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The Alkaloids

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A Specialist Periodical Report

The Alkaloids

Volume 4

A Review of the Literature Published between
July 1972 and June 1973

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Foreword

This fourth volume in the series of *Specialist Periodical Reports* on Alkaloids follows the pattern established by its predecessor, and comprises summaries of progress in the whole field of alkaloid chemistry for the period July 1972—June 1973. In addition there is also included a more extended review of the aporphine alkaloids, in which are discussed developments in this sub-group of benzyloquinoline alkaloids since the last comprehensive survey was compiled. The length of this chapter reflects the continuing enormous activity in this area, and amply illustrates the versatility of biosynthetic processes in the construction of substituted aporphines. It is hoped that Dr. Shamma's account, which includes a reference list of the 107 aporphines known up to the summer of 1973, will prove invaluable to all chemists interested in the structural and biosynthetic relationships in the aporphine group.

My request last year for reprints of papers in the less accessible journals has met with some response, for which I hasten to acknowledge my appreciation. The Senior Reporter and all contributors hope that alkaloid chemists will continue to send us such reprints, which help substantially in the prompt compilation of these Reports.

Once again it is a pleasure to acknowledge the enthusiastic co-operation of my colleagues, in circumstances that in some respects become more difficult with each succeeding year. As always, we shall welcome suggestions concerning the presentation of future Reports.

J. E. SAXTON

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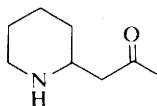
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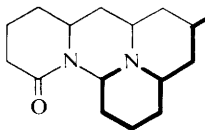
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1 Piperidine, Pyridine, and Pyrrolidine Alkaloids

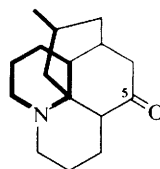
Lycopodine.—Pelletierine (1) serves as a specific precursor for cernuine (2)^{1,2} and lycopodine (3).^{2,3} The reasonable hypothesis that these alkaloids were modified dimers of pelletierine had to be abandoned when it was discovered that pelletierine gave only one each of the two C₈N units (heavy bonding) of (2) and (3).



(1) Pelletierine

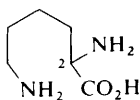


(2)

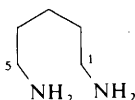


(3) Lycopodine

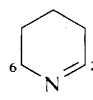
The results were surprising as lysine (4), cadaverine (5), and Δ^1 -piperideine (6) had all been built equally into each of the two C₈N units of lycopodine and cernuine.¹⁻³ It followed, therefore, that if lycopodine is formed from two pelletierine-like units, these units must either be identical or, if different, be derived from



(4) Lysine



(5) Cadaverine

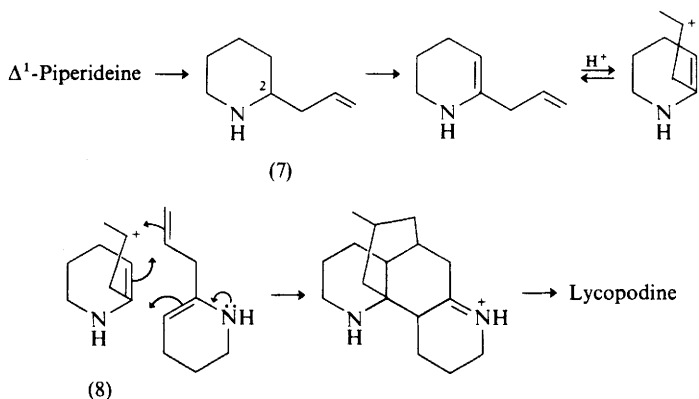
(6) Δ^1 -Piperideine

Δ^1 -piperideine (6) with the same overall dilution by non-labelled pools. Two models were proposed which could account for the incorporation of pelletierine, one (Scheme 1)^{2,3} in which it could substitute for one of the two identical units, *i.e.* (8), and the other where it was an obligatory intermediate and precursor for

¹ Y. K. Ho, R. N. Gupta, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1971, **49**, 3352.

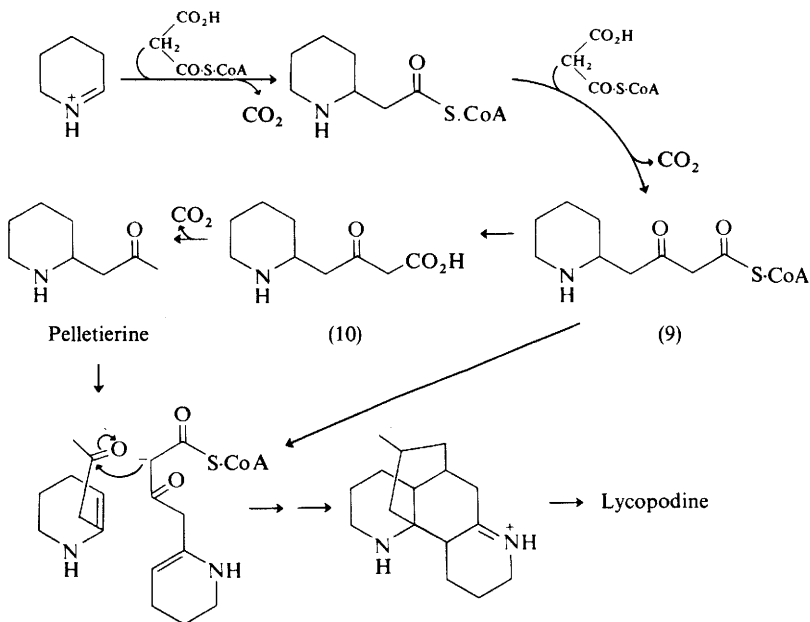
² R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1973, vol. 3, p. 28.

³ M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1970, **48**, 2911.



Scheme 1

one of the C_8N units (Scheme 2);²⁻⁴ it is a consequence of the equal labelling of both halves of lycopodine by Δ^1 -piperidineine, lysine, and cadaverine that in this scheme the steady-state concentration of pelletierine and (10) be small compared with (9).



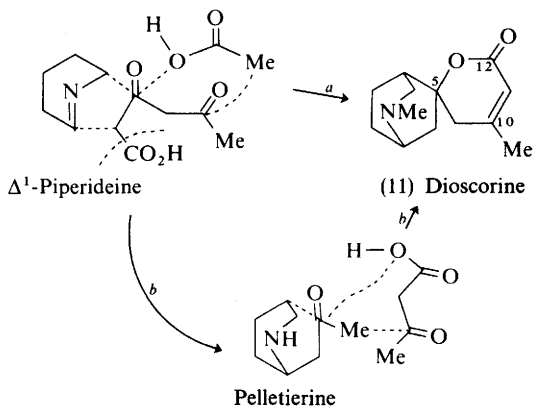
Scheme 2

⁴ J.-C. Braekman, R. N. Gupta, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1972, **50**, 2591.

The failure of $[2-^{14}\text{C}]$ -2-allylpiperidine [as (7)] to label C-5 of lycopodine (3) specifically in *Lycopodium tristachyum* provided evidence against the first hypothesis.⁴ Evidence was then adduced which showed that pelletierine (1) was very probably a normal intermediate in lycopodine biosynthesis. Firstly, the presence of pelletierine (1) in *L. tristachyum* was demonstrated. $[2-^{14}\text{C}]\text{-}\Delta^1$ -Piperidine [as (6)] together with a large quantity of inactive pelletierine was administered to the plant; a similar experiment was carried out with $[1,5-^{14}\text{C}_2]\text{-cadaverine}$ [as (5)]. Radioactive pelletierine was isolated at the end of each experiment.

