB vinyl quartet attributable to C(9)–C(10)-protons, confirming that only the expected change had occurred. The terminus of the nitrogen-containing bridge of cancentrine was established by comparison of its n.m.r. spectrum with that of the morphine alkaloid codeine. The very similar splitting pattern and chemical shift of the C(9)–C(10)-protons in both systems ruled out the alternative

C(14) or C(10)-to-nitrogen bonding arrangement. The position of the acetoxy-group in (316; R = Ac) and thus the hydroxy-group in cancentrine was deter-mined by examination of their n.m.r. spectra and by n.o.e. measurements. Cancentrine is a unique dimeric alkaloid constructed from morphine and cularine subunits and represents a formidable challenge for biogenetic-type synthesis.

(316)   (317)

(318)
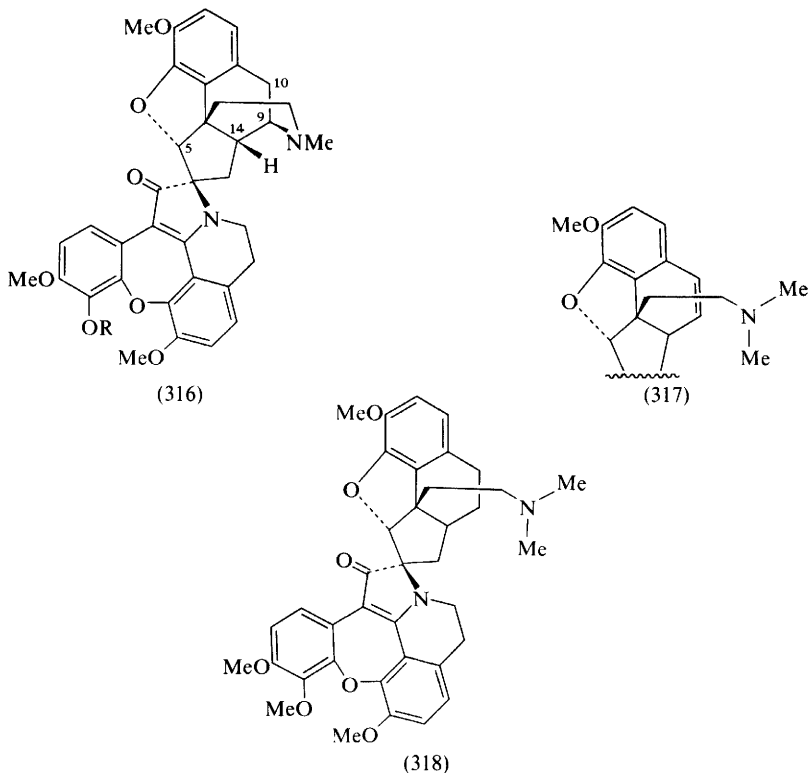
The methylation of the known[24] alkaloid thalisopidine to its O-methyl ether has been reported.[273]

The following four new total syntheses of dimeric benzylisoquinoline alkaloids have been reported: (−), (−)-OO-dimethylcurine (288; R = Me),[274] O-methyl-thalicberine (323; R = Me),[275] (±)-O-methyltiliacorine (331),[276] and (±)-obaberine (286; R¹ = R² = R³ = Me).[277] The synthesis of O-methylthalic-berine, the first reported example of the bisbenzylisoquinoline alkaloids, is

[273] Kh. G. Pulatova, Z. F. Ismailov, and S. Yu. Yunuscv, *Khim. prirod. Soedinenii*, 1969, 5, 609 (*Chem. Abs.*, 1970, 73, 4071d).
[274] T. Kametani, H. Iida, and K. Sakurai, *J. Chem. Soc. (C)*, 1971, 1024.
[275] E. Fujita and A. Sumi, *Chem. and Pharm. Bull. (Japan)*, 1970, 18, 2591.
[276] B. Anjaneyulu, T. R. Govindachari, and N. Viswanathan, *Tetrahedron*, 1971, 27, 439.
[277] T. Kametani, K. Wakisaka, and K. Kigasawa, *J. Heterocyclic Chem.*, 1970, 7, 509.
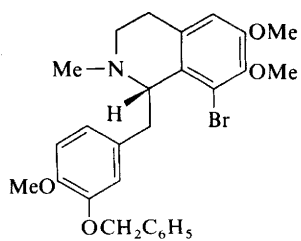
(319)
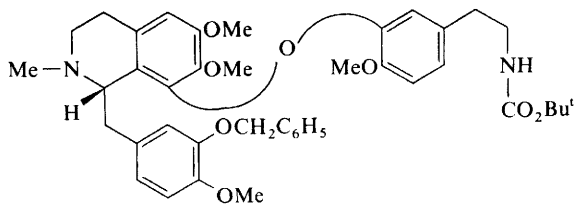
(320)
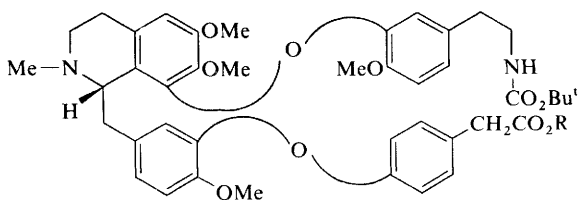
(321)
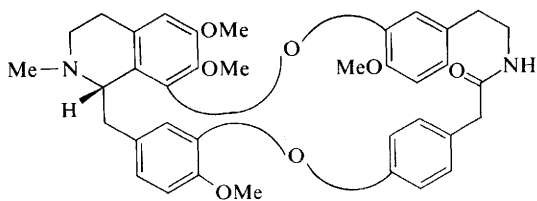
(322)
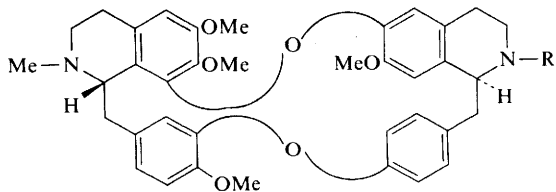
(323)
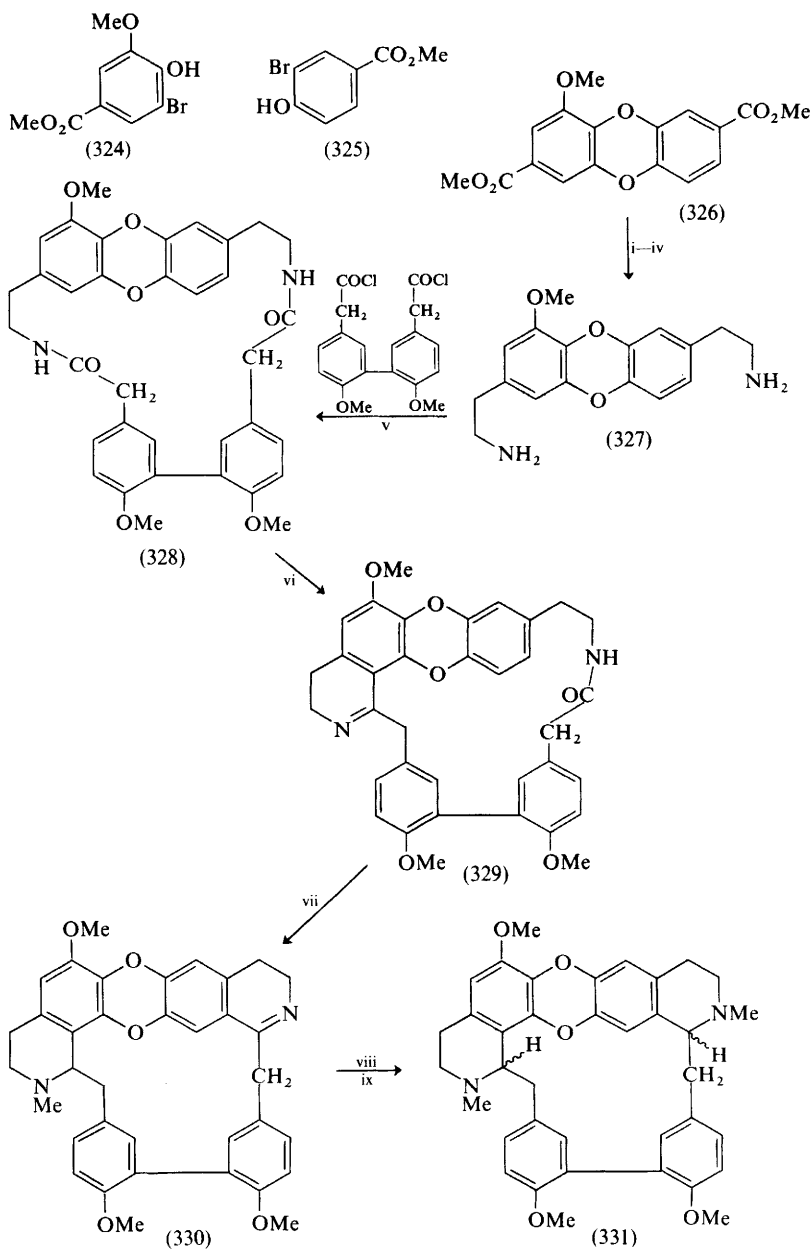
Reagents: i, LiAlH$_4$, THF; ii, SOCl$_2$, iii, KCN, iv, H$_2$, Raney Ni; v, KOH, CHCl$_3$; vi, POCl$_3$, C$_6$H$_6$; vii, MeI, then MeOH, NaBH$_4$, then POCl$_3$, 100 °C; viii, H$_2$, PtO$_2$; ix, CH$_2$O, HCO$_2$H.

Scheme 21

representative.[275] The norlaudanidine derivative (319), prepared *via* a Bischler–Napieralski condensation, was resolved and the (S)-(+)-chiral substance was treated with N-t-butoxycarbonyl-3-hydroxy-4-methoxyphenethylamine under Ullmann condensation conditions to yield compound (320). Hydrogenolysis followed by a second Ullmann reaction with methyl *p*-bromophenylacetate gave the bis-diphenyl ether (321; R = Me) which was converted into the *p*-nitrophenyl ester (321; R = *p*-NO$_2$·C$_6$H$_4$·) and the latter, after removal of the t-butoxycarbonyl group, was cyclized to compound (322). Bischler–Napieralski reaction of (322) followed by sodium borohydride reduction gave (323; R = H) as a single product, indicating that the latter reaction had proceeded stereoselectively. N-Methylation gave the naturally-occurring alkaloid O-methylthalicberine (323; R = Me).

The occurrence of the dibenzo-*p*-dioxan unit in (±)-O-methyltiliacorine (331) presented problems not encountered in the synthesis of other dimeric benzylisoquinoline alkaloids.[276] Firstly, the Ullmann reaction of methyl 5-bromovanillate (324) with methyl 3-bromo-4-hydroxybenzoate (325) gave all theoretically possible dimethoxycarbonyl-dibenzo-*p*-dioxans, from which the desired diester (326) could be obtained only by extensive chromatography. Compound (326) was then readily converted into the bisamine (327) (as shown in Scheme 21), which was condensed with the diacid chloride of 2,2'-dimethoxybiphenyl-5,5'-diacetic acid under high dilution conditions to yield the bisamide (328). Attempts to effect a double Bischler–Napieralski cyclization under vigorous conditions were synthetically very inefficient but milder conditions gave the monocyclized product (329). Possibly as a result of less molecular flexibility in (329) in comparison to (328), the second Bischler–Napieralski cyclization could now be effected under forcing conditions to yield (330). Reduction and methylation yielded a diastereoisomeric mixture from which (±)-O-methyltiliacorine (331) could be isolated as the major product, thus completing the synthesis. Other alkaloids containing the dibenzo-*p*-dioxan system which have been synthesized were briefly reviewed.[276]

9
Amaryllidaceae and Related Alkaloids

BY V. A. SNIECKUS

An expert introduction to this class appears in a general text on the chemistry of alkaloids.[1] The Amaryllidaceae sub-family, Amaryllidoideae, has been reviewed from the point of view of occurrence in Switzerland.[2]

Polarographic analyses of galanthamine and related alkaloids in *Ungernia victoris*[3] and quantitative u.v. determination of methylapogalanthamine hydrochloride[4] have been reported. The rate of alkaloid accumulation in *U. tadshikorum*, *U. trisphaera*, and *U. victoris* has been studied.[5] The toxicity of galanthamine hydrobromide has been convincingly demonstrated.[6]

New alkaloid isolation studies are summarized in the Table. The structure and stereochemistry of clividine [1; C(3a) α-H; C(5) α-OH; $R^1 + R^2 = O$], obtained from *Clivia miniata*, has been determined by chemical correlation with other previously isolated alkaloids of this group.[7] Its gross structure was compared with that of dihydrohippeastrine [1; C(3a) α-H; C(5) β-OH; $R^1 + R^2 = O$] but attempts to correlate the structures of these two alkaloids by conversion into a common ketone failed. This could be explained on the basis of their stereochemical difference at C(5)-OH, as evidenced by the fact that partial reduction of clividine followed by periodic acid treatment of the resulting hemiacetal [1; C(3a) α-H; C(5) α-OH; $R^1 = H$, $R^2 = OH$] resulted in 96% uptake, whereas the same sequence of reactions on dihydrohippeastrine showed only 16% oxidation. For the purpose of correlation, hippeastrine (2; $R^1 = OH$, $R^2 = H$) was oxidized with manganese dioxide to the ketone (2; $R^1 + R^2 = O$) which by consecutive lithium aluminium hydride reduction and catalytic reduction gave 5-epi-α-tetrahydrohippeastrine (3). The last was transformed into [1; C(3a) α-H; C(5) α-OH; $R^1 = R^2 = H$] under vigorous acid conditions, and the lithium

[1] W. C. Wildman in 'Chemistry of the Alkaloids,' ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, p. 151.
[2] R. Jaspersen-Schib, *Pharm. Acta Helv.*, 1970, **45**, 424.
[3] A. D. Volodina, E. K. Dobronravova, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1970, **6**, 450 (*Chem. Abs.*, 1970, **74**, 897a).
[4] A. D. Volodina, E. K. Dobronravova, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1970, **6**, 277 (*Chem. Abs.*, 1970, **73**, 94 415w).
[5] A. Abdusamotov, S. A. Khamidkhodzhaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 60 (*Chem. Abs.*, 1971, **74**, 136 536q).
[6] V. V. Mikhno and V. Kramarenko, *Farm. Zhur.* (*Kiev*), 1970, **25**, 68 (*Chem. Abs.*, 1970, **73**, 43 354t).
[7] W. Doepke and M. Bienert, *Tetrahedron Letters*, 1970, 3245.

Table *Isolation of Amaryllidaceae and related alkaloids*

Species	Alkaloid (Structure)	Ref.
Clivia miniata	Cliviasine [1; C(5) β-OH; $R^1 + R^2 = O$] Clividine [1; C(5) α-OH; $R^1 + R^2 = O$]	} 7, 8
Galanthus caucasicus	Galanthamine (4; $R^1 = OH, R^2 = H$) Galanthusine (5) Lycorine (6; $R^1 + R^2 = CH_2, R^3 = R^4 = H$)	} 9, 10
G. nivalis	[Galanthamine, Hippeastrine (2; $R^1 = OH, R^2 = H$), Lycorine, Narwedine (4; $R^1 + R^2 = O$), Nivalidine (7), Tazettine (8)]*	} 11
Leucojum vernum	(Galanthamine, Lycorine)* Tazettine	} 12
Narcissus tazetta	Pseudolycorine (6; $R^1 = R^3 = R^4 = H, R^2 = Me$)	13
Sceletium joubertii	Dehydrojoubertiamine (9) Dihydrojoubertiamine (9; *a,b*: *c,d*-tetrahydro) Joubertiamine (9; *c,d*-dihydro)	} 14
S. strictum	*O*-Acetylmesembrenol (10; $R^1 = OAc, R^2 = H$, $R^3 = Me$) 4'-*O*-Demethylmesembranol (10; $R^1 = OH$, $R^2 = R^3 = H$; *a,b*-dihydro) 4'-*O*-Demethylmesembrenol (10; $R^1 = OH$, $R^2 = R^3 = H$) Mesembrenol (10; $R^1 = OH, R^2 = H, R^3 = Me$)	} 15

* Known alkaloid, previously isolated from the same species but usually of a different locality. *Cf.* J. J. Willaman and H.-L. Li, *Lloydia*, 1970, 33, No. 3A (Suppl.) and R. A. Raffauf, 'A Handbook of Alkaloids and Alkaloid-Containing Plants,' Wiley·Interscience, New York, 1970.

aluminium hydride reduction and acid treatment sequence on clividine also yielded [1; C(3a) α-H; C(5) α-OH; $R^1 = R^2 = H$]. The stereochemistry of C(3a), C(5), C(5a), C(11b), and C(11c) was clarified by n.m.r. spectral analysis. Since the absolute configuration of hippeastrine was known, clividine was assigned the 5-epi-α-dihydrohippeastrine structure [1; C(3a) α-H; C(5) α-OH; $R^1 + R^2 = O$] and the same absolute configuration. Cliviasine is dihydrohippeastrine [1; C(3a) α-H; C(5) β-OH; $R^1 + R^2 = O$] and clivonine is dihydro-5a-epihippeastrine [1; C(5) β-OH; C(5a) β-OC(O)—; $R^1 + R^2 = O$].[8]

[8] W. Doepke and M. Bienert, *Pharmazie*, 1970, **25**, 700.

[9] I. D. Kalashnikov, *Issled. Obl. Lek. Sredstv.*, 1969, 228; From *Ref. Zhur. Biol. Khim.*, 1970, Abstr. No. 14F1106 (*Chem. Abs.*, 1971, **74**, 136 420x).

[10] D. M. Tsakadze, A. Abdusamatov, R. Razakov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 773 (*Chem. Abs.*, 1971, **74**, 100 246f).

[11] I. D. Kalashnikov, *Khim. prirod. Soedinenii*, 1970, **6**, 380 (*Chem. Abs.*, 1971, **74**, 127 734e); *Farm. Zhur.* (*Kiev*), 1970, **25**, 4 (*Chem. Abs.*, 1970, **73**, 91 195p).

[12] I. D. Kalashnikov and M. V. Savicheva, *Farmatsiya* (*Moscow*), 1970, **19**, 26 (*Chem. Abs.*, 1970, **73**, 38 477f).

[13] E. Furusawa, S. Furusawa, S. Morimoto, and W. Cutting, *Proc. Soc. Exp. Biol. Med.*, 1971, **136**, 1168 (*Chem. Abs.*, 1971, **74**, 139 262h).

[14] R. R. Arndt and P. E. J. Kruger, *Tetrahedron Letters*, 1970, 3237.

[15] P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli, and R. L. Hawks, *J. Org. Chem.*, 1970, **35**, 3512.

(1)   (2)   (3)

(4)   (5)   (6)
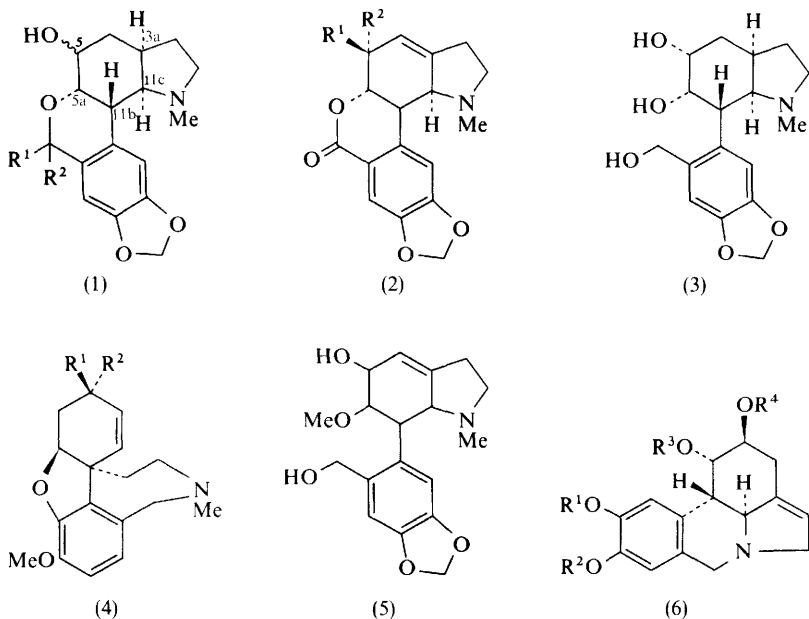
Aside from those mentioned in the Table, three other alkaloids were detected in *Galanthus caucasicus*, but were not identified.[9] It is possible that galanthusine (5), isolated[10] from the same species, may be correlated with the degradation product (3) of clividine and hippeastrine (see above).[7] *Leucojum vernum* yielded the alkaloids listed in the Table and three others which were not characterized.[12] Pseudolycorine (6; $R^1 = R^3 = R^4 = H$, $R^2 = Me$), from *Narcissus tazetta*, and the residual alkaloid extract from this species appear to show excellent activity against a specific type of leukaemia.[13]

The alkaloids of structure (9), isolated from *Sceletium joubertii*, represent the first non-mesembrine compounds to be obtained from this species.[14] Joubertiamine (9; *c,d*-dihydro) showed in its mass spectrum a base peak at m/e 58, suggesting the formation of the fragment $CH_2 : \overset{+}{N}Me_2$. A weaker peak corresponding to a fragment at m/e 72 was attributed to the *NN*-dimethylaziridinium ion, indicating the presence of a *NN*-dimethylaminoethyl side-chain. The u.v. and i.r. spectra were consistent with the presence of a monohydric phenol and $\alpha\beta$-unsaturated six-membered-ring ketone respectively. The most important information was obtained from its n.m.r. spectrum, which showed four aromatic protons appearing as doublets at τ 2.95 (2H) and τ 3.43 (2H), $J = 8$ Hz, and two olefinic proton signals as two doublets at τ 3.92 (1H) and τ 2.96 (1H), $J = 10$ Hz. The above information led to the unique assignment of structure (9; *c,d*-dihydro) for joubertiamine. The other alkaloids, dehydrojoubertiamine (9) and dihydrojoubertiamine (9; *a,b*:*c,d*-tetrahydro) were correlated with joubertiamine.
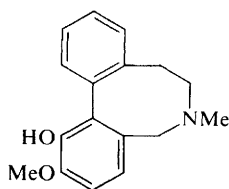
(7)
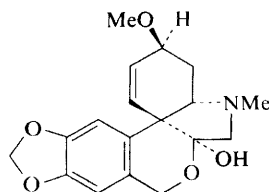
(8)
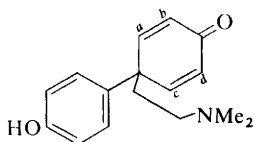
(9)

Mesembrenol (10; R^1 = OH, R^2 = H, R^3 = Me) proved to be the major alkaloid isolated from *Sceletium strictum*.[15] Functional group analysis by chemical and spectral methods and comparison with known alkaloids suggested the mesembrane skeleton for this alkaloid. It had been established that the mass spectra of mesembrine alkaloids possessing a 3a-dimethoxyphenyl substituent show a prominent peak at m/e 219 attributed to the ion (11; R = Me). This peak was intensely represented in the spectrum of mesembrenol, implying that the double bond and the hydroxy-group must be placed in ring B in structure (10). Their location as shown in (10; R^1 = OH, R^2 = H, R^3 = Me) was based on Jones oxidation to ($\pm$)-mesembrenone (10; R^1 + R^2 = O, R^3 = Me). A reasonable mechanism for the racemization process observed in this reaction, involving the N-protonated ketone (10; R^1 + R^2 = O, R^3 = Me; NHMe for NMe) and the symmetrical dienone (12), was proposed. The stereochemistry of the C(6)-hydroxy-group and the absolute configuration of mesembrenol were established by its hydrogenation to (−)-mesembranol (10; R^1 = OH, R^2 = H, R^3 = Me; a,b-dihydro). The relative and absolute configurations had been concurrently established by X-ray analysis of 6-epimesembranol methiodide.[16] Aside from the known alkaloids mesembrenone, mesembrine, and mesembranol, O-acetyl-mesembrenol (10; R^1 = OAc, R^2 = H, R^3 = Me) and two phenolic alkaloids were also isolated. One of the phenolic compounds (m.p. 219.5—220 °C) was characterized as an O-demethylmesembrenol on the basis of its mass spectrum and methylation with diazomethane to (+)-mesembrenol. Similarly, the other (m.p. 201 °C) was shown to be a dihydro-derivative of the alkaloid of m.p. 219.5—220 °C on the basis of its mass spectrum and conversion to (−)-mesembranol by treatment with diazomethane. Thus the two phenolic alkaloids are an O-demethylmesembrenol and an O-demethylmesembranol respectively, in which the phenolic hydroxy-group is located at the same but as yet undetermined site.

[16] P. Coggan, D. S. Farrier, P. W. Jeffs, and A. T. McPhail, *J. Chem. Soc.* (*B*), 1970, 1267.

This problem was solved by a radioisotope dilution method. O-Demethyl-mesembranol was equilibrated with tritium oxide and treated with diazo$[^3H_2]$-methane. The isolated product was diluted with inactive mesembranol and oxidized to give radio-labelled veratric acid $(13; R^1 = Me, R^2 = CT_3)$. Careful treatment of the latter with hydrobromic acid gave isovanillic acid $(13; R^1 = H, R^2 = CT_3)$ with no loss of label. Further demethylation of isovanillic acid gave inactive protocatechuic acid $(13; R^1 = R^2 = H)$. Thus it was demonstrated that all of the tritium label in the veratric acid must be located at the 4-methoxy-group (the group corresponding to the 4'-methoxy-group of the parent compound) and the nature of the oxidative degradation requires that 4'-O-demethylmesembranol and 4'-O-demethylmesembrenol be assigned structures $(10; R^1 = OH, R^2 = R^3 = H; a,b$-dihydro) and $(10; R^1 = OH, R^2 = R^3 = H)$ respectively.

(10) (11) (12)

(13) (14)
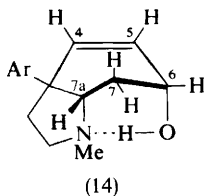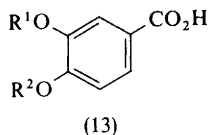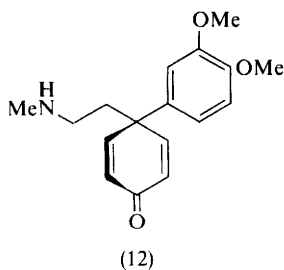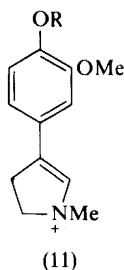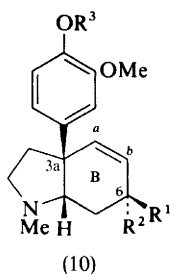
In view of the previous surprising findings that some of the mesembrane alkaloids exist in conformations in which ring B has a chair form, with the aryl substituent occupying a quasi-axial position, a closer spectral examination of the conformational features of mesembrenol $(10; R^1 = OH, R^2 = H, R^3 = Me)$, 6-epimesembrenol $(10; R^1 = H, R^2 = OH, R^3 = Me)$, and mesembrenone $(10; R^1 + R^2 = O, R^3 = Me)$ was undertaken.[15] For example, the i.r. spectrum of 6-epimesembrenol in solution showed no free OH-stretching mode but rather a strongly hydrogen-bonded OH at 3385 cm^{-1}, thus indicating that the alkaloid must exist almost exclusively in the rigid half-chair conformation (14). Support for this representation was obtained by examination of its n.m.r. spectrum, which showed the two olefinic hydrogens as a quartet [$C(4)$-H] and an octet [$C(5)$-H] at δ 5.73 and 6.12 respectively with $J_{5,6} = 5.5$ Hz and $J_{4,6} = 0$ Hz. Model studies showed that in conformation (14) the value of the dihedral angle which $C(6)$-H makes with $C(4)$- and $C(5)$-hydrogen atoms is close to 0°, thus giving rise to the

observed maximum vicinal and minimal allylic coupling, a situation which had been well documented in other cases. Double-resonance experiments showed that the fine splitting observed in the signal due to $C(4)$-H was due to long-range coupling with the $C(7a)$-H signal at δ 2.55. In this decoupling, the eight-line pattern of $C(5)$-H remained unchanged and therefore the fine splitting in this signal must be due to coupling to the $C(7a)$-hydrogen atom, which is related to $C(5)$-H in a distorted W arrangement. Similar analyses of the n.m.r. spectra of mesembrenol (10; $R^1 = OH$, $R^2 = H$, $R^3 = Me$) and mesembrenone (10; $R^1 + R^2 = O$, $R^3 = Me$), together with c.d. studies on the latter, fully supported analogous conformational representations for these two alkaloids.
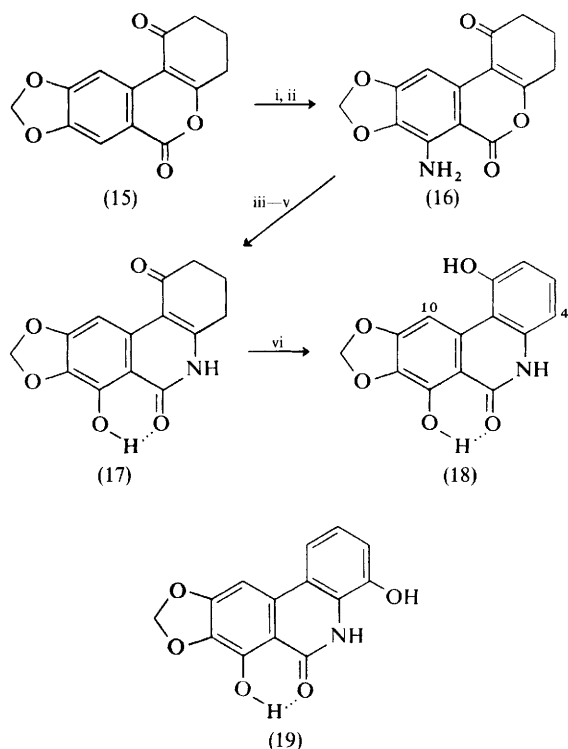
Reagents: i, HNO_3, -10 °C; ii, H_2, Raney Ni; iii, H_2SO_4, $NaNO_2$, -5 °C; iv, $Cu(NO_3)_2$, 20 °C; v, NH_3, MeOH; vi, 30% Pd–C, boiling naphthalene.

Scheme 1

Details of the synthetic work which led to the structural revision of narciprimine from the originally assigned (18) to the structure (19) have appeared.[17] Condensation of 6-bromopiperonylic acid with dihydroresorcinol gave directly the

[17] A. Mondon and K. Krohn, *Chem. Ber.*, 1970, **103**, 2729.

benzopyrone (15) in 65% yield, which by successive nitration and reduction produced the amino-derivative (16), as shown in Scheme 1. Conversion of the latter into the related phenol, followed by ammonolysis gave the phenanthridine-dione (17), which on dehydrogenation yielded the phenanthridone derivative (18). Each step of the synthesis was explored in detail and conditions for maximum yields were established, procedures of investigation which are now almost expected from this group of workers. Comparison of the n.m.r. spectrum of the synthetic compound (18) with that of narciprimine showed distinct differences. In particular, compound (18) showed the expected strongly deshielded and shielded signals at δ 8.40 and 6.78 or 6.9, assignable to protons at C(10) and C(4) respectively. Full interpretation of the n.m.r. spectra of the two isomers led to the assignment of structure (19) for narciprimine. A synthesis of narciprimine, involving a photochemical reaction as the key step, has been previously reviewed.[18]

The structural revision of narciprimine led to a more detailed investigation[17] into the identity of the related alkaloid narciclasine, which had been assigned structure (20) by other workers. On the basis of interpretation of u.v. and n.m.r. spectra in comparison with those of other alkaloids of this structural type and of chemical degradation, the revised structure (21) for narciclasine has been advanced. Synthetic work towards the final solution of this structural problem is under way.[17]

The molecular structures and absolute configurations of two 5,10-ethano-phenanthridine alkaloids, 6-hydroxybuphanidrine (22) methiodide and haeman-thamine *p*-bromobenzoate (23), have been determined by *X*-ray analysis.[19] An important first paper on the ^{13}C n.m.r. spectral analysis of several Amarylli-daceae alkaloids (among them buphanamine, lycorenine, tazettine, deoxy-tazettine, montanine, and galanthine) using sophisticated proton decoupling techniques requires the careful attention of alkaloid chemists.[20] The ^{1}H n.m.r.

(20)　　　　　　　　(21)
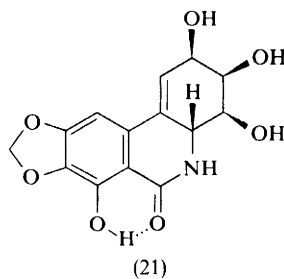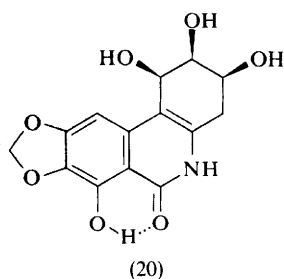
[18] 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1970, vol. 1, p. 142.
[19] J. C. Clardy, F. M. Hauser, D. Dahm, R. A. Jacobson, and W. C. Wildman, *J. Amer. Chem. Soc.*, 1970, **92**, 6337.
[20] J. D. Roberts, W. O. Crain, jun., and W. C. Wildman, *J. Amer. Chem. Soc.*, 1971, **93**, 990.

OMe

O

O

MeO   OH

(22)

OMe

O$_2$C·C$_6$H$_4$·Br-*p*

O

O

N

(23)
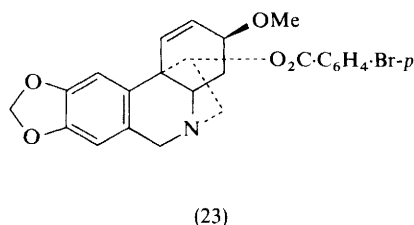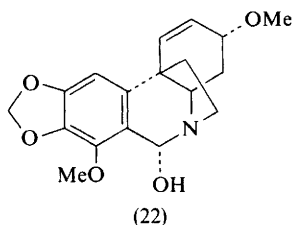
spectra of alkaloids of structural types (2) and (4) have been studied in detail for the purpose of stereochemical assignment.[21]

Stereospecific syntheses of haemanthidine (29) and tazettine (8) have been announced.[22] The lactam acid (24), prepared previously in eight steps and 14% overall yield, was converted (see Scheme 2) *via* iodolactone and epoxy-acid salt (0.1M-NaOH treatment) intermediates to the methoxy-lactone (25). Saponification of (25) followed by a reaction involving unusual conditions and a normal mesylation gave compound (26). In contrast to derivatives obtained previously by functionalization of the double bond in (24), compound (26) possessed the required stereochemistry for later *trans*-elimination to the desired $\Delta^{2,3}$-olefin. The compound (27) exhibiting a bridge to nitrogen, was now readily formed in four steps and was transformed to nortazettine (28) by taking advantage of the presence of the axial mesylate function to direct the required stereospecificity in the sodium borohydride reduction step. Since nortazettine had previously been converted into tazettine (8), the synthesis of the latter alkaloid had been achieved. It was shown that the internal Cannizzaro reaction, long observed in the conversion of the alkaloid haemanthidine (29) into nortazettine (28), was also operating in the transformation (27) → (28). In order to block this conversion, (27) was treated with a hindered borane (refluxing disiamylborane–THF) and the resulting diol was transformed into ($\pm$)-haemanthidine (29) by successive acetylation elimination {hot 1,5-diazabicyclo[3,4,0]non-5-ene (DBN)}, and reductive deacetylation steps. The initial acetylation reaction was required in order to block the aforementioned internal hydride transfer from occurring during the base-catalysed elimination step.

Two alternative syntheses of ($\pm$)-galanthamine (4; R^1 = OH, R^2 = H) to the one reviewed earlier[23] have been developed.[24,25] In one of these, phenolic oxidative coupling of amides (30; R = H, X = H$_2$, Y = O) and (30; R = CH$_2$·C$_6$H$_5$, X = H$_2$, Y = O) using potassium ferricyanide gave poor yields of the enones (31; R = H, X = H$_2$, Y = O) and (31; R = CH$_2$·C$_6$H$_5$, X = H$_2$,

[21] M. R. Yagudaev, Kh. A. Abduazimov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 94 (*Chem. Abs.*, 1970, **73**, 45 641*h*); *ibid.*, p. 235 (*Chem. Abs.*, 1970, **73**, 25 708*g*).

[22] J. B. Hendrickson, T. L. Bogard, and M. E. Fisch, *J. Amer. Chem. Soc.*, 1970, **92**, 5538.

[23] Ref. 18, p. 140.

[24] T. Kametani, C. Seino, K. Yamaki, S. Shibuya, K. Fukumoto, K. Kigasawa, F. Satoh, M. Hiiragi, and T. Hayasaka, *J. Chem. Soc.*, (*C*), 1971, 1043.