The presence and synthesis of pelletierine from lycopodine precursors was thus demonstrated but its obligatory participation in lycopodine biosynthesis was not proven. Secondly, therefore, the ability was examined of inactive pelletierine to dilute radioactivity from one of the C_8N units following simultaneous administration of labelled Δ^1 -piperidine or cadaverine. Difficulties normally experienced with this type of experiment in plants were obviated since labelling of the C_8N unit not derived from pelletierine served as an internal standard. It was found that pelletierine very effectively diluted activity in both experiments from the C_8N unit (heavy bonding) of (3), consonant with its being an obligatory intermediate in lycopodine biosynthesis. All the experimental evidence is accommodated in Scheme 2, which also allows for the non-intact incorporation of β -hydroxybutyrate and acetoacetate.⁵

Dioscorine.—Full details of the mode of incorporation of acetate into dioscorine (11) have been published.⁶ The results are consistent with either variant, *a*⁶ and *b*,⁴ of a pathway involving condensation of four acetate units with a lysine-derived unit, plausibly Δ^1 -piperidine (Scheme 3); as indicated in path *b*, pelletierine may be involved. Administration of $[2-^{14}\text{C}]\text{lysine}$ [as (4)] to the tropical



Scheme 3

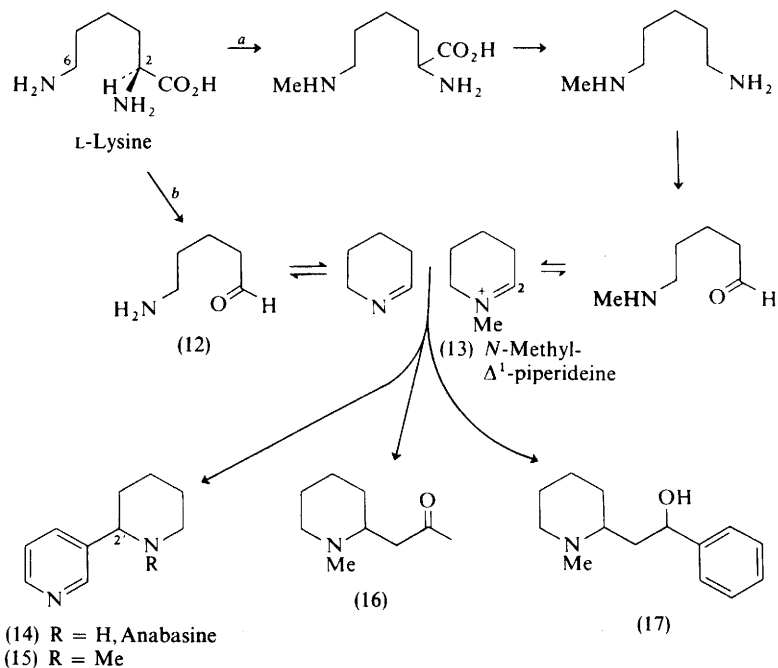
⁵ M. Castillo, R. N. Gupta, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1970, **48**, 1893.

⁶ E. Leete and A. R. Pinder, *Phytochemistry*, 1972, **11**, 3219; preliminary communication: E. Leete and A. R. Pinder, *Chem. Comm.*, 1971, 1499; R. B. Herbert, in ref. 2, p.25.

yam, *Dioscorea hispida*, however, gave dioscorine (11) with little radioactivity; whilst $[6-^{14}\text{C}]\text{-}\Delta^1\text{-piperideine}$ [as (6)] was better used, the labelling pattern was essentially the same as that from $[1-^{14}\text{C}]\text{acetate}$, arising presumably by catabolism of the radioactive $\Delta^1\text{-piperideine}$ to acetate.⁶ These poor incorporations were rationalized by suggesting that, at the time of feeding, some compound, derivable from lysine, was not being actively synthesized but that it was available for condensation with acetate. This hypothetical compound could not be pelletierine for $[1-^{14}\text{C}]\text{acetate}$ incorporation would result in labelling of C-10 and C-12 but not C-5, and in fact almost equal labelling of these positions is observed.

It is worth noting that incorporation of acetate into dioscorine was only achieved with considerable difficulty and it seems possible that the administered lysine and $\Delta^1\text{-piperideine}$ are not reaching the site of alkaloid synthesis, in which case pelletierine (1) may yet prove to be a precursor for dioscorine (11).

Anabesine.—Study of the biosynthesis of the piperidine ring of alkaloids like anabesine (14), *N*-methylpelletierine (16), and sedamine (17) has proved most interesting. Two pathways (Scheme 4, paths *a* and *b*) have been proposed⁷ which are consistent with the experimental results, in particular the incorporation of L-lysine without intervention of symmetrical intermediates or loss of hydrogen

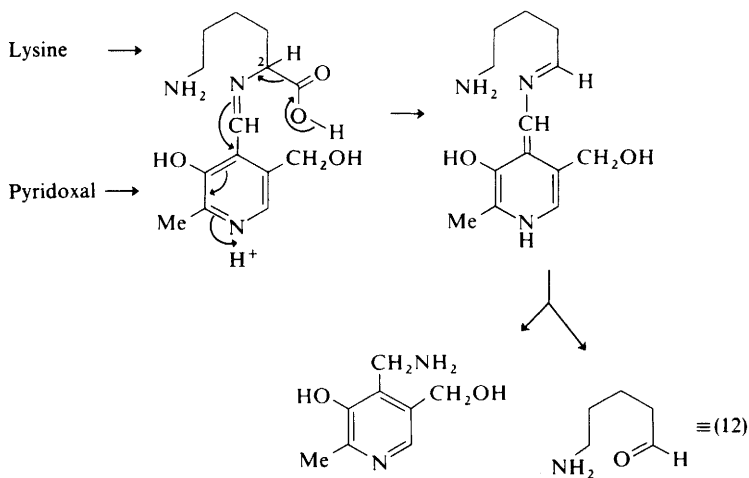


Scheme 4

⁷ (a) E. Leete, *Accounts Chem. Res.*, 1971, **4**, 100; (b) R. N. Gupta and I. D. Spenser, *Phytochemistry*, 1970, **9**, 2329; R. B. Herbert, in ref. 2, p. 25.

from C-2 or C-6. *N*-Methyl- Δ^1 -piperideine (13) is implicated as an intermediate in path *a*, and its role in the biosynthesis of anabasine (14) in *Nicotiana glauca* and *N. tabacum* has been examined by administration of [2- 14 C]-labelled material.⁸ Similar results were obtained for both plants. Thus efficient incorporations into (–)-anabasine (14) and (–)-*N*-methylanabasine (15) were recorded and without randomization of the label. However, the specific activity of the *N*-methylanabasine, unlike that of the anabasine, was the same as the specific activity of the precursor, *i.e.*, no dilution by inactive alkaloid had occurred in the plant. The failure of these plants to produce *N*-methylanabasine normally was confirmed by g.l.c. analysis of crude alkaloid extracts and also by the failure to dilute it out of the plants after administration of DL-[2- 14 C]lysine. The formation of *N*-methylanabasine (15) from *N*-methyl- Δ^1 -piperideine (13) in *Nicotiana*, therefore, is an aberrant one. The synthesis of unnatural alkaloids by *Nicotiana* had been reported earlier⁹ and this then is a further example. The configuration of the *N*-methylanabasine at C-2' was found to be the same as that of natural anabasine and nicotine.