[25] T. Kametani, K. Shishido, E. Hayashi, C. Seino, T. Kohno, S. Shibuya, and K. Fukumoto, *J. Org. Chem.*, 1971, **36**, 1295.
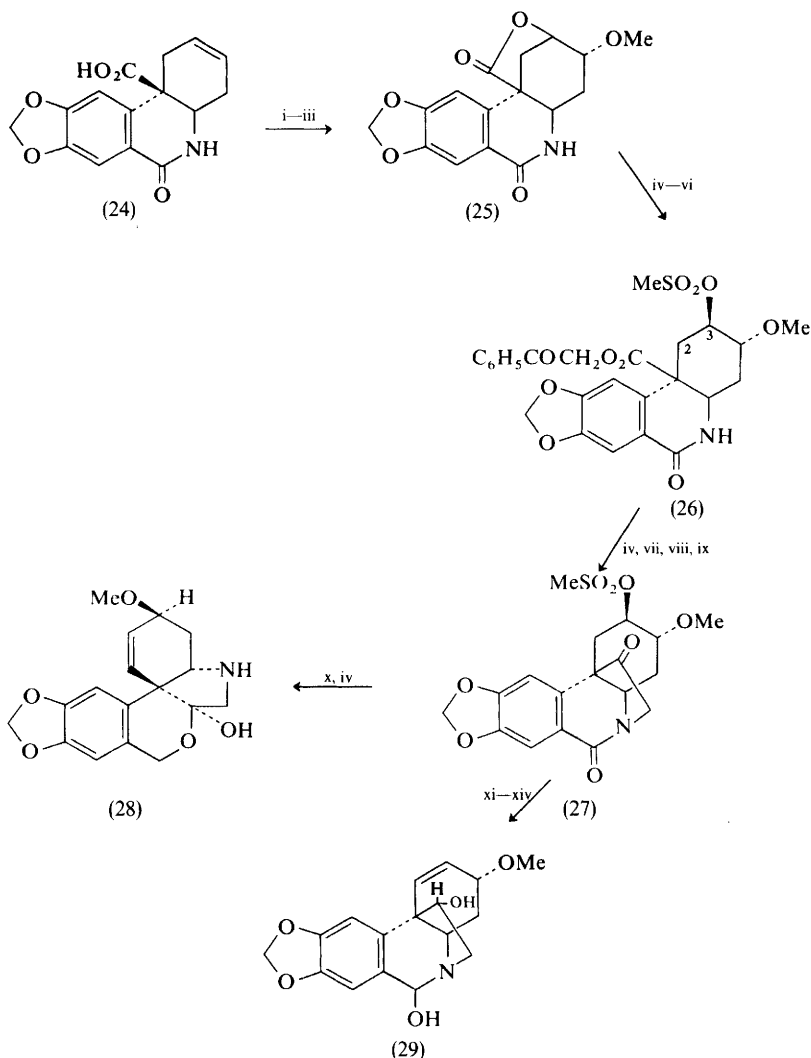
Reagents: i, KI_3, $NaHCO_3$; ii, 0.1M-NaOH; iii, BF_3–MeOH; iv, base; v, $C_6H_5COCH_2Br$, DMF; vi, $MeSO_2Cl$, pyridine; vii, $SOCl_2$; viii, CH_2N_2; ix, dry HCl; x, $NaBH_4$, Pr^iOH; xi, disiamylborane, THF; xii, Ac_2O; xiii, DBN; xiv, $LiAlH_4$.

Scheme 2

$Y = O$).[24] The latter was converted by lithium aluminium hydride reduction and methylation into ($\pm$)-*N*-benzylgalanthamine iodide [4; $R^1 = OH$, $R^2 = H$; $MeN \cdot CH_2 \cdot C_6H_5 \, I^-$ for NMe] which was identical with a sample prepared from ($\pm$)-galanthamine. On the other hand, oxidative coupling of the amide (30; $R = Me$, $X = O$, $Y = H_2$) under similar conditions gave the enone (31;

R = Me, X = O, Y = H$_2$) which could be converted into a mixture of ($\pm$)-galanthamine (4; R^1 = OH, R^2 = H) and ($\pm$)-epigalanthamine (4; R^1 = H, R^2 = OH) by reduction with lithium aluminium hydride. Another synthesis of galanthamine by the same group of workers involves only a slight variation on the above synthetic scheme.[25] In a separate investigation intended to provide conditions for *O*-demethylation, treatment of galanthamine with hot potassium hydroxide and hydrazine in water–diethylene glycol gave a number of products including nivalidine (7), anhydro-*O*-demethylgalanthamine (32; R = H) and its nitrogen-containing-bridge isomer, and anhydrogalanthamine (32; R = Me).[26] The last was converted under the same conditions or in boiling hydrochloric acid into nivalidine.

(30)   (31)

(32)
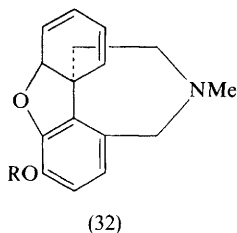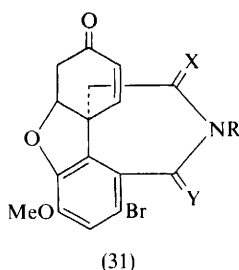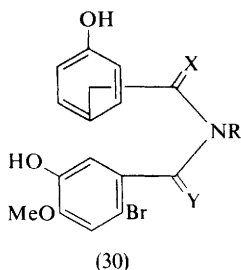
The total synthesis of dihydrolycorine (38), the sole hydrogenation product of lycorine (6; R^1 + R^2 = CH$_2$, R^3 = R^4 = H) and an alkaloid in its own right, has been reported.[27] Scheme 3 shows how treatment of the Diels–Alder adduct (33) with methanol gave a mixture of two half-esters which were directly subjected to Friedel–Crafts cyclization to give the indanone ester (34) and a rearrangement product. Attempted Schmidt ring expansion on (34) failed, but a prior reduction–oxidation sequence followed by treatment with sodium azide and hydrolysis produced the desired lactam (35) and an isomeric compound whose structure remains undetermined. Lactam (35) was readily converted into a chain-extended

[26] T. Kametani, K. Yamaki, S. Shibuya, K. Fukumoto, K. Kigasawa, F. Satoh, M. Hiiragi, and T. Hayasaka, *J. Chem. Soc. (C)*, 1971, 590.
[27] H. Irie, Y. Nishitani, M. Sugita, and S. Uyeo, *Chem. Comm.*, 1970, 1313.

carboxylic acid which was cyclized to the iodolactone (36). Treatment of this unstable compound with acid resulted in facile rearrangement to the imide (37), which was transformed to dihydrolycorine (38) to complete the synthesis. The conditions for the ultimate multi-functional reduction step may be noted; the yield in this step was only 5%.

(33) (34)

(35) (36)

(37) (38)
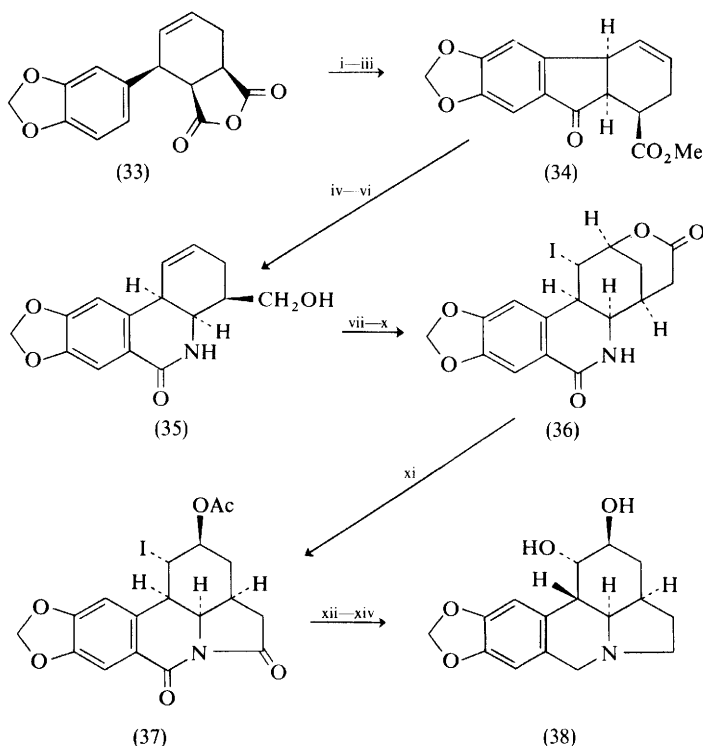
Reagents: i, MeOH; ii, PCl$_5$; iii, SnCl$_4$, CH$_2$Cl$_2$; iv, LiAlH$_4$; v, MnO$_2$; vi, NaN$_3$, CCl$_3$CO$_2$H; vii, TsCl, pyridine; viii, KCN, MeCN; ix, HCl, HOAc; x, KI$_3$, NaHCO$_3$, H$_2$O; xi, Ac$_2$O, HOAc; xii, LiCl, DMF; xiii, *m*-Cl·C$_6$H$_4$·CO$_3$H; xiv, LiAlH$_4$–ZnCl$_2$.

Scheme 3

A new synthesis of (±)-crinan (43), a compound possessing the basic ring skeleton of the alkaloid crinine, using a stereoselective photocyclization reaction has been devised.[28] The imine (39), readily prepared from 2-allylcyclohexanone and benzylamine, was acetylated with piperonyloyl chloride to give the *N*-acylenamine (40). Photolysis of (40) in methanol solution gave compound (41) (15% yield) whose structure and stereochemistry were established by spectral means and by consideration of the proposed electrocyclic nature of the reaction.

[28] I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Comm.*, 1970, 1669.

Successive ozonolysis and lithium aluminium hydride reduction provided the amino-alcohol (42) which upon catalytic debenzylation followed by treatment with thionyl chloride gave (±)-crinan (43). Alternatively, compound (42) was converted *via* its tosylate into the corresponding iodide, which upon hydrogenolysis also produced (±)-crinan. It may be envisaged that the key photocyclization step could also be used for the synthesis of functionalized crinan alkaloids.

(39)

(40)   (41)

(42)   (43)
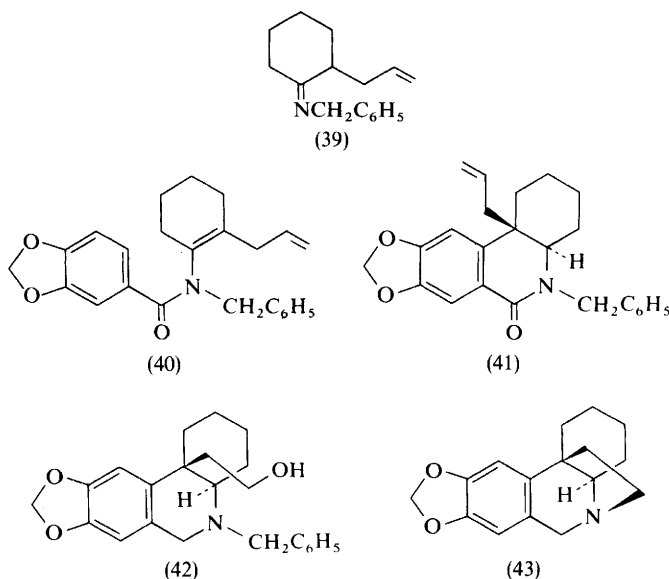
A different approach which likewise may have generality for crinan alkaloid synthesis has been reported.[29] This approach utilizes two key reactions which may now be accepted as general principles in alkaloid synthesis: (*a*) the acid-catalysed thermally-induced rearrangement of cyclopropyl imines (45) → (46), which had been used previously for the preparation of mesembrine (10; $R^1 + R^2 = O, R^3 = Me$; *a,b*-dihydro), and (*b*) the methyl vinyl ketone annelation to an endocyclic enamine[(46) → (47)], which has also been applied in the synthesis of mesembrine as well as *Erythrina*, hasubanan, and *Aspidosperma* alkaloids. Piperonyl cyanide (44) was converted (Scheme 4) into the cyclopropyl imine (45) in three steps. The latter was transformed *via* the enamine (46) into compound (47) using the two key reactions adduced above. Successive reduction and debenzylation provided the alcohol (48) which was subjected to a Pictet–Spengler reaction under carefully defined conditions to give (±)-3-epi-elwesine (49), a known minor alkaloid of *Galanthus elwesii*. A modification of the annelation reaction [(46) → (47)] to cyclic enamines, indicated conceptually by

[29] R. V. Stevens and L. E. DuPree, jun., *Chem. Comm.*, 1970, 1585.

[(50) → (51) or (52)], has been presented in preliminary form.[30] This method, which has been generalized, holds the advantages that rings of different sizes may be formed and that the reactive enamine functions obtained in the products [(51) or (52)] may serve as handles for further modification.

(44)   (45)   (46)

(47)

(48)   (49)
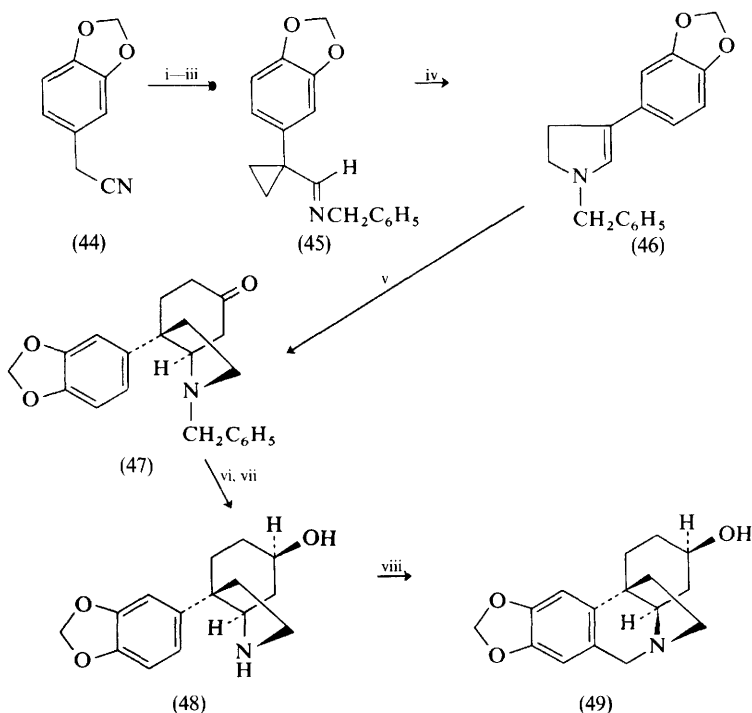
Reagents: i, $(CH_2Br)_2$, $LiNH_2$; ii, Bu^i_2AlH; iii, $C_6H_5CH_2NH_2$, $CaCl_2$, C_6H_6; iv, NH_4Cl, heat; v, $CH_2=CHCOMe$, H^+; vi, $NaBH_4$; vii, conc. HCl, H_2, Pd–C, MeOH; viii, 6M-HCl, CH_2O, MeOH.

Scheme 4

The first total synthesis of chiral cherylline (55), a rare phenolic Amaryllidaceae alkaloid, has been fully described.[31] Resolution of the previously synthesized (±)-phenethylamine (53) with (−)-diacetone-2-keto-L-gulonic acid gave the (2R)-(+)- and (2S)-(−)-L-gulonate salts, which were transformed into the diastereomeric hydrobromides; the latter were formylated, subjected to Bischler–Napieralski cyclization conditions, and debenzylated to yield the (4R)-(+)- and (4S)-(−)-dihydroisoquinoline (54) hydrochlorides. These were separately selectively O-demethylated, quaternized with methyl iodide, and reduced with

[30] D. A. Evans, *J. Amer. Chem. Soc.*, 1970, **92**, 7593.
[31] A. Brossi and S. Teitel, *J. Org. Chem.*, 1970, **35**, 3559.
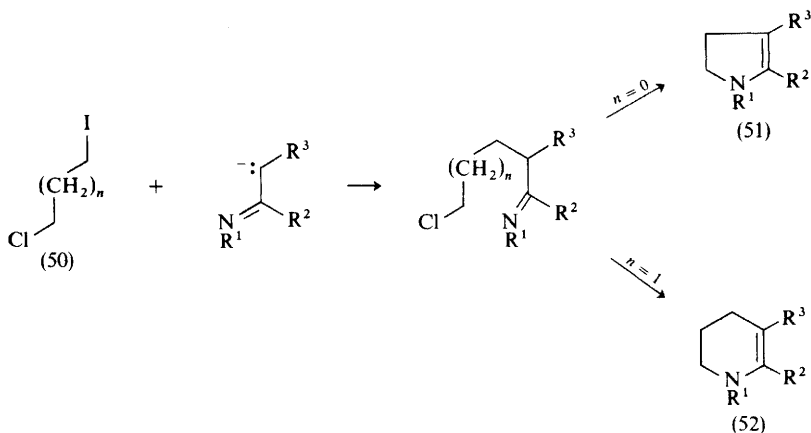
sodium borohydride to produce respectively (+)-cherylline (unnatural isomer) and the alkaloid, (−)-cherylline (55).
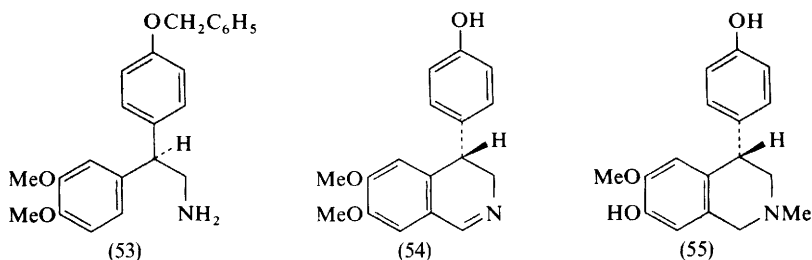
Syntheses of specifically[32] and stereospecifically[33] tritiated *O*-methylnorbelladine have been published; the latter synthesis[33] has proved useful in biosynthetic studies of certain Amaryllidaceae alkaloids.

[32] C. Fuganti, D. Ghiringelli, P. Grasselli, and M. Mazza, *Gazzetta*, 1970, **100**, 739.
[33] A. R. Battersby, J. E. Kelsey, and J. Staunton, *Chem. Comm.*, 1971, 183.

10
Erythrina and Related Alkaloids

BY V. A. SNIECKUS

A lucid introduction to this group has been published as part of a general text on the chemistry of alkaloids.[1] The relatively small and novel group of *Cephalotaxus* alkaloids which show inhibitory activity against experimental lymphoid leukemia has been briefly reviewed in a volume dedicated primarily to the interests of medicinal chemists.[2]

   A small number of new *Erythrina* and Homoerythrina alkaloids have been isolated from plant sources. Details have appeared[3] of the structural elucidation of erythroculine (1), an unusual $C(15)$-methoxycarbonyl-substituted alkaloid from *Cocculus laurifolius*. Routine spectral examination provided evidence for the nature of the skeleton (tetracyclic) and the presence of three methoxy-groups and one trisubstituted double bond. Additionally, the i.r. spectrum showed a band at $1710\ cm^{-1}$ attributed to a carbonyl function. Lithium aluminium hydride reduction of (1) gave erythroculinol (2; $R^1 = Me$, $R^2 = CH_2OH$) which showed the following salient spectral features: in the i.r., a band at $3600\ cm^{-1}$ and no carbonyl absorption; in the n.m.r., absence of a signal due to one of the methoxy-groups and instead a new singlet ($\tau 5.36$) due to a hydroxymethylene group; in the u.v., maxima at 280 and 284 nm (compare with maximum at 304 nm for erythroculine). Treatment of erythroculine with boron trichloride gave a phenol (2; $R^1 = H$, $R^2 = CO_2Me$) whose i.r. spectrum showed bands at 3200 and $1675\ cm^{-1}$. The large shift of the carbonyl absorption band in this compound compared to the alkaloid suggested the presence of an intramolecular hydrogen bond between the phenolic hydroxy-group and the ester, thus requiring that these functions be located *ortho* to each other. Further evidence for the substitution pattern of ring D was also obtained from the n.m.r. spectra: of the two signals in erythroculine due to the aromatic protons at $\tau 3.29$ and 2.51, the former appeared broad and possibly coupled to benzylic protons. The sharp signal at $\tau 2.51$ appeared at higher field by 0.54 p.p.m. in erythroculinol (2; $R^1 = Me$, $R^2 = CH_2OH$), indicating that this proton is located at the *ortho* position to the methoxycarbonyl group. That the coupled proton was situated *ortho* to the

[1] A. Mondon in 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, p. 173.
[2] M. Shamma, *Ann. Rep. Med. Chem.*, 1969, 323.
[3] Y. Inubushi, H. Furukawa, and M. Juichi, *Chem. Pharm. Bull. (Japan)*, 1970, **18**, 1951.

methoxy-group was confirmed by acid-catalysed deuterium exchange experiments on both erythroculine and erythroculinol. For example, it was observed that the relative intensity of the higher field signal ($\tau 3.29$) to the downfield signal ($\tau 2.51$) in erythroculine decreased upon exchange and, in fact, that the latter signal was unaffected. The environment of the nitrogen in erythroculine was established by Hofmann degradation of the alcohol ($2; R^1 = Me$, $R^2 = CH_2OH$) and the information on the relative positions of the double bond and the non-aromatic methoxy-group was obtained from its mass spectrum. The latter showed a predominant and diagnostic $M - 58$ peak due to a retro-Diels–Alder fragmentation involving the loss of methoxyethylene. A classical degradation route of erythroculine gave the biphenyl derivative (3) thus establishing the relative position of the methoxycarbonyl group as indicated in structure (1). Finally, this was firmly defined and the complete stereochemistry was established by a neat chemical correlation of erythroculine with the known tetrahydroerysotrine ($4; R = OMe$). Catalytic hydrogenation of erythroculine followed by lithium aluminium hydride reduction and treatment with silver oxide in 85 % phosphoric acid yielded the aldehyde ($4; R = CHO$). The latter was subjected to a Baeyer–Villiger oxidation with performic acid, and the resulting product was treated with diazomethane to yield tetrahydroerysotrine ($4, R = OMe$). Erythroculine (1) represents only the third example of the biogenetically interesting $C(15)$-methoxycarbonyl *Erythrina* alkaloids.

A new alkaloid, 11-methoxyerythraline ($5; R^1 + R^2 = CH_2$, $R^3 = OMe$) has been isolated from *Erythrina lysistemon* and its structure has been established mainly by comparison of its spectral data with those of known alkaloids possessing similar functional features.[4] In particular, the n.m.r. spectrum of 11-methoxy-erythraline was very similar to that of the known erythristemine ($5; R^1 = R^2 = Me$, $R^3 = OMe$) and exhibited the additional feature of well-separated peaks for all the protons, which facilitated its detailed interpretation with the aid of the INDOR technique. The same plant species also yielded erysotrine ($5; R^1 = R^2 = Me$, $R^3 = H$). Catalytic reduction of erysotrine gave the dihydro product ($2; R^1 = Me$, $R^2 = OMe$) resulting from 1,4-addition of hydrogen. Its structure was suggested on the basis of a characteristic base peak at $M - 58$ and similarity of n.m.r. spectrum to those of other alkaloids containing a 1,6 double bond. The claim[4] that erysotrine has not been previously isolated from natural sources is incorrect since it had been reported somewhat earlier that this alkaloid, together with erythraline ($5; R^1 + R^2 = CH_2$, $R^3 = H$) and erysodine ($5; R^1 = R^3 = H$, $R^2 = Me$) had been obtained from *Erythrina suberosa*.[5] Erythraline together with erysovine ($5; R^1 = Me$, $R^2 = R^3 = H$) have been found in *Erythrina variegata* var. *orientalis*.[6]

The seeds of *Erythrina lithosperma* have yielded an alkaloid, erythrinine ($C_{30}H_{36}O_5N_4$), whose structure has not been elucidated.[7] Erythrinine contains

[4] R. M. Letcher, *J. Chem. Soc.* (*C*), 1971, 652.
[5] H. Singh and A. S. Chawla, *J. Pharm. Sci.*, 1970, **59**, 1179.
[6] H. Singh and A. S. Chawla, *Planta Med.*, 1971, **19**, 71.
[7] S. P. Tandon, K. P. Tiwari, and A. P. Gupta, *Proc. Nat. Acad. Sci., India, Sect. A*, 1969, **39**, 263 (*Chem. Abs.*, 1970, **73**, 77 454r).

(1)   (2)   (3)

(4)   (5)
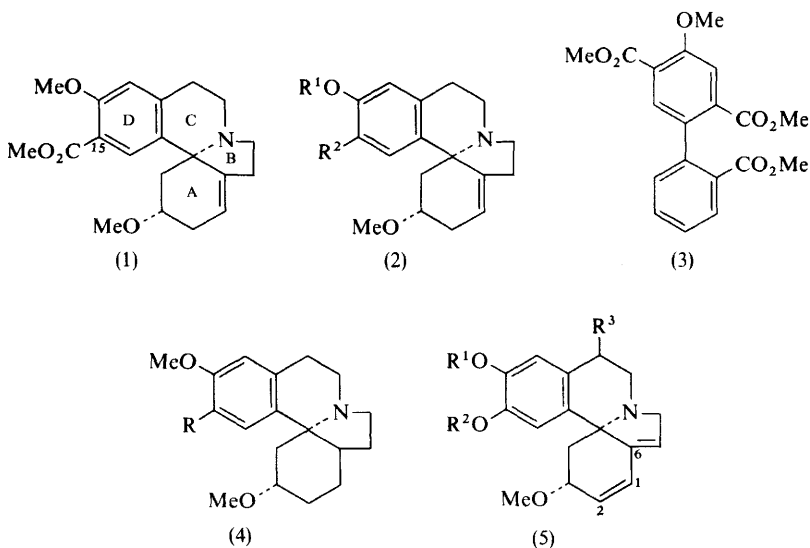
four methoxy-groups, a CONH function and all nitrogen atoms as part of ring systems.

Recent investigations have shown that the *Phelline* genus (Ilicaceae), indigenous to New Caledonia, is rich in Homoerythrina alkaloids. Two alkaloids whose structures (6; R = H and Me) have not as yet been fully elucidated were isolated from *Phelline billardieri*.[8] On the other hand, details of the structural determination of seven alkaloids from *P. comosa* have now appeared.[9] The major alkaloids, $(7; R^1 + R^2 = CH_2)$ and $(7; R^1 = R^2 = Me)$ both showed in their n.m.r. spectra appropriate signals for two *para* aromatic protons; additionally, the former exhibited the presence of a methylenedioxy singlet at δ 5.86 and the latter two singlets at δ 3.76 and 3.84, attributed to two aromatic methoxy-groups. From the n.m.r. spectra it was also clear that both alkaloids possessed a non-aromatic methoxy-group and a disubstituted double bond. Examination of their mass spectra confirmed that the two structures differed only in the substitution of the aromatic ring. The major peaks $(M - 31)$ and $(M - 73)$ were readily interpreted in terms of fragments $(8; R^1 + R^2 = CH_2$ or $R^1 = R^2 = Me)$ and $(9; R^1 + R^2 = CH_2$ or $R^1 = R^2 = Me)$ respectively, but one other intense peak at $M - 45$, present in the spectra of both alkaloids, remained unexplained. von Braun reaction on $(7; R^1 + R^2 = CH_2)$ and $(7; R^1 = R^2 = Me)$ resulted in aromatization typical of the *Erythrina* alkaloids to give the cyanoamides (10; $R^1 + R^2 = CH_2$) and $(10; R^1 = R^2 = Me)$ respectively. One of these (10; $R^1 + R^2 = CH_2$) was found to be identical with the product of the same degradation

[8] N. M. Hoang, N. Langlois, B. C. Das, and P. Potier, *Compt. rend.*, 1970, **270**, C, 2154.

[9] N. Langlois, B. Das, P. Potier, and L. Lacombe, *Bull. Soc. chim. France*, 1970, 3535.

carried out on (11; R = H), an alkaloid previously isolated from *Schelhammera pedunculata*[10] and also found in *Phelline comosa*. The gross structure was thus established. The elucidation of the stereochemistry was carried out with the aid of 100 MHz n.m.r. spectra. In deuteriated benzene, it was possible to analyse completely the proton pattern of ring A. In particular, the large coupling constant between $C(3)$-H and $C(4)$-H ($J = 10.7$ Hz) indicated that the former was pseudo-axially oriented. Treatment of (7; $R^1 + R^2 = CH_2$) with 10% hydrochloric acid yielded the allylic alcohol (12) whose n.m.r. spectrum showed a triplet due to $C(4ax)$-H ($J_{4ax, 4eq} \sim J_{4ax, 3eq} = 11$ Hz) indicating that the $C(3)$-OH function was in a pseudo-equatorial arrangement and thus that no epimerization had taken place in the acid-catalysed reaction. Finally, the alcohol (12) was found to be identical with another alkaloid isolated from *Schelhammera pedunculata* whose structure and stereochemistry had been conclusively established.[10] Thus the stereochemistry of (7; $R^1 + R^2 = CH_2$) was defined. Likewise, the stereochemistry of (7; $R^1 = R^2 = Me$) is probably represented by that of (12) with the remaining uncertainty as to the configuration of C(5) which could not be determined by c.d. studies.

(6)   (7)   (8)

(9)   (10)   (11)
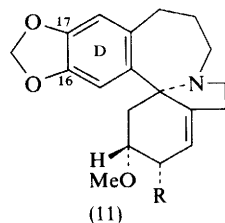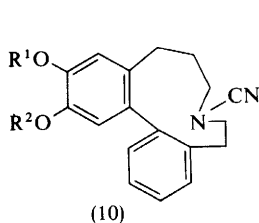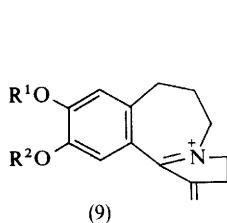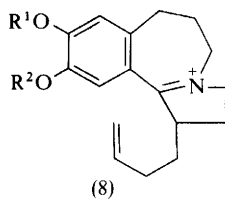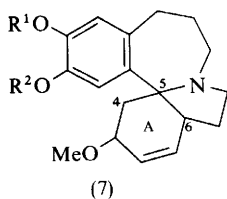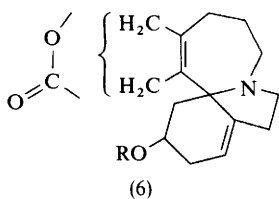
Similar spectral and other degradation studies completely define the structures of two other alkaloids as (11; R = OH) and (11; R = H).[9] As noted earlier, the compound (11; R = H) was found to be identical with an alkaloid isolated from another plant source. Another alkaloid was assigned the gross structure and stereochemistry of (11; R = H), except that ring D was shown to contain one methoxy-group rather than the methylenedioxy function. The location of the methoxy-function [either C(16) or C(17)] remains to be assigned.

[10] 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1970, Vol. 1, p. 148.

Interpretation of spectral data of the two remaining new alkaloids obtained from *Phelline comosa* (13; $R^1 + R^2 = CH_2$) and (13; $R^1 = R^2 = Me$) led to the inescapable conclusion that one of the four oxygen-containing functions must form part of an epoxide ring and this was confirmed by lithium aluminium hydride reduction of the two alkaloids to yield the alcohols (14; $R^1 + R^2 = CH_2$, $R^3 = H$) and (14; $R^1 = R^2 = Me$, $R^3 = H$) respectively. The mass spectra of the alcohols showed peaks at *m/e* 232 and *m/e* 216, respectively, attributed to the C/D ring fragment of (14) (dotted line) and confirmed by studies of the corresponding deuteriated alcohols (14; $R^1 + R^2 = CH_2$, $R^3 = D$) and (14; $R^1 = R^2 = Me$, $R^3 = D$) obtained by lithium aluminium deuteride reduction of the epoxide-containing alkaloids. On the other hand, catalytic hydrogenation of these alkaloids gave the allylic alcohols (15; $R^1 + R^2 = CH_2$, $R^3 = H$) and (15; $R^1 = R^2 = Me$, $R^3 = H$) whose structures were established by detailed n.m.r. spectral analysis with the aid of decoupling experiments. Finally, compound (15; $R^1 + R^2 = CH_2$, $R^3 = H$) was transformed by successive treatment with thionyl chloride and lithium aluminium hydride into the alkaloid (11; $R = H$) of known structure and stereochemistry, thus confirming the configurations of the $C(3)$-OMe function and the $C(5)$-spiro-centre in (13; $R^1 + R^2 = CH_2$) as written. Compounds (13; $R^1 + R^2 = CH_2$) and (13; $R^1 = R^2 = Me$) represent the first examples of *Erythrina* and Homoerythrina alkaloids exhibiting an epoxide function. Apparently the presence of alkaloids in *Phelline* poses taxonomic problems.

A detailed analysis of the mass spectra of *Erythrina* alkaloids has been published.[11] The mass spectra of compounds possessing the conjugated 1,6-diene system [*e.g.* erythraline, (5; $R^1 + R^2 = CH_2$, $R^3 = H$)] showed similar fragmentation patterns which may be summarized by Scheme 1. The major pathways

(12)

(13)

(14)

(15)

(16)

(17)
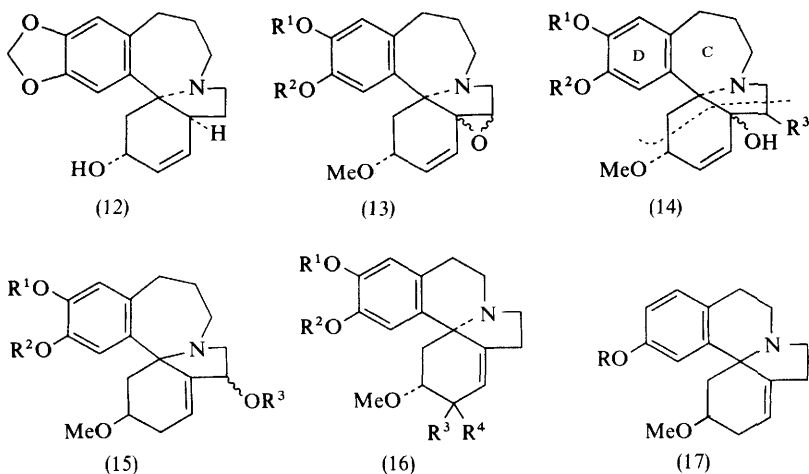
[11] R. B. Boar and D. A. Widdowson, *J. Chem. Soc.* (*B*), 1970, 1591.

were shown not to involve the aromatic ring D by the observation that the mass spectrum of a $C(17)$-deuteriated compound differed from that of the undeuteriated alkaloid only in that all the abundant peaks were displaced upwards by one mass unit. Metastable ions for $(M - 31)$ and $(M - 58)$ peaks were observed and studies with $C(2)$-deuteriated erythraline indicated that loss of deuterium, and thus loss of $C(2)$ occurred only in the formation of fragments from cleavage at e and f (Scheme 1). On the other hand, the mass spectra of alkaloids exhibiting a 1,6 double bond [*e.g.* erythratine $(16; R^1 + R^2 = CH_2, R^3 = OH, R^4 = H)$] were similar to the above group only in that an ion $(M - 58)$ corresponding to a retro-Diels–Alder reaction was again prominent. The ions $M - 15$ and $M - 31$ were of minor importance in the spectra of the alkaloids with 1,6-unsaturation. Examination of the spectra of erythratine, erythratine benzoate, chloroerythramine $(16; R^1 + R^2 = CH_2, R^3 = Cl, R^4 = H)$, and $C(2)$-deuteriated erythratine $(16; R^1 + R^2 = CH_2, R^3 = OH, R^4 = D)$, together with detection of appropriate metastable peaks, led to the interpretation outlined in Scheme 2 for the deuteriated alkaloid. Analysis of the spectrum of chloroerythramine gave definite information about the constitution of the base peak at m/e 241. Two pathways for fragmentation were deduced for this compound: (a) loss of Cl and HCl from the molecular ion $(m/e$ 333) and formation of erythraline $(5; R^1 + R^2 = CH_2, R^3 = H)$ and (b) loss of $MeOCH CHCl$ to give an ion at m/e 241 which further lost H to give m/e 240, and a retro-Diels–Alder fragmentation to an ion at m/e 275. The last ion $(M - 58)$ apparently could not fragment in the manner observed for erythratine $(16; R^1 + R^2 = CH_2, R^3 = OH, R^4 = H)$ but rather underwent loss of Cl to yield the ion at m/e 240. Metastable peaks confirmed the two distinct pathways for the formation of the m/e 240 ion.

$(5; R^1 + R^2 = CH_2, R^3 = H)$

a, $M - 15$
b, $M - 31$
c, $M - 32$
d, $M - 58$
e, $M - 71$
f, $M - 84$
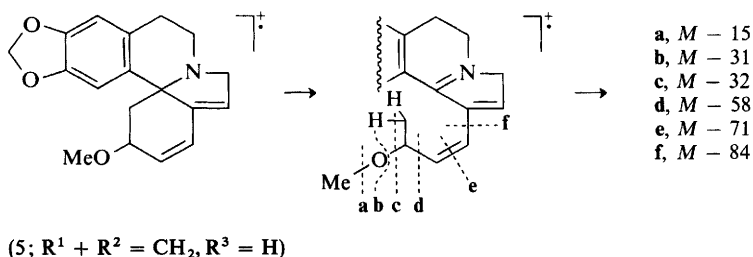
Scheme 1

The fragmentation pattern observed in the mass spectrum of erythratinone $(16; R^1 + R^2 = CH_2, R^3 + R^4 = O)$ showed a major difference in that there was complete absence of the erythratine-type fragmentation to an ion at m/e 241. Instead, a strong peak at $M - 43$ $(m/e$ 270) was observed for erythratinone, attributed to the preference of this compound to undergo fragmentation by loss of carbon monoxide (Scheme 2).[11]
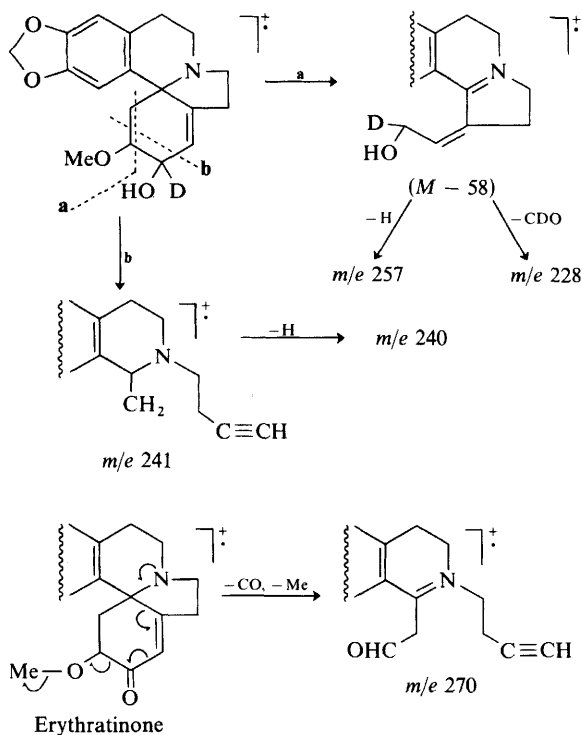
Scheme 2

The mass spectra of cocculine (17; R = H), cocculidine (17; R = Me), deuteriococculidine (17; R = D) and a degradation product of cocculidine have been studied.[12]

The early structural elucidation and synthetic studies by Boekelheide and by Mondon on aromatic *Erythrina* alkaloids led to the assignment of *cis* stereochemistry at the ring A/B junction (*e.g.* (20; X = H$_2$)]. Since that time, the German group have been interested in preparing corresponding *trans* systems, and the details of their studies have now appeared.[13—15] One such study concerned a reinvestigation of the pioneering work of Belleau, who had assigned the structure (19) to the product obtained by successive polyphosphoric acid and lithium aluminium hydride reactions on the ketolactam (18).[13] Compound (19) was shown not to be identical with the *cis*-isomer (20; X = H$_2$) which had been

[12] S. Yu. Yunusov and R. Razakov, *Khim. prirod. Soedinenii*, 1970, **6**, 74 (*Chem. Abs.*, 1970, **73**, 35 585d).