It follows that *N*-methyl- Δ^1 -piperideine is unlikely to be a normal intermediate in anabasine biosynthesis and its incorporation into nicotine must be the result of the action of a non-specific demethylating enzyme on (13) or (15). The biosynthesis of anabasine (14) probably proceeds therefore by path *b*, Scheme 4, and the conversion of lysine into (12) without loss of hydrogen from C-2 is accounted for by a reasonable mechanism involving pyridoxal, as shown in Scheme 5.



Scheme 5

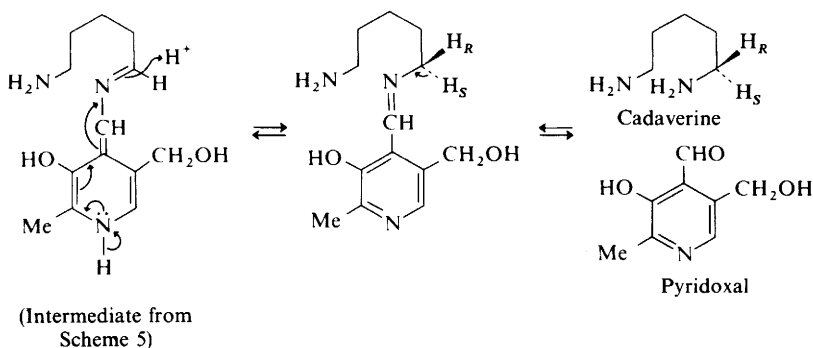
⁸ E. Leete and M. R. Chedekel, *Phytochemistry*, 1972, **11**, 2751.

⁹ (a) M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, **93**, 7021; *ibid.*, 1970, **92**, 5528; (b) E. Leete, G. B. Bodem, and M. F. Manuel, *Phytochemistry*, 1971, **10**, 2687; (c) R. B. Herbert, in ref. 2, p. 32.

The idea that ϵ -*N*-methyl-lysine (Scheme 4, path *a*) is a precursor for *N*-methylpiperidine alkaloids like sedamine (17) must apparently also be abandoned: although ϵ -*N*-methyl-lysine has been detected in *Sedum acre* plants, administration of [*methyl*- ^{14}C]methionine together with [^3H]lysine to these plants gave ϵ -*N*-methyl-lysine with a $^3\text{H}:^{14}\text{C}$ ratio quite different from that of sedamine (17), which indicated therefore that ϵ -*N*-methyl-lysine was not a precursor of this alkaloid.¹⁰

It may be concluded then that of the two pathways outlined in Scheme 4, path *a* is not followed in the biosynthesis of piperidine alkaloids. Path *b* is in accord with many of the results obtained for piperidine alkaloid biosynthesis but cannot be regarded as a general hypothesis as it stands, for ceruine (2) and decodine are derived from lysine *via* a symmetrical intermediate, reasonably cadaverine.¹¹ It has been suggested⁴ that cadaverine (5) may be a normal intermediate common to the biosynthesis of piperidine alkaloids. The degree of dissociation of the enzyme-cadaverine complex formed on decarboxylation of lysine would decide whether the incorporation of lysine into a piperidine alkaloid occurs in non-symmetrical or symmetrical manner. Incorporation of cadaverine into *N*-methylpelletierine (16) has been found¹² to proceed in stereospecific fashion with retention of the *pro-R* and loss of the *pro-S* hydrogen at C-1.

By using these ideas the pathway illustrated in Schemes 4 (path *b*) and 5 can be made general for the biosynthesis of all piperidine alkaloids with the implication of cadaverine as a pyridoxal-linked intermediate by an extension of Scheme 5.



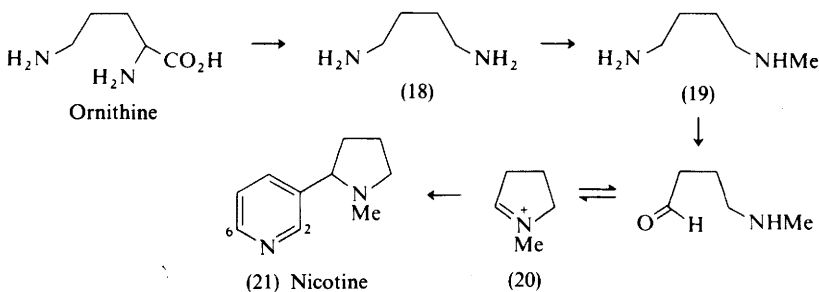
The importance of this sequence relative to that outlined in Scheme 5 would decide whether lysine is symmetrically or unsymmetrically incorporated into the piperidine alkaloids.

¹⁰ E. Leistner, R. N. Gupta, and I. D. Spenser, Abstracts 10th Annual Symposium Phytochemistry Society N. America, in part. Quoted as a footnote in ref. 8.

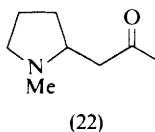
¹¹ R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *Chem. Comm.*, 1970, 409; S. H. Koo, R. N. Gupta, I. D. Spenser, and J. T. Wrobel, *Chem. Comm.*, 1970, 396; R. B. Herbert, in ref. 2, p. 26.

¹² I. D. Spenser, 23rd International Congress of Pure and Applied Chemistry, Boston, July 1971. Symposium 0-13. Abstr. No. 91, p. 36, based on unpublished results of E. W. Leistner and I. D. Spenser. Quoted in ref. 4.

Nicotine.—These results for the piperidine alkaloids are in marked contrast to those observed with pyrrolidine alkaloids like hygrine (22) and nicotine (21) where the pathways from ornithine proceed *via* *N*-methylated derivatives. The route to hygrine (22) and its relatives must necessarily involve non-symmetrical intermediates^{13,14} whereas that to nicotine must involve at least one symmetrical intermediate, *i.e.* putrescine (18); the proposed biosynthetic pathway¹⁵ to nicotine (21) is illustrated in Scheme 6.



Scheme 6



The pathway to nicotine has received further support in the isolation of two enzymes from tobacco roots,¹⁶ one of which, putrescine *N*-methyltransferase, will catalyse the formation of *N*-methylputrescine (19) from putrescine (18). The other enzyme which was isolated was *N*-methylputrescine oxidase. It catalysed the conversion of *N*-methylputrescine (19) into *N*-methylpyrrolinium salt (20). This enzyme oxidized putrescine and cadaverine at a rate 40% that found for *N*-methylputrescine whilst other amines were unaffected, thus showing reasonable specificity for *N*-methylputrescine.

It has long been known¹⁷⁻²⁰ that nicotinic acid [as (23)] is a precursor of the pyridine ring of nicotine (21) and that the pyrrolidine ring becomes attached to

¹³ D. G. O'Donovan and M. F. Keogh, *J. Chem. Soc. (C)*, 1969, 223.

¹⁴ R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1, p. 10.

¹⁵ D. Gross, in 'Biosynthese der Alkaloide', ed. K. Mothes and H. R. Schütte, VEB Deutscher Verlag der Wissenschaften, Berlin, 1969, p. 234.

¹⁶ S. Mizusaki, Y. Tanabe, M. Noguchi, and E. Tamaki, *Phytochemistry*, 1972, **11**, 2757.

¹⁷ R. F. Dawson, D. R. Christman, R. C. Anderson, M. L. Solt, A. F. D'Adamo, and U. Weiss, *J. Amer. Chem. Soc.*, 1956, **78**, 2645.