[13] A. Mondon and B. Neffgen, *Chem. Ber.*, 1970, **103**, 3050.

[14] A. Mondon, *Chem. Ber.*, 1971, **104**, 270.

[15] A. Mondon and P. R. Seidel, *Chem. Ber.*, 1971, **104**, 279.

prepared previously by an alternative synthesis. The latter was also obtained
from *cis*-erythrinane (21; R = H) and from 16-methoxy-*cis*-erythrinane (21;
R = OMe) thus firmly establishing its stereochemistry. The intriguing possibility
existed, therefore, that Belleau's base (19) exhibited a *trans*-A/B ring stereo-
chemistry. Repetition of the original polyphosphoric acid cyclization reaction
on (18) gave a mixture of spirolactams (20; X = O) and (22) in ratios 3:1 (at
100 °C) or 1:3 (150 °C). Reduction of the 3:1 mixture with lithium aluminium
hydride gave mainly the *cis*-base (20; X = H$_2$) while reduction of the 1:3 mixture
under the same conditions did yield the base (picrate m.p. 178–179 °C) described
by Belleau. However, n.m.r. and mass spectral measurements showed that this
compound is not a *trans*-A/B erythrinane but, rather, corresponds to the hexa-
hydro-*cis*-erythrinane (23). The stereochemistry at positions 12 and 13 in
compound (23) was not established; an attempt to do this by catalytic reduction
of (20; X = H$_2$) under forceful conditions failed.

(18)   (19)   (20)

(21)   (22)   (23)
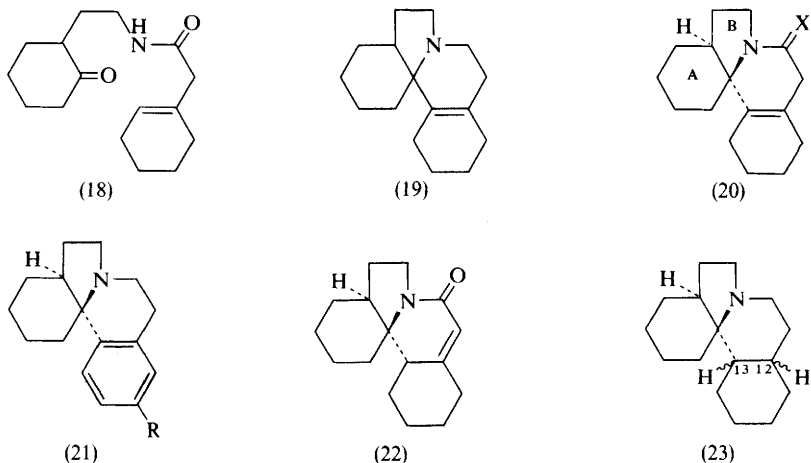
The first ring A/B-*trans* erythrinane compound (25; β-OH) was obtained,
together with the epimeric alcohol (25; α-OH) and other products, by Wolff–
Kishner reduction of the 6α-bromoketolactam (24).[14] As an interesting sidelight,
the reaction of (25) with mineral acid was undertaken. Dissolution of (25; α-OH)
in 50 % sulphuric acid produced a yellow colour due to the intermediate imminium
cation (26). Basification of this solution with sodium carbonate gave the known
isomeric hydroxylactam (27). A similar colour change was observed when
(25; β-OH) was dissolved in sulphuric acid, indicating the intermediacy of (26), but
a product was not isolated in this case, presumably owing to some further re-
arrangement. The mass spectra of the two isomeric hydroxylactams (25; α-OH)
and (25, β-OH) differed significantly in that only in the latter was there observed a
$M - 18$ peak. This is probably due to the sterically unhindered nature of the
C(6)-OH function in (25; β-OH) leading to facile loss of a molecule of water.

Two other interesting products, assigned structures (28) and (29), were obtained in the Wolff–Kishner reduction of compound (24).[14]

MeO   OMe
(24)

MeO   OMe
(25)

MeO   OMe
(26)

MeO   OMe
(27)

MeO   OMe
(28)

MeO   OMe
(29)
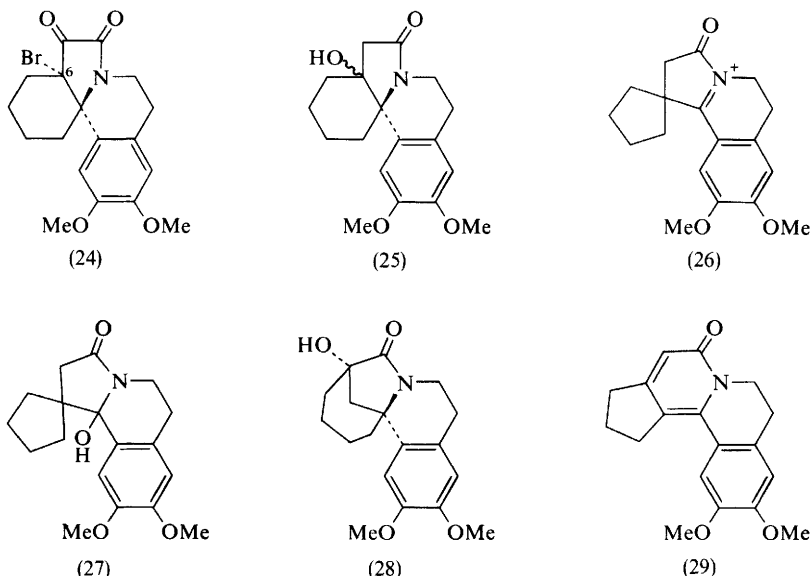
The enol-lactam (30), which has occupied a central role in the synthesis of *Erythrina* alkaloids, has been converted in an unprecedented reaction into the dimeric isomers [31; $C(6)$-α-O] and [31; $C(6)$-β-O].[15] This reaction may be effected in benzene, pyridine, or acetic acid solution in the presence of lead tetra-acetate. The structures of the products were elucidated by spectral and chemical means. As enol ethers, these compounds were found to exhibit surprising stability to mineral acids. However, catalytic reduction of [31; $C(6)$-α-O] under neutral conditions gave the starting enol-lactam (30) and the 7β-hydroxylactam (32; $R^1 = OH$, $R^2 = R^3 = H$). The dimer [31; $C(6)$-β-O] yielded only compound (32; $R^1 = OH$, $R^2 = R^3 = H$). Similarly, sodium borohydride reduction of the dimer mixture in hot isopropanol led to cleavage products (32; $R^1 = OH$, $R^2 = R^3 = H$) and (32; $R^1 = R^3 = H$, $R^2 = OH$). Besides the dimeric products, compound (32; $R^1 + R^2 = O$, $R^3 = OAc$) was also isolated from the lead tetra-acetate oxidation in low yields. Attempts to discover conditions for the formation of preparative amounts of (32; $R^1 + R^2 = O$, $R^3 = OAc$), a compound of more potential usefulness for alkaloid synthesis, were fruitless. The other question of interest, whether or not the *trans*-dimer [31; $C(6)$-β-O] could be converted into a monomeric *trans*-erythrinane system, remains to be answered.

The dienone (34), a proposed intermediate in the biosynthesis of *Erythrina* alkaloids, has been obtained by the phenolic oxidative coupling reaction of the norprotosinomenine derivative (33) with potassium ferricyanide in the presence

(30)

(31)

(32)

(33)

(34)

(35)
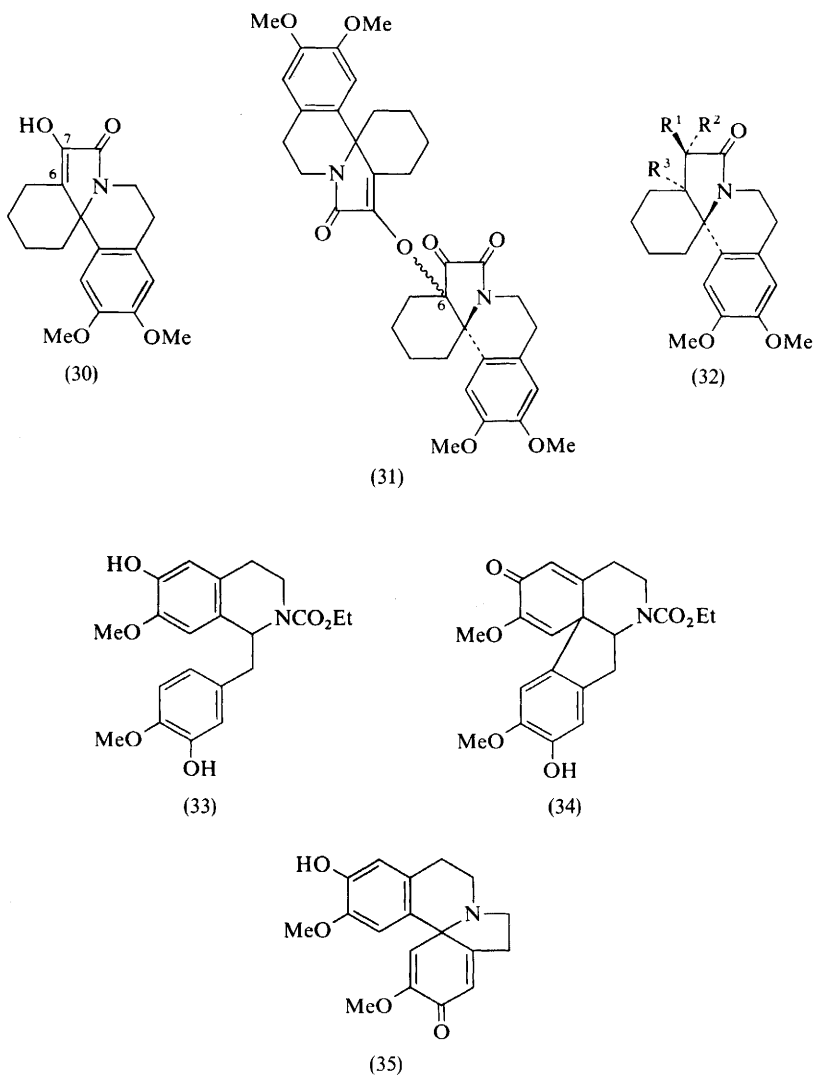
of ammonium acetate and ammonia.[16] Unfortunately, simulation of the next proposed biosynthetic step, the conversion of the 'proerythrinandienone' into an *Erythrina* skeleton [(34) → (35)] was apparently not investigated in sufficient detail (see also Chapter 8, Section 3D).

[16] T. Kametani, R. Charubala, M. Ihara, M. Koizumi, and K. Fukumoto, *Chem. Comm.*, 1971, 289.

11
Indole Alkaloids

BY J. A. JOULE

The material is presented in a similar order to that used in last year's report[1a] on this group of alkaloids, but this year bis-indole alkaloids are included in this section. Within each sub-section the order is (i) mention of full reports which contain material already reviewed, (ii) isolation of known alkaloids from different plants, (iii) new physical measurements on known alkaloids or systems, (iv) new chemistry of known alkaloids or systems, (v) new structures, together with supporting chemical and physical evidence, (vi) synthesis of model systems, (vii) partial synthesis of alkaloids, (viii) total synthesis of alkaloids.

1 Simple Alkaloids

Non-tryptamines.—In the *Murraya* carbazoles area, more details[2] of the structural work on murrayacine[1a] (1a) have been given. The alkaloid isomahanimbine[1a] (1b) has unfortunately been given a second name*, mahanimbicine, in an independent structure determination.[3] The hexacyclic bicyclomahanimbicine was also isolated in this investigation;[3] it is related to the tetracyclic mahanimbicine (= isomahanimbine) as bicyclomahanimbine is[1a] to mahanimbine, and can likewise be obtained from the tetracyclic compound by acid treatment.

Murraya exotica has yielded[5] 3-formylindole; it would be intriguing to know if the biogenesis of this simple indole is related to that of the *Murraya* carbazoles, for which it has been postulated that the methyl-substituted C or A rings are derived from an indole by interaction with an isoprene unit.

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1 a J. A. Joule in 'The Alkaloids,' ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1971, vol. 1, p. 150; b A. R. Battersby, *ibid.*, p. 31.
2 D. P. Chakraborty, K. C. Das, and B. K. Chowdhury, *J. Org. Chem.*, 1971, **36**, 725.
3 S. P. Kureel, R. S. Kapil, and S. P. Popli, *Chem and Ind.*, 1970, 958.
4 a S. P. Kureel, R. S. Kapil, and S. P. Popli, *Experientia*, 1969, **25**, 790; b N. S. Narasimhan, M. V. Paradkar, and S. L. Kelkar, *Indian J. Chem.*, 1970, **8**, 473; c D. P. Chakraborti, K. C. Das, and A. Islam, *J. Indian Chem. Soc.*, 1970, **47**, 1197.
5 B. K. Chowdhury and D. P. Chakraborty, *Phytochemistry*, 1971, **10**, 481.

* Koenimbidine 1a (1c) was termed both koenigicine[4a] and koenidine[4b] in another set of parallel investigations; the number and similarity of names for the twenty-one *Murraya* and *Clausena* alkaloids is very confusing; it is to be hoped that at least any newly-discovered compounds in this series can be named as derivatives either of one of the known alkaloids or of the basic tetracyclic nucleus.

The phenolic carbazoles mahanine[4b] (1d), koenine[4b] (1e), koenigine[4b] (1f), and heptazoline[4c] (which is 8-hydroxyheptaphylline[1a]) from *Clausena heptaphylla* have been characterized by the spectral methods[1a] now standard for this group.
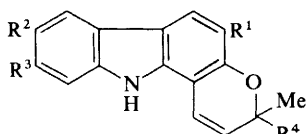
(1)	R¹	R²	R³	R⁴
a;	CHO	H	H	Me
b;	H	Me	H	$(CH_2)_2CH:CMe_2$
c;	Me	MeO	MeO	Me
d;	Me	H	HO	$(CH_2)_2CH:CMe_2$
e;	Me	HO	H	Me
f;	Me	MeO	HO	Me
g;	Me	MeO	H	Me
h;	Me	H	H	$(CH_2)_3 \cdot C(OH)Me_2$
i;	Me	H	H	$(CH_2)_2CH:CMe_2$
j;	Me	H	H	Me

(1i) $\xrightarrow{\text{i, ii}}$ (1h)
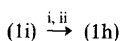
Reagents: i, $m\text{-}Cl \cdot C_6H_4CO_3H$; ii, $LiAlH_4$.

Scheme 1

Koenine[4b,6] and koenigine[4b] were *O*-methylated to give koenimbine (1g) and koenimbidine (1c) respectively. The structure of mahanimbine (1h) was established by partial synthesis[7] (Scheme 1) from mahanimbine (1i). 2-Hydroxy-6-methylcarbazole reacts with citral to give (±)-isomahanimbine (1b).[3] 2-Hydroxy-3-methylcarbazole and 2,6-dihydroxy-3-methylcarbazole have been converted[6] into girinimbine (1j) and koenine (1e), respectively, by reaction with 3-hydroxy-3-methylbutyraldehyde dimethylacetal; Scheme 2 shows the total syntheses of koenine (1e) and koenimbine (1g).

+ structural isomer
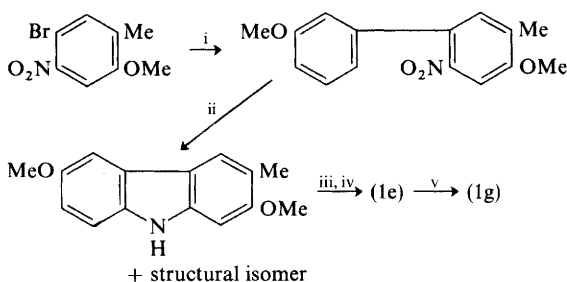
Reagents: i, $Cu\text{--}m\text{-}MeO \cdot C_6H_4I$; ii, $(EtO)_3P$–heat; iii, pyridine–HCl at 220 °C; iv, $Me_2C(OH)\text{-}CH_2CH(OMe)_2$–pyridine at 160 °C; v, $Me_2SO_4\text{--}K_2CO_3\text{--}Me_2CO$.

Scheme 2

⁶ S. P. Kureel, R. S. Kapil, and S. P. Popli, *Chem. and Ind.*, 1970, 1262.
⁷ S. P. Kureel, R. S. Kapil, and S. P. Popli, *Experientia*, 1970, **26**, 1055.

Non-isoprenoid Tryptamines.—The relative stereochemistry at C(8a) in gene-serine (2) has now been established,[8] most simply by observing[8a] a nuclear Overhauser effect between the *cis*-related C(3a)-methyl group and the C(8a)-hydrogen. The aromatic-ring oxygen substituent (MeNHCO$_2$—) in physo-stigmine can be removed[9] to give deoxyeseroline (10% yield) by irradiation at 300nm in propan-2-ol.

The relative stereochemistry and preferred conformation shown in (3) have been assigned[10] to elaeocarpidine. The alkaloid itself and the 7,20-dideuterio-derivative had strong Bohlmann absorption, showing the N(4) lone pair to be axial; since the C—D stretching frequencies, 1990 and 1935 cm^{-1}, of C(7)—D and C(20)—D, are consistent with these bonds being *trans*-diaxially related to one and two lone pairs respectively, the configuration and conformation (3) follow. The assignment is in accord with the failure to epimerize C(7) in acid or base and with the formation of only the natural isomer in a synthesis[10] which could in principle have given the alternative stereoisomer as well.

Isolated from the woad plant, *Isatis tinctoria*, as a bistetramethylammonium salt, and co-occurring with glucobrassicin (4a) and neoglucobrassicin (4b), there has been obtained another 3-indolylglucosinolate (4c), which is the first natural indole *N*-sulphonate to be recognized.[11] The location of the sulphonate sub-stituent was established by the absence of the characteristic i.r. and n.m.r. spectral
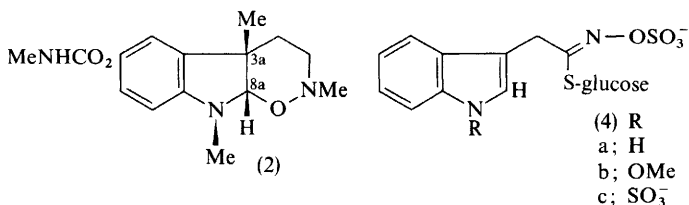
properties of indole *N*-hydrogen and the presence of an n.m.r. signal (2.62τ) for indole α-hydrogen comparable to that (2.74τ) observed for the corresponding proton of (4a). Surprisingly, the u.v. spectrum of (4c) was affected by neither acid nor base.

Methyl tryptophan ester derivatives having —NHMe and —ṄMe$_3$ groups have been isolated from *Aotus subglauca*[12a] and *Abrus precatorius*[12b], respectively. *Shepherdia* species have given,[13a] as well as 6-hydroxytryptamine, 7-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline and 7-acetoxy-2-acetyl-1-methyl-1,2,3,4-tetrahydro-β-carboline; from *Picrasma* species[13b,c] 1-ethyl-4-methoxy-β-

[8] [a] B. Robinson and D. Moorcroft, *J. Chem. Soc. (C)*, 1970, 2077; [b] F. G. Riddell, D. A. R. Williams, C. Hootelé, and N. Reid, *J. Chem. Soc. (B)*, 1970, 1739.
[9] E. F. Travecedo and V. I. Stenberg, *Tetrahedron Letters*, 1970, 4539.
[10] G. W. Gribble, *J. Org. Chem.*, 1970, **35**, 1944.
[11] M. C. Elliott and B. B. Stowe, *Phytochemistry*, 1970, **9**, 1629.
[12] [a] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1971, **24**, 439; [b] S. Ghosal and S. K. Dutta, *Phytochemistry*, 1971, **10**, 195.
[13] [a] W. A. Ayer and L. M. Browne, *Canad. J. Chem.*, 1970, **48**, 1980; [b] E. Sanchez and J. Comin, *Anales Asoc. quim. argentina*, 1969, **57**, 57 (*Chem. Abs.*, 1971, **74**, 39 128a); [c] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1970, **23**, 629;
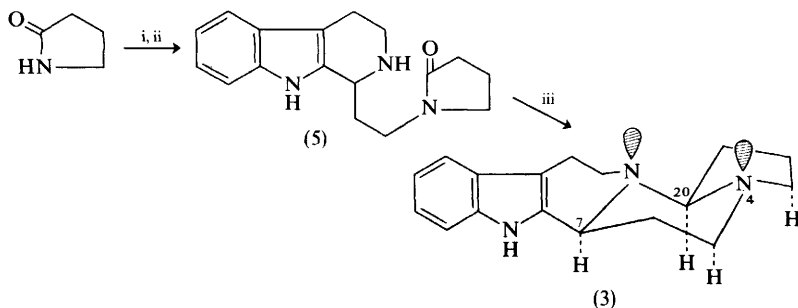
Reagents: i, $Cl(CH_2)_2CH(OEt)_2$–NaH; ii, 3-indolyl-$(CH_2)_2NH_2$; iii, $LiAlH_4$–pyrrolidine–THF at 0 °C.

Scheme 3

carboline (crenatine), 1-ethyl-4,8-dimethoxy-β-carboline (crenatidine), 7-methoxy-carbonyl-β-carboline, and 4-methoxy-1-vinyl-β-carboline have been obtained; ruine[13d] from *Peganum harmala* is 8-glucosyloxy-7-methoxy-1-methyl-β-carboline.

A synthesis[10] (Scheme 3) of ($\pm$)-elaeocarpidine avoids the production of dihydroelaeocarpidine during lithium aluminium hydride treatment of the intermediate (5) by reduction, using low temperatures, in the presence of pyrrolidine; it is considered that the secondary amine traps the partially reduced amide in the form of an N(4)–C(20)—NC_4H_8 adduct until hydrolytic work-up breaks the N—C—N systems and allows cyclization to proceed.

2 Isoprenoid-tryptamine and -tryptophan Alkaloids

Non-terpenoid Alkaloids.—De-*N*-methylation of lysergic acid and derivatives can be achieved using a variant[14] of the classical von Braun procedure which involves successive treatments with cyanogen bromide and zinc–acetic acid (or hydrogen–Raney nickel).

Ergoxine-type counterparts of natural alkaloids known in the ergotamine and ergotoxine series, but not in the ergoxine series, having valine and leucine units in the polypeptide moiety, have been synthesized[15] by adaptations of previously developed methods.

The ammonia enamine derivative[16a] of cyclopiazonic acid[16b] (6), also isolated from *Penicillium cyclopium*, was shown to have the nitrogen attached at C*; it accumulated in the later stages of fermentation and could be prepared *in vitro* by treating cyclopiazonic acid with aqueous ammonia. Bis-secodehydrocyclo-piazonic acid (7),[16a] the concentration of which reached a maximum in the early stages of fermentation, was shown to be converted *in vivo* into cyclopiazonic acid. One interesting aspect of the structure elucidation of (7) is that the C(13)-location of the isopentenyl substituent was indicated by the occurrence of ions,

[13] [d] L. Mettleship and M. Slaytor, *Phytochemistry*, 1971, **10**, 231.
[14] T. Fehr, P. A. Stadler, and A. Hofmann, *Helv. Chim. Acta*, 1970, **53**, 2197.
[15] P. Stutz, P. A. Stadler, and A. Hofmann, *Helv. Chim. Acta*, 1970, **53**, 1278.
[16] [a] C. W. Holzapfel, R. D. Hutchinson, and D. C. Wilkins, *Tetrahedron*, 1970, **26**, 5239; [b] C. W. Holzapfel, *ibid.*, 1968, **24**, 2101.

e.g. (8), in the mass spectra of both bis-secodehydrocyclopiazonic acid and cyclo-piazonic acid. To produce such ions from the former, a cyclization must occur in the spectrometer and of course can only do so when the alkenyl group is located as shown.

(8), *m/e* 154
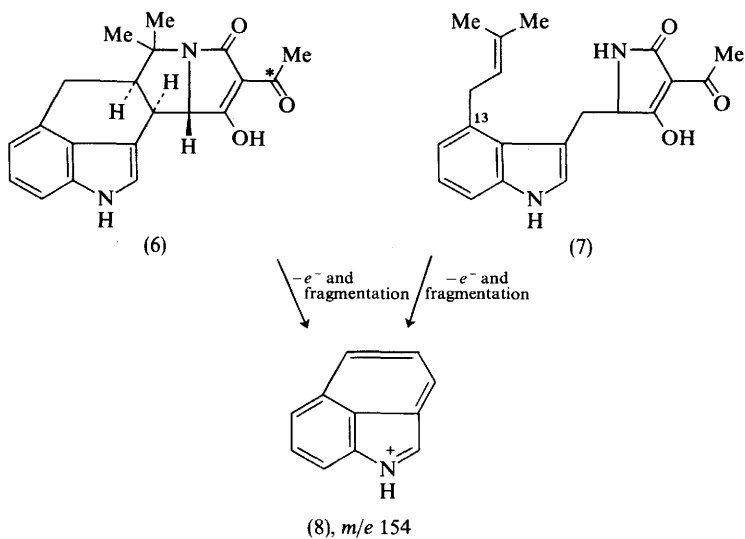
Monoterpenoid Alkaloids.—The numbering system used for this group is that originally evolved for the yohimbine skeleton and since extrapolated[1b] to all the skeletal types on the basis of the well-established[1b] biogenetic relationships between them.

The considerable differences in chemical shift positions observed for N(1)-hydrogen signals in indole, indoline, and hydroxyindole alkaloids have been noted.[17]

Yohimbine–Corynantheine (and Related Oxindoles) Group. α-Yohimbine (9a) has been isolated[18] from *Aspidosperma excelsum*. The alcohol (9b) can be produced[19] from apoyohimbine (9c) by sequential catalytic reduction, epimerization at C(16), and lithium aluminium hydride reduction, or more easily by the lithium aluminium hydride treatment of β-yohimbine 17-*O*-tosylate (9d).

By transformation[1a] of quinine into 19,20β-dihydrocinchonamine (10), the C(3) stereochemistry has been settled[20a] (α-hydrogen). Quinidine was similarly transformed[1a] into 3-epi-10-methoxy-19,20β-dihydrocorynantheol (11a).[20b]

[17] M. A. Yagudaev, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 89 (*Chem. Abs.*, 1970, **73**, 35 564w).
[18] R. H. Burnell and Nguyên-Thi-Sen, *Phytochemistry*, 1971, **10**, 895.
[19] J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Heterocyclic Chem.*, 1970, **7**, 623.
[20] *a* Y. K. Sawa and H. Matsumura, *Tetrahedron*, 1970, **26**, 2923; *b* Y. K. Sawa and H. Matsumura, *ibid.*, p. 2931.

(9)   R^1 R^2 R^3
a;   α-H   β-MeO$_2$C   α-HO
b;   β-H   α-HOCH$_2$ H
c;   β-H   MeO$_2$C   H, 16,17-dehydro
d;   β-H   α-MeO$_2$C   β-TsO

(10)
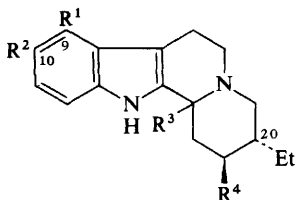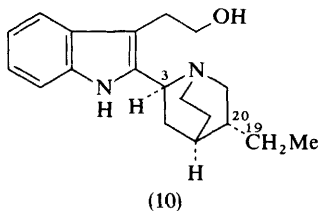
(11) R^1 R^2 R^3 R^4
a;   H   MeO   β-H   HO(CH$_2$)$_2$
b;   HO   H   α-H   MeOCH:C(CO$_2$Me)

(12) R
a;   β-H
b;   α-H

Gambirine from *Neonauclea schlechteri* is 9-hydroxy-19,20β-dihydrocory-nantheine (11b).[21] Mitrajavine (12a) from *Mitragyna javanica* can be converted[22] into its C(3)-epimer (12b) by the standard sequence of mercuric acetate followed by zinc–acetic acid.

In a study[23] of the minor alkaloids of *Alstonia constricta* the structure (13) for alstonidine was confirmed and the stereochemistry deduced from a detailed n.m.r. examination. The absence of a complex overlapping pattern for aliphatic hydrogens in such β-carbolines facilitates a complete analysis (see ref. 1a and below). This study also showed vincamajine, 17-*O*-(3,4,5-trimethoxycinnamoyl)-vincamajine, 17-*O*-(3,4,5-trimethoxybenzoyl)quebrachidine, and alstonilidine (14) to be present. The structure of the last was again susceptible to n.m.r. analysis

[21] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1970, **23**, 1285.
[22] E. J. Shellard and K. Sarpong, *Tetrahedron*, 1971, **27**, 1725.
[23] W. D. Crow, N. C. Hancox, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1970, **23**, 2489.

[see τ and J values on (14)]. Alstonilidine is another in the group of β-carboline alkaloids which lack the C(21)—N(4) bond.

(13)

(14)
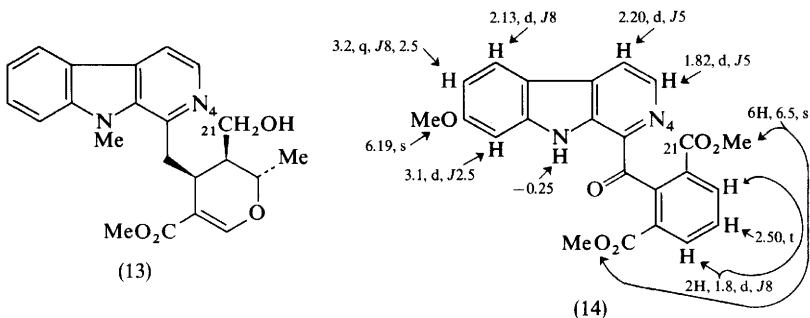
Talbotine[24] (15) from *Pleiocarpa talbotii* Wernham is a tetrahydro-version of this type; it has the C(16)—N(1) linkage which is also present in mavacurine, and indeed the present base was degraded (Scheme 4) to ε_1-mavacurine (16), the

(15)

(16)
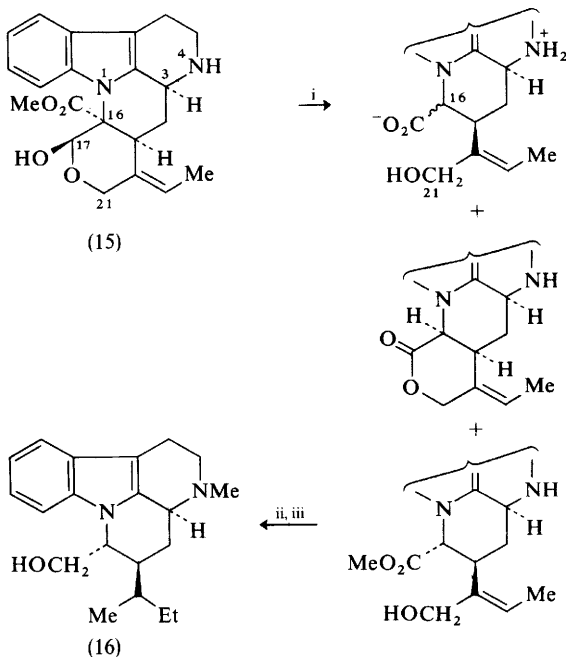
Reagents: i, MeONa–MeOH (retro-Claisen loss of HCO_2H); ii, H_2–Pd/C–HCHO; iii, LiAlH$_4$.

Scheme 4

[24] M. Pinar, M. Hanaoka, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1971, **54**, 15.

Emde degradation product of mavacurine. The absolute stereochemistry of (15) was established by applying Horeau's method to talbotine $C(17)$-O-methyl ether. It is significant that the method[1a] of comparing molecular rotation differences on $N(4)$-acetylation gave unambiguously the wrong result.

Herbavine is a heteroyohimbine oxindole with two aromatic methoxy-groups.[25]

Quite the most intriguing new indole alkaloidal structural type to appear this year is that of ervatamine (17b) which occurs, together with 20-epi-ervatamine (17c) and 19,20-dehydroervatamine (17a), in *Ervatamia orientalis*.[26a] A description of the degradations (Scheme 5) which led to the structural assignments is included in this sub-section on the basis of a possible biogenetic relationship to alkaloids in this class (see below).

(17) R
a; CO_2Me
b; CO_2Me; 19,20-dihydro, C(20)-H-?
c; CO_2Me; 19,20-dihydro, C(20)-H-?
d; CH_2OH
e; CH_2OAc

Reagents: i, H_2–catalyst; ii, re-oxidation; iii, $LiAlH_4$; iv, CrO_3–pyridine; v, MeI; vi, 'mild conditions'; vii, Bu^tOH–Bu^tO^-.
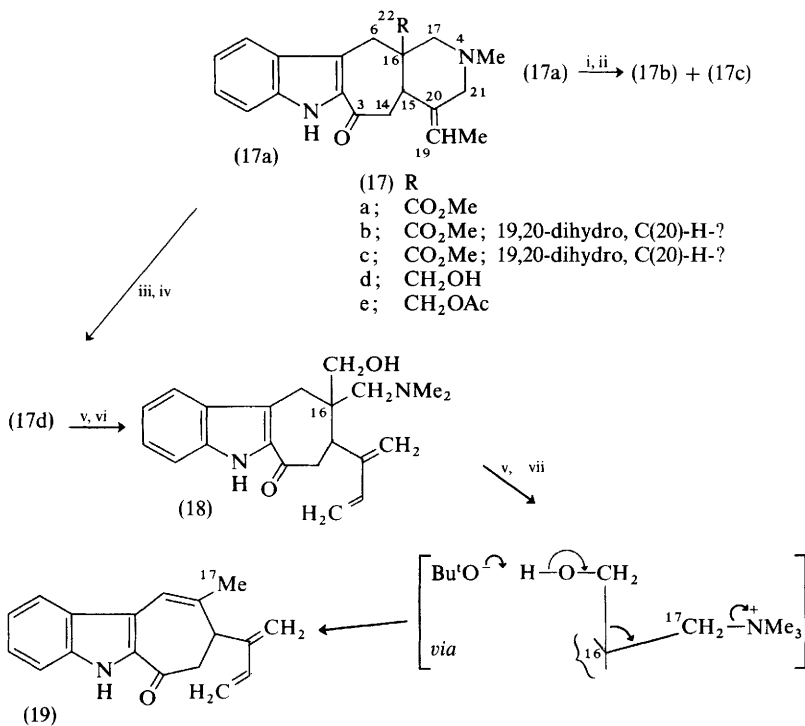
Scheme 5

[25] E. Z. Dzhakeli and K. S. Mudzhiri, *Soobshch. Akad. Nauk Gruz.*, S.S.R., 1970, **57**, 353 (*Chem. Abs.*, 1970, **73**, 25 723h).
[26] [a] J. R. Knox and J. Slobbe, *Tetrahedron Letters*, 1971, 2149; [b] J. P. Kutney, V. R. Nelson, and D. C. Wigfield, *J. Amer. Chem. Soc.*, 1969, **91**, 4278.

19,20-Dehydroervatamine (17a), which has an ethylidene function, was converted, by hydrogenation followed by re-oxidation at C(3), into ervatamine together with a minor amount of 20-epi-ervatamine. These last two, then, have ethyl groups and are the two possible epimers at C(20).

The quaternary environment of the ester function was demonstrated by reduction, mild re-oxidation of the benzylic C(3)-hydroxy-group giving (17d) and then acetylation to give (17e), in the n.m.r. spectrum of which there could be seen a clean AB quartet for the $C(22)-H_2OAc$ group.

One Hofmann cycle on the keto-alcohol (17d) gave (18), in which the conjugated diene unit could be recognized. A second cycle led to the loss of formaldehyde (no β-hydrogen; 1,3-hydroxyamine system) and a product (19) which is considered to arise by conjugation in the reaction medium of the first formed product. These experiments, taken with the characteristic 2-acylindole u.v. absorption, led to the assignment of (20) as a part structure for 19,20-dehydroervatamine. Of the remaining two carbon atoms, one, as CH_2, was shown to be attached to the C(3)-carbonyl carbon by borohydride reduction and dehydration, when an α-vinylindole, recognizable from its u.v. absorption and having two olefinic hydrogens [at C(3) and C(14)], was produced. The remaining carbon must then be attached to all three available and unspecified sites, C(14), C(16), and C(20).

(20)
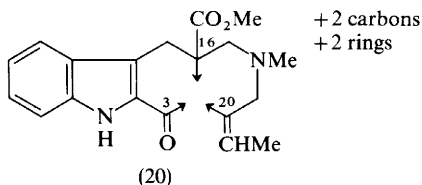
This new structural type poses fascinating biogenetic questions: if one imagines the C(6)—C(16) bond broken, then the remaining aliphatic skeleton is of the standard corynantheine type (implied by the reviewer's numbering) but with the exceptional features that C(17) is attached to N(4) (as in vallesiachotamine), and the presence of the entirely novel C(16)—C(6) bond: this would imply that C(6) is the stump of the original tryptamine two-carbon unit, as has been demonstrated[26b] to be the case for a similar 3-indolylmethylene in apparicine.

Alstoniline has been synthesised[27] by the method employed recently[1a] for dihydrogambirtannine.

Sarpagine–Ajmaline–Picraline Group. Picralinal has been isolated[28] from *Alstonia scholaris*. The value which natural-abundance ^{13}C n.m.r. can have in analysing alkaloid structures has been exemplified[29] by a study of the complex gelsemine molecule. It was possible to assign signals for all twenty carbon atoms

[27] J. A. Beisler, *Chem. Ber.*, 1970, **103**, 3360.
[28] R. C. Rastogi, R. S. Kapil, and S. P. Popli, *Experientia*, 1970, **26**, 1056.
[29] E. Wenkert, C-J. Chang, A. O. Clouse, and D. W. Cochran, *Chem. Comm.*, 1970, 961.

by an examination of the spectra of gelsemine and a few simple derivatives and a knowledge of chemical shifts. In such a complex molecule each of the carbon atoms is in a sufficiently different environment as to be distinguishable from its fellows.