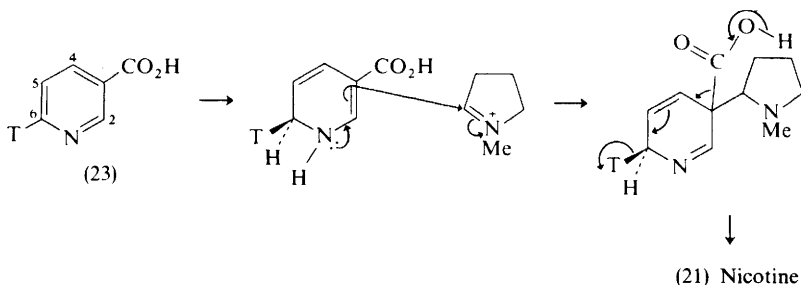
¹⁸ R. F. Dawson, D. R. Christman, A. F. D'Adamo, M. L. Solt, and A. P. Wolf, *Chem. and Ind.*, 1958, 100.

¹⁹ R. F. Dawson, D. R. Christman, A. F. D'Adamo, M. L. Solt, and A. P. Wolf, *J. Amer. Chem. Soc.*, 1960, **82**, 2628.

²⁰ K. S. Yang, R. K. Gholson, and G. R. Waller, *J. Amer. Chem. Soc.*, 1965, **87**, 4184; T. A. Scott and J. P. Glynn, *Phytochemistry*, 1967, **6**, 505.

the position from which the carboxy-group is lost.²⁰ The mechanism by which nicotinic acid and the pyrrolidine ring become linked has not been established, however. Germane to a consideration of the mechanism of this reaction are results obtained from feeding experiments with variously tritiated/deuteriated nicotinic acids in excised root cultures of *N. tabacum*. It was found^{18,19} that [2-³H]-, [4-²H]-, and [5-³H]-nicotinic acids [as (23)] were incorporated approximately ten times more efficiently than [6-³H]nicotinic acid. An explanation for the loss of tritium from C-6 was offered by suggesting that 6-hydroxynicotinic acid was an intermediate between nicotinic acid and nicotine. This was shown to be unlikely when 6-hydroxy[¹⁵N]nicotinic acid failed to be incorporated.¹⁹ It was also shown that [6-³H]nicotinic acid did not undergo loss of tritium while present in the culture medium.

It was suggested then^{19,21} that 1,6-dihydronicotinic acid might be an intermediate and that the results could be accounted for by the mechanism shown in Scheme 7;²² it is necessary to postulate, as is likely, that hydrogen introduction and removal are stereospecific otherwise tritium would be preferentially retained by a primary isotope effect.



Scheme 7

The above results warranted further examination which has now been carried out²² and the results provide confirmation of those obtained earlier. Thus [2-³H]nicotinic acid was found to be a much more efficient precursor (8—35 times) for nicotine (21) than [6-³H]nicotinic acid, and the label from [2-³H]nicotinic acid was essentially all located at C-2 of nicotine (*cf.* ref. 19). Surprisingly, degradation of the nicotine, obtained after administration of the [6-³H]nicotinic acid, revealed that only 40—58 % of the residual activity was located at C-6, the remainder being located on the other carbons of the pyridine ring. It was also confirmed by administering doubly labelled nicotinic acid that little of the tritium was lost from C-2 or C-6 of nicotinic acid over the period of the other feedings.

Whilst it is clear that more experiments are needed to establish the mechanism whereby (20) and nicotinic acid [as (23)] become linked, it seems as if a pathway which involves complete loss of tritium from C-6 is the main one involved in

²¹ R. F. Dawson, *Amer. Sci.*, 1960, **48**, 321.

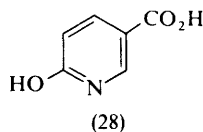
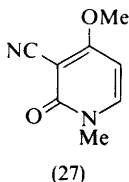
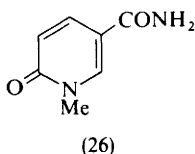
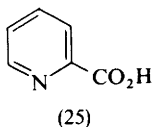
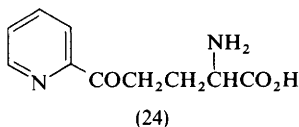
²² E. Leete and Y.-Y. Liu, *Phytochemistry*, 1973, **12**, 593.

nicotine biosynthesis. The residual tritium from C-6 of nicotinic acid could arise by hydrogen shifts not connected with formation of the nicotine skeleton, supported by variable efficiencies of incorporation of $[2\text{-}^3\text{H}]$ - compared with $[6\text{-}^3\text{H}]$ -nicotinic acid, under different experimental conditions.

Recent criticism²³ of a degradation procedure for nicotine obtained after $^{14}\text{CO}_2$ feeding experiments has been challenged by the original authors.²⁴ They cite their original control experiments, now supported by additional experiments, which unlike the other work²³ demonstrates that formaldehyde obtained by oxidation of *NN*-dimethylglycine derived from nicotine does not include label from the *N*-methyl groups. The original discrepancy between $^{14}\text{CO}_2$ and tracer feeding experiments still stands therefore.

Miscellaneous Pyridine Alkaloids.—Preliminary results on the biosynthetic pathway to proferrosamine A (24), a metabolite of *Pseudomonas roseus fluorescens*, have been obtained.²⁵ An exceptionally efficient incorporation of picolinic acid (25) suggested that it was an immediate precursor. DL-[3,4- $^{14}\text{C}_2$]Glutamic acid was also incorporated with activity confined to the picolinic acid moiety.

Nicotinic acid and nicotinamide have been found to be precursors for *N*-methyl-5-carboxamide-2-pyridone (26), a new alkaloid found in young greenhouse-grown *Trewia nudiflora*.²⁶ The mechanism of hydroxylation of this and related alkaloids, *e.g.* ricinine (27), is unknown. In the conversion of nicotinic acid into the related derivative (28) in the bacterium *Pseudomonas fluorescens*,



the oxygen originates from water and not molecular oxygen.²⁷ Consequently the reaction cannot be mediated by a mixed function oxidase and it represents a so far unique example of such a hydroxylation in an aromatic system.

²³ E. Leete, *Chem. Comm.*, 1971, 1524; R. B. Herbert, in ref. 2, p. 32.

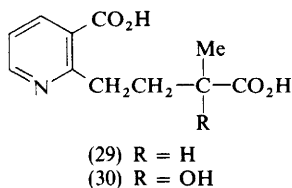
²⁴ A. A. Liebman, B. P. Mundy, M. L. Rueppel, and H. Rapoport, *J.C.S. Chem. Comm.*, 1972, 1022.

²⁵ M. Pouteau-Thouvenot, J. Padikkala, M. Barbier, A. Helbling, and M. Viscontini, *Helv. Chim. Acta*, 1972, **55**, 2295.

²⁶ S. D. Sastry and G. R. Waller, *Phytochemistry*, 1972, **11**, 2241.

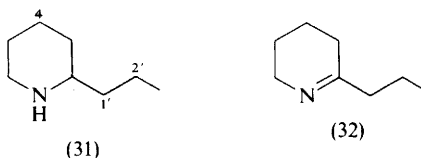
²⁷ A. L. Hunt, D. E. Hughes, and J. M. Lowenstein, *Biochem. J.*, 1957, **66**, 2P.

Hydrolysis of the complex ester alkaloids present in *Tripterygium wilfordii* yields either wilfordic acid (29) or hydroxywilfordic acid (30), for which [6-¹⁴C]-nicotinic acid and [carbonyl-¹⁴C]nicotinamide adenine nucleotide (NAD) serve



as efficient precursors.²⁸ Interestingly, nicotinic acid is more efficiently incorporated into the root alkaloids than NAD, the reverse being observed in the alkaloids of leaves and stems.