The Hofmann degradations[30] (Scheme 6) of taberpsychine (21a) (= anhydro-vobasinol[1a]) and dihydrotaberpsychine (21b) proceed on opposite sides of the nitrogen. The dihydrotaberpsychine methine (22) was the key to this structural study: the sequence indole—$CH:CH·CH(C)·CH_2OCH(C)$—indole could be traced by n.m.r. and u.v., and this established the presence of the eight-membered ring.

Reagents: i, H_2–Pt–AcOH; ii, MeI; iii, Bu^tOK–Bu^tOH–heat.
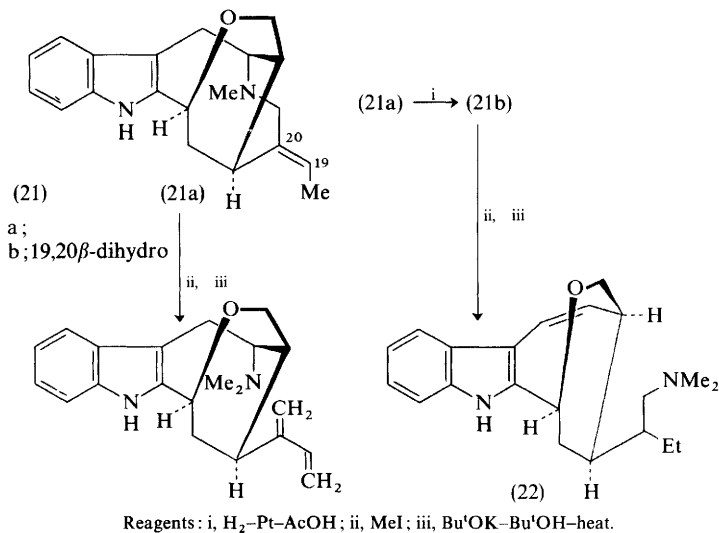
Scheme 6

The fourth alkaloid, gardneramine (23),[31] from *Gardneria nutans* turns out to be just as fascinating as the other three.[1a] The carbon skeleton is of the sarpagine type but with the modification that C(3) is attached to C(7) and not, as in the standard form, to C(2); the only other known alkaloid with this skeleton is voachalotine oxindole.[1a] The present base is the first alkaloid to be recognized having an N(1)-imino-ether system. The structure was settled by X-ray analysis[31b] of the 3,4-seco-3-bromo-4-cyanide, but many of the key features were deduced independently by a chemical study; some of the degradations[31a] are shown in Scheme 7. It was shown, for example, that the imino-ether grouping could be cleaved reversibly, either in the alkaloid itself or the cyanobromide, by treatment with aqueous formic acid to open and by base treatment of the open tosylate to reclose.

[30] R. H. Burnell and J. D. Medina, *Canad. J. Chem.*, 1971, **49**, 307.
[31] *a* S. Sakai, N. Aimi, A. Kubo, M. Kitagawa, M. Shiratori, and J. Haginiwa, *Tetrahedron Letters*, 1971, 2057; *b* N. Aimi, S. Sakai, Y. Iitaka, and A. Itai, *ibid.*, p. 2061.

(23)
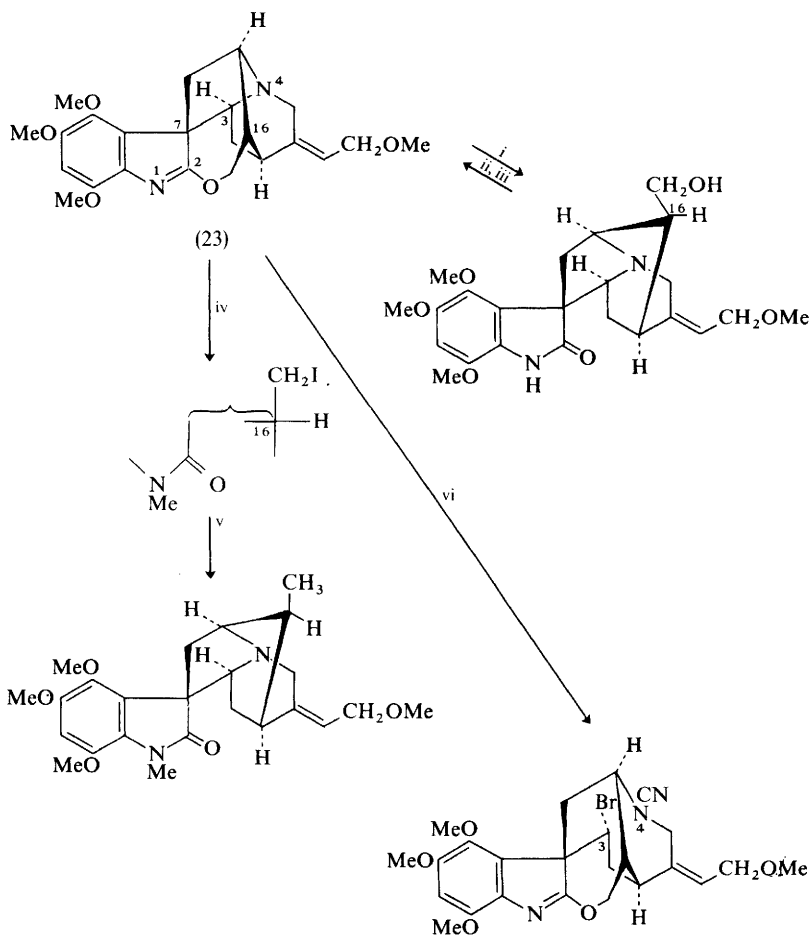
Reagents: i, aq. HCO$_2$H, heat; ii, TsCl; iii, KOH–EtOH; iv, MeI–PhH; v, Zn–AcOH; vi, CNBr.

Scheme 7

N(1)-Demethylseredamine[32] (24a) has been identified as a constituent of *Rauwolfia sumatrana* Jack; as well as sandwicine (24b), isosandwicine (24c) has been isolated from *R. vomitoria*,[33] and vinorine (24d)[34] and majoridine (24e)[35] from *Vinca* species. Raucaffricine (24f)[36] from *R. caffra* is the first of the ajmaline

[32] M. Hanaoka, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1970, **53**, 1723.
[33] F. Ronchetti, G. Russo, E. Bombardelli, and A. Bonati, *Phytochemistry*, 1971, **10**, 1385.
[34] H. Meisel, W. Döpke, and E. Grindemann, *Tetrahedron Letters*, 1971, 1291.
[35] J. L. Kaul, J. Trojánek, and A. K. Bose, *Coll. Czech. Chem. Comm.*, 1970, **35**, 116.
[36] M. A. Khan and A. M. Ahsan, *Tetrahedron Letters*, 1970, 5137.

type carrying a sugar to be isolated; what is interesting is that, although like the sugar of vincoside[1a] (the proposed common biogenetic precursor for all the monoterpenoid indole alkaloid types) it is situated at C(21), the sugar is D-(+)-galactose, and not glucose as in vincoside.

Vincovine,[37] another *Vinca* base, has the structure (25). Picrinine (vincaridine[38a]) (26a) and vincaricine[38a,b] (26b) from *Vinca erecta* react[38a] with zinc–hydrochloric acid to give indoles.[38c]

(24)	R^1	R^2	R^3	R^4	R^5
a;	H	MeO	H	H	H
b;	Me	H	H	H	α-HO, 19,20α-dihydro
c;	Me	H	H	H	β-HO, 19,20β-dihydro
d;	—	H	H	H	H, 1,2-dehydro
e;	Me	H	Ac	MeO	H
f;	—	H	Ac	H	galactose-O, 1,2-dehydro

(25)

(26) R
a;   H
b;   MeO
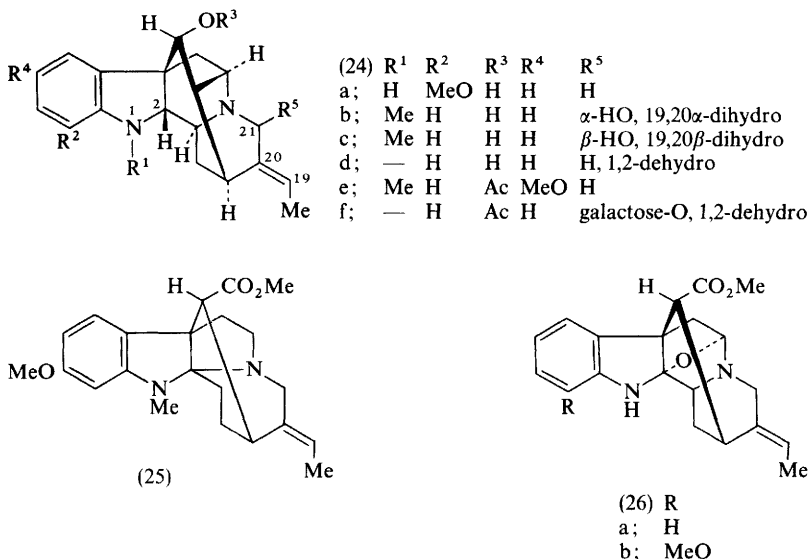
Strychnine–Akuammicine–Condylocarpine–Uleine Group. Details[39] have appeared of a synthesis[1a] of the (±)-dasycarpidones and (±)-epi-uleine. Ellipticine, apparicine, and isoreserpiline have been isolated from *Ochrosia silvatica*[40a] and the last two, together with 10-methoxy-19,20-dihydrocorynantheol, from *O. vieillardii*.[40b]

The material responsible for the colour in the classical Otto reaction on strychnine (Scheme 8), and other strychnine derivatives having the N(1)—C: O grouping, has been isolated and assigned[41] the dimeric, dicationic structure (27), both on spectrocopic grounds and on its reduction to 10,10′-bistrychnine.

[37] H. Meisel and W. Döpke, *Tetrahedron Letters*, 1971, 1285.
[38] [a] D. A. Rakhimov, Kh. T. Il'yasova, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 521 (*Chem. Abs.*, 1970, **73**, 25 722g); [b] H. T. Il'yasova, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 327 (*Chem. Abs.*, 1969, **70**, 88 026s); [c] see A. Z. Britten, J. A. Joule, and G. F. Smith, *Tetrahedron*, 1967, **23**, 1971.
[39] L. J. Dolby and H. Biere, *J. Org. Chem.*, 1970, **35**, 3843.
[40] [a] J. P. Cusson and M. Schmid, *Phytochemistry*, 1970, **9**, 1353; [b] C. Kan-Fan, B. C. Das, P. Potier, and M. Schmid, *ibid.*, p. 1351.
[41] K. Rehse, *Arch. Pharm.*, 1970, **303**, 518 (*Chem. Abs.*, 1970, **73**, 56 285w).
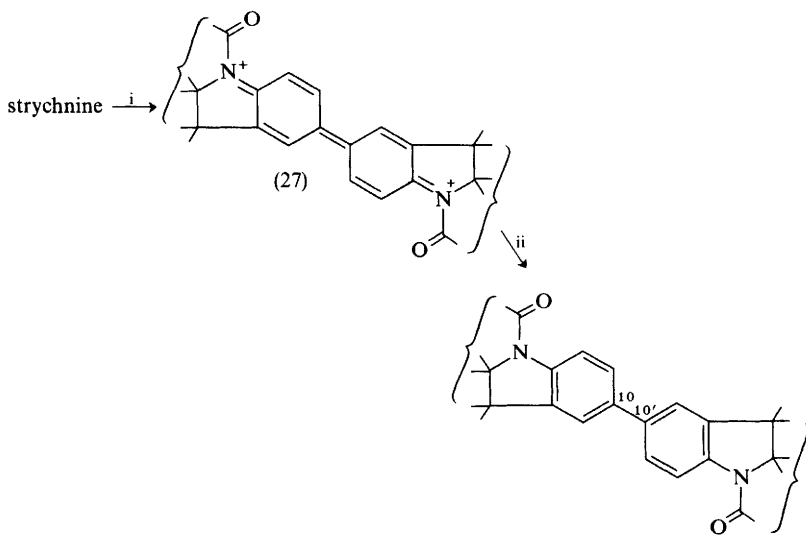
(27) as $\{[Cr(HSO_4)_4(H_2O)_2]\}_2$,$12H_2O$ salt

Reagents: i, CrO_3–50% H_2SO_4 at 0°C; ii, SO_2–50% H_2SO_4.

Scheme 8

Full details[42] of the chemical and spectroscopic studies on dichotine (28a) and 11-methoxydichotine (28b) have been published. Notable among the transformations, some of which are shown in Scheme 9, are the opening of the $N(1) \rightarrow C(12)$ ring followed by hydrolysis and trapping of the C_2-fragment and the cleavage of the $N(1)$—$C(2)$ bond. It is interesting that the $N(1)$—$C(2)$—OH system was unaffected by sodium borohydride but reduced by lithium aluminium hydride; the $N(4)$—$C(21)$:O system was unaffected by either reagent. The dehydrogenation to dehydrodichotamine (29) occurs under extraordinarily mild conditions.

16-Hydroxy-α- and 16-hydroxy-β-colubrines have been isolated[43] from *Strychnos nux vomica* and partially synthesised from the corresponding colubrines by the standard procedure of N(4) oxidation and then reaction with potassium chromate.

The oxindole [both stereoisomers at C(7)] rearrangement products of an intermediate used previously in syntheses[1a] of D/E *trans*-heteroyohimbine types, were converted into their imino-ethers (30). A cyclization, C(16) as nucleophile

[42] N. C. Ling and C. Djerassi, *J. Amer. Chem. Soc.*, 1970, **92**, 6019.
[43] G. B. Marini-Bettolo, E. F. delle Monache, C. Galetti, M. A. Ciasca Rendina, and A. Villar del Fresno, *Ann Chim. (Italy)*, 1970, **60**, 444 (*Chem. Abs.*, 1970, **73**, 109 942s).

Reagents: i, NaBH$_4$; ii, H$_3$O$^+$; iii, 2,4-(O$_2$N)$_2$C$_6$H$_3$NHNH$_2$; iv, Me$_2$SO$_4$–K$_2$CO$_3$; v, LiAlH$_4$; vi, Pd/C–EtOH; vii, H$_2$–Pt–EtOH.

Scheme 9

→ C(2) as electrophile, which it was hoped would lead to an akuammicine system could not be effected; cyclization to give a carbocyclic D ring was the only change observed[44b] (Scheme 10[44a]).

As well as an improved method[45a] for inserting the C(17) carbon in a previous synthesis[1a] of dihydronorfluorocurarine, a neat development[45b] (Scheme 11) of the established route has allowed the synthesis of (±)-norfluorocurarine (31)

---

[44] [a] A. J. Gaskell, H.-E. Radunz, and E. Winterfeldt, *Tetrahedron*, 1970, **26**, 5353; [b] see also E. Winterfeldt and H. Riesner, *Synthesis*, 1970, 261.

[45] [a] J. Harley-Mason and C. G. Taylor, *Chem. Comm.*, 1970, 812; [b] G. C. Crawley and J. Harley-Mason, *ibid.*, 1971, 685.

Reagents: i, CH_2Cl_2–$Et_3O^+BF_4^-$; ii, Bu^tOK–Bu^tOH; iii, HCl–$MeOH$.

Scheme 10
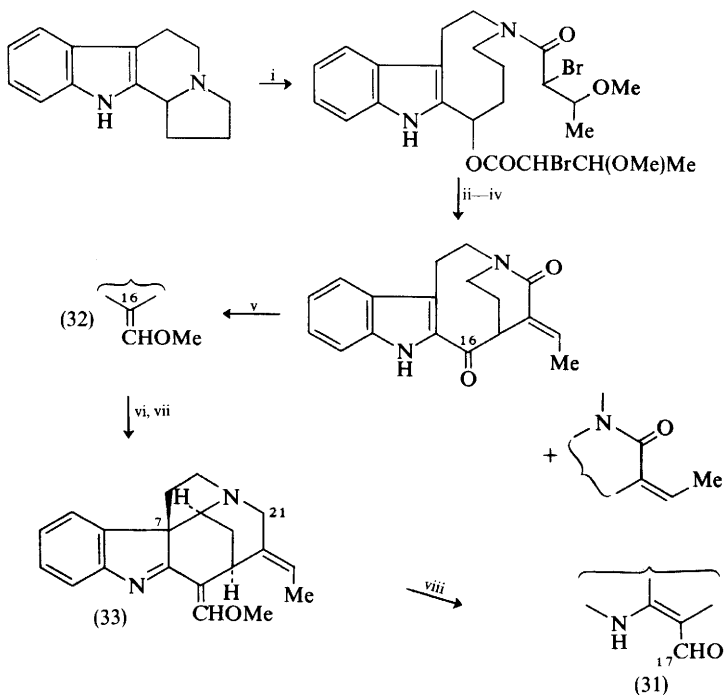
Reagents: i, $[MeCH(OMe)CHBrCO]_2O$–$MeCN$; ii, mild base; iii, $Pb(OAc)_4$; iv, Me_3CCH_2ONa–THF–heat; v, $MeOCH{:}PPh_3$; vi, AlH_3; vii, O_2–Pt; viii, H_3O^+.

Scheme 11

itself, and thus for the first time of an indole alkaloid with a natural ethylidene group. It is very interesting that in the cyclization step, $(32) \rightarrow (33)$, no isomer from an alternative C(21) to C(7) linking could be observed.

Two new successful routes[46,47] to the dasycarpidone–uleine type have been described. The first, which has been used to make de-ethyldasycarpidone[46a] and the ($\pm$)-dasycarpidones (34a and b) (Scheme 12[46b]) utilizes, as a key step, the reaction of methyl 3-ethylisonicotinate *N*-oxide with the indolyl Grignard reagent in the presence of benzoyl chloride. After quaternization, reduction, and hydrolysis of the product (35), cyclization was effected as before,[1a] using polyphosphoric acid.

(34)	R^1	R^2	R^3
a;	O	α-Et	Me
b;	O	β-Et	Me
c;	CH_2	α-Et	Me
d;	CH_2	β-Et	Me
e;	CH_2	α-Et	CHO
f;	CH_2	β-Et	CHO.
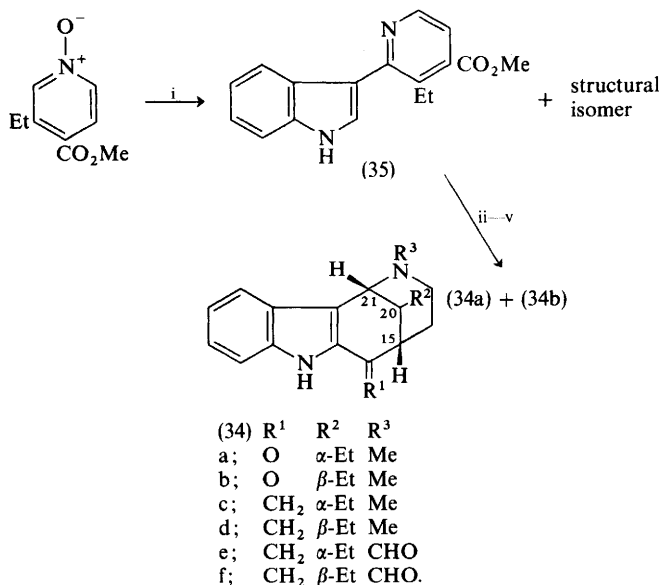
Reagents: i, 1-indolyl-MgBr–PhCOCl; ii, MeI; iii, H_2–Pt; iv, aq. KOH; v, PPA.

Scheme 12

Routes[47] to ($\pm$)-uleine (34c) (Scheme 13) and ($\pm$)-epi-uleine (34d) (Scheme 14) which are stereoselective, and so provide synthetic confirmation for the relative stereochemistry of these two bases, give the methylene compounds directly without the necessity of going by way of the ketones.

The key processes which controlled the stereochemistry were as follows. Firstly, the catalytic reduction of (36) gave two stereoisomeric products, of which (37), in which hydrogen had been added on the side opposite to the bulky indole residue and *cis* [thus ensuring that hydrogens at C(21), C(20), and C(15)

[46] [a] T. Kametani and T. Suzuki, *J. Chem. Soc.* (*C*), 1971, 1053; [b] T. Kametani and T. Suzuki, *J. Org. Chem.*, 1971, **36**, 1291.
[47] G. Büchi, S. J. Gould, and F. Näf, *J. Amer. Chem. Soc.*, 1971, **93**, 2492.
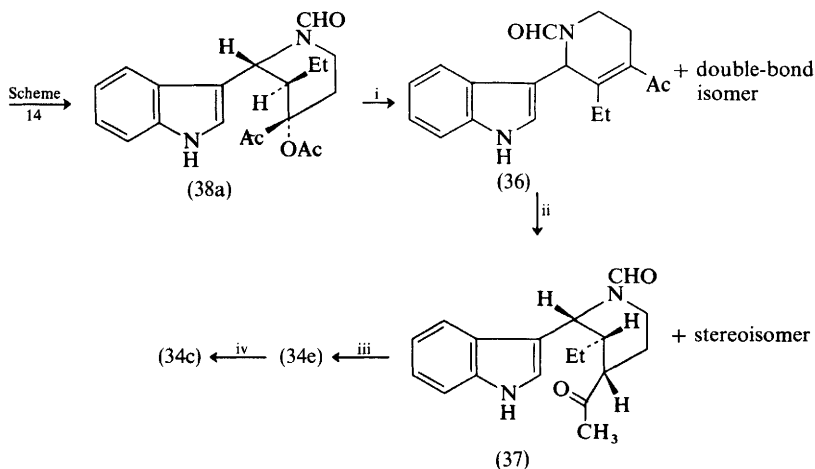
Reagents: i, heat; ii, H_2–Pd–pyridine; iii, BF_3,Et_2O; iv, $LiAlH_4$.

Scheme 13

were *cis*], was the isomer necessary for the eventual formation of uleine (34c). Secondly, for the epi-uleine system (34d), the crucial step was the formation of the *trans*-piperidine (38) by cyclization *via* (39), a chair-like transition state with the large substituents 'equatorial'.
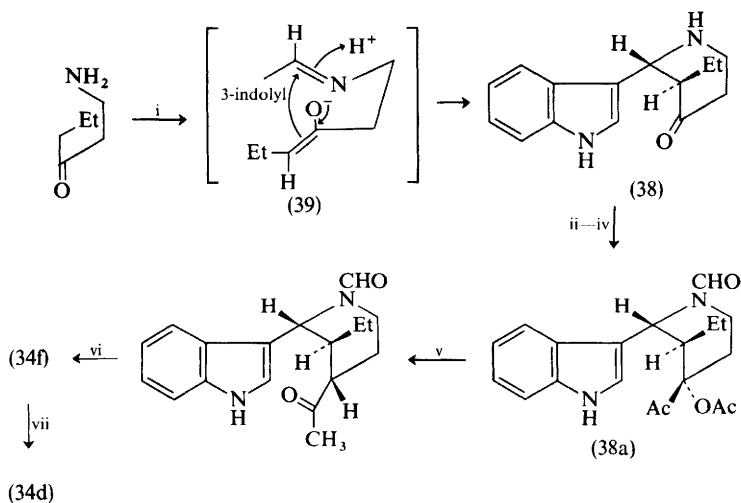
Reagents: i, 3-indolyl-CHO–pH9; ii, HCO_2H–Ac_2O; iii, HC⋮CK–Bu^{t}OH–THF; iv, $Hg(OAc)_2$–AcOH; v, Li–NH_3(liq.); vi, BF_3,Et_2O; vii, $LiAlH_4$.

Scheme 14

Eburnamine–Aspidospermine–Aspidofractinine Group. An X-ray analysis[48] of obscurinervine hydrobromide has confirmed the structure arrived at earlier by chemical and spectroscopic means.

It was shown[49a] that (+)-vincadifformine (40a), with none of the (−)-form, was present as major alkaloid in young shoots of *Amsonia tabernaemontana* and that its place was taken by (+)-1,2-dehydroaspidospermidine (41a) after blooming. In a related study[49b] it was shown (Scheme 15) that the indolenine (41a) was reduced normally, that is without ring opening, to (41b) with borohydride at 0 °C in ethanol, but at reflux temperatures it gave (−)-quebrachamine (42a), in the previously recognized reductive cleavage. This could be very useful since the less selective reagent lithium aluminium hydride (or lithium borohydride in dioxan[49c]) has had to be used previously to bring about reduction without cleavage in such systems.

Reduction with formic acid[50] provides a way of cleaving the $C(21)$—$C(7)$ bond (Scheme 15) in (−)-vincadifformine (40b) and (−)-tabersonine (40c); previously it was necessary to remove the ester group and reduce the resulting indolenine (for example as above). Formic acid is unique in providing of itself both a proton, to produce a concentration of indoleninium cation (43), which in
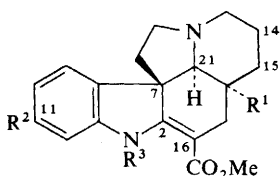
(40)	R^1	R^2	R^3
a;	Et	H	H, all opposite absolute configuration
b;	Et	H	H
c;	Et	H	H, 14,15-dehydro
d;	MeCH(OH) [20]	H	H
e;	MeCH(OH) [20]	MeO	H
f;	Ac	H	H
g;	Ac	MeO	H
h;	MeCH(OH)	H	H, $2\beta,16\beta$-dihydro
i;	MeCH(OH)	MeO	H, $2\beta,16\beta$-dihydro
j;	Et	MeO	H, stereochemistry not implied
k;	Et	MeO	H, 14,15-dehydro, stereochemistry not implied
l;	Et	MeO	H, 14,15-dehydro-14,15-epoxide, stereochemistry not implied
m;	Et	H	H, $2\beta,16\beta$-dihydro, all opposite absolute configuration.
n;	Et	H	$MeO_2C, 2\beta,16\beta$-dihydro, all opposite absolute configuration.

[48] J. Kahrl, T. Gebreyesus, and C. Djerassi, *Tetrahedron Letters*, 1971, 2527.
[49] [a] B. Zsadon and P. Kaposi, *Tetrahedron Letters*, 1970, 4615; [b] B. Zsadon, R. Hubay, E. Egry, M. Rakli, and M. Sarkazi, *Magyar Kém. Folyóirat*, 1970, **76**, 466 (*Chem. Abs.*, 1971, **74**, 13 312*f*); [c] J. A. Joule and G. F. Smith, *Proc. Chem. Soc.*, 1959, 322.
[50] M-J. Hoizey, L. Olivier, J. Lévy, and J. Le Men, *Tetrahedron Letters*, 1971, 1011.

(41)
a; all opposite absolute configuration
b; 1,2β-dihydro; all opposite absolute configuration
c; 14,15-dehydro

(41c)   (41a)

(42f)   (41a)

(42a)

(41b)
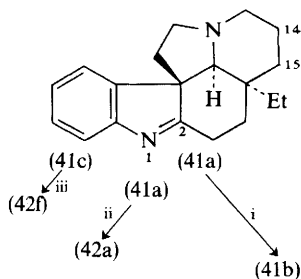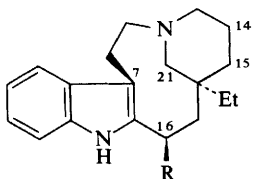
(42)   R
a;   H   all opposite absolute configuration
b;   CO$_2$Me
c;   CO$_2$Me,   14,15-dehydro
d;   H,   14,15-dehydro-14,15-α-epoxide, all
                 opposite absolute configuration
e;   H,   14β-hydroxy-15α-hydroxy-, all opposite
                 absolute configuration
f;   H,   14,15-dehydro

(42b) +   (42c) + C(16)-
C(16)-epimer   epimer + (42f)

(43)   (44)

(40b)   (40c)
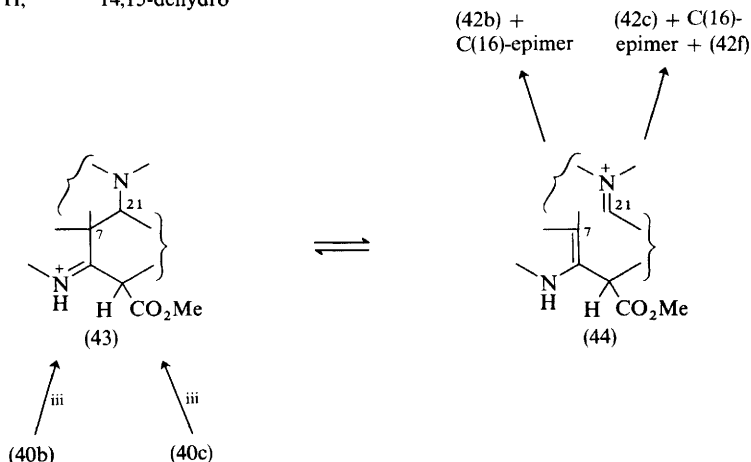
Reagents: i, NaBH$_4$–EtOH at 0 °C; ii, NaBH$_4$–EtOH at 80 °C; iii, HCO$_2$H–HCONH$_2$ at 100 °C.

Scheme 15

turn leads to a concentration of the required ring-opened species (44), and hydride ion (+ carbon dioxide) to trap the ring-opened species. It is intriguing to wonder why it should be that it is the ring-opened immonium intermediate (44) which is reduced rather than more simply (43). Formic acid similarly reduced the (−)-tabersonine indolenine (41c), with C(7)—C(21) cleavage, to give (+)-14,15-dehydroquebrachamine (42f).

The stereochemistry of minovincinine (40d) and 11-methoxyminovincinine (40e) has been settled[51a,b] by Horeau's method [for C(20)] and by interconversions with the corresponding minovincines (40f and g) (for the other centres). The 2,16-dihydro-alcohols (40h and i) spontaneously lactonize.

Ervinceine (40j), ervamycine (40k), and ervincinine (40l) have been given[51c] overall structures, without stereochemistry, which show that they correspond to the 11-methoxy-derivatives of vincadifformine, tabersonine, and lochnericine respectively.

As well as (+)-1,2-dehydroaspidospermidine (41a) (= eburenine), eburine (40m) and eburcine (40n) have been obtained from *Hunteria eburnea*.[51d]

Voaphylline (42d) from *Voacanga africana* is 14,15-dehydro-(−)-quebracha-mine-14,15-β-epoxide; also isolated in this study[51e] were the corresponding diol (42e) and voaphylline 7-hydroxyindolenine.

The intermediate (45a) previously employed[1a] in a synthesis of aspidospermine has been neatly prepared[52] by a potentially general method which has already been applied to the syntheses of several other alkaloid systems. The key step is the reaction of a cyclic enamine, in this case (46a), with methyl vinyl ketone and the formation of a homocyclic ring and the required carbonyl function. Scheme 16

(46) R
a;   Et
b;   PhCH₂O-
      CH₂CH₂

(45) R
a;   Et
b;   PhCH₂OCH₂CH₂
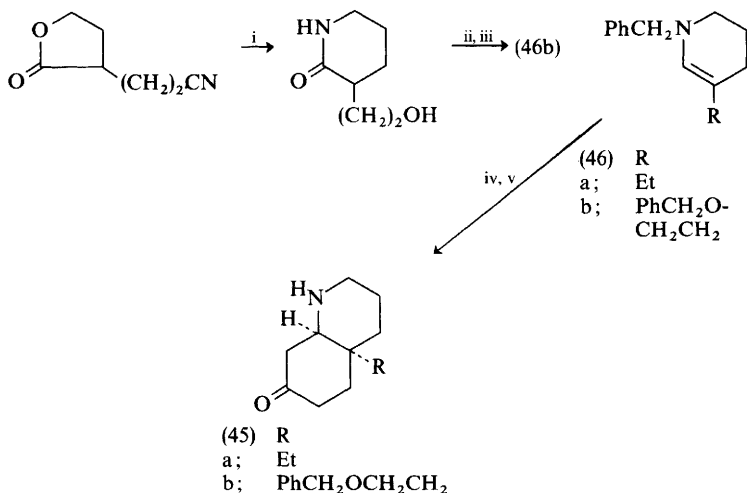
Reagents: i, H₂–Ni; ii, PhCH₂Br–MeSOCH₂K–DMSO; iii, Bu^i₂AlH; iv, MeCOCH:CH₂–glycol–
heat; v, H₂–Pd/C.

Scheme 16

[51] *a* W. Döpke and H. Meisel, *Tetrahedron Letters*, 1970, 749; *b* W. Döpke, H. Meisel, and E. Gründemann, *Tetrahedron Letters*, 1971, 1287; *c* D. A. Rakhimov, V. M. Mali-kov, M. R. Yagudaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 226 (*Chem. Abs.*, 1970, **73**, 45 652*n*); *d* L. Olivier, F. Quirin, P. Maupérin, J. Lévy, and J. Le Men, *Compt. rend.*, 1970, **270**, C, 1667; *e* N. Kunesch, J. Poisson, and J. Guilhem, *Bull. Soc. chim. France*, 1971, 1919.
[52] R. V. Stevens, R. K. Mehra, and R. L. Zimmerman, *Chem. Comm.*, 1969, 877.

shows how the approach was used to make (45b), which is of potential value for the synthesis of the C(18)-oxygenated *Aspidosperma* alkaloids such as lima-spermine.

In another study[53] aimed towards this *Aspidosperma* variation, the bicyclic compound (47) was prepared and transformed (Scheme 17) into (48), which unfortunately has the undesired stereochemistry at C(20)–C(21).
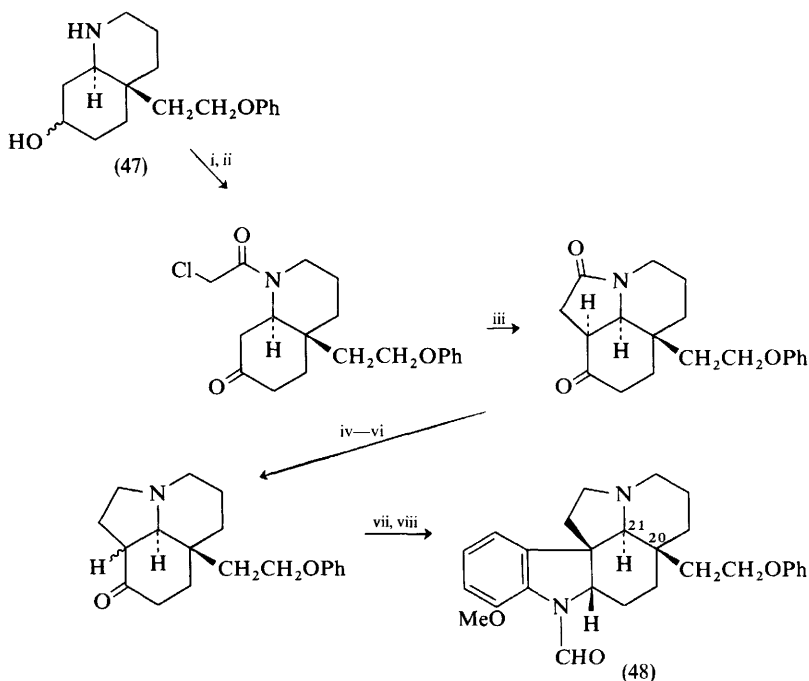
Reagents: i, $ClCH_2COCl$–NaOH; ii, H_2CrO_4–Me_2CO; iii, Bu^tOK–Bu^tOH; iv, glycol–H^+; v, $LiAlH_4$; vi, H_3O^+; vii, o-MeO·$C_6H_4NHNH_2$; viii, HCO_2H.

Scheme 17

A splendid synthesis[54] (Scheme 18) of ($\pm$)-minovine (49), which has an $N(1)$-methyl group, takes advantage of the possibility of introducing a substituent into the α-position of an N-alkylindole by way of metallation. In a biogenetically patterned step the intermediate (50) reacted, by a process which may be electro-cyclic or may be ionic, with the cyclic enamine (51). The two-carbon tryptamine bridge was introduced as a final stage; the alkylation of the indole β-position in this way was a notable feature of a model synthesis described previously.[1a]

[53] I. Inoue and Y. Ban, *J. Chem. Soc.* (*C*), 1970, 602.
[54] F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, 1970, **92**, 3492.
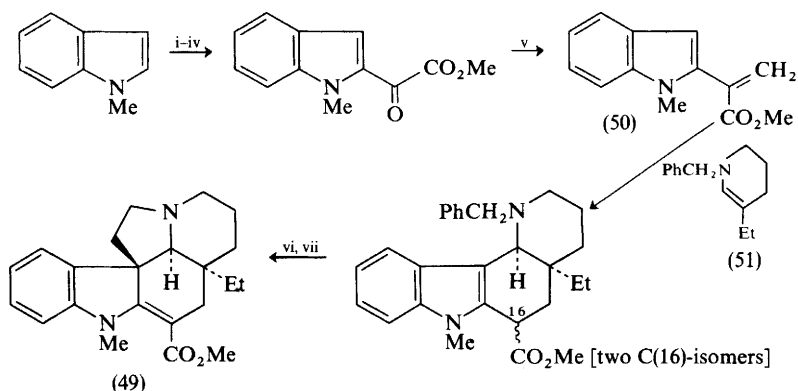
Reagents: i, Bu^{n}Li; ii, (EtO$_2$C)$_2$; iii, aq. KOH; iv, CH$_2$N$_2$; v, CH$_2$:PPh$_3$; vi, H$_2$–Pd/C–HCl; vii, BrCH$_2$CH$_2$Br–Na$_2$CO$_3$–DMF.

Scheme 18
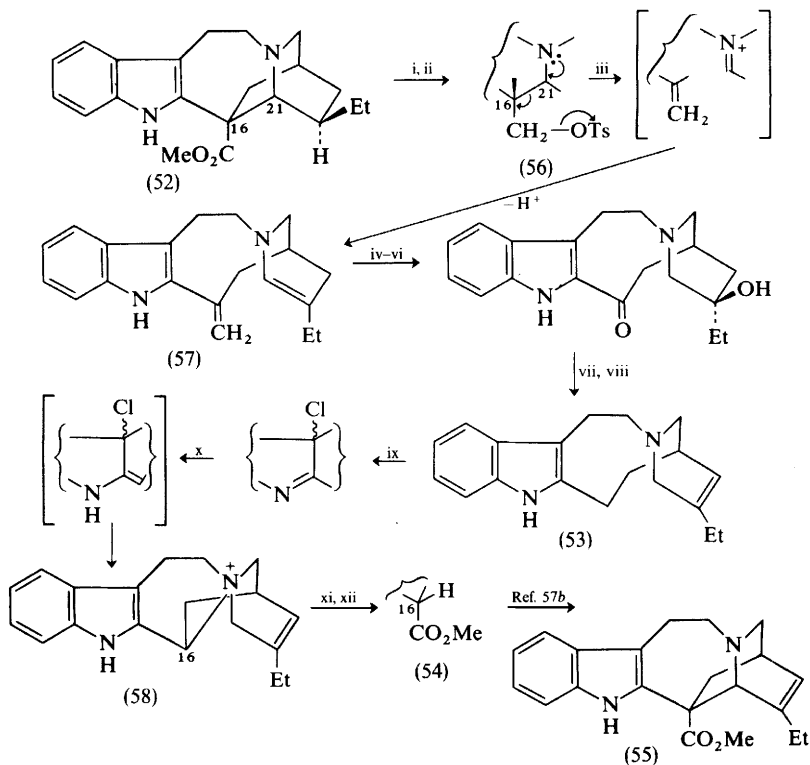
Reagents: i, LiAlH$_4$; ii, TsCl; iii, Et$_3$N; iv, OsO$_4$; v, NaBH$_4$; vi, HIO$_4$; vii, LiAlH$_4$–N-methylmorpholine; viii, conc. H$_2$SO$_4$; ix, Bu^{t}OCl; x, AcONa–AcOH; xi, KCN–DMF; xii, hydrolysis and esterification.

Scheme 19

Ibogamine–Cleavamine Group. Voalutein, the indoxyl corresponding to voacan-gine, has been isolated[55] from *Voacanga thouarsii* and has been partially synthe-sized by aerial oxidation of the Grignard derivative of voacangine followed by acid-catalysed rearrangement.

Extension[56a] of the potential[56b] of 1,4,5,6-tetrahydro-3-acyl- or -3-alkoxy-carbonylpyridines to the preparation of the isoquinuclidine system of the *Iboga* bases has not yet proved possible.

Dihydrocatharanthine (52) has been converted[57a] into isovelbanamine, velbanamine, cleavamine (53), 16-β-methoxycarbonylcleavamine (54), and catharanthine[57a,b] (55) (Scheme 19). A Grob fragmentation (56) → (57), of a type previously recognized for voacanginol,[57c] proved an efficient means for breaking the C(16)—C(21) bond and moving from the pentacyclic ibogamine series to the tetracyclic cleavamine series. The ester function was neatly introduced *via* cyanide by displacement on the benzylic salt (58), itself prepared by way of the 7-chloroindolenine of cleavamine.

Skeletal Rearrangements and Interconversions. Several new rearrangements have been observed in a thoroughly worked out study[58] of the reactions of alkaloids which can give rise to $C(2):N(1)^+$ in acid, by direct protonation of indolenine $C:N$, or otherwise by $C(16)$-protonation of a β-aminoacrylate unit. Zinc–acetic acid, as well as effecting some straightforward reduction in each case, converted akuammicine (59) (Scheme 20[58a]) into a compound (60) having a de(methoxycarbonyl)corynantheine-type skeleton and (61a), having a skeleton not yet recognized in Nature; tabersonine (40c) similarly gave 16-methoxy-carbonyl-14,15-dehydrovallesamidine (62a) and the 1,16-secovincamine-type system (63) (Scheme 21[58b]); the tabersonine indolenine (41c) gave (62b) (Scheme 22[58c]), which was catalytically reduced to vallesamidine itself; and the akuam-micine indolenine (64) gave (Scheme 23[58c]) compound (61b). Tabersonine, by alcoholic treatment of the corresponding 16-chloroindolenine (65), was converted (Scheme 24[58d]) into several products, of which (66) and (67) were the main ones; only the former has a skeleton which occurs naturally, for example in vincadine.

All the zinc–acetic acid reductions[58a—c] can be fitted nicely into a common pattern (Scheme 25): after formation of indoleninium cation, reduction can occur immediately (products of Type A) or after a formal* $C(7) \rightarrow C(2)$ alkyl shift

[55] A. Goldblatt, C. Hootelé, and J. Pecher, *Phytochemistry*, 1970, **9**, 1293.
[56] *a* E. Wenkert, K. G. Dave, I. Dainis, and G. D. Reynolds, *Austral. J. Chem.*, 1970, **23**, 73; *b* E. Wenkert, *Accounts Chem. Res.*, 1968, **1**, 78.
[57] *a* J. P. Kutney and F. Bylsma, *J. Amer. Chem. Soc.*, 1970, **92**, 6090; *b* J. P. Kutney, R. T. Brown, E. Piers, and J. R. Hadfield, *ibid.*, p. 1708; *c* U. Renner, K. A. Jaeggi, and D. A. Prins, *Tetrahedron Letters*, 1965, 3697.
[58] *a* W. B. Hinshaw, J. Lévy, and J. Le Men, *Tetrahedron Letters*, 1971, 995; *b* P. Maupérin, J. Lévy, and J. Le Men, *ibid.*, p. 999; *c* J. Lévy, P. Maupérin, M. Döé de Maindreville, and J. Le Men, *ibid.*, p. 1003; *d* C. Pierron, J. Garnier, J. Lévy, and J. Le Men, *ibid.*, p. 1007.

* This migration can be interpreted either as a 1,5-alkyl shift[58] or as the result of reverse Mannich cleavage of the C(7)—C(3) [or C(21)] bond followed by Mannich condensation at the indole α-position, C(2).

(59)

(61)   R
a;   MeO$_2$C
b;   H

(61a) $\xrightarrow{i}$ (60)

(61a) $\xrightarrow{ii}$ (60)

(60) + trace
C($\boldsymbol{3}$)-epimer

Reagents: i, Zn–CuSO$_4$–AcOH–reflux; ii, Bu^{t}OK.

Scheme 20

(40c)

(63)

(62)
a; MeO$_2$C
b; H
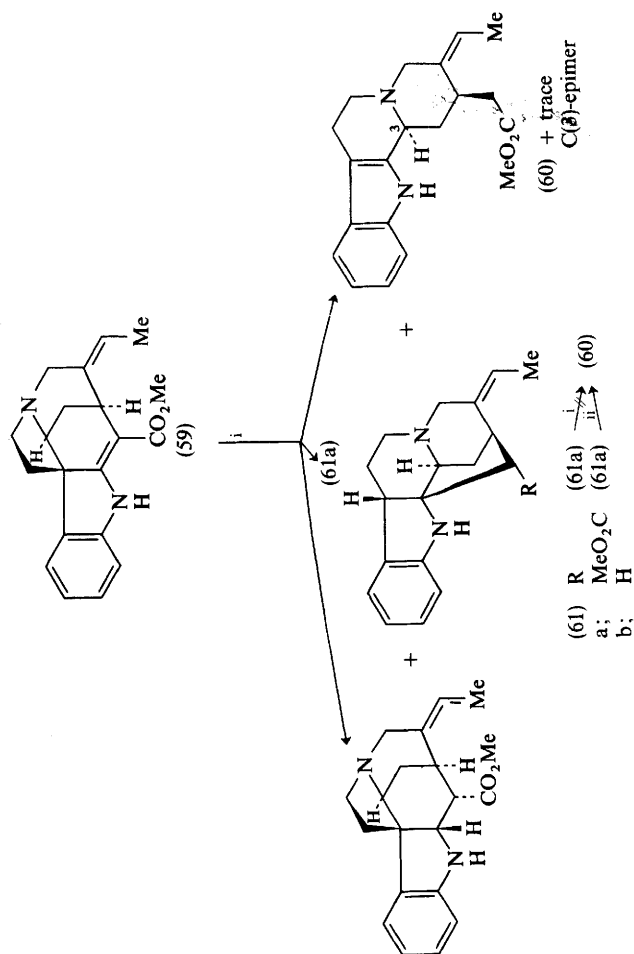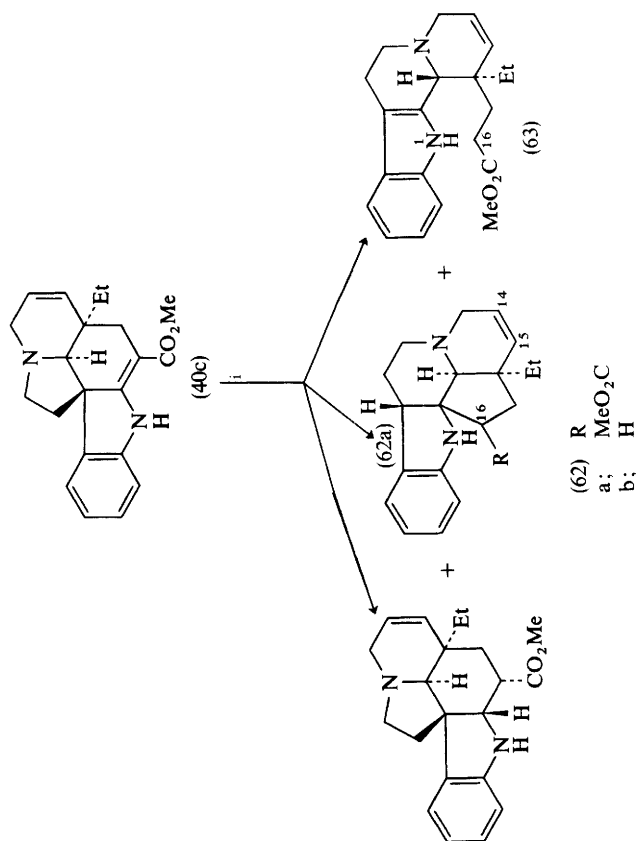
Reagent: i, Zn–CuSO$_4$–AcOH at 100 °C.

Scheme 21

(41c)
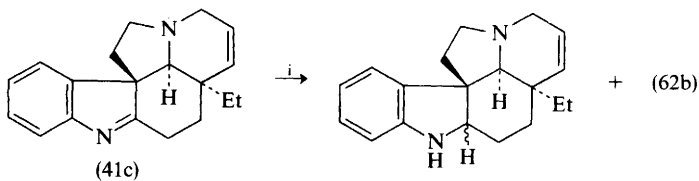
Reagent: i, Zn–CuSO$_4$–AcOH at 100—110 °C.

Scheme 22

(64)　　　　(Ac)
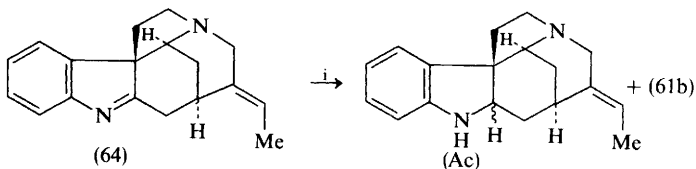
Reagent: i, Zn–CuSO$_4$–AcOH at 110 °C.

Scheme 23

$$(40c) \underset{iii}{\overset{i}{\rightleftarrows}}$$

(65)

(66)

(67)

Reagents: i, Bu^{t}OCl; ii, EtOH–reflux for 5 min; iii, Bu^{t}OK.
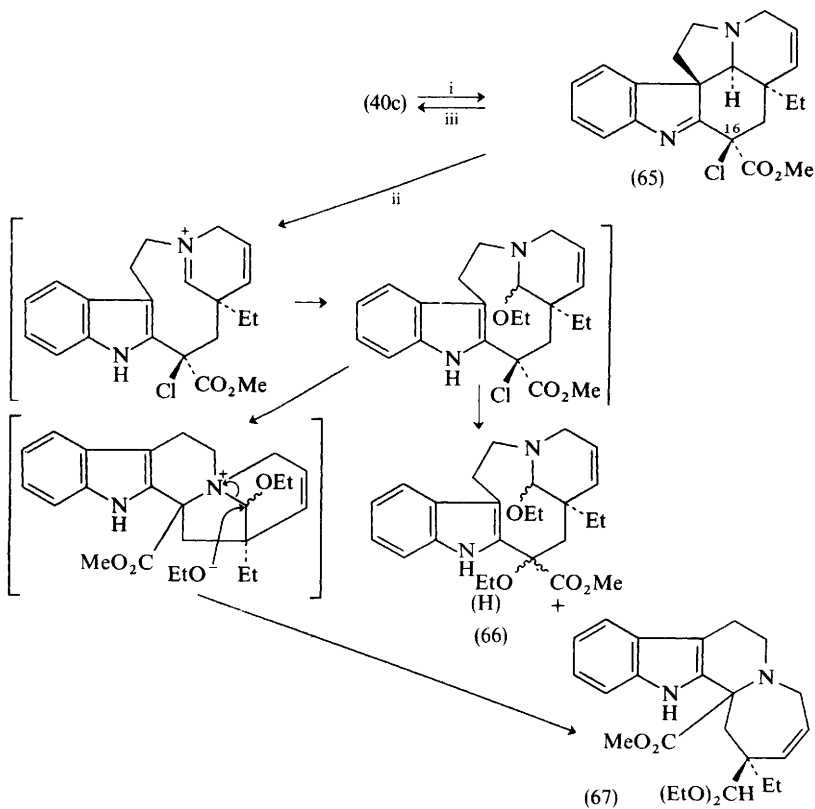
Scheme 24

(products of Type B), or after the shift *and* with fragmentation (products of Type C); this last type is only observed when C(16) is capable of acting as a leaving group, *i.e.* carries an ester function. The reductive fragmentations can be represented as proceeding by way of a concentration of free, unprotonated indolenine (Scheme 25). This may be significant in rationalizing the formation of these rearrangement products in the present case, in contrast with comparable zinc–sulphuric acid treatments which lead predominantly to straightforward reduction (→ 2,16-dihydro-products).
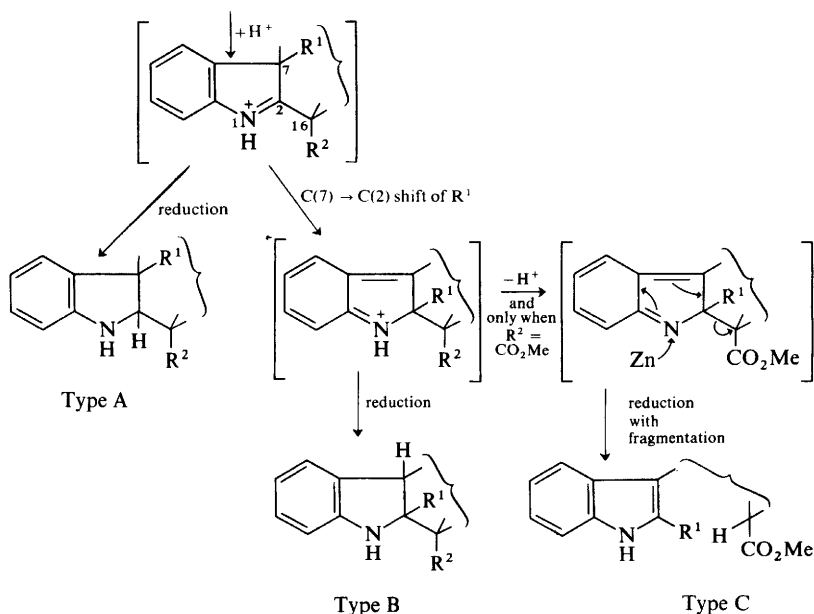
Scheme 25

In the alcoholic treatments[58d] of the 16-chloroindolenine (65) from tabersonine (Scheme 24), the ring-opened vincadine system (66) is formed by trapping with alcohol addition after $N(1)$-protonation and C(7)—C(21) reverse Mannich cleavage of the usual type; the unnatural system (67) is believed to arise by a further rearrangement of the initial product as shown.

3 Biogenetically Related Quinoline Alkaloids

Details have been published[59] of the photocatalysed $C(9)$-deoxygenation of quinine alkaloids. The natural-abundance ^{13}C n.m.r. spectrum (see also p. 217) of quinine has been interpreted[60] using the spectra of simple models for chemical shifts. Of several 2'-alkyl- and 2'-aryl-quinine and -quinidine derivatives which

[59] V. I. Stenberg and E. F. Travecedo, *J. Org. Chem.* 1971, **35**, 4131.
[60] W. O. Crain, W. C. Wildman, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 990.

were synthesised[61] by reaction of organometallic reagents with $N(1')$-oxides, the aryl compounds, in particular the p-trifluoromethylphenyl derivatives, showed increased potency against malaria, though coupled with increased phototoxicity.

The configurations at $C(4')$ of the hexahydroquinines were established[62] by conversions[1a] (see also p. 213) to the corresponding $N(1')$—$C(2')$ cleaved quinolizines in which the stereochemistry could be assigned by n.m.r.

Cinchonidone (68) was shown to be present in *Cinchona ledgeriana*.[63]

(68)   (69)
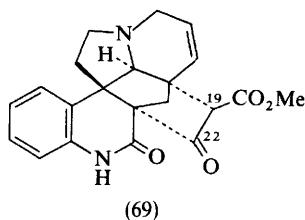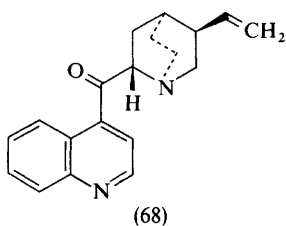
Meloscandonine from *Melodinus scandens*[64] has been given the structure (69) in which, at least formally, it appears that the original $C(22)$ ester carbon has become attached to $C(19)$, an unprecedented link.

(70)

(71)
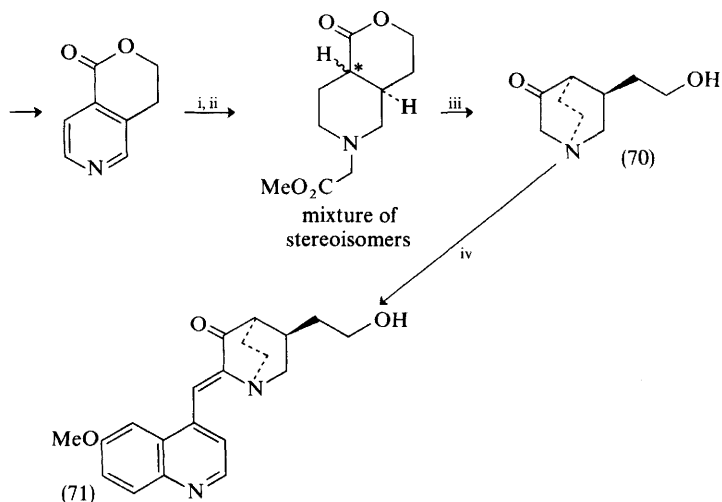
Reagents: i, $BrCH_2CO_2Me$; ii, H_2–catalyst; iii, EtONa–PhMe (epimerization at C^* of 'wrong' isomer before cyclization); iv, 6-MeO·C_9H_5N-4-CHO–EtONa.

Scheme 26

[61] J. P. Yardley, R. E. Bright, L. Rane, R. W. A. Rees, P. B. Russell, and H. Smith, *J. Medicin. Chem.*, 1971, **14**, 62.

[62] Y. K. Sawa and H. Matsumura, *Tetrahedron*, 1960, **26**, 2919.

[63] A. R. Battersby and R. J. Parry, *Chem. Comm.*, 1971, 31.

[64] M. Plat, M. Hachem-Mehri, M. Koch, U. Scheidegger, and P. Potier, *Tetrahedron Letters*, 1970, 3395.

A stereoselective synthesis (Scheme 26[65]) of a 3-quinuclidone (70) allows an aldol condensation to be used to build up the complete quinine skeleton, as in (71).

Ajmalicine[66a], and several synthetic tetrahydro-β-carbolines,[66] have been converted in high yields, by aerial oxidation in the presence of strong base, into compounds having portions of the skeleton of camptothecin. Thus ajmalicine[66a] (72) gave (73) (Scheme 27) with the complete ring system though with incorrectly
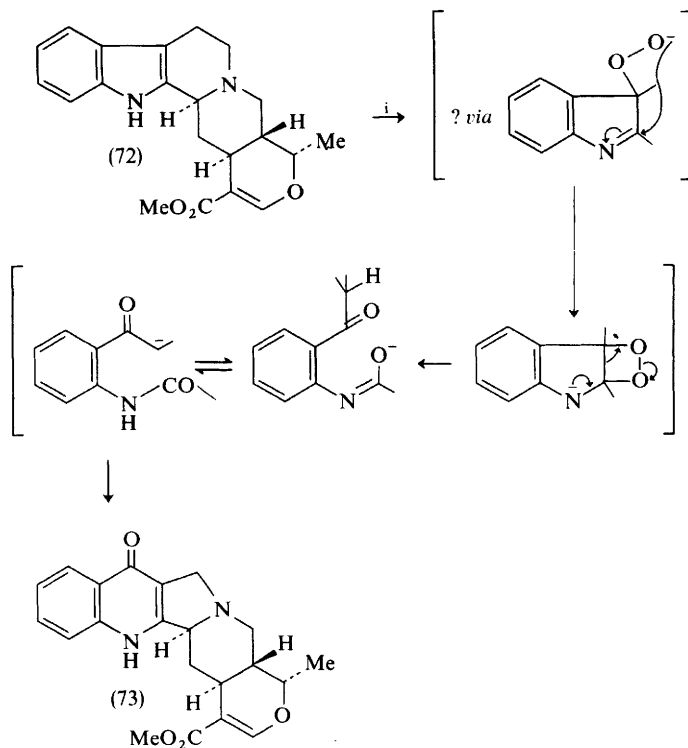
Reagent: i, O_2–Bu^{t}OK–DMSO at room temperature.

Scheme 27

placed substituents and at the wrong oxidation level. A synthetic tetrahydro-β-carboline similarly treated[66b] (Scheme 28) led to (74) which, apart from substituents, has the A to D rings of camptothecin at the correct oxidation level. It is suggested that these transformations may involve a four-membered dioxo-ring intermediate and a final intramolecular aldol condensation (Scheme 27).

[65] D. L. Coffen and T. E. McEntee, *Chem. Comm.*, 1971, 539.
[66] [a] E. Winterfeldt, *Annalen*, 1971, **745**, 23; [b] E. Winterfeldt and H. Radunz, *Chem. Comm.*, 1971, 374.
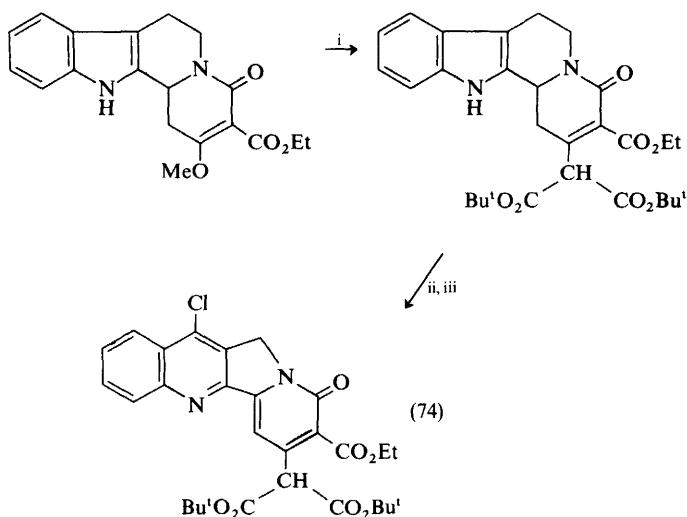
Reagents: i, $CH_2(CO_2Bu^t)_2$–NaH; ii, O_2–Bu^{t}OK–DMSO; iii, SOCl$_2$–DMF (chlorination and dehydrogenation).

Scheme 28

Further tri- and tetra-cyclic analogues[67] of camptothecin have been synthesised.

4 Bisindole Alkaloids

Calycanthine co-occurs[68] with pyrrolizidine alkaloids in *Bhesa archboldiana*. The absorption and c.d. spectra of calycanthine and caracurine II have been extended[69] to 53 000 cm^{-1}; theoretical curves match the experimental ones moderately well.

Chaetocin[70a] (75a) and verticillin A[70b] (75b), metabolites of *Chaetomium minutum* and a species of *Verticillium* from *Coltricia cinnamomea* respectively, are closely related dimers (Scheme 29) with S$_2$-bridged diketopiperazine systems reminiscent of gliotoxin, sporidesmin, and aranotin.

The base peak (76) in the mass spectrum of chaetocin represents the favoured loss of sulphur and water and splitting in half to give the stabilized, conjugated ion. The structure of chaetocin, which was shown by labelling experiments to

[67] M. Shamma and L. Novák, *Coll. Czech. Chem. Comm.*, 1970, **35**, 3280; T. Kametani, H. Nemoto, H. Takeda, and S. Takano, *Tetrahedron*, 1970, **36**, 5753.

[68] C. C. J. Culvenor, S. R. Johns, J. A. Lamberton, and L. W. Smith, *Austral. J. Chem.*, 1970, **23**, 1279.

[69] W. S. Brickell, S. F. Mason, and D. R. Roberts, *J. Chem. Soc. (B)*, 1971, 691.

[70] *a* D. Hauser, H. P. Weber, and H. P. Sigg, *Helv. Chim. Acta*, 1970, **53**, 1061; *b* H. Minato, M. Matsumoto, and T. Katayama, *Chem. Comm.*, 1971, 44.
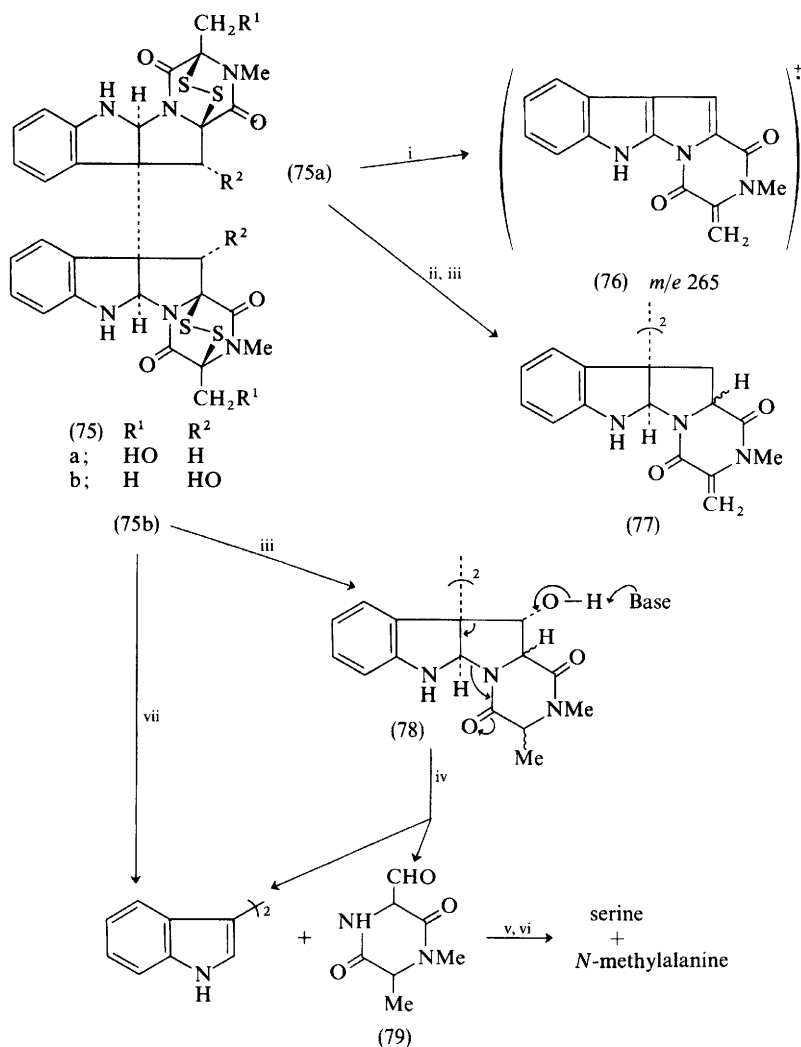
Reagents: i, $-e^-$ and fragmentation; ii, Ac_2O; iii, Al–Hg; iv, 5% aq. KOH at room temperature; v, $NaBH_4$; vi, 6N-HCl; vii, aq. KOH–heat.

Scheme 29

incorporate tryptophan, was settled by X-ray analysis and its absolute configuration was decided by c.d. comparisons with the other natural epidithiapiperazine-diones.

Aluminium amalgam reduction of the diacetate of chaetocin resulted in removal of the sulphur bridges and the elimination of acetic acid to give (77). Analogous

treatment of verticillin also resulted in desulphurization and gave (78), a compound which, in a key degradation, gave a quantitative yield of 3,3′-bi-indolyl and the diketopiperazine aldehyde (79) on mild base treatment [arrows in (78)]. The structural features of the aldehyde (79) were elucidated by degradation to serine and *N*-methylalanine. Aqueous alkali treatment of the metabolite itself also gave 3,3′-bi-indolyl.

The relative stereochemistry of the two hydroxy-groups in verticillin was assigned on the basis that both are hydrogen-bonded to carbonyl oxygen. The absolute configuration is the same as that of chaetocin, as shown, again by c.d. comparisons.

As well as macralstonine[71a] and others, a new alkaloid,[71b] alstonisidine, has been isolated from *Alstonia muelleriana.* The structure (80) suggested for this dimer rests on spectral measurements, principally the presence of several ions in its mass spectrum which have the same mass numbers as characteristic fragment ions of authentic macroline and ajmaline alkaloids, the formation of a mono-*O*-acetate, of a triol with lithium aluminium hydride (fission of N—C—O), and the detection of formaldehyde after acid treatment. Formaldehyde was also detected after a model acid treatment of quebrachidine (81) and it is suggested that this rather surprising result can be explained, for both the dimer, believed to contain a quebrachidine unit, and for quebrachidine itself as shown [arrows in (81) and (82)].
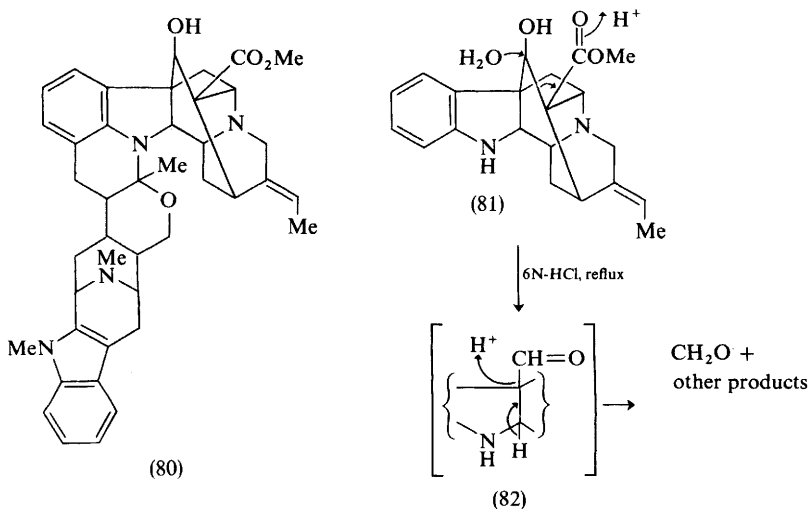
Details[72a] have been published of the isolation and spectral properties of iso-voafoline, voafoline, voafolidine, and folicangine from *Voacanga africana*; the

[71] *a* J. M. Cook and P. W. Le Quesne, *Phytochemistry*, 1971, **10**, 437; *b* J. M. Cook and P. W. Le Quesne, *J. Org. Chem.*, 1971, **36**, 582.
[72] *a* N. Kunesch, B. C. Das, and J. Poisson, *Bull Soc. chim. France*, 1970, 4370; *b* V. Agwada, M. B. Patel, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1970, **53**, 1567.

isolation[72b] of vobtusine, callichiline, voacangine, and conoflorine from *Hedranthera barteri* has been described.

In continued studies[73] of the dimerization of tetrahydrocarbazole derivatives to give the central chromophoric section of the calabash curare alkaloids, it has been shown that the presence of an ethylamino-side-chain can be tolerated; thus (83a) gives (84a) and (83b) gives (84b) (Scheme 30).

(83) R   (84) R
a;   Me $\xrightarrow{\text{i}}$ a;   Me
b;   CO$_2$Me $\xrightarrow{\text{i}}$ b;   CO$_2$Me
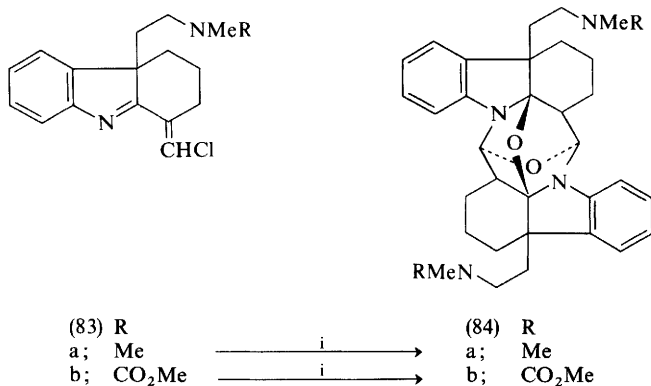
Reagent: i, 2N-HCl at room temperature.

Scheme 30

[73] H. Fritz and S. H. Eggers, *Annalen*, 1970, **736**, 33.

12
Lycopodium Alkaloids

BY V. A. SNIECKUS

This group has been concisely and lucidly reviewed in a general book on the chemistry of alkaloids.[1]
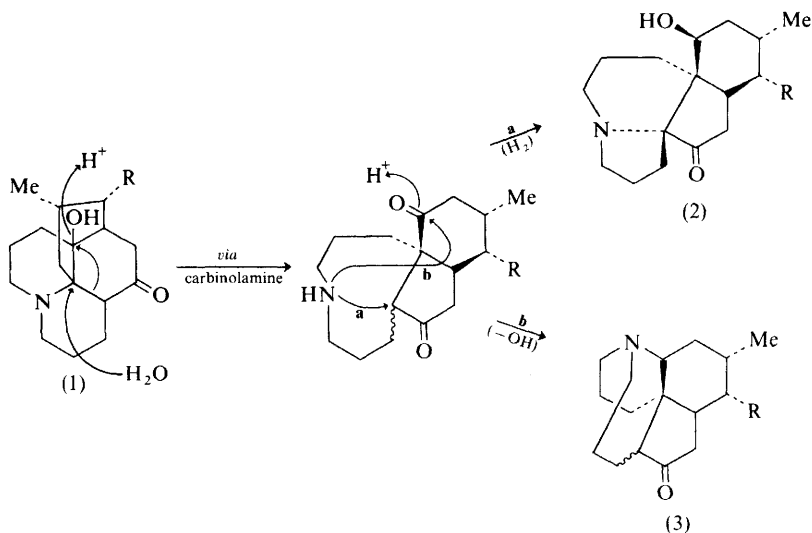
Scheme 1

Details of the structural elucidation of two unusual alkaloids, serratinidine (6) from *Lycopodium serratum* var. *serratum f. serratum* and fawcettidine (10) from *L. fawcetti* have been reported.[2] Following an ingenious proposal for the bio-genetic inter-relationships of the common lycodoline (1), serratinine (2), and serratinidine (3) type structures (Scheme 1), the chemical correlation of the last two alkaloids was achieved as outlined in Scheme 2. The final product (6) was

[1] D. B. MacLean in 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, p. 469.
[2] H. Ishii, B. Yasui, R. Nishino, T. Harayama, and Y. Inubushi, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1880.

found to be identical with a sample of the alkaloid. Since the structure and complete stereochemistry of serratinine had been established earlier by *X*-ray analysis,[3] serratinidine was assigned the absolute stereostructure as written (6), with the configuration of the C(4)-side-chain and C(5)-acetoamide groups remaining to be assigned. This interconversion rests crucially on the mechanism of the first reaction, the reductive rearrangement of the serratinine derivative (4; Scheme 2) promoted by zinc in acetic acid solution. Numerous other correlations of (5) with known degradation products of serratinine were carried out in order to establish its skeleton and carbinolamine character.

The structure of fawcettidine (10) was indicated from the similarity of its i.r. and n.m.r. spectra and basicity to those of serratinine.[2] Transformation of a serratinine derivative (7) into fawcettidine was thus envisaged and ultimately achieved by the sequence outlined in Scheme 3. The required intermediate (8) for the reductive rearrangement to (9) and (10) was obtained in four conventional steps. On the basis of previous studies, the alkaloid fawcettimine had been assigned structure (9). Unfortunately, direct comparison of synthetic (9) with the natural product could not be effected.
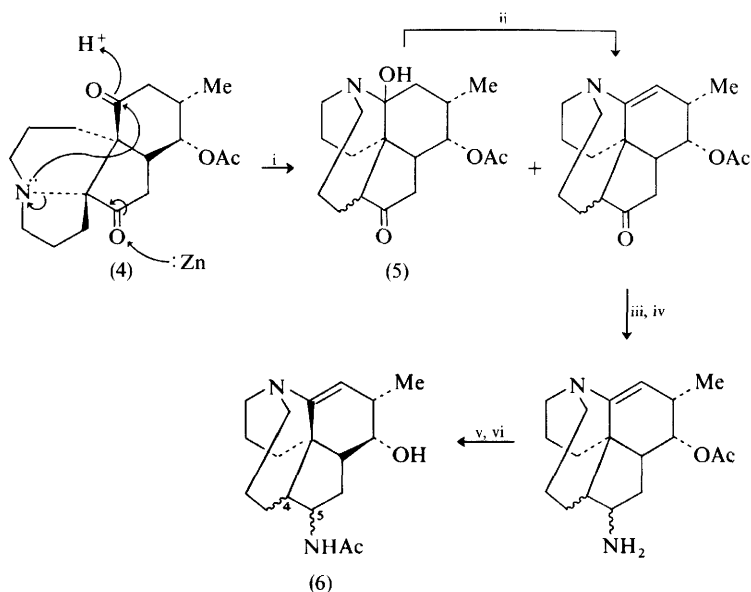
Reagents: i, Zn, HOAc; ii, POCl$_3$, pyridine, or HO$_2$CCO$_2$H, HOAc; iii, NH$_2$OH,HCl, pyridine; iv, Raney Ni, H$_2$; v, Ac$_2$O; vi, 5% NaOH, EtOH.