Coniine.—Unlike most of the piperidine alkaloids, coniine (31) is derived in Nature from acetate and not lysine. Full details²⁹ of the fascinating discovery of its mode of biosynthesis have been published. Results additional to those already reviewed^{30,31} are as follows. [1-¹⁴C]Hexanoic acid was incorporated into coniine (31), with activity confined to C-4. This is an example of a fairly rarely observed elongation of a medium length fatty acid.^{7a} A rapid equilibration of coniine (31) and γ -coniceine (32) is known to occur in hemlock³² and it was



observed here that [2'-¹⁴C]coniine was incorporated into its biological precursor γ -coniceine with the natural (+)-isomer much more efficiently converted than (−)-coniine.

An enzyme has been isolated³³ from hemlock leaves which catalyses transamination between alanine and 5-oxo-octanal (33), a precursor for coniine, a finding which strengthens the position of 5-oxo-octanal as an intermediate in coniine biosynthesis. The products of the enzymic transformation were γ -coniceine (32) and pyruvic acid. This reaction was shown to be irreversible *in vivo* when (−)-[¹⁵N,1'-¹⁴C]coniine [as (31)] and similarly labelled γ -coniceine were re-isolated after 9 days in hemlock without change in isotope ratio.²⁹ The

²⁸ H. J. Lee and G. R. Waller, *Phytochemistry*, 1972, **11**, 2233.

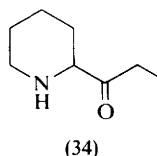
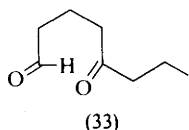
²⁹ E. Leete and J. O. Olsen, *J. Amer. Chem. Soc.*, 1972, **94**, 5472.

³⁰ R. B. Herbert, in ref. 14, p. 1.

³¹ J. Staunton, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1972, Vol. 2, p. 26.

³² J. W. Fairburn and P. N. Suwal, *Phytochemistry*, 1961, **1**, 38.

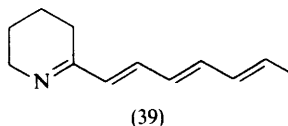
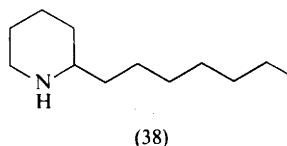
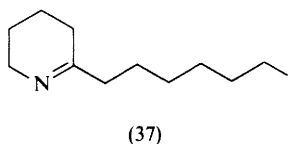
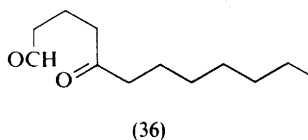
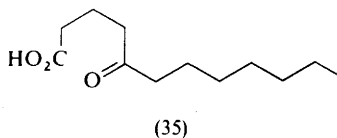
³³ M. F. Roberts, *Phytochemistry*, 1971, **10**, 3057.



coniceine efficiently labelled a new alkaloid, conhydrinone (34), discovered during the course of these experiments.

Attention was drawn to the much more efficient use of $[2-^{14}\text{C}]$ acetate compared with $[1-^{14}\text{C}]$ acetate in the biosynthesis of coniine as well as other metabolites, which is the consequence of acetate entering the Krebs cycle. Acetate arising at the end of the cycle will be labelled on both carbon atoms if derived from $[2-^{14}\text{C}]$ acetate but devoid of activity if derived from $[1-^{14}\text{C}]$ acetate.^{7a,34} The results with coniine were consistent with this.

Nigrifactin.—Although the biosynthesis of piperidine alkaloids from plants has been studied extensively, nigrifactin (39) is the first such compound from microbial sources to be examined.³⁵ The results of experiments with $[^{14}\text{C}]$ - and $[^{13}\text{C}]$ -labelled acetic acid showed that nigrifactin was elaborated by the linear combination of six acetate units. The pathway to nigrifactin thus resembles that to the plant alkaloid coniine (31) and further similarities are apparent in the incorporation of labelled 5-oxododecanoic acid (35), 5-oxododecanal (36), and the piperidine derivatives (37) and (38). Although the incorporations of these compounds were specific they were significantly lower than those obtained for acetic acid. Further, the incorporations of the bases (37) and (38) were at least an order

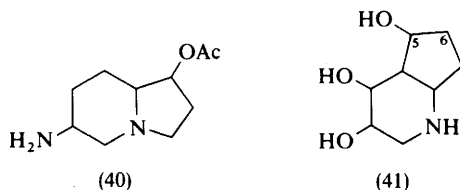


³⁴ I. D. Spenser, *Comp. Biochem. Physiol.*, 1968, **20**, 256.

³⁵ T. Terashima, E. Idaka, Y. Kishi, and T. Goto, *J.C.S. Chem. Comm.*, 1973, 75.

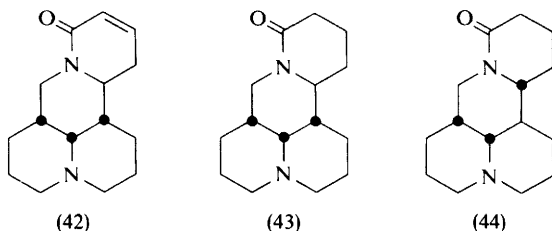
of magnitude lower than those of (35) and (36). It was felt that the sparing solubility of (35) through (38) in the culture medium as well as the open question of cell permeability may have given rise to the low incorporation values. The results thus do not allow one to decide conclusively whether the bases (37) and (38) in fact lie on the main biosynthetic pathway to nigrifactin and at what point the additional double bonds are introduced. It will be interesting to see if more definite results can be obtained using disrupted cells.

***Rhizoctomia leguminicola* Bases.**—Slaframine (40) is elaborated by the fungus *Rhizoctomia leguminicola* from the entire skeleton of pipecolic acid³⁶ and a new alkaloid, (41), isolated from this fungus has been found in preliminary experiments to be similarly derived.³⁷ L-Pipecolic acid is known in other living systems to derive preferentially from the D-isomer of lysine,^{37a} and a lower incorporation of L-lysine compared with DL-precursor was accordingly observed. The derivation of these bases from pipecolic acid is unusual, for the biosynthesis of other piperidine alkaloids from lysine does not involve pipecolic acid and the route to these alkaloids begins with the L-isomer of lysine (see above).



The origin of the two carbon atoms not accountable for by pipecolic acid (C-5 and C-6) is unknown; DL-[1-¹⁴C]- and DL-[3-¹⁴C]-serine were not incorporated.

Quinolizidine Alkaloids.—Sophocarpine (42) and matrine (43) have been shown to be incorporated into, respectively, matrine (43) and sophocarpine (42) and also their N-oxides in *Sophora alopecuroides*.³⁸ They were not incorporated into



³⁶ H. P. Broquist and J. J. Snyder, in 'Microbial Toxins', ed. S. Kadis, A. Ciegler, and S. J. Ajl, Academic Press, New York, 1971, Vol. 7, p. 319.

³⁷ F. P. Guengerich, S. J. DiMari, and H. P. Broquist, *J. Amer. Chem. Soc.*, 1973, **95**, 2055.

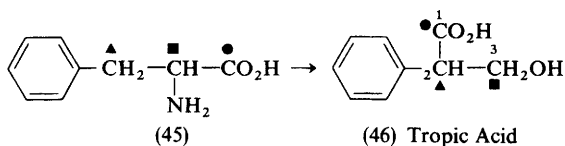
^{37a} T. J. Gilbertson, *Phytochemistry*, 1972, **11**, 1737; J. A. Grove, T. J. Gilbertson, R. H. Hammerstedt, and L. M. Henderson, *Biochim. Biophys. Acta*, 1969, **184**, 329; R. H. Aldag and J. L. Young, *Planta*, 1970, **95**, 187; R. B. Herbert, in ref. 2, p. 25.

³⁸ J. K. Kuschmuradov, D. Gross, and H. R. Schütte, *Phytochemistry*, 1972, **11**, 3441.

sophoridine (44), indicating that the configurational differences between sophoridine (44) and the matrine type are fixed at an early stage of biosynthesis. [1,5- $^{14}\text{C}_2$]-Cadaverine was but poorly incorporated into the alkaloids of this plant, and its role in the biosynthesis of these bases was thus uncertain. Cadaverine, however, is incorporated satisfactorily into similar quinolizidine alkaloids in *Goebelia pachycarpa* and other plants.³⁹

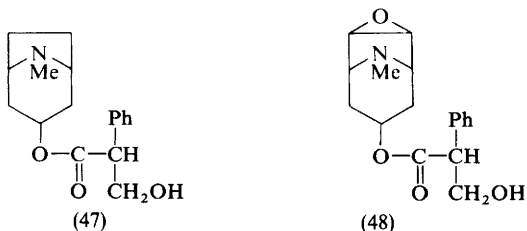
Cryogenine.—The work which was carried out on the incorporation of phenylalanine into cryogenine has appeared in full.⁴⁰ There are additional degradations which support the original conclusions.⁴¹

Tropane Alkaloids.—It is well established that the carbon atoms of the side-chain of phenylalanine (45) become those of the side-chain of the tropic acid (46) moiety of scopolamine and hyoscyamine (Scheme 8).⁴² Phenylacetic acid and tryptophan



Scheme 8

have been found also to act as precursors for tropic acid, the former being elaborated to tropic acid (46) with inclusion of a C_1 unit. Suitable C_1 units like carbon dioxide (as sodium bicarbonate), formate, formaldehyde, or methionine were not specifically incorporated, however.⁴² Compounds which give formic acid as a result of metabolism have been tested: both DL-[indolyl-2- ^{14}C]tryptophan and L-[3- ^{14}C]serine served as reasonably efficient precursors for the tropic acid moiety of hyoscyamine (47) and scopolamine (48) in *Datura innoxia* root-tissue, as indeed did [^{14}C]formic acid.⁴³ In each case the label was largely confined



³⁹ B. A. Abdusalamov, A. A. Takanaev, Kh. A. Aslanov, and A. S. Sadykov, *Biochemistry (U.S.S.R.)*, 1971, **36**, 239; R. B. Herbert, in ref. 2, p. 31; H. R. Schütte, in ref. 15, p. 324.

⁴⁰ A. Rother and A. E. Schwarting, *Phytochemistry*, 1972, **11**, 2475.

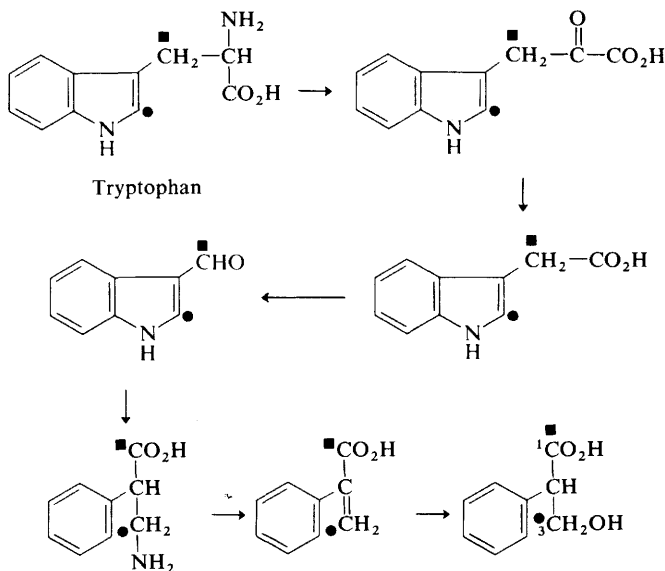
⁴¹ A. Rother and A. E. Schwarting, *Chem. Comm.*, 1969, 1411; R. B. Herbert, in ref. 14, p. 6.

⁴² H. W. Liebisch, in ref. 15, p. 183.

⁴³ N. W. Hamon and J. L. Eyolfson, *J. Pharm. Sci.*, 1972, **61**, 2006.

to C-1 and C-3 of the tropic acid [as (46)] derived from the alkaloids with substantially heavier labelling of C-1 by the serine and formate. This complemented the results obtained with $[1-^{14}\text{C}]$ phenylacetic acid where a similarly efficient incorporation was recorded with heavier labelling of C-3 than C-1.

The distribution of label in the tropic acid isolated after the tryptophan feeding was different from that from formate, that is C-3 was more heavily labelled than C-1. Labelling of C-3 is in accord with a pathway proposed as a result of the specific incorporation of label from $[3-^{14}\text{C}]$ tryptophan into C-1 of tropic acid;⁴⁴ these results are depicted in Scheme 9.⁴³ $[\text{Benzene ring-}U-^{14}\text{C}]$ tryptophan was incorporated also into tropic acid and the activity was confined to the aromatic ring.⁴³ Thus the whole skeleton of tropic acid can be derived from tryptophan.



Scheme 9

Labelling of C-1 in addition to C-3 by $[\text{indolyl-2-}^{14}\text{C}]$ tryptophan can be explained as being the result of tryptophan catabolism whereby the labelled carbon atom is released as formate, but why significant activity appears in C-1 when C-3 is heavily labelled, or *vice versa* in the other cases, is unclear. DL- $[1-^{14}\text{C}]$ Phenylalanine gave tropic acid with heavy labelling of C-1 but again labelling of the other atom (C-3) was heavier than any of the other carbon atoms in the molecule.⁴³

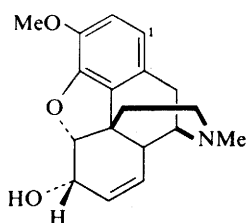
It may be concluded from these results and those obtained before that the tropic acid moiety of scopolamine and hyoscyamine can arise by three different pathways beginning with phenylalanine, phenylacetic acid, or tryptophan.

⁴⁴ A. M. Goodeve and E. Ramstad, *Experientia*, 1961, 17, 124.

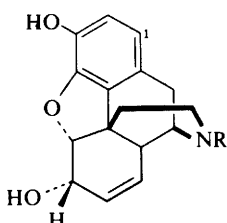
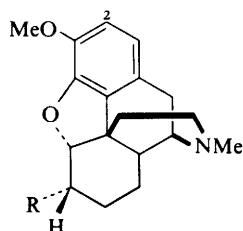
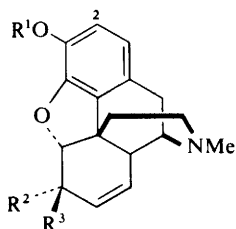
2 Isoquinoline Alkaloids

Morphine Alkaloids.—An interesting new development in the study of the biosynthesis of secondary metabolites is the testing of modified precursors as substrates for conversion in the intact living system into unnatural products. The conversion of 5-fluoronicotinic acid into 5-fluoronicotine,^{9b} and of various C-methyl derivatives of *N*-methyl- Δ^1 -pyrroline into the corresponding methylated nicotine derivatives^{9a} has already been reviewed;^{9c} the role of *N*-methyl- Δ^1 -piperidine (13) in anabasin biosynthesis is discussed above. The results of such studies can yield further information on biosynthesis and in particular provide insight into the specificity of enzyme function. These transformations are also of potential use for the synthesis of molecules not easily accessible chemically and here one might expect that the enzymes which regulate the biosynthesis of secondary metabolites will show less substrate specificity than those concerned with primary metabolic processes.