Scheme 2

[3] 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1970, Vol. 1, p. 339.

(7) (8) (10) (9)
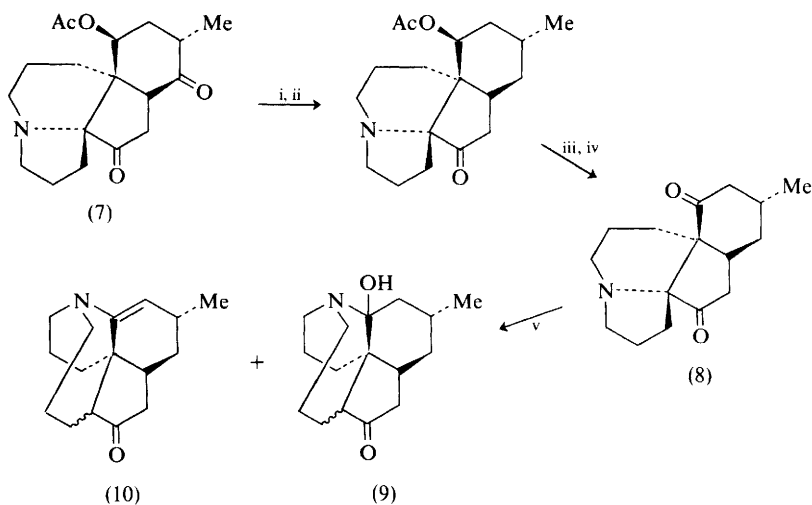
Reagents: i, HSCH$_2$CH$_2$SH, BF$_3$,Et$_2$O; ii, Raney Ni, H$_2$; iii, OH$^-$; iv, Jones reagent; v, Zn, HOAc.

Scheme 3

Continuation of previous activity[4] has led to the synthesis of a tricyclic derivative (17) which may be potentially useful for the preparation of *Lycopodium* alkaloids.[5] In a different approach from that reviewed last year,[4] the ketocarbamate (11) was transformed into the oxiran (12) by Corey's procedure (Scheme 4); attempts to use a Wittig reaction for a one-carbon chain-extension process failed. Treatment of (12) with ethyl sodiomalonate gave poor yields of the spiro-lactone (13), but this compound could be obtained in 61% yield by modification of the attacking nucleophilic reagent. Hydrolysis and decarboxylation were effected in one step. The product was smoothly transformed into the tricyclic lactam (14) possessing the important bridgehead hydroxy-group. Unexceptional reactions then led to the carbamate (15) which, upon hydroboration, gave the alcohol (16) as the major product. The other possible alcohol [C(6)-OH rather than C(7) in (16)] was detected only by t.l.c. and g.l.c. The large preference for the formation of the equatorial alcohol (16) may be the result of steric control. Mercuric acetate was ineffective at functionalizing the C(6)–C(7) double bond of (15). Oxidation of (16) gave compound (17), possessing certain features which may serve for further elaboration to alkaloid structures.

Comparison of structures (17) and (1) clearly shows that the former could serve as a biogenetic model for the first step of the lycodoline to serratinine rearrangement (1) → (2). In point of fact, treatment of (17) with acid gave compound (18), thus lending some credence to the proposed biogenetic route.[5]

[4] Ref. 3, p. 341.
[5] Z. Horii, S.-W. Khim, T. Imanishi, and T. Momose, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 2235.
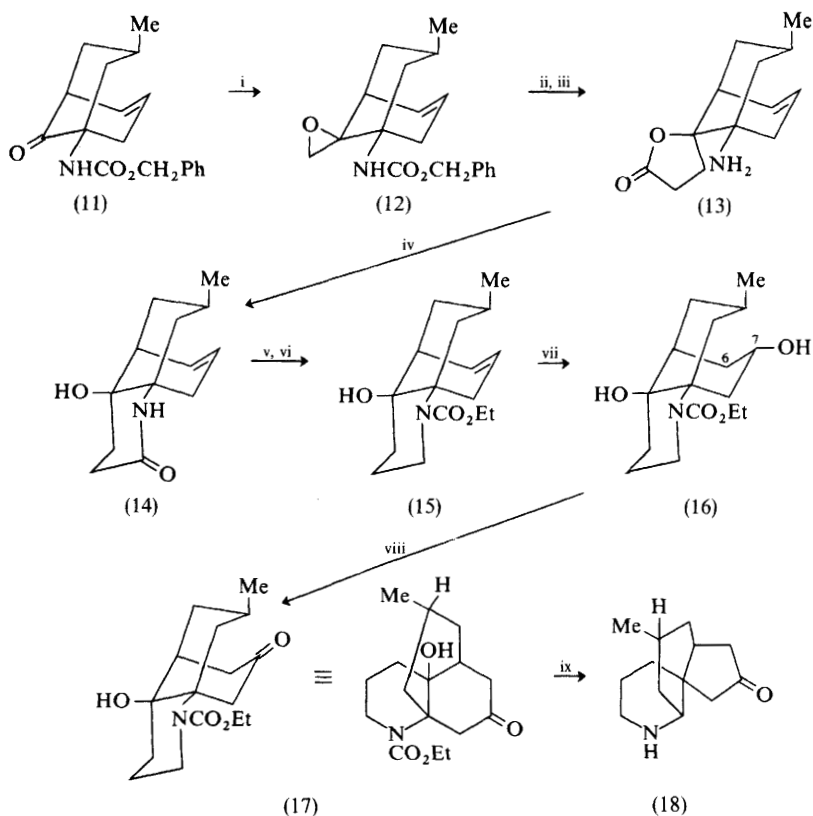
Reagents: i, Me$_2$S=CH$_2$, DMSO; ii, EtO$_2$CCH(OEt)CO$_2$Et, Mg, EtOH; iii, conc. HCl,
HOAc; iv, Triton B, EtOH; v, LiAlH$_4$; vi, ClCO$_2$Et, K$_2$CO$_3$; vii, B$_2$H$_6$;
viii, Jones reagent; ix, conc. HCl, 48% HBr, HOAc.

Scheme 4

(19)
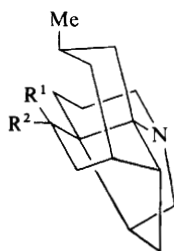
Owing to the availability of only small amounts of material, the structure of another novel alkaloid, lycopecurine (19; $R^1 = OH$, $R^2 = H$) from *Lycopodium alopecuroides* has been elucidated with the aid of *X*-ray crystallographic analysis. A future report will deal with the isolation of dehydrolycopecurine (19; $R^1 + R^2 = O$) from *L. inundatum*, and its correlation with lycopecurine.[6]

[6] W. A. Ayer and N. Masaki, *Canad. J. Chem.*, 1971, **49**, 524.

13

Recent Developments in Diterpenoid Alkaloid Chemistry

BY S. W. PELLETIER AND L. H. WRIGHT

1 Introduction

Since last year's Specialist Report, the emphasis in the diterpenoid alkaloid field has focused on structure determination, both by X-ray crystallography and by chemical and spectral methods. Some interesting synthetic approaches to diterpenoid alkaloids have also been reported. The total volume of work on diterpenoid alkaloids reported this year, however, is much less than in Chapter 16 of last year's Report, which covered a longer period and was intended to give a background to the subject.

The numbering system for the alkaloids used in this chapter is based upon the standard skeletons atisane, kaurane, and aconane and corresponds with the proposal suggested by J. W. Rowe and endorsed by O. E. Edwards, K. Wiesner, and the author. Thus the atisine, veatchine, and lycoctonine systems are numbered as in (1), (2), and (3), respectively.[1]

(1)
Atisine Skeleton

(2)
Veatchine Skeleton

(3)
Lycoctonine Skeleton
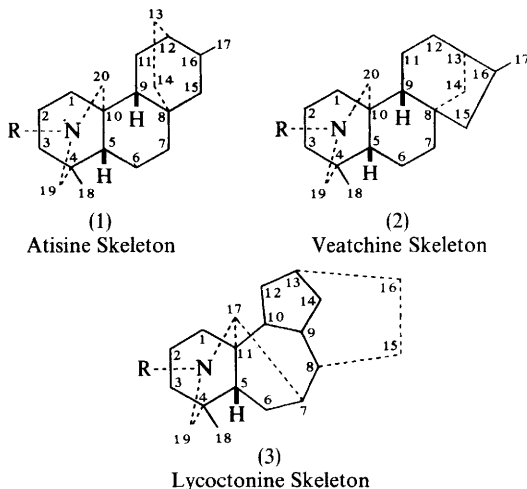
[1] cf. S. W. Pelletier and L. H. Keith in 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand Reinhold Company, New York, 1970, p. 504.

Because of a shift in emphasis and the absence of further work on the *Daphniphyllum* alkaloids, the outline of this Report differs somewhat from that in Chapter 16 of Volume 1.

2 New Structures

Anhydroignavinol ($C_{20}H_{27}NO_4$).—Alkaline hydrolysis of ignavine, a diterpenoid alkaloid of *Aconitum sanyoense* Nakai, *A. tasiromontanum* Nakai, and *A. japonicum*, affords anhydroignavinol. This base was reported by Ochiai *et al.* to have a molecular formula of $C_{20}H_{25}NO_4$ (mol. wt. 343).[2] Chemical and spectral data had led to the assignment of partial formulae (4) and (5) to ignavine and anhydro-ignavinol, respectively. Anhydroignavinol was believed to arise from ignavine

(4)   (5)
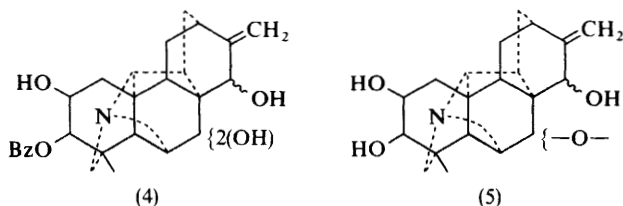
by saponification of the benzoate group at position 3 with subsequent dehydration between two hydroxy-groups to form an ether linkage.[2b] Recent high-resolution mass spectral studies indicate that the molecular ion of anhydroignavinol has m/e 345.1936, and therefore the molecular formula must be $C_{20}H_{27}NO_4$.[3] A single-crystal X-ray analysis of the methiodide showed the correct structure of anhydroignavinol to be (6), with $R = 0.119$.

(6)
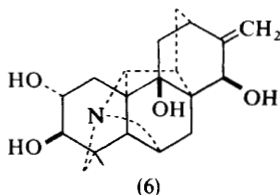
Since the previous chemical studies had assigned the benzoate group of ignavine as being attached to C(3), the nature and position of the remaining oxygen demanded by the ignavine formula ($C_{27}H_{31}NO_6$) requires explanation. Either an obscure transformation occurs in going from ignavine to anhydro-ignavinol, or more likely, the molecular formula originally assigned to ignavine

[2] [a] E. Ochiai, T. Okamoto, T. Sugasawa, H. Tani, and H. S. Hai, *J. Pharm. Soc. Japan*, 1952, **72**, 816; [b] E. Ochiai and T. Okamoto, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 556.
[3] S. W. Pelletier, S. W. Page, and M. G. Newton, *Tetrahedron Letters*, 1970, 4825.

is incorrect and should be $C_{27}H_{33}NO_6$. Ignavine would therefore be a hydrate of the benzoate ester of anhydroignavinol.

Hypognavinol ($C_{20}H_{27}NO_4$).—Hypognavinol, the alkaline hydrolysis product of hypognavine ($C_{27}H_{31}NO_5$, from *Aconitum sanyoense*), had been assigned by Japanese investigators either structure (7) or (8) on the basis of chemical and spectral evidence.[4—6] Recently, an X-ray crystallographic study of hypognavinol methiodide defined the location of the diol system and the tertiary hydroxy-group as shown in structure (9) ($R = 0.087$).[7]

(7)   (8)

(9)
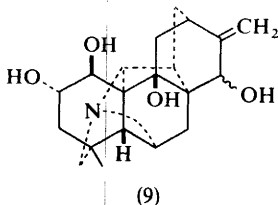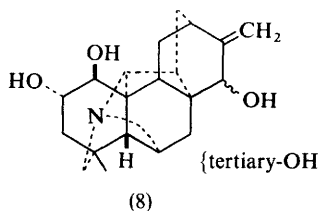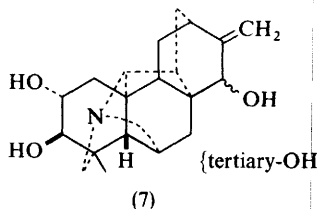
The Japanese workers had proposed on steric grounds that the benzoyloxy-group of hypognavine is in a β-configuration. Studies of models suggest, however, that the steric difference between a benzoyl group on the β-C(1)-hydroxy-group or on the α-C(2)-hydroxy-group would be slight.[7] The site of the benzoyl group in hypognavine therefore remains in doubt.

Hypognavinol and anhydroignavinol join the recently reported miyaconitine[8] as alkaloids of the modified atisine type bearing a hydroxy-group at C(9).

Vakognavine ($C_{34}H_{37}NO_{10}$).—The highly oxygenated alkaloid vakognavine was isolated from *Aconitum salmatum* Don.[9] Spectral data indicated the presence of a benzoate (δ 7.62,5H), a tertiary methyl (δ 1.12,s,3H), three acetates, and an N-methyl group (δ 2.07,s,6H; δ 2.18,s,3H; δ 2.33,s,3H) in the compound. The isolation of a compound identified as 1,9-dimethyl-7-ethylphenanthrene from the

[4] E. Ochiai, T. Okamoto, T. Sugasawa, H. Tani, and S. Saki, *Pharm. Bull. (Japan)*, 1953, **1**, 152.
[5] S. Saki, *J. Pharm. Soc. Japan*, 1956, **76**, 1054.
[6] S. Saki, *Pharm. Bull. (Japan)*, 1957, **5**, 1; *Chem. and Pharm. Bull. (Japan)*, 1958, **6**, 448; 1959, **7**, 50, 55.
[7] S. W. Pelletier, S. W. Page, and M. G. Newton, *Tetrahedron Letters*, 1971, 795.
[8] Y. Ichinohe and M. Yamaguchi, *Tetrahedron Letters*, 1970, 2323.
[9] N. Singh and A. Singh, *J. Indian Chem. Soc.*, 1965, **42**, 49.

selenium dehydrogenation products led the Indian workers to postulate a songorine-type skeleton (10).[10]

(10)
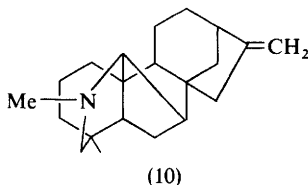
A recent X-ray crystallographic study of vakognavine hydriodide has shown the structure of the cation to be (11) ($R = 0.14$). The presence of the aldehyde group at C(19) in the free base (12) is indicated in the n.m.r. spectrum by absorption at $\delta = 9.43$.[11] Vakognavine is the first example of an N,19-seco-diterpenoid

(11)   (12)
                             Vakognavine
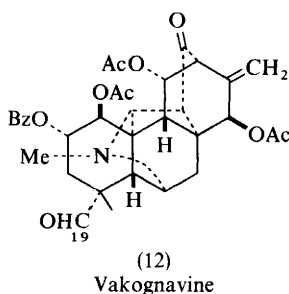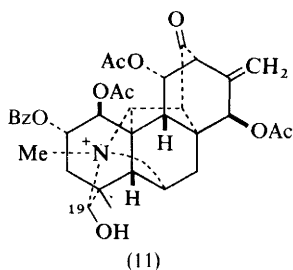
alkaloid reported and an interesting subject for biogenetic speculation. The structure having C(19) in an aldehyde group is a possible alternative to the pseudokobusine (13) structure as an intermediate in the biosynthesis of the hetisine-type skeleton (14).

(13)   (14)
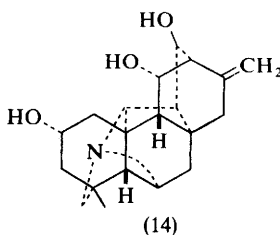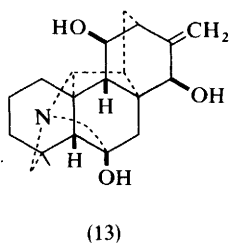
[10] N. Singh and S. S. Jaswal, *Tetrahedron Letters*, 1968, 2219.
[11] L. H. Wright, S. W. Pelletier, M. G. Newton, and K. N. Iyer, *American Crystallographic Assoc. Abstr. of Papers*, Summer Meeting, August 1971, C7.

Lappaconidine ($C_{22}H_{35}NO_6$).—A new alkaloid from *Aconitum leucostomum* (*excelsum*) has been shown by n.m.r. spectroscopy to possess two methoxy-groups and an *N*-ethyl group. The base formed tetra-acetate and tetramethyl derivatives. The latter was identical with trimethyl-lappaconine. The base peak at $M - 17$ in the mass spectrum of lappaconidine led the Russian investigators to suggest the presence of a hydroxy-group at C(1) and structure (15) for lappaconidine.[12] Although the configuration of the substituent groups in lappaconidine is not indicated in the Russian paper, because of the correlation with lappaconine the groups must have the configurations shown in structure (15).

(15)
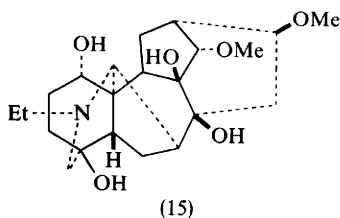
Lappaconitine ($C_{32}H_{44}N_2O_8$).—Lappaconitine is an acetylanthranilic ester of lappaconine, whose structure has been shown by *X*-ray analysis to be (16).[13] Russian workers have now shown that the oxidation of lappaconine with chromium trioxide in acetone affords a product identical with that obtained by a similar oxidation of lappaconitine and subsequent hydrolysis. The oxidation product was identified as a lactam containing a ketone in a five-membered ring. Reasoning that only a vicinal diol system could give rise to such a product, the Russian workers assigned the ester moiety of lappaconitine (17) to position 4.[14]

(16; R = H)

(17; R = CO·C_6H_4·NHCOMe-*o*)
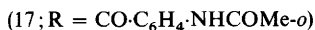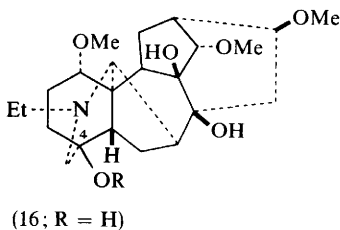
[12] V. A. Telnov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 639.
[13] G. I. Birnbaum, *Acta Cryst.*, 1970, **B26**, 755.
[14] V. A. Telnov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 583.

Talatizamine ($C_{24}H_{39}NO_5$) and Cammaconine ($C_{23}H_{37}NO_5$).—Talatizamine, an alkaloid isolated from *Aconitum talassicum* M. Pop. and from *A. variegatum*, had been shown to possess as functional groups an *N*-ethyl group, one primary and one secondary hydroxy-group, and three methoxy-groups.[15,16] The mass spectrum of talatizamine is similar to that of the lycoctonine alkaloids. Pyrolysis of diacetyltalatizamine proceeded with the loss of acetic acid to afford pyro-acetyltalatizamine and isopyroacetyltalatizamine, products which are character-istic of lycoctonine-type alkaloids with a $C(8)$-hydroxy-group and a $C(16)$-methoxy-group. Hydrogenolysis of the 'pyro'-derivative with lithium aluminium hydride confirmed the presence of a $C(16)$-methoxy-group, and an n.m.r. study placed this group in a β-configuration. Further n.m.r. studies located an α-hydroxy-group attached to $C(14)$ and a methoxy-group at $C(18)$. By mass spectroscopy the second methoxy-group was assigned a position attached to $C(1)$.[17]

Both talatizamine and isotalatizidine upon treatment with methyl iodide and sodium hydride afforded 1,8,14-tri-*O*-methylisotalatizidine (18).[18] Since the structure of isotalatizidine had been established as (19),[19] this correlation proves the structure of talatizamine to be (20). Pyroacetyltalatizamine and isopyro-acetyltalatizamine have structures (21) and (22), respectively.
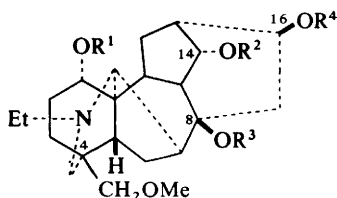
(18; $R^1 = R^2 = R^3 = R^4 = Me$)
(19; $R^1 = R^2 = R^3 = H$; $R^4 = Me$)
(20; $R^1 = R^4 = Me$; $R^2 = R^3 = H$)
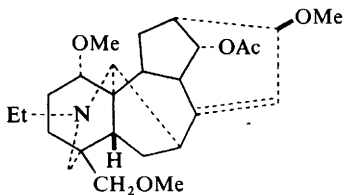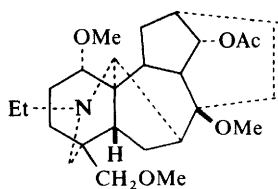
(21)   (22)

[15] R. A. Konovalova and A. P. Orekhov, *Zhur. obshchei Khim.*, 1940, **10**, 745.
[16] S. Yu. Yunusov, E. V. Sichkova, and G. F. Potiemkin, *Zhur. obshchei Khim.*, 1954, **24**, 2237.
[17] M. S. Yunusov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 90.
[18] M. A. Khaimova, M. D. Palamareva, N. M. Mollov, and V. P. Krestev, *Tetrahedron*, 1971, **27**, 819.
[19] S. W. Pelletier, L. H. Keith, and P. C. Parthasarathy, *J. Amer. Chem. Soc.*, 1967, **89**, 4146.

Cammaconine, an alkaloid of *Aconitum variegatum*, has been shown to contain three hydroxy-groups, two methoxy-groups, and an *N*-ethyl group, on the basis of n.m.r. evidence.[18] Methylation of cammaconine afforded 1,8,14-tri-*O*-methyliso-talatizidine (18). This reaction demonstrates that cammaconine possesses the same skeleton, oxygen location, and stereochemistry as isotalatizidine, but a different pattern of *O*-methylation.

Oxidation of cammaconine with Sarett reagent afforded two products, dehydro-oxocammaconine (23) and didehydro-oxocammaconine (24). Both products showed spectral characteristics for two methoxy-groups, an *N*-ethyl group, a hydroxy-group, a cyclopentanone moiety, and a tertiary lactam in a six-membered ring. The second product also possessed an i.r. absorption band characteristic of a cyclohexanone. There was no evidence of an aldehyde proton in the n.m.r. spectra of either product.

(23; R = β-OH, H)
(24; R = O)

(25)
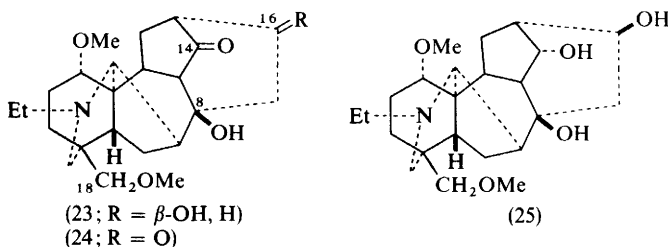
The structural correlation of cammaconine with isotalatizidine establishes the tertiary hydroxy-group of cammaconine as being attached to C(8) and a secondary hydroxy-group at C(14). To avoid identity with isotalatizidine, cammaconine must be assigned structure (25) and is the first example of an aconitine- or lycoctonine-type alkaloid with a β-hydroxy-group at C(16),[18] instead of the usual β-methoxy-group at this position.

Absolute Configuration of Condelphine ($C_{25}H_{39}NO_6$) and its Relatives.— Condelphine from *Delphinium confusum* and *D. denudatum* has been assigned[19] structure (26) on the basis of chemical and spectral evidence. The configuration of the C(15)-methoxy-group was unassigned and the absolute configuration of the molecule was assumed by analogy with that of other diterpenoid alkaloids.

An *X*-ray crystallographic study of condelphine hydriodide showed that the assigned structure of condelphine is correct and that the C(15)-methoxy-group has a β-orientation (27).[20] Moreover, application of the anomalous dispersion method has shown that the assumed absolute configuration is correct. Since condelphine has been correlated with isotalatizidine (28), talatizidine, talatiz-amine, and cammaconine, all of these alkaloids have the same absolute con-figuration as condelphine.

[20] S. W. Pelletier, and D. L. Herald, unpublished work.

OH

Et - - N

H

CH$_2$OMe

OR^1 ^{15}

R^2

^{16}

OH
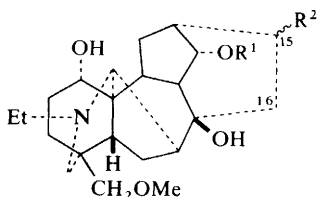
(26; R^1 = Ac; R^2 = ⎯OMe)
Condelphine   (27; R^1 = Ac; R^2 = β-OMe)
Isotalatizidine (28; R^1 = H; R^2 = β-OMe)

A Revision of Structure for Certain Delphinine and Aconitine Alkaloids.⎯The configuration of the ring A methoxy-group in delphinine was assigned[21] many years ago on the basis of a direct structural correlation[22] of delphinine with aconitine. The corresponding ring A methoxy-group of aconitine had been assigned the configuration *trans* to the nitrogen bridge on the basis of what appeared to be a sound conformational argument.[23] A similar conformational argument seemed valid when this substituent was studied in delphinine.[21] Summarized below is evidence which demonstrates that the configuration of the ring A methoxy-group in delphinine (and in several other aconitine-type alkaloids) must be reversed. The fact that the conformational arguments led to assignment of the erroneous configuration of the ring A methoxy-group reflects the basic uncertainty about the conformation of ring A in the delphinine alkaloids.

The total synthesis of a racemic delphinine degradation product, thought to be (29) (one enantiomer shown), and its identification with the 'natural' degradation product has been reported.[24] Resolution of the 'identical racemate' *via* the L-camphorsulphonamide derivative and the identification of one enantiomer with the 'natural' degradation product has also been reported.[25] However, a subsequent X-ray crystallographic study of the 'identical racemate' in the form of its acid oxalate has proved that its actual structure is (30) (one enantiomer shown).[26] In view of this result delphinine must possess an α-equatorial methoxy-group at C(1) (*cis* to the nitrogen bridge) instead of the formerly assigned β-axial methoxy-group, and accordingly should be assigned structure (31).

By virtue of chemical correlations, the structures of the following alkaloids must also be revised to indicate an α-equatorial methoxy-group at C(1): aconitine (32), mesaconitine (33), jesaconitine (34), indaconitine (35), pseudaconitine (36),

[21] K. Wiesner, D. L. Simmons, and R. H. Wightman, *Tetrahedron Letters*, 1960, No. 15, p. 23.
[22] K. Wiesner, D. L. Simmons, and L. R. Fowler, *Tetrahedron Letters*, 1959, No. 18, p. 1.
[23] F. W. Bachelor, R. F. C. Brown, and G. Büchi, *Tetrahedron Letters*, 1960, No. 10, p. 1.
[24] K. Wiesner, E. W. K. Jay, C. Demerson, T. Kanno, J. Křepinský, Lizzie Poon, T. Y. R. Tsai, A. Vilim, and C. S. Wu, *Experientia*, 1970, **26**, 1030.
[25] K. Wiesner, E. W. K. Jay, and Lizzie Poon, *Experientia*, 1971, **27**, 363.
[26] K. B. Birnbaum, K. Wiesner, E. W. K. Jay, and Lizzie Jay (Poon), *Tetrahedron Letters*, 1971, 867.
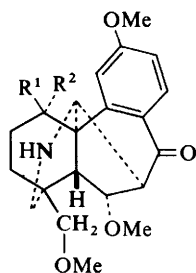
(29; R¹ = OMe; R² = H)
(30; R¹ = H; R² = OMe)

(31)
Delphinine
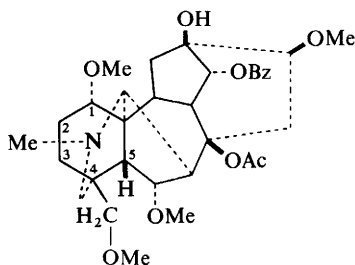
hypaconitine (37), deoxyaconitine (38), chasmaconitine (39), bikhaconitine (40), and chasmanthinine (41). (*cf.* ref. 27).
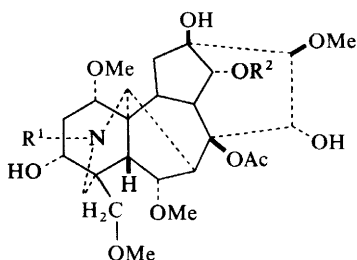
          R¹   R²
(32; Et   Bz)
(33; Me   Bz)
(34; Et   CO·C₆H₄·OMe-*p*)
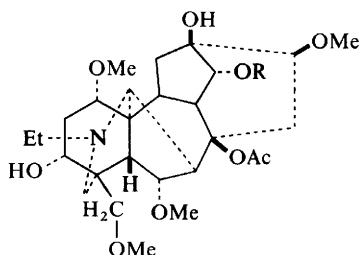
Indaconitine (35; R = Bz)
Pseudaconitine [36; R = CO·C₆H₃(OMe)₂-*m, p*]
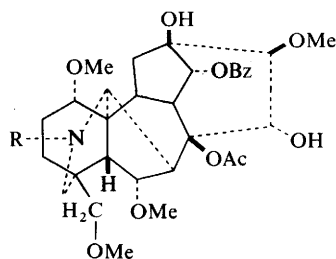
Hypaconitine (37; R = Me)
Deoxyaconitine (38; R = Et)
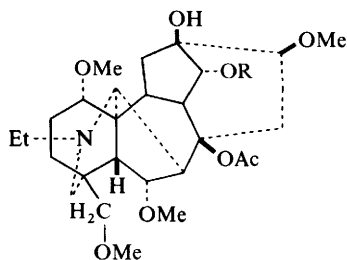
Chasmaconitine (39; R = Bz)
Bikhaconitine [40; R = CO·C₆H₃(OMe)₂-*m, p*]
Chasmanthinine [41; R = CO·CH:CH·C₆H₅]

3 Chemistry and Synthesis

Lappaconine Rearrangements.—In their study of lappaconitine, Russian chemists observed an acid-catalysed rearrangement of lappaconine (16). Treatment of (16) with sulphuric acid produced an amorphous solid whose molecular formula differed from that of the starting material by the loss of methanol and water. Spectral data led to the suggestion that the reaction had proceeded *via* a pinacolinic-type rearrangement to afford the product (42) which possesses a denudatine-type skeleton.[14]

(16)   (42)
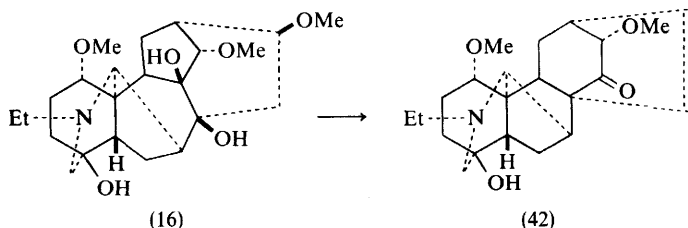
Some controversy has appeared with regard to the cleavage of oxolappaconine (43) by lead tetra-acetate to dehydro-seco-oxolappaconine. Canadian workers[28] have proposed that the scission produces the intermediate (44) which in turn undergoes an aldol condensation to afford (45). Structure (45) was assigned on evidence from its i.r. spectrum (1645 cm^{-1}, CO—N; 1710 cm^{-1}, CO in a five-membered ring conjugated with a double bond). Only a single ketonic absorption was present in the spectrum.[28] Telnov and co-workers have reported, however, that there is no absorption characteristic of an $\alpha\beta$-unsaturated ketone in the u.v. spectrum of this compound.[14]

(43)   (44)

(45)
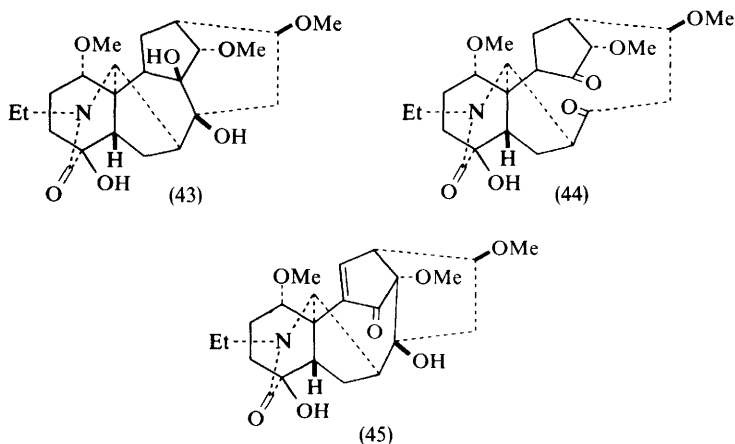
[27] L. H. Keith and S. W. Pelletier in 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand Reinhold Company, New York, 1970, pp. 564–568.
[28] N. Mollov, T. Tada, and L. Marion, *Tetrahedron Letters*, 1969, 2189.

Diacetyltalatizamine Pyrolysis.—The pyrolysis of diacetyltalatizamine (46) in glycerol affords a product differing from the starting material by the loss of methanol, acetic acid, and an acetyl group. Spectral evidence showed that the compound contained two methoxy-groups (δ 3.24,3.20,s), an *N*-ethyl group (δ 0.97,t), and no acetate groups. The presence of a single hydroxy-group was demonstrated by formation of a monoacetate, and the site was fixed at C(14) by n.m.r. spectroscopy (δ 3.96,t,1H, $J = 4.5$ Hz). Structure (47) was assigned to the product.[29] The authors suggest that the product is generated by an ionic hydrogenation process. The formation of the carbonium ion (48) is succeeded by the abstraction of hydride from the glycerol solvent to afford (49), which then proceeds to the final product.[29]

(46; R = OAc)
(48; R = +)
(49; R = H)

(47)
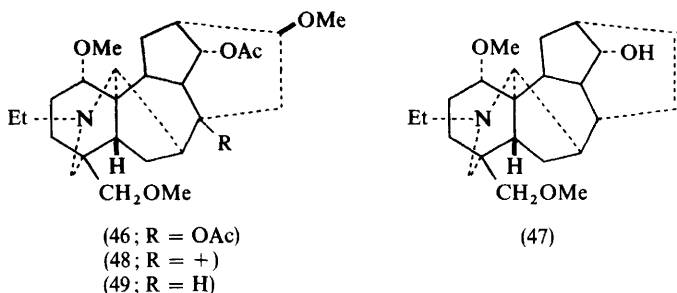
Synthesis of an Atisine-type Intermediate.—Two synthetic routes to the tricyclic dione (50) were explored by Beames and Mander.[30] Using an approach analogous to one developed by Masamune,[31] they converted 1,2,3,4-tetrahydro-7-hydroxy-2-naphthoic acid (51) into the bromide (52). The reaction of the latter with t-butoxide produced a 3:1 mixture of the dienone ethers (54) and (55). The use of deblocking and oxidation reactions furnished the diketone (50). Reduction of (50) with borohydride furnished a 2:3 mixture of the alcohols (56) and (57).

(51; R = CO₂H)
[52; R = CH(OTHP)CH₂Br]
(53; R = COCHN₂)

(54; R¹ = OTHP; R² = H)
(55; R¹ = H; R² = OTHP)
(56; R¹ = OH; R² = H)
(57; R¹ = H; R² = OH)

(50)
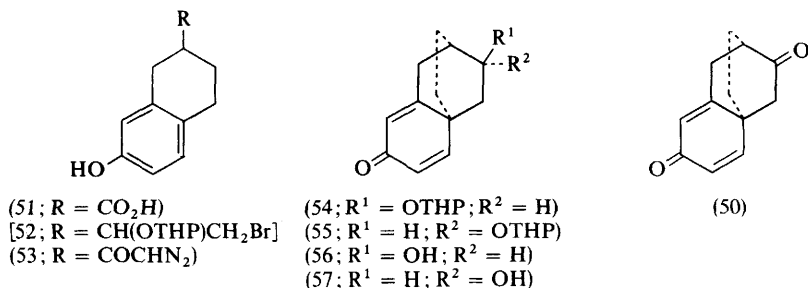
[29] M. S. Yunusov, V. A. Telnov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii,* 1970, **6**, 774.
[30] D. J. Beames and L. N. Mander, *Austral. J. Chem.,* 1971, **24**, 343.
[31] S. Masamune, *J. Amer. Chem. Soc.,* 1964, **86**, 288.

The second approach to (50) was more direct. Acetylation of (51) was followed by sequential treatment with oxalyl chloride and excess diazomethane to afford, after hydrolysis, the diazoketone (53). Boron trifluoride etherate in nitromethane proved to be the best system to catalyse the cyclization of (53) to (50). This route may provide a useful intermediate for syntheses of atisine-type alkaloids.

Synthesis of a Veatchine-type Intermediate.—A recent synthesis[32] of gibberellin-A$_{15}$ involves an intermediate of interest for the synthesis of diterpene alkaloids. Enmein (58) had previously been converted to the alcohol (59).[33] Oxidation of this alcohol afforded an aldehyde which was converted to its oxime. Removal of the blocking group afforded (60). The nitrone (61), prepared by treatment of (60) with bromonium azide, was photolysed to (62). The resemblance of this intermediate to several alkaloids of the veatchine-type is obvious. Minor variations of this scheme may prove to be of synthetic interest.

(58)

(59; R^1 = THP; R^2 = CH$_2$OH)
(60; R^1 = H; R^2 = CH=NOH)

(61)   (62)
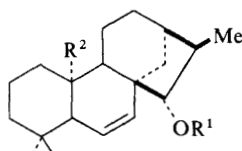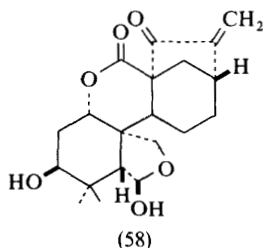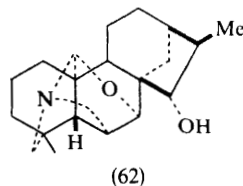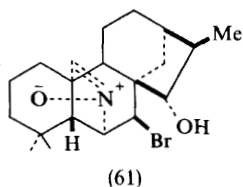
The authors wish to thank Dr. Ionel Haiduc for translation of several Russian articles into English. We are grateful to Dr. Samuel Page for checking the manuscript.

[32] M. Somei and T. Okamoto, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2135.
[33] M. Somei, K. Shudo, T. Okamoto, and M. Natsume, *Abstr. Papers, 24th Meeting of the Pharmaceutical Society of Japan*, 1967, 460.

14

Steroidal Alkaloids of the Apocynaceae and the Buxaceae

BY F. KHUONG-HUU and R. GOUTAREL

Introduction

The present report follows that which was published in 1971 in volume one of this publication.[1] The following sections outline further work published from June 1970 to July 1971 and are limited to steroidal alkaloids of the Apocynaceae and Buxaceae.

PART I: Alkaloids of the Apocynaceae

A review of steroidal alkaloids by Sato has recently been published in a book entitled 'Chemistry of the Alkaloids' edited by Pelletier.[2]

The *Holarrhena* and *Paravallaris* Alkaloids

A. Steroidal Alkaloids and Amines.—Lanitine (1), 2α-hydroxy-*N*-methylpara-vallarine,[3] and its 2β-hydroxy isomer (2), have been isolated from the stem bark of *Kibatalia gitingensis*.[4]

Oxidation of 18-benzoylaminoprogesterone (3) with chromium trioxide afforded as the main product the lactam (4) (etianic acid series) together with a smaller yield of the imine (5).[5]

(1)   (2)
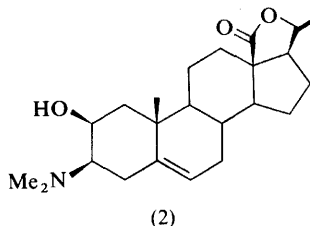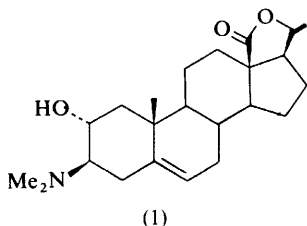
[1] R. Goutarel, 'The Alkaloids,' ed. J. E. Saxton, (Specialist Periodical Report), Chemical Society, London, 1971, Vol. 1, p. 382.

[2] 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand–Reinhold, New York, 1970.

[3] A. Cave, P. Potier, and J. Le Men, *Ann. pharm. franc.*, 1967, **25**, 107.

[4] R. M. Bernal-Santos, *Philipp. J. Sci.*, 1967, **96**, 411 (*Chem. Abs.*, 1971, **74**, 10 364p).

[5] A. Kasal, *Coll. Czech. Chem. Comm.*, 1970, **35**, 3821.
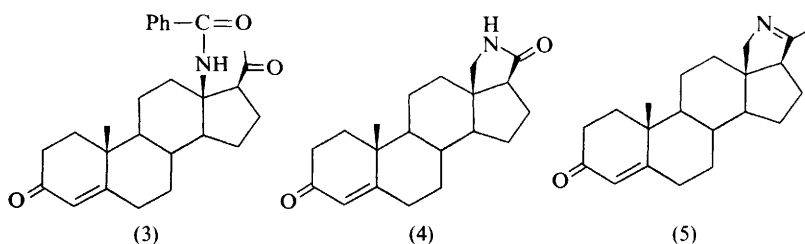
The equilibrium between the open and closed form of the aldehyde-amide formed from acylated derivatives of Δ^1-pyrrolines (conkurchine series[6]) has been studied for the N-benzoyl (6) and the N-acetyl (7) compounds.[7] It appears that for the benzoyl derivative (6) the equilibrium is such that the open form is favoured, whereas for the acetyl derivative (7) the cyclic form predominates [there is an absence of C=O aldehydic vibrations in the i.r. of (7)]. However, in both cases, reduction with sodium borohydride gave the two corresponding alcohol amides.

The pyrroline (9), methylated in position 20, has been prepared by the action of methylmagnesium iodide on the methoxylated imine (8). The reactivity of this pyrroline has been studied and compared to that of conkurchine. Reactions have also been carried out on the imine (9) for the preparation of 18,20-substituted derivatives of 20-methyl-5α-pregnane such as the tertiary amine (10) and the ether (11).[8]
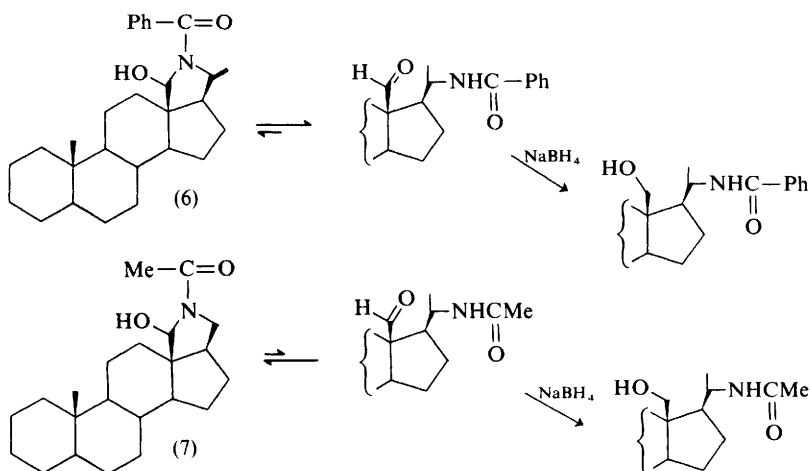
[6] M.-M. Janot, M. Truong-Ho, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. chim. France*, 1963, 1977.
[7] Q. Khuong-Huu, C. Monneret, J. Einhorn, G. Ratle, X. Monseur and R. Goutarel, *Compt. rend.*, 1970, **271**, C, 1142.
[8] J. P. Alazard and X. Lusinchi, *Compt. rend.*, 1970, **271**, C, 1386.

(8) (9) (10) (11)
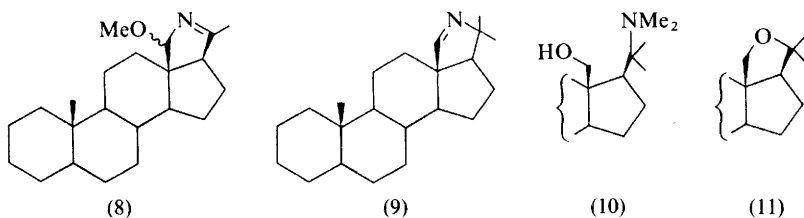
In a study of the reduction of steroidal imines with lithium aluminium hydride and sodium borohydride, Lusinchi[9] found that with an excess of lithium aluminium hydride the methoxylated imine (8) afforded the two isomeric imines, (12) and (13), together with *N*-demethylconanine (14), in a ratio dependent on the time of the reaction. The absence of *N*-demethylheteroconanine indicated that the reduction at position 20 was stereospecific. The imine (12) was found to result from initial reduction of the 20-*N*-imine, while the imine (13) was suggested to be derived from an enamine derivative, as in Scheme 1.

(8) (12) (13) (14)
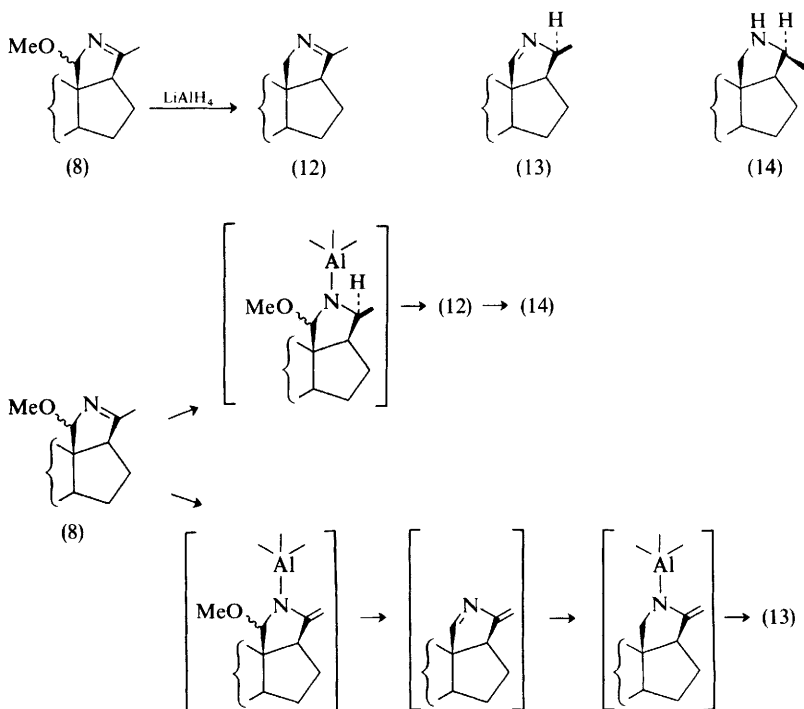
Scheme 1

[9] P. Milliet, A. Picot, and X. Lusinchi, *Tetrahedron Letters*, 1971, 1195.

By contrast, the imines (8), (12), and (13) were quantitatively and rapidly reduced to *N*-demethylconanine (14) with sodium borohydride.

The 12β-hydroxy- (16), 12α-hydroxy- (17), and 12-keto- (18) derivatives of *N*-demethyl-5α-20(*N*)-conen-3-one have been prepared from holarrhenine (15). The 12α-hydroxy-derivative has been obtained by Elks reduction[10] of 12-keto-dihydroconimine.[11]

(15)

(16)   (17)   (18)
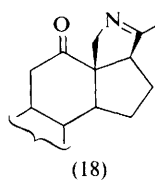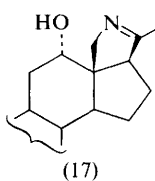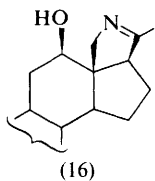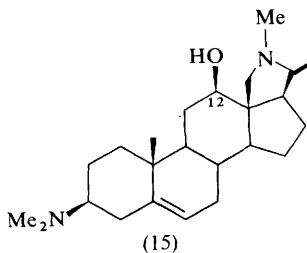
Treatment of the oxaziran (19), monodeuteriated in position 18α, with methanolic potassium hydroxide in the presence of water, by Emmons' procedure,[12] gives rise to the deuteriated ketone (20). This result prompted Lusinchi to suggest that the first stage of the reaction occurred by a concerted *trans* E2-type elimination[13] (see Scheme 2).

(19)   →   (20)

$$B^- \quad H \quad O \quad H-B \qquad R^1R^2C{=}O + NH_3$$
$$R^1{-}\underset{R^2}{\overset{H}{C}}{-}N{-\!-}\underset{R^4}{\overset{}{C}}{-}R^3 \rightarrow R^1{-}\underset{R^2}{\overset{}{C}}{=}N{-}\underset{R^4}{\overset{OH}{C}}{-}R^3 \xrightarrow{\text{H}_2\text{O}} + R^3R^4C{=}O$$
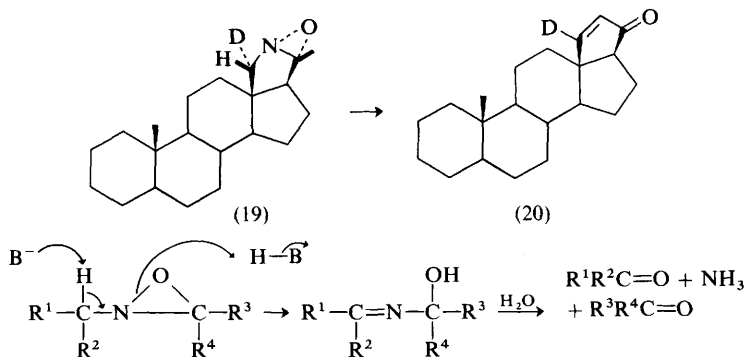
Scheme 2

[10] J. Elks and G. H. Phillips, *J. Chem. Soc.*, 1956, 3420.
[11] G. Lukacs, G. Roblot, A. Picot, and X. Lusinchi, *Ann. pharm. franc.*, 1970, **28**, 363.
[12] W. D. Emmons, *J. Amer. Chem. Soc.*, 1957, **79**, 5739.
[13] J. P. Jeanniot, X. Lusinchi, P. Milliet, and J. Parello, *Tetrahedron*, 1971, **27**, 401.

A method for the preparation of secondary amines from cyanamides has been demonstrated for the preparation of the amine (22) using dihydroisoconessimine (21) as the starting material. Under alkaline conditions, hydrogen peroxide

(21)

(22)

(23) a; R = CN
b; R = $CONH_2$
c; R = H
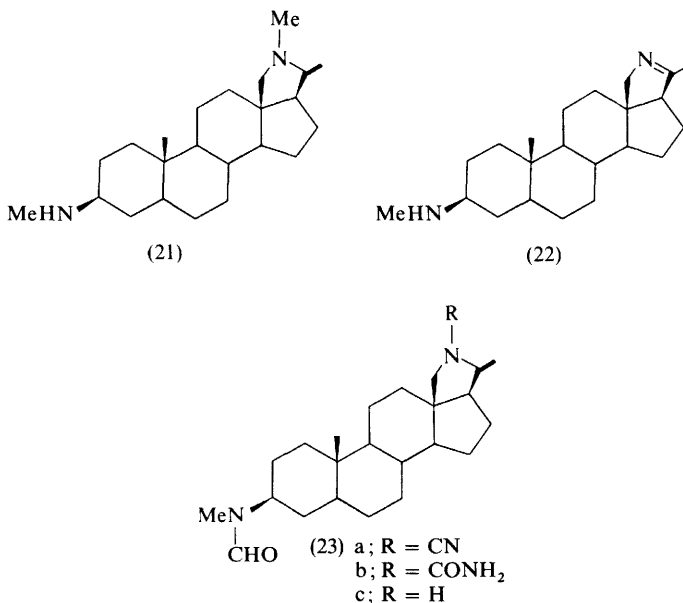
transformed the cyanamide (23a) to the urea (23b) which in turn was converted by nitrous acid into the secondary amine (23c). Chlorination of N-20, followed by treatment with MeOH–Na, gave the derivative (22).[14]

B. Amino-glyco-steroids.—Partial syntheses of holantogenin (24) and anhydro-holantogenin (25), the steroidal moieties of the amino-glyco-steroids, holanto-sines A, B, C, and D,[15] have been realised by two independent schools by similar

(24)

(25)
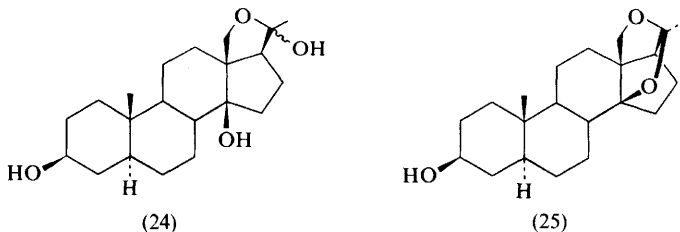
[14] P. Longevialle, A. Picot, L. Diatta, and X. Lusinchi, *Bull. Soc. chim. France*, 1970, 4057.
[15] Q. Khuong-Huu, C. Monneret, P. Choay, J. M. Tekam, I. Kabore, and R. Goutarel, *Bull. Soc. chim. France*, 1970, 864.

(26)   (27)
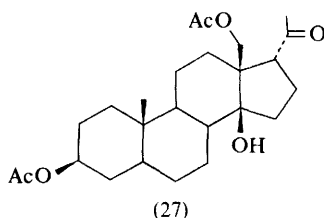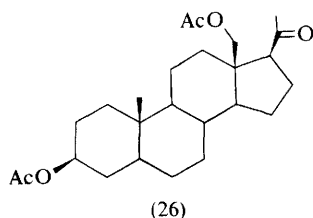
pathways.[16] The keto-acetate (26), which was prepared by ring-opening of 3β-acetoxy-18-hydroxy-5α-pregnan-20-one (18→20 hemiacetal), was hydroxylated in the 14β position by standard classical methods.[17] Saponification of the hydroxy-derivative (27) afforded holantogenin (24), which could be transformed by sublimation into anhydroholantogenin (25).

C. Mass and N.M.R. Spectra of Steroidal Amines.—A study has recently been made[18] of the mass spectral fragmentation pattern of the dimer (28), obtained by reduction of the cyanamide of conanine with lithium aluminium hydride.[19] As with certain benzylamines, a major fragment has been interpreted to arise from a heterolytic rupture of the $C\overset{+}{-}N=$ bond.

m/e 314

(28)
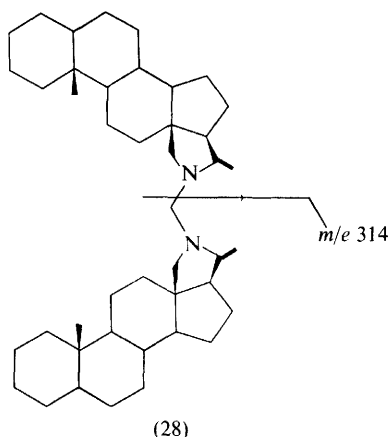
In the mass spectral fragmentation pattern of 3β-N-demethyl-5α-20(N)-conene (22), after [^{2}H] labelling in positions 2 and 4, it was demonstrated that hydrogen transfer occurred from C-2 to C-4, giving an insight into the mechanism leading to ions a, characteristic of 3-amino-steroids:[14]

[16] B. P. Schaffner, F. L. Berner-Fenz, and H. Wehrli, *Helv. Chim. Acta*, 1970, **53**, 2266;
P. Choay, C. Monneret, and Q. Khuong-Huu, *Compt. rend.*, 1971, **272**, C, 782.
[17] Pl. A. Plattner, L. Ruzicka, H. Heussler, and E. Angliker, *Helv. Chim. Acta*, 1947, **30**, 385.
[18] P. Longevialle, A. Picot, and X. Lusinchi, *Compt. rend.*, 1970, **271**, C, 859.
[19] A. Picot and X. Lusinchi, in press.

(22) $\xrightarrow{-e}$ →

$(a = \overset{+}{\underset{H}{MeN}}\!\!=\!\!\overset{\scriptscriptstyle\diagup}{})$

$- MeN\!\!=\!\!\overset{\scriptscriptstyle\diagup}{}$

$\xrightarrow[*]{-CH_3\cdot}$

ions $M - a + 1$
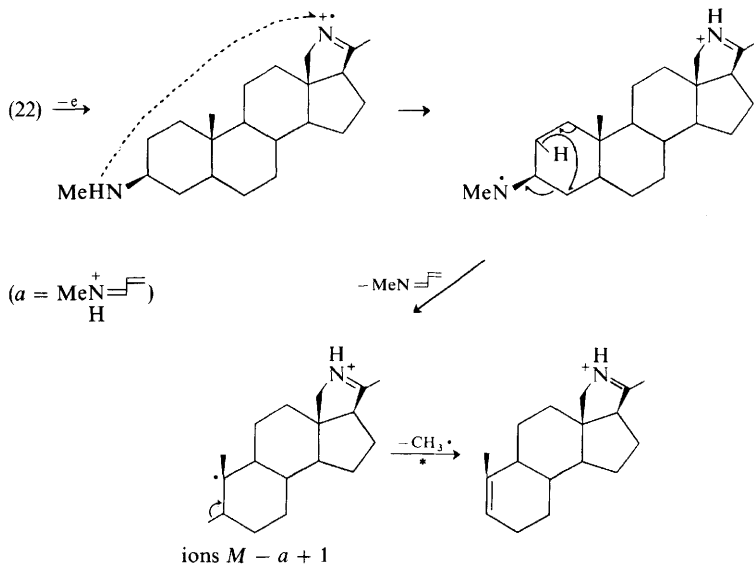
The presence of a hydroxy-group in steroidal amines, amides, and imines may profoundly influence their fragmentation patterns in the mass spectrometer. This fragmentation is initiated by the rearrangement of the hydroxylic hydrogen to the nitrogen-containing groups, resulting in characteristic ions of the OH site in the molecule. That may occur when the two groups are remote from each other,[20] as illustrated by the example in Scheme 3.

A study of the n.m.r. spectra of compounds belonging to the pyrrolidine series has resulted in a conformational analysis of ring E of conanine and heteroconanine by observing the signals from the non-equivalent N-CH$_2$ protons.

Examination of the n.m.r. spectra of some monodeuteriated pyrrolidines specifically labelled in the 18α position permitted the assignment of the preferred configuration of conanine as (29), and of heteroconanine as (30). These assignments were supported by the fact that the *trans*-proton with respect to the lone pair of the nitrogen is displaced upfield.[21]

As for a hydroxy-group it was found that a primary amino function is able to complex with tris(dipivalomethanato)europium, Eu(dpm)$_3$, and the resulting n.m.r. spectrum can be used for the resolution of protons which are in close proximity to the complexing agent. An axial or pseudoaxial amino-group has been found interesting for this purpose.[22]

[20] P. Longevialle, J. Einhorn, J. P. Alazard, L. Diatta, P. Milliet, C. Monneret, Q. Khuong-Huu, and X. Lusinchi, *Org. Mass Spectrometry*, 1971, **5**, 171.

J. P. Jeanniot, X. Lusinchi, J. Parello, and D. Z. Simon, *Tetrahedron Letters*, 1971, 235.

[22] L. Lacombe, F. Khuong-Huu, A. Pancrazi, Q. Khuong-Huu, and G. Lukacs, *Compt. rend.*, 1971, **272**, C, 668.

M − 30   m/e 85

M − 30   m/e 300

Scheme 3

R = H or D   R = H or D
(29)   (30)
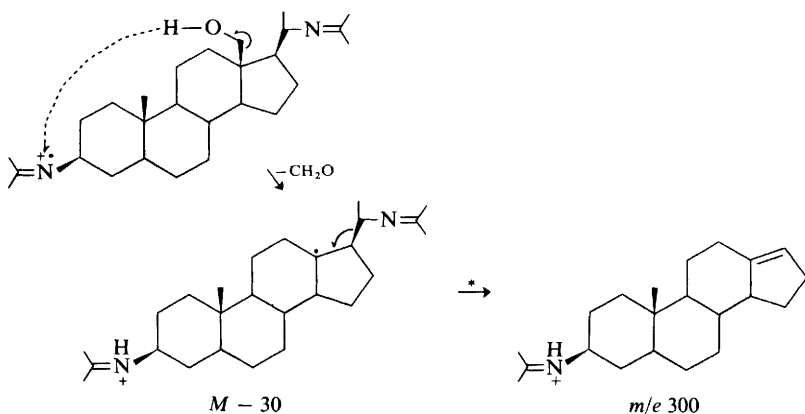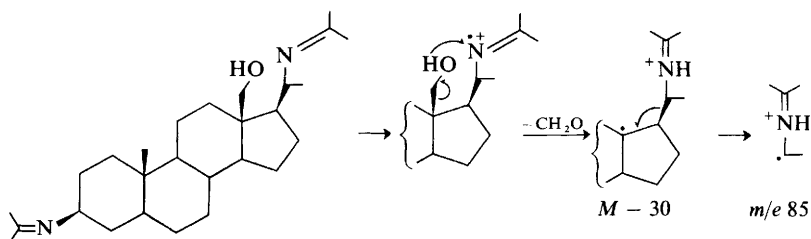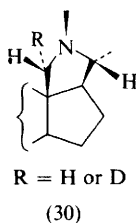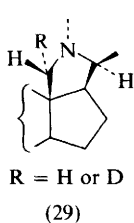
PART II: Alkaloids of the Buxaceae

1 The *Buxus* Alkaloids

A review on this subject has been published by Brown in a chapter entitled 'Abnormal Steroidal Alkaloids', in the book 'Chemistry of the Alkaloids' edited by Pelletier.[2]

Two alkaloids, buxpapine, m.p. 111—112 °C, $[\alpha]_D$ + 7.5, $C_{27}H_{34}H_2O$, and buxpapamine, m.p. 205—206 °C, $[\alpha]_D$ + 92, $C_{28}H_{30}N_2O$, have been isolated from the strong-base fraction of the alkaloids of *Buxus papilosa*.[23]

[23] M. Ikram, G. A. Miana, and F. Mahmud, *Pakistan J. Sci. Ind. Res.*, 1968, **11**, 253 (*Chem. Abs.*, 1969, **71**, 779*b*).

Cyclobuxine B has been isolated from the leaves of *Buxus sempervirens* from the acetone-insoluble portion of the strong bases and, after chemical and spectral analysis, has been assigned structure (31).[24]

(31)
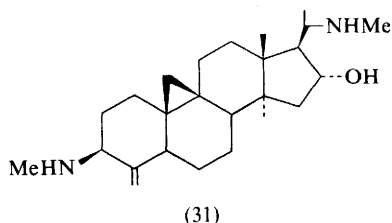
The structures of previously isolated alkaloids A, D, and G from *Buxus balearica* have been elucidated.[25] Alkaloid D has been identified as *N*-isobutyroylcycloxobuxidine F,[26] alkaloid G as cycloxobuxidine F, and, although alkaloid A has an n.m.r. spectrum similar to *N*-isobutyroylcycloxobuxine F (baleabuxine),[27] the mixed melting point of these two alkaloids suggested that they were dissimilar. Alkaloid A is thought to be epimeric with baleabuxine and has been named pseudobaleabuxine.

The alkaloids cyclobuxine D, cyclovirobuxine D, buxtauine (principal alkaloid), cycloprotobuxine C, cyclobuxoxazine C, buxpiine, and two unidentified alkaloids, alkaloid M and another with molecular ion peak in the mass spectrum at *m/e* 422, have been isolated from *Buxus wallichiana* Baillon.[28]

The interconversion between cyclobuxine D and cyclobuxosuffrine (from *Buxus microphylla*) led to the assignment to cyclobuxosuffrine of structure (32) with the *C*(4)-methyl in the α-equatorial position.[29] Cyclobuxine D has been transformed by known pathways[30] to the ketone (33), which in turn has been reduced to the 16β alcohol (34) with lithium aluminium hydride. Oxidative deamination of (34) was found to be accompanied by epimerization of the *C*(4)-methyl group to the α-equatorial position, with the resulting keto-alcohol (35) having a positive o.r.d. curve.[31] Reduction of the oxime of (35) with lithium aluminium hydride afforded the primary amine (36a) which, upon methylation, gave the tertiary amine (36b). Oxidation of this amino-alcohol afforded the amino-ketone (37), which was found to be identical with the product obtained by hydrogenation of cyclobuxosuffrine.

[24] Z. Voticky, V. Paulik, and B. Sedlack, *Chem. Zvesti*, 1969, **23**, 752 (*Chem. Abs.*, 1970, **73**, 35 591c).
[25] I. O. Kurakina, N. O. Proskurnina, A. U. Stepanyants, *Khim. prirod. Soedinenii*, 1970, **6**, 231.
[26] F. Khuong-Huu, D. Herlem-Gaulier, Q. Khuong-Huu, E. Stanislas, and R. Goutarel, *Tetrahedron*, 1966, **22**, 3321.
[27] D. Herlem-Gaulier, F. Khuong-Huu, and R. Goutarel, *Bull. Soc. chim. France*, 1966, 3478.
[28] A. Vassova, J. Tomko, Z. Voticky, and J. L. Beal, *Pharmazie*, 1970, **25**, 363.
[29] T. Nakano and Z. Voticky, *J. Chem. Soc.* (*C*), 1970, 590.
[30] T. Nakano and S. Terao, *J. Chem. Soc.*, 1965, 4512.
[31] C. Djerassi, 'Optical Rotatory Dispersion', McGraw-Hill, New York, 1960, p. 90.

(32)

(33)

(34)

(35)

(36) a; R^1 = R^2 = H
b; R^1 = R^2 = Me

(37)
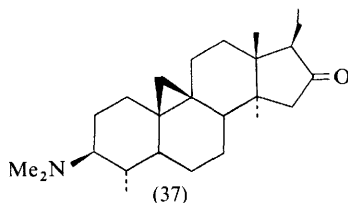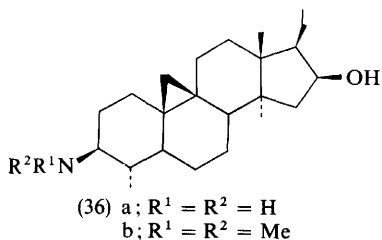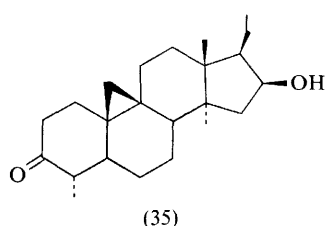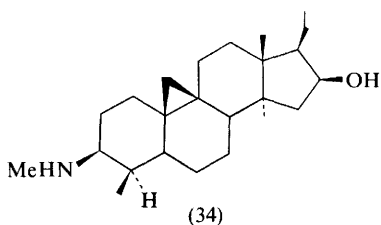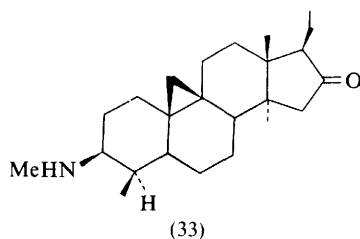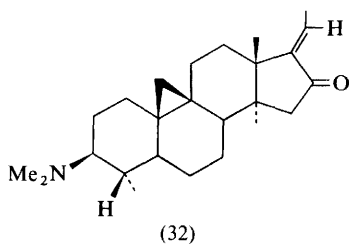
An approach to the total synthesis of cycloxobuxine and cycloprotobuxine alkaloids has been attempted starting from lanosterol.[32] The pregnane derivative (38a), prepared from lanosterol,[33] was transformed into the 11β-nitrite ester (38b), which was irradiated in benzene solution containing iodine. After oxidation of the resulting iodide, the 11-oxo-19-iodo-derivative was transformed, through an alumina column, into 11-oxo-9β,19-cyclo-derivative (39) (cycloxobuxine skeleton). Reduction of (39) with lithium aluminium hydride gave a mixture of the triol (40) and the diol (41), the latter being oxidized to the diketone (42).

(38) a; R = H
b; R = NO
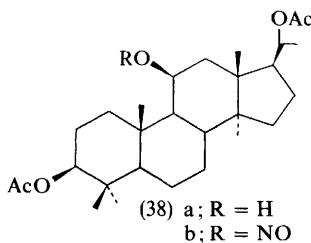
[32] T. Nakano, M. Alonso, and A. Martin, *Tetrahedron Letters*, 1970, 4929.
[33] W. Voser, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta.*, 1952, **35**, 503; A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lenin, *J. Chem. Soc.*, 1953, 2548.

(39)

(40)

(41)

(42)
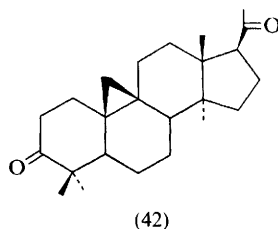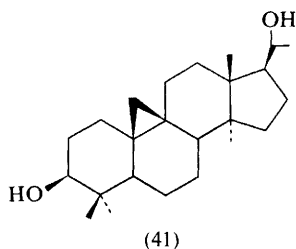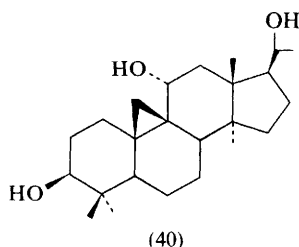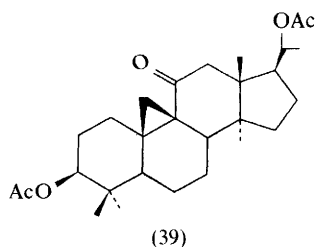
2 *Sarcococca* Alkaloids

Alkaloid C from *Sarcococca pruniformis* has been identified as 3α-methoxy-20α-dimethylaminopregn-5-ene (43). Emde degradation of (43) followed by catalytic hydrogenation afforded 3α-methoxy-5α-pregnane (44), identical with a sample prepared from 5α-pregnan-3-one.[34]

(43)

(44)
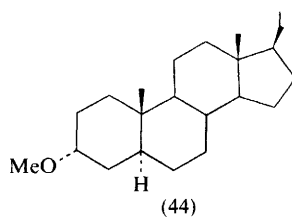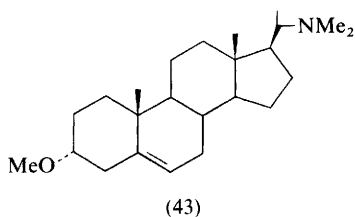
PART III: Biological Notes

Amoebicidal and trichomonacidal activities[35] and cardiovascular properties[36] of steroidal derivatives of the alkaloid paravallarine, from *Paravallaris microphylla*, have been investigated.

[34] J. M. Kohli, A. Zaman, and A. R. Kidwai, *Phytochemistry*, 1971, **10**, 442.
[35] R. Bellon, J. Le Men, P. Forgacs, P. De Lajudie, O. Albert, and M. Aurousseau, *Chim. Ther.*, 1969, **4**, 420; P. De Lajudie, O. Albert, M. Aurousseau, P. Forgacs, M. Collin, and R. Tiberghien, *Chim. Ther.*, 1970, **5**, 129.
[36] R. Bellon, J. Le Men, J. Provost, R. Tiberghien, P. Forgacs, H. Eyraud, and M. Aurousseau, *Chim. Ther.*, 1970, **5**, 41.

A pharmacologically useful derivative of conessine, 3β-(dimethylamino)-cona-4,6-dienine-3-(*N*-ethiodide) (45) has been prepared by the action of ethyl iodide on 3β-(dimethylamino)-cona-4,6-dienine.[37]

(45)
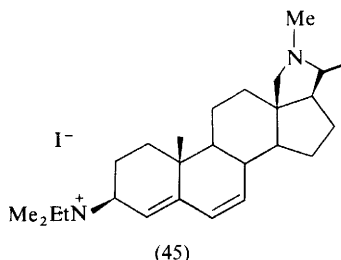
The antimicrobial properties of funtumine and funtumidine have been made use of in the manufacture of biocides.[38] A study has also been made on the antimicrobial properties of 20α- and 20β-aminopregna-3,5-dienes and 20α- and 20β-aminopregn-5-enes.[39]

A study of the variation of the supercoils in closed circular DNA by binding of antibiotics and drugs, such as the diamino-steroid irehdiamine A (IDA), has revealed that IDA is exceptional in that it appears to uncoil the double helix by a non-intercalative mechanism.[40]

The synthesis of steroids with amino-groups in positions 3 and 17 has been achieved[41] and their selective interaction with nucleic acids studied.[42]

[37] Neth. Appl. 6908, 367 (*Chem. Abs.*, 1971, **74**, 3796c).
[38] G. R. Wende and K. W. Ledig, U.S.P., 3 515 784 (*Chem. Abs.*, 1970, **73**, 56 290u).
[39] Y. Nagai and Y. Kurosawa, *Agric. Biol. Chem.*, 1970, **34**, 805 (*Chem. Abs.*, 1970, **73**, 42 590c).
[40] M. Waring, *J. Mol. Biol.*, 1970, **54**, 247.
[41] R. Glaser and E. J. Gabbay, *J. Org. Chem.*, 1970, **35**, 2907.
[42] R. Glaser, *Diss. Abs.*, 1970, **31B**, 1160.

15
Miscellaneous Alkaloids

BY V. A. SNIECKUS

1 Muscarine Alkaloids

A review on the structure and biological activity of this group has appeared.[1] A shorter review of the same nature dealing with alkaloids from *Amanita muscaria* is not readily accessible.[2] Parenthetically, it may be noted that the poisonous nature of this mushroom is not due to muscarine but to component(s) as yet unknown.[3]

A detailed investigation of muscarine and muscarine-isomer content in the genus *Inocybe* has been completed.[4] Normuscarine and norepimuscarine were found in all the species examined. Norallomuscarine was detected in most species whereas norepiallomuscarine was rarely found. *I. lacera*, *I. geophylla*, and *I. cinnamomea* were found to be particularly rich in epimuscarine. The significance of these findings in terms of pharmacologic activity and taxonomic analysis was discussed.

A new report on the synthesis of racemic muscarine and its stereoisomers, proceeding along conventional lines, has appeared.[5]

2 Imidazole Alkaloids

A brief introduction to this proportionally small group of alkaloids forms part of a general text on alkaloids.[6] Papers dealing with t.l.c. analysis[7] and kinetics of hydrolysis[8] of pilocarpine (1) have appeared.