The ultimate precursor for morphine (50) is codeine (49), from which it arises by demethylation.⁴⁵ The substrate specificity of the enzyme or enzymes involved in this reaction has been studied⁴⁶ in *Papaver somniferum* with the codeine derivatives dihydrocodeine (52), isocodeine (54), codeine methyl ether (55), dihydrodeoxycodeine (53), and 1-bromocodeine. By feeding codeine with a



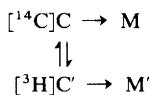
(49) Codeine

(50) R = Me, Morphine
(51) R = H(52) R = OH
(53) R = H(54) R¹ = Me, R² = H, R³ = OH
(55) R¹ = Me, R² = OMe, R³ = H
(56) R¹ = H, R² = OMe, R³ = H.

⁴⁵ H. R. Schütte, in ref. 15, p. 371; G. W. Kirby, *Science*, 1967, **155**, 170.

⁴⁶ G. W. Kirby, S. R. Massey, and P. Steinreich, *J.C.S. Perkin I*, 1972, 1642.

^{14}C -label on the *N*-methyl group in admixture with the $[2\text{-}^3\text{H}]$ -labelled codeine derivative it was possible to compare directly the efficiency of conversion of unnatural precursor (C') into unnatural morphine derivative (M') with that of codeine (C) into morphine (M) and also to determine any interconversion of precursors ($\text{C} \rightleftharpoons \text{C}'$) (see Scheme 10). Both $[2\text{-}^3\text{H}]$ codeine and $[N\text{-methyl-}^{14}\text{C}]$ -codeine were known to be incorporated into morphine without significant loss or scrambling of label^{47,48} and this was confirmed. The incorporation of the unnatural precursors was also shown to be without randomization of label.



Scheme 10

Both codeine methyl ether (55) and codeine (49), as had been previously observed,⁴⁵ were incorporated into morphine, with (55) also being transformed into morphine methyl ether (56); it was clear that cleavage of both the 3-methoxy- ($\text{C}' \rightarrow \text{M}'$) and 6-methoxy-groups ($\text{C}' \rightarrow \text{C}$) occurred readily, the latter process leading to tritium-labelled morphine. It had been shown that codeine methyl ether is not a normal constituent of *P. somniferum*⁴⁹ although it was observed here that the methylation of administered codeine could occur to a small extent.

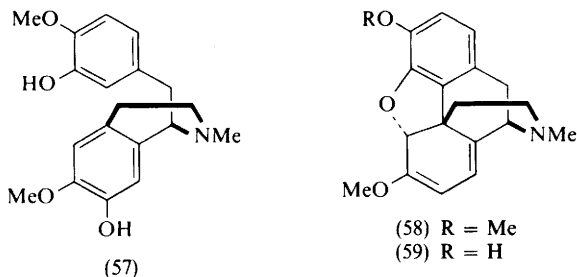
In experiments with the other administered compounds no significant inter-conversions, $\text{C} \rightleftharpoons \text{C}'$, were observed. These substrates were efficiently converted, however, into their respective morphine derivatives except for bromocodeine. This inhibited its own demethylation and a low yield of the morphine derivative resulted. It was clear from the surprisingly high efficiencies observed for the transformations of the codeine derivatives, (52) and (53), that neither the hydroxy-group nor the 7,8-double bond is important for binding to the demethylating enzyme but as isocodeine (54) was less efficiently demethylated than codeine perhaps a hydroxy-group *cis* to the ethanamine bridge may hinder such binding.

It has been established that of four dihydroxy-dimethoxy-1-benzylisoquinolines, only reticuline (57) is incorporated into morphine.⁴⁸ Consequently no general non-specific enzyme(s) for demethylation is functioning in *P. somniferum* but it is likely that the above demethylation reactions occur with the same enzyme(s) responsible for the demethylation of codeine to morphine and that it is an enzyme or enzyme system with fairly wide substrate specificity but nonetheless confined to the codeine-type skeleton. This implies that the phenol corresponding to thebaine (58), namely oripavine (59), previously isolated from other *Papaver*

⁴⁷ A. R. Battersby, J. A. Martin, and E. Brochmann-Hanssen, *J. Chem. Soc. (C)*, 1967, 1785; D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, 1965, 2423; A. R. Battersby, D. M. Foulkes, M. Hirst, G. V. Parry, and J. Staunton, *J. Chem. Soc. (C)*, 1968, 210.

⁴⁸ A. R. Battersby, D. M. Foulkes, and R. Binks, *J. Chem. Soc.*, 1965, 3323.

⁴⁹ H. I. Parker, G. Blaschke, and H. Rapoport, *J. Amer. Chem. Soc.*, 1972, **94**, 1276; R. B. Herbert, in ref. 2, p. 18.



species, may be expected to occur in *P. somniferum*, and also the phenolic analogues of intermediates lying between thebaine (58) and morphine (50).

The demethylation reactions associated with the late stages of morphine biosynthesis have been the subject of another approach which seeks to assign a positive role for the morphine alkaloids in the metabolism of *P. somniferum*.⁵⁰

It is a general observation that plant alkaloids undergo turn-over, lending support to the view that alkaloids play an active role in plant metabolic processes. Morphine, for example, undergoes rapid turn-over and appears to be broken down into non-alkaloidal products. Early steps could involve *N*-demethylation, and normorphine (51) could therefore be implicated.⁵⁰ Its presence in the plant *P. somniferum* had first to be established. This was done and it was shown to be present during the life-cycle of the plant.⁵⁰ From the isolation of radioactive normorphine after administration of labelled morphine it followed that normorphine was a degradation product of morphine. Like the reactions which lead from thebaine to morphine,^{49,51} however, this reaction too was shown to be irreversible. It appears that the major if not the only breakdown pathway for morphine involves an initial demethylation to normorphine. The formation of normorphine completes a sequence of demethylations which begins at thebaine. Taken with the high turn-over of morphine and normorphine observed here as the result of ¹⁴CO₂ feeding, it was suggested tentatively that the active metabolic role which may be assigned to the alkaloids of the demethylation sequence from thebaine (58) to normorphine (51) may be that of methylating agents.

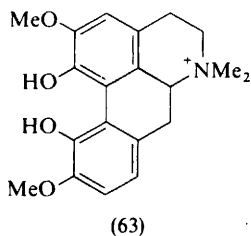
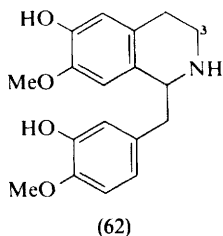
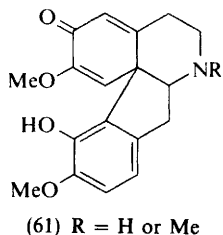
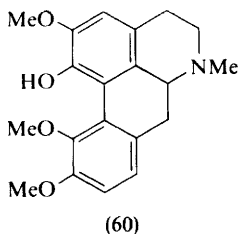
Magnoflorine.—In contrast to the delightfully novel pathway to the *Dicentra eximia* alkaloids, e.g. corydine (60), which has been found to proceed via the dienone (61) from norprotosinomenine (62),⁵² the biosynthesis of magnoflorine (63) has proved more prosaic, proceeding apparently by an *ortho-ortho* coupling of reticuline.⁵³ Thus (+)-[*N*-methyl-¹⁴C]reticuline [as (57)] was incorporated but (±)-[3-¹⁴C, 7-*O*-methyl-³H]norprotosinomenine [as (62)] was not. The successful incorporation was obtained with an *Aquilegia* species, which contrasts with an

⁵⁰ R. J. Miller, C. Jolles, and H. Rapoport, *Phytochemistry*, 1973, **12**, 597.