Two new alkaloids, cypholophine (2; R = H) and O-acetylcypholophine (2; R = Ac), have been isolated from *Cypholophus friesianus* and their structures

[1] R. W. Baker, C. H. Chothia, P. Pauling, and T. J. Petcher, *Nature*, 1971, **230**, 439.
[2] N. F. Buchwald, *Natur. Verden*, 1970, 230 (*Chem. Abs.*, 1971, **74**, 136 339c).
[3] C. H. Schweitzer, *Muenchen. Med. Wochschr.*, 1970, **112**, 1085 (*Chem. Abs.*, 1970, **73**, 107 758n).
[4] P. Catalfomo and C. H. Eugster, *Helv. Chim. Acta*, 1970, **53**, 848.
[5] F. V. Mudryi, V. V. Smirnov, and S. B. Zotov, *Khim. geterotsikl. Soedinenii*, 1970, 579.
[6] R. K. Hill in 'Chemistry of the Alkaloids,' ed. S. W. Pelletier, Van Nostrand Reinhold, New York, 1970, p. 385.
[7] R. Tulus and G. Iskender, *Istanbul Univ. Eczacilik Fak. Mecmuasi*, 1969, **5**, 130 (*Chem. Abs.*, 1970, **73**, 69 887u).
[8] P.-H. Chung, T.-F. Chin, and J. L. Lach, *J. Pharm. Sci.*, 1970, **59**, 1300.

have been confirmed by synthesis.[9] The structure of cypholophine (2; R = H) was deduced on the basis of spectral data and chemical degradation. The 100 MHz n.m.r. spectrum was particularly informative and showed, among other absorptions required by structure (2), two triplet signals at $\delta 3.57$ and 2.60 ($J = 6$ Hz) which could be assigned to CH_2OH and CH_2-2-imidazole protons respectively on the basis of double-resonance studies. The mass spectrum of cypholophine showed the molecular-ion peak at m/e 318, a peak at m/e 300 ($-H_2O$), and the other important peaks as indicated in structure (2; R = H). Acetylation of cypholophine yielded O-acetylcypholophine (2; R = Ac), identical with the minor alkaloid isolated from *C. friesianus*. Comparison of the n.m.r. spectra of the two alkaloids showed the expected downfield shift of 0.45 p.p.m. in the triplet signal due to the CH_2OH upon acetylation. A short synthesis (Scheme 1) of cypholophine was accomplished which yielded 8 g of the alkaloid, an amount not normally obtained in synthetic natural-product work! In one approach, the crude α-bromo-ketone (5) was readily prepared from the α-diazo-ketone (4) and allowed to react with 2-iminotetrahydropyran hydrochloride (6) in basic solution to give directly the alkaloid (2; R = H). In an alternative synthesis giving a poorer overall yield, the diazo-ketone was converted into the α-ketol (3). Oxidation of the latter in the presence of 5-hydroxyvaleraldehyde and NH_4OAc gave compound (2; R = H). In the course of this work some other new imidazole derivatives have been prepared.[9]

Reagents: i, 48 % HBr; ii, MeOH, NH₃;
ii, Cu(OAc)₂, HOAc; iv, Ba(OH₂, H₂O;
v, Bi₂O₃, NH₄OAc, OHC(CH₂)₃CH₂OH.
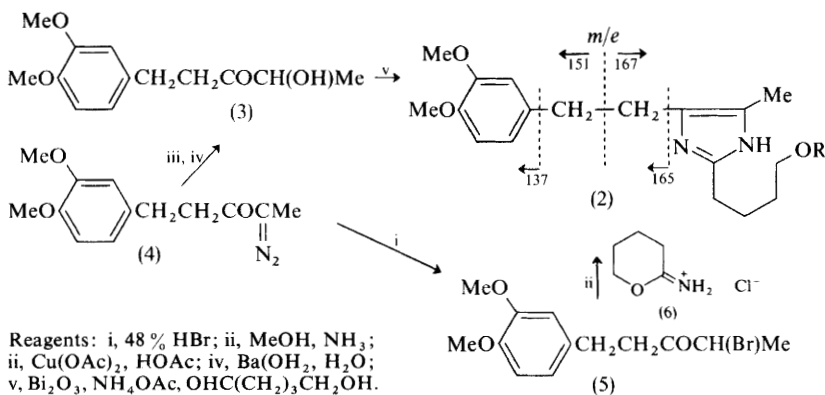
Scheme 1
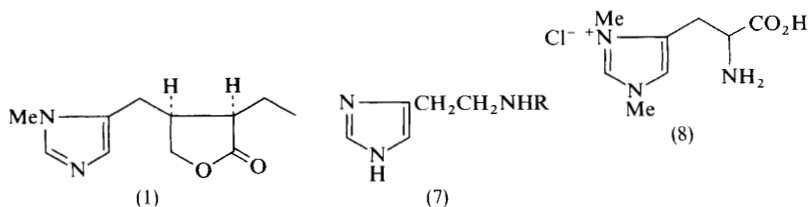
[9] N. K. Hart, S. R. Johns, J. A. Lamberton, J. W. Loder, and R. H. Nearn, *Austral. J. Chem.*, 1971, **24**, 857.

An imidazole alkaloid has been isolated for the first time from a cactus species.[10] Dolichotheline (7; $R = COCH_2CH_2CHMe_2$) has been obtained from *Dolichothele sphaerica* and its structure has been established on the basis of spectral and degradative evidence and confirmed by synthesis from histamine (7; $R = H$) and isovaleric anhydride. This represents only the second report of a chemical investigation in the genus *Dolichothele*.

The isolation of histidine, the imidazolium derivative (8), and other non-protein amino-acids from the seaweed *Gracilaria secundata* may be of general interest.[11]

Purine Alkaloids

A book on caffeine and related derivatives has been published.[12] Effective thin-layer chromatographic[7] and combination t.l.c.–counter-current partition[13] methods for the analysis of caffeine have been developed. The content of 4-*O*-caffeoylquinic acids in roots, stems, and leaves of tobacco plants grown in complete and N-deficient nutrient solutions has been quantitatively determined.[14]

Two new purine derivatives, deoxyeritadenine (11) and 3-(6-amino-9*H*-purin-9-yl)propionic acid (12; $R = CH_2CO_2H$) have been isolated from *Leontinus*
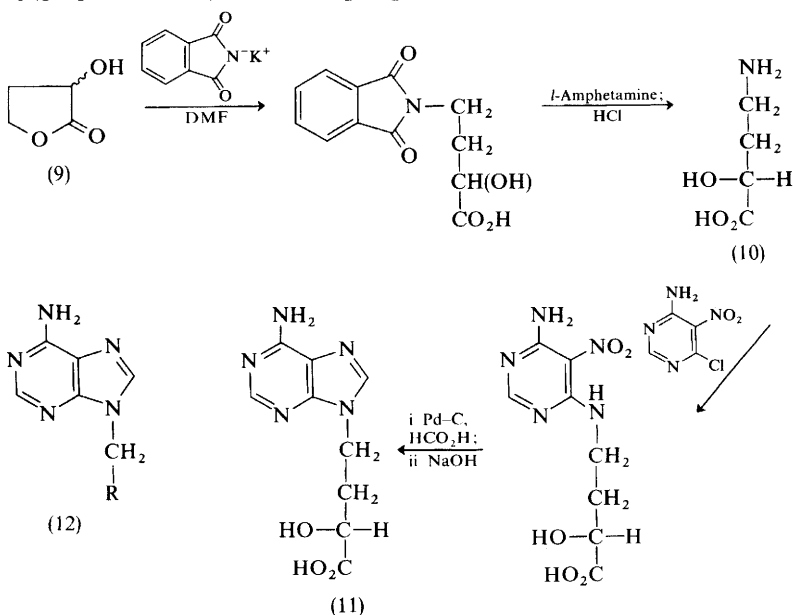
[10] H. Rosenberg and A. G. Paul, *Phytochemistry*, 1970, **9**, 655.
[11] J. C. Madgwick, B. J. Ralph, J. S. Shannon, and J. J. H. Simes, *Arch. Biochem. Biophys.*, 1970, **141**, 766.
[12] 'Coffein und Andere Methylxanthine,' ed. F. Heim and P. T. Hermann, Schattauer, Stuttgart, 1969.
[13] V. E. Chichiro, *Farmatsiya* (*Moscow*), 1970, **19**, 44 (*Chem. Abs.*, 1971, **74**, 45 633c).
[14] G. M. Armstrong, L. M. Rohrbough, E. L. Rice and S. H. Wender, *Phytochemistry*, 1970, **9**, 945.

edodes.[15] The structure of (11) rests on spectroscopic evidence and synthesis [(9) → (10) → (11)]. The carbon atom carrying the hydroxy-group in (11) was shown to have *R*-configuration by transformation of the resolved amino-acid (10) into the corresponding γ-lactone which exhibited a negative Cotton effect. The structure of the minor component (12; R = CH₂CO₂H) was confirmed by synthesis from adenine and ethyl acrylate. Eritadenine, the major constituent of *L. edodes*, had been previously shown to possess structure [12; R = CH(OH)-CH(OH)CO₂H].[15]

Chemical degradation of triacanthine (13) for the purpose of structural verification has been undertaken.[16] Potassium permanganate oxidation of (13) gave the side-chain diol, which was converted into acetone and the aldehyde (14; R = CH₂CHO) by periodate oxidation. Reduction of (14; R = CH₂CHO) with zinc in acetic acid produced adenine (14; R = H) and acetaldehyde, while catalytic hydrogenation gave the corresponding alcohol (14; R = CH₂CH₂OH). Heating (13) in the presence of barium hydroxide yielded the imidazole derivative (15) and a mole of carbon dioxide and a mole of ammonia were evolved.

The synthesis of caffeoylcholine and other caffeine derivatives has been carried out for the purpose of pharmacological activity and chemotaxonomic studies in relation to components isolated from *Cleome pungens.*[17]

A new general purine synthesis has been reported.[18] Treatment of 5-nitrouracil derivatives (16; R^1 = Me, R^2 = H or *vice versa*) with arylhydrazones (ArCH:NNR$_2^3$, R^3 = H or Me) gave theophylline (17; R^1 = Me, R^2 = H) and xanthine (17; R^1 = H, R^2 = Me) derivatives respectively in good yield. A brief mechanistic investigation of this reaction was also undertaken.

(13)　　　　　　　　(14)　　　　　　　　(15)

(16)　　　　　　　　(17)　　　　　　　　(18)
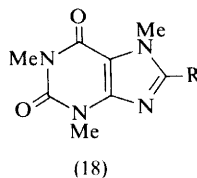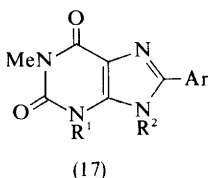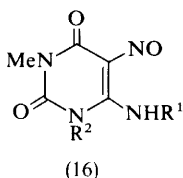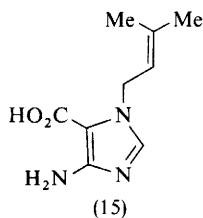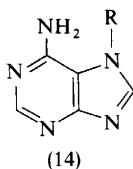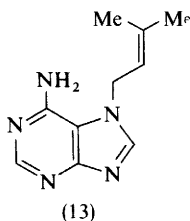
[15] Y. Saito, M. Hashimoto, H. Seki, and T. Kamiya, *Tetrahedron Letters*, 1970, 4863.
[16] A. S. Belikov, *Lek. Rast.*, 1969, **15**, 362 (*Chem. Abs.*, 1971, **74**, 142 142z).
[17] F. Pagani and G. Romussi, *Farmaco, Ed. Sci.*, 1970, **25**, 727 (*Chem. Abs.*, 1971, **74**, 10 323z).
[18] F. Yoneda, K. Ogiwara, M. Kanahori, and S. Nishigaki, *Chem. Comm.*, 1970, 1068.
[19] S. Jerumanis and A. Martel, *Canad. J. Chem.*, 1970, **48**, 1716.

The photochemical reaction of caffeine (18; R = H) with cyclic ethers in the presence of sensitizers has been investigated.[19] Substitution into the imidazole ring of caffeine, as exemplified by the reaction with diethyl ether to give [18; R = CH(Me)OEt] and (18; R = Et), was generally observed.

4 *Securinega* Alkaloids

The structures of securinol B (19; R^1 = H, R^2 = OH) and C (20), isolated previously[20] from the leaves of *S. suffruticosa*, have been determined by means of spectral data and chemical correlation with known alkaloids.[21] The n.m.r. spectrum of securinol B showed a one-proton triplet at $\tau4.34$ (J = 1.5 Hz) which was attributed to the olefinic $C(3)$-proton coupled to the $C(4)$-methylene protons. On the basis of this fact and by comparison with the spectra of known alkaloids, the position of the hydroxy-group was located at $C(5)$. Thus securinol B is an epimer of securinol A (19; R^1 = OH, R^2 = H) and may be named as 4,5-dihydro-viroallosecurinin-5β-ol (19; R^1 = H, R^2 = OH). Previous work had shown the presence of a long-range 'W-type' coupling between the $C(5\beta)$- and $C(11$-*exo*)-protons in dihydrosecurinine [part structure (21)]. The proton attached to $C(5)$ appeared as an octet (J = 9.5, 5, and 2 Hz). Inspection of models of a derivative (19; R^1 = H, R^2 = OSO_2Me) of securinol B indicated that the only manner in which the large diaxial coupling $J_{5\alpha,4\beta}$ = 9.5 Hz could be explained was to have the conformation (22; R = OSO_2Me) in which the mesylate group occupied an equatorial position in the near-boat A ring. The other couplings ($J_{5\alpha,4\alpha}$ = 5 Hz and $J_{5\alpha,5a\beta}$ = 2 Hz) were thus also reasonably explained. In securinol B (19; R^1 = H, R^2 = OH), a signal at $\tau6.20$ appeared as a broad multiplet, which suggested a similar conformation (22; R = OH) for the alkaloid.

Reflux of the mesylate of securinol B in collidine gave viroallosecurinine (23), of known structure and absolute configuration. Similar treatment of the mesylate of securinol C (20) yielded allosecurinine (24), which suggested that the former was 4,5-dihydroallosecurinine with a hydroxy-group at $C(4)$ or $C(5)$. Evidence in favour of the location of the hydroxy-group at $C(4)$ was obtained from the mass spectrum and by comparison with known $C(5)$-OH securinine alkaloids, from which securinol C was found to be different. In the n.m.r. spectrum of securinol C the broad quartet at $\tau5.55$ (J = 9.5 and 4.5 Hz) suggested that the $C(4)$-hydroxy-group existed in an equatorial position and thus could be assigned a β-configuration if ring A possessed a part-boat conformation (22), as deduced for securinol B (19; R^1 = H, R^2 = OH).

The synthesis of fused butenolides *via* the reaction of α-ketols with lithium ethoxyacetylide had been previously developed in connection with the synthesis of *Securinega* alkaloids.[22] This synthesis has now been generalized

[20] Z. Horii, M. Ikeda, Y. Tamura, S. Saito, K. Kotera, and T. Iwamoto, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 1307.

[21] Z. Horii, M. Yamauchi, M. Ikeda, and T. Momose, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2009.

[22] Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura, S. Saito, N. Shigematsu, K. Kotera, H. Yoshikawa, Y. Sato, H. Nagai, and N. Sugimoto, *Tetrahedron*, 1967, **23**, 1165.

(19)   (20)   (21)

(22)   (23)   (24)
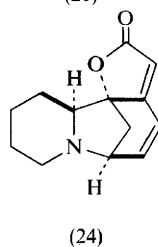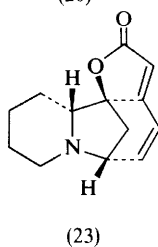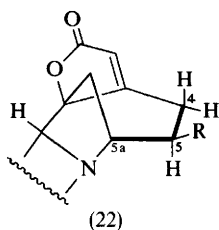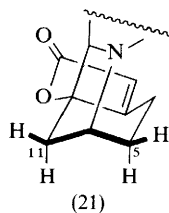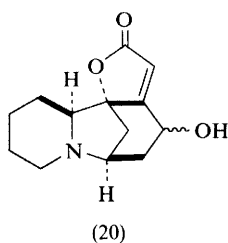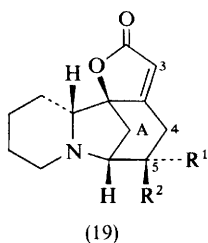
[e.g. (25) → (26), R = H or Me], and applied to the preparation of dihydrose-curinine (28).[23] Treatment of the known α-ketol (27) under the same conditions as described for (25) gave synthetic dihydrosecurinine (28) which was found to be identical with the natural product.

(25)   (26)

(27)   (28)
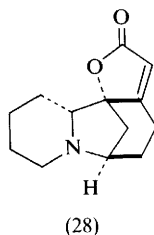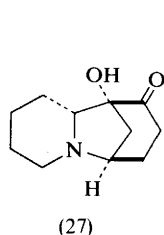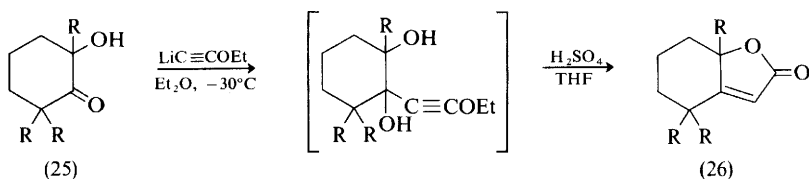
5 Peptide Alkaloids

The minor alkaloid aralionine B from the leaves of *Araliorhamnus vaginata* has been shown to possess structure (29).[24] The structure elucidation followed the now conventional lines of extensive application of n.m.r. spectroscopy and mass

[23] Z. Horii, M. Ito, I. Minami, M. Yamauchi, M. Hanaoka, and T. Momose, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1967.

[24] R. Tschesche, E. Frohberg, and H. W. Fehlhaber, *Chem. Ber.*, 1970, **103**, 2501.

spectrometry, coupled with hydrolytic studies.[25] The peptide-alkaloid-containing species *Zizyphus jujuba* var. *spinosus*[25] has been shown to contain ebelin lactone, which is an interesting triterpenoid derivative.[26]

A synthesis of norphalloin (30), a component of the Green Deathcap toadstool *Amanita phalloides*, has been accomplished.[27] Advantage was taken of the susceptibility of a 3-substituted indole to electrophilic attack at the 2-position by sulphenyl chlorides. Treatment of the t-butoxycarbonyl-tripeptide (Boc-tri-peptide)(31) as its sulphenyl chloride with the tryptophan-containing tetrapeptide (32) gave the heptapeptide thioether (33). The latter was cyclized to an amide at the unprotected pyrrolidine nitrogen by a mixed anhydride method; saponification, removal of the Boc blocking group, and again subjection to a mixed anhydride synthesis of amides, gave norphalloin (30). If the attempted cyclization reaction of (33) was processed by chromatography in the presence of ammonium salts rather than triethylammonium salts, a carboxamide isolated as the urethane (34) was obtained. Saponification, removal of the Boc group, and internal amide formation as before gave the non-toxic 18-membered-ring compound (34; amide bond at dotted line).
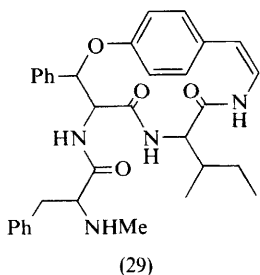
(29)
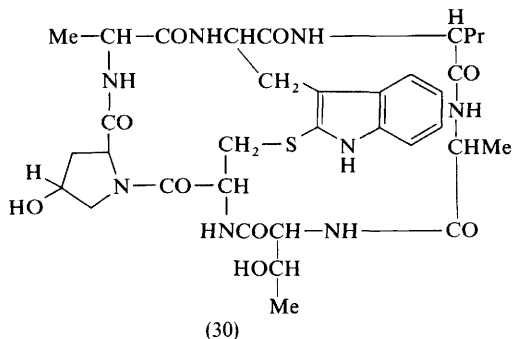
(30)
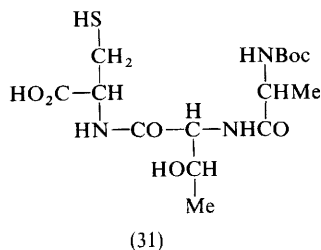
(31)
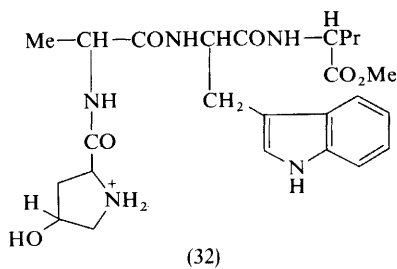
(32)

[25] 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1971, vol. 1, p. 444.

[26] S. Shibata, Y. Nagai, O. Tanaka, and O. Doi, *Phytochemistry*, 1970, **9**, 677.

[27] F. Fahrenholz, H. Faulstich, and T. Wieland, *Annalen*, 1971, **743**, 83.

Me—CHCONHCHCONH————CPr
                                                        CO₂Me

(33)

Me—CHCONHCHCONH————CPr
                                                        CO₂Me

(34)

(35)
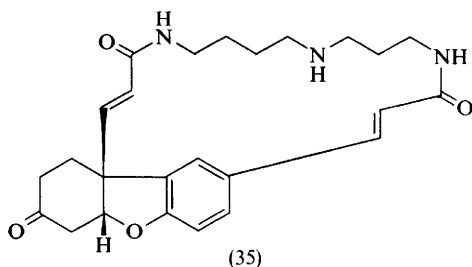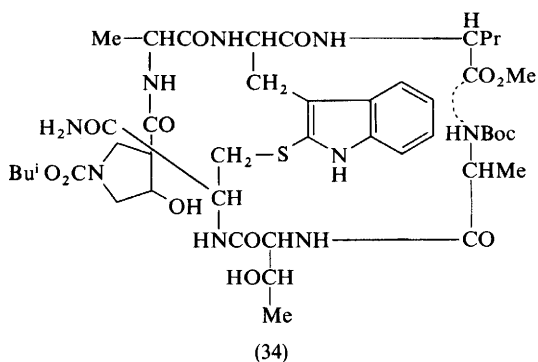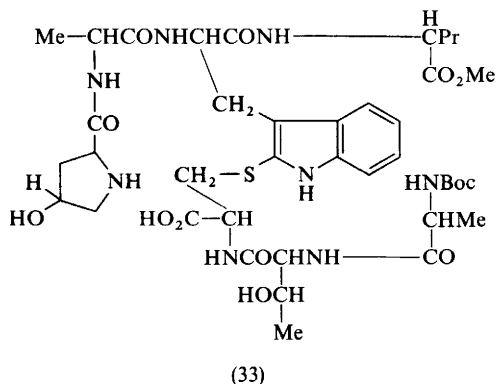
The absolute stereochemistry of the spermidine-based alkaloid lunarine, isolated from *Lunaria biennis*, has been determined by two groups on two different heavy-atom salts.[28,29] The final representation (35) is the reverse of that arbitrarily selected and jointly published by these workers in preliminary form.

[28] J. A. D. Jeffreys and G. Ferguson, *J. Chem. Soc. (B)*, 1970, 826.
[29] C. Tamura and G. A. Sim, *J. Chem. Soc. (B)*, 1970, 991.

6 Unclassified Alkaloids

Various unclassified alkaloids (aniline and anthranilic acid derivatives, cinnamic acid amides, guanidine bases, and oxazoles) are briefly reviewed in a general text on alkaloids.[30]

The format adopted in Volume 1 of this series[31] will be followed. Reference to earlier work on a particular species or contained alkaloid which has been summarized[31] will be indicated by the appropriate page number in parenthesis following the botanical name.

Alchornea floribunda and *A. hirtella* (Euphorbiaceae)

A pharmacologically active compound, alchorneine (36) has been characterized by chemical and spectroscopic methods.[32]

Alchornea javanensis (Bl.) Muell. Arg. (Euphorbiaceae) (Vol. 1, p. 458)

Details of the structural elucidation of alchornine (37), alchornidine [(38) or (39)], and two guanidine alkaloids [(40) and (41)] have appeared.[33] The main structural features of alchornine were obtained from the 100 MHz n.m.r. spectrum, although this in itself was not sufficient to assign a unique structure for the alkaloid. Singlets were observed at δ 1.26 and 1.28, assigned to the two $C(7)$-methyl groups. An additional three-proton multiplet at δ 1.71 was shown by double-resonance experiments to be weakly coupled to both vinyl protons at $C(10)$ and thus could be assigned to the $C(9)$-methyl function. A sharp two-proton singlet at δ 2.44 [$C(6)$-protons] and two one-proton multiplets at δ 4.84 and 4.98 [$C(10)$-protons] were readily identified. Double-resonance experiments showed that the vinyl protons at $C(10)$ were coupled to each other and also to the $C(9)$-methyl and $C(2)$-protons. The last, giving a quartet at δ 4.41 ($J_{2,3} = 9$ and 6 Hz), was also assigned on the basis of a double-resonance study. Finally, quartets at δ 3.95 ($J_{gem} = 11.0$ Hz) and 3.53 were assigned to the $C(3)$-protons [completing the AMX pattern with $C(2)$-H], and a broad singlet at δ 6.90 was identified as the $N(8)$-H. Hydrogenation of alchornine gave dihydroalchornine (42), whose n.m.r. spectrum showed peaks at δ 0.85 (d, 3H, $J = 7$ Hz), 0.92 (d, 3H, $J = 7$ Hz), and 1.65 (m, 1H) which clearly indicated the presence of an isopropyl substituent. Other absorptions were consistent with the derived structure. On the other hand, lithium aluminium hydride reduction of alchornine gave 5-deoxyalchornine (43). The salient features of the n.m.r. spectrum of (43) were two-proton triplets at δ 3.33 ($J = 6$ Hz) and 1.87 ($J = 6$ Hz) which could be assigned to the $C(5)$- and $C(6)$-protons respectively. Thus in alchornine and dihydroalchornine the lactam carbonyl must be adjacent to the isolated methylene group at $C(6)$ (δ 2.44, s). Firm evidence for placing the isopropenyl group at $C(2)$ rather than at $C(3)$ came from the relationship of alchornine with alchornidine.

[30] A. Brossi and B. Pecherer in 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, p. 11.

[31] Ref. 25, p. 458.

[32] F. Khuong-Huu-Laine, J. P. Leforestier, G. Maillard, and R. Goutarel, *Compt. rend.*, 1970, **270**, C, 2070.

[33] N. K. Hart, S. R. Johns, J. A. Lamberton, and R. I. Willing, *Austral. J. Chem.*, 1970, **23**, 1679.
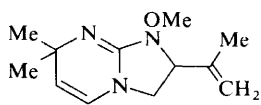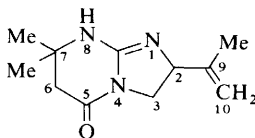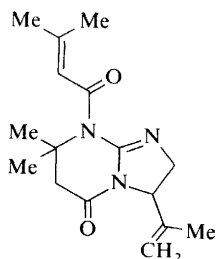
(36)   (37)   (38)
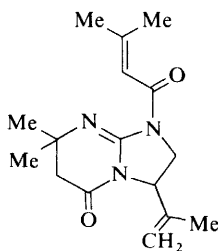
(39)   (40)   (41)

(42)   (43)   (44)

(45)
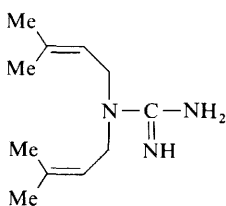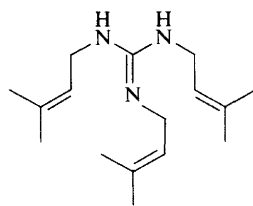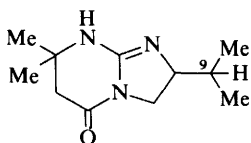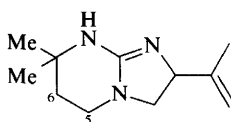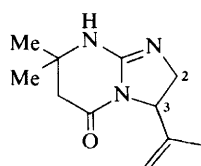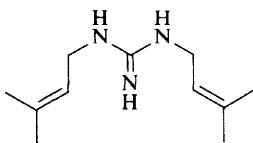
Alchornidine [(38) or (39)] was isolated only once from the leaves of *A. javanensis*, owing to the facility with which it underwent hydrolysis. The absence of an NH group was conclusively established by failure to observe any change in the mass spectrum of the alkaloid after carrying out a D_2O exchange directly in the spectrometer inlet. Basic hydrolysis of alchornidine gave alchornine and 2,2-dimethylacrylic acid, indicating that alchornidine must be the *N*-acyl derivative of alchornine. That this was not the case was shown by subjecting alchornidine to mild acidic hydrolysis conditions which were known not to affect alchornine. Under these conditions, alchornidine gave isoalchornine (44) which could be readily converted into alchornine by treatment with base. This conversion, which must be occurring

by ring opening and alternative ring closure, shows that alchornine is the thermo-dynamically more stable isomer. The n.m.r. spectrum of isoalchornine showed significant differences from that of alchornine, which allowed definite assignment of the position of the isopropenyl group. The important feature was the presence of an AMX system {δ 3.36 [q, 1H, J = 13 and 5.0 Hz, C(2)-H], 3.87 [q, 1H, J = 10 Hz, C(2)-H], and 4.72 [q, 1H, C(3)-H]}, whose assignments were confirmed by double-resonance studies. Clearly, the methine signal at δ 4.72 can be assigned to the C(3)-proton in isoalchornine, on the basis of the expected deshielding effect of the C(5)-carbonyl group in comparison with the methine signal in alchornine (δ 4.41). Conversely, the methylene protons in alchornine would be expected to be more strongly deshielded than those in isoalchornine and therefore must be located at C(3).

Although the chemical shift difference between the two C(7)-methyl signals (δ 1.19 and 1.29) in the n.m.r. spectrum of alchornidine suggested that the 2,2-dimethylacrylyl substituent was located at the N(8) position and thus favoured structure (39) for the alkaloid, no definite proof of this was obtained. The mass spectra of alchornine (37), alchornidine [(38) or (39)], and isoalchornine (44) were consistent with the proposed structures.

Evidence has been presented that the alkaloid isolated from *Alchornea javanensis* and originally formulated as (45) possesses the symmetrical structure (40).[33] This structure was conclusively established by successive hydrogenation and hydrolysis with barium hydroxide, which yielded *NN*-di-isopentylamine. The structure of the other guanidine alkaloid isolated from this species was shown to be *NN'N"*-tri-isopentenylguanidine (41) by spectral and degradative evidence and by unambiguous synthesis of its hexahydro-derivative.

Antirrhinum majus

4-Methyl-2,6-naphthyridine (46) has been isolated from the aerial parts.[34] The structure was assigned on the basis of comparison of spectral data with that of known naphthyridines and related N-heterocycles.

Aralia mandshurica and *A. schmidtii*

These species may contain alkaloids.[35]

Centaurea alexandrina, C. calcitrapa, C. glomerata, and *C. pallescens.*

Alkaloids have been isolated but not characterized.[36]

Fagara macrophylla (Rutaceae)

The presence of fagaramide (*N*-isobutyl-3,4-methylenedioxycinnamide) has been confirmed.[37] More complicated alkaloids were also isolated from this species.

[34] K. J. Harkiss and D. Swift, *Tetrahedron Letters*, 1970, 4773.

[35] I. F. Gribovskaya and N. I. Grinkevich, *Agrokhimiya*, 1970, 124 (*Chem. Abs.*, 1971, **74**, 39 126*y*); G. K. Shreter and V. I. Shashlova, *Farmatsiya (Moscow)*, 1970, **19**, 35 (*Chem. Abs.*, 1971, **74**, 67 630*b*).

[36] Z. F. Ahmed, F. M. Hammouda, A. M. Rizk and S. I. Ismail, *Planta Med.*, 1970, **18**, 227.

[37] F. Fish and P. G. Waterman, *J. Pharm. Pharmacol.*, 1971, **23**, 67.

Galbanum oil

Acid extraction yielded the following pyrazine derivatives: tetramethylpyrazine, 2,6-diethyl-3-methylpyrazine (47), 2,3-dimethyl-5-ethylpyrazine, 2-methoxy-3-isopropoxy-5-methylpyrazine, and 2,6-dimethoxy-3-isopropoxy-5-methylpyrazine.[38] All structures were confirmed by synthesis. Pyrazine derivatives had previously been isolated from green peas (*Pisum sativum*).[39]

Galega officinalis (Leguminosae)

Galegine (48; R = H) and hydroxygalegine (48; R = OH) have been isolated and their distribution in various parts of the plant was studied.[40]

Nigella damascena (Ranunculaceae)

Isolation and structural elucidation of damascenine (49) have been described.[41]

(46)   (47)   (48)

(49)   (50)

(51)
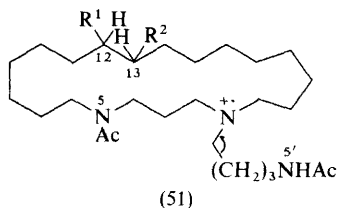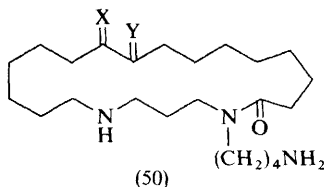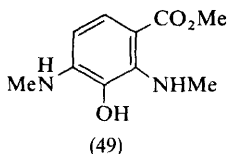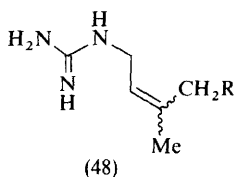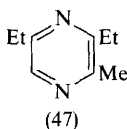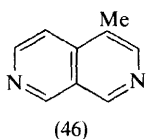
Oncinotis inandensis Wood et Evans (Apocynaceae)

Another novel alkaloid, inandenine, has been isolated as an inseparable mixture of isomers (50; X = O, Y = H$_2$) and (50; X = H$_2$, Y = O).[42] Spectral and

[38] J. W. K. Burrell, R. A. Lucas, D. M. Michalkiewicz, and G. Riezebos, *Chem. and Ind.*, 1970, 1409.
[39] Ref. 25, p. 460.
[40] J. Schaefer and M. Stein, *Biol. Zentr.*, 1969, **88**, 755 (*Chem. Abs.*, 1970, **73**, 22 112x).
[41] W. Doepke and G. Fritsch, *Pharmazie*, 1970, **25**, 69.
[42] H. J. Veith, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1970, **53**, 1355.

chemical evidence showed that inandenine contained a lactam ring, no carbon–carbon double bond, a spermidine $[H_2N(CH_2)_3N'H(CH_2)_4N''H_2]$ fragment in which the three nitrogen atoms exist in secondary, primary, and N-acyl forms, and a keto-function in the lactam ring. The absence of N-, O-, and C-methyl groups was also indicated. The question as to the position of the lactam nitrogen was answered by comparison of the mass spectrum of the 5,5',O-triacetyldeoxy-derivative (51, $R^1 = OAc$, $R^2 = H$ and $R^1 = H$, $R^2 = OAc$) with that of inandenine. Only the former showed an intense peak due to α-cleavage as indicated in structure (51). This fragmentation pathway was confirmed by studying deuteriated derivatives. Furthermore, comparison of the mass spectrum of (51) with that of $NN'N''$-triacetylspermidine showed certain differences, significantly the presence of a strong peak at m/e 129 in the latter which implied that the central nitrogen atom effects an α-cleavage of a trimethylenediamine unit $[CH_2\overset{+}{=}NH(CH_2)_3NHAc]$. The absence of the m/e 129 ion in the mass spectrum of (51) indicated that the trimethylenediamine and not the tetramethylenediamine portion of spermidine was involved in the macrocyclic ring of the alkaloid, and that therefore the ring must be 21-membered.

The key information to the elucidation of the structure of inandenine was obtained from examination of the mass spectra of the ethyleneketals [(52), (53)] in comparison with those of other degradation products. Apart from certain similar fragmentation patterns observed for all these compounds, the ethylene-ketals [(52), (53)] showed strong signals at m/e 243 and 257 as well as at m/e 426 and 440. This could only be explained by the fragmentation pattern indicated (Scheme 2) and led to the conclusion that inandenine was a 1 : 1 mixture of the two isomers (50; X = O, Y = H_2) and (50; X = H_2, Y = O).

Ottonia vahlii [syn. *Piper ovatum* (Vahl)] (Piperaceae)

Piperovatine (p-MeOC$_6$H$_4$CH$_2$CH=CHCH=CHCONHBu^i) has been isolated from the leaves, roots, and stems.[43] The structure was initially indicated from spectral determinations and subsequently confirmed by synthesis involving a Wittig reaction as the key step.

Phakellia flabellata

Dibromophakellin (54; $R^1 = R^2 = Br$, $R^3 = H$) has been isolated from this marine sponge.[44] The structure was revealed from a 220 MHz n.m.r. spectrum of phakellin (54; $R^1 = R^2 = R^3 = H$), which was obtained by catalytic hydrogenation. Confirmation of structure was secured from the X-ray crystallographic analysis of its monoacetyl derivative (54; $R^1 = R^2 = Br$, $R^3 = Ac$). Another alkaloid, 4-bromophakellin (54; $R^1 = Br$, $R^2 = R^3 = H$), has apparently been isolated from this species.

Pterogyne nitens Tul. (Leguminosae) (Vol. 1, p. 460)

Pterogynine, which is apparently identical with the guanidine alkaloid obtained

[43] S. J. Price and A. R. Pinder, *J. Org. Chem.*, 1970, **35**, 2568.
[44] G. M. Sharma and P. R. Burkholder, *Chem. Comm.*, 1971, 151.

(52)

a ↓   ↓ b

$^+$O—O
$(CH_2)_8CH_2OAc$
m/e 257

m/e 426

(53)

a ↓   ↓ b

$(CH_2)_7CH_2OAc$
m/e 243

m/e 440

Scheme 2

(54)
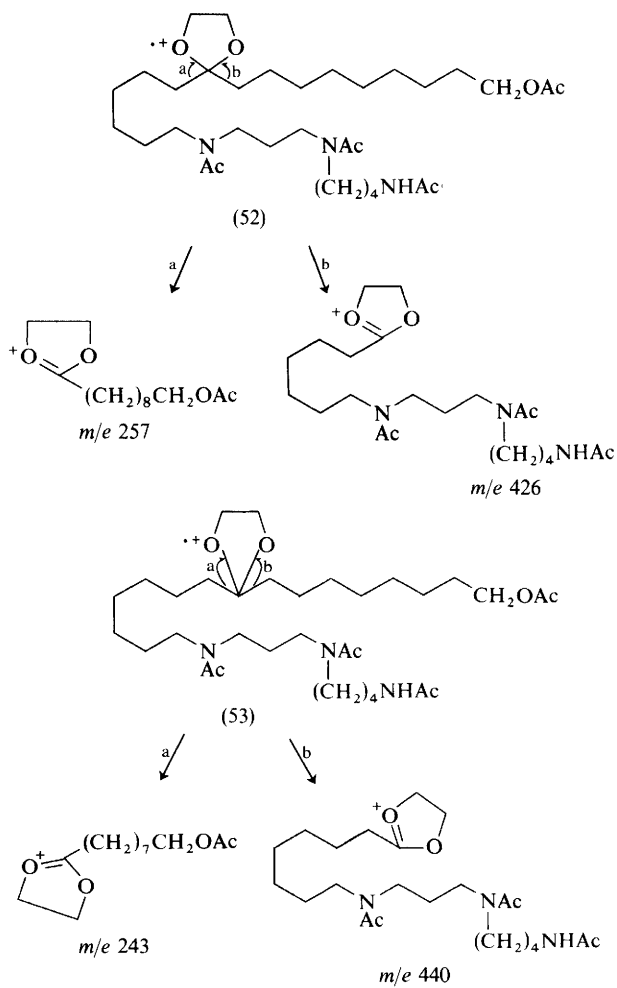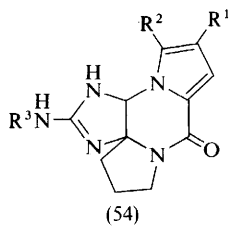
from *Alchornea javanensis* (*loc. cit.*), must also possess the revised structure (40), rather than (45) as previously deduced.

Thymus transcaspicus and *Ziziphora turcomanica*

Alkaloids isolated from these species have not been characterized.[45]

[45] M. O. Karryev, *Izvest. Akad. Nauk Turkm. S.S.R.*, *Ser. Biol. Nauk*, 1971, 35 (*Chem. Abs.*, 1971, **75**, 1238u).

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