⁵¹ R. F. Stermitz and H. Rapoport, *Nature*, 1961, **189**, 310.

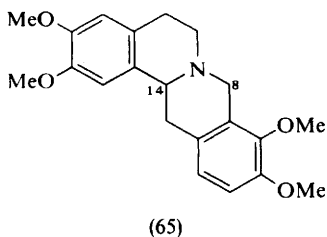
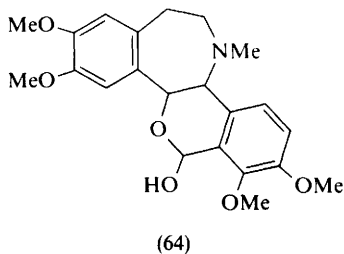
⁵² A. R. Battersby, J. L. McHugh, J. Staunton, and M. Todd, *Chem. Comm.*, 1971, 985; J. Staunton, in ref. 31, p. 12.

⁵³ E. Brochmann-Hanssen, C.-H. Chen, H.-C. Chiang, and K. McMurtrey, *J.C.S. Chem. Comm.*, 1972, 1269.



earlier negative result with *Papaver somniferum*.⁵⁴ On both occasions magnoflorine was isolated by dilution with inactive carrier and it is possible that the *P. somniferum* contained no magnoflorine, thus illustrating the dangers of this particular application of the technique of dilution analysis.

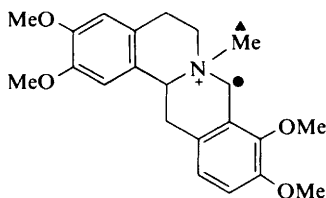
Alpinigenin.—Of all the alkaloids derived from the benzylisoquinoline skeleton, only the spirobenzylisoquinoline alkaloids, *e.g.* ochotensimine, and those of the rheoadine type, *e.g.* alpinigenin (64), have been little studied. A plausible route⁵⁵ to the rheoadine-type alkaloids involves initial oxidative cleavage of the N—C-14 or N—C-8 bond [as (65)] of a tetrahydropprotoberberine. Tetrahydro-[8-¹⁴C]palmatine [as (65)] and its *N*-methyl derivative, labelled as shown in (66), were both incorporated specifically⁵⁶ into alpinigenin (64) in *Papaver bracteatum* in accord with this suggestion. A role for the quaternary *N*-methyl function in



⁵⁴ E. Brochmann-Hanssen, C.-C. Fu, and L. Y. Misconi, *J. Pharm. Sci.*, 1971, **60**, 1880; R. B. Herbert, in ref. 2, p. 19.

⁵⁵ F. Šantavý, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1970, Vol. 12, p. 430.

⁵⁶ H. Rönsch, *European J. Biochem.*, 1972, **28**, 123.



(66)

aiding the ring-opening reaction was therefore suggested. Although the *N*-methyl label was completely retained in the derived alpinigenin an enormous difference in the level of incorporation of the two precursors was found, which must call into question whether (66) is a normal intermediate.

Colchicine.—Results which delineate the biological route to colchicine (70) had been reported, in essence,⁵⁷ before the appearance of these reviews. But the publication of a series of full papers^{58–60} provides a fresh opportunity to discuss the remarkable pathway by which this non-basic alkaloid arises in *Colchicum*.

Ring A and carbons 5, 6, and 7 of colchicine (70) derive from phenylalanine via cinnamic acid.^{61,62} The labels from [ring-4-¹⁴C]- and [3-¹⁴C]-tyrosine were incorporated into colchicine (70) in *Colchicum* and were located at C-9 and C-12, respectively;^{59,61a,62} [1-¹⁴C]- and [2-¹⁴C]-tyrosine were not specifically incorporated.^{61a} (It is apparent from the results that conversion of phenylalanine into tyrosine in *Colchicum* does not occur. Similar results have been obtained with other plants.) Formation of the tropolone ring is thus by expansion of the aromatic ring of tyrosine with inclusion of the benzylic carbon atom. It is interesting to note that the fungal tropolones, *e.g.* stipitatic acid (71), have different origins, being derived from acetate,^{63b} but their formation resembles that of colchicine in that the tropolone ring is formed apparently by expansion of an aromatic six-membered ring.^{63a,64}

⁵⁷ A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *Chem. Comm.*, 1966, 603; A. C. Barker, A. R. Battersby, E. McDonald, R. Ramage, and J. H. Clements, *ibid.*, 1967, 390; A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Santavý, *ibid.*, 1965, 228; A. R. Battersby and R. B. Herbert, *Proc. Chem. Soc.*, 1964, 260; A. R. Battersby, *Pure Appl. Chem.*, 1967, **14**, 117; D. Gross, in ref. 15, p. 359.

⁵⁸ A. R. Battersby, R. B. Herbert, L. Pijewska, F. Šantavý, and P. Sedmera, *J.C.S. Perkin I*, 1972, 1736.

⁵⁹ A. R. Battersby, T. A. Dobson, D. M. Foulkes, and R. B. Herbert, *J.C.S. Perkin I*, 1972, 1730.

⁶⁰ A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *J.C.S. Perkin I*, 1972, 1741.

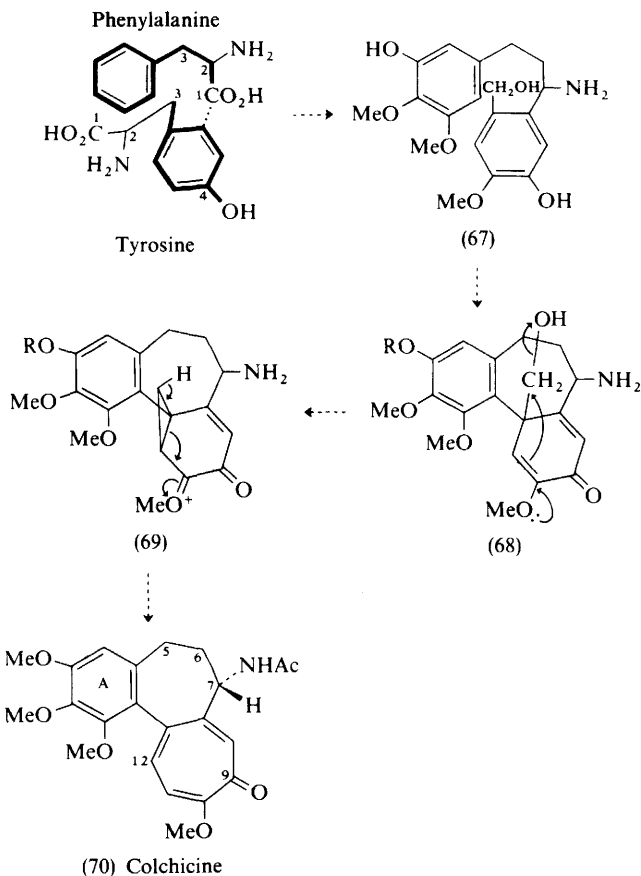
⁶¹ (a) A. R. Battersby and J. J. Reynolds, *Proc. Chem. Soc.*, 1960, 346; A. R. Battersby, R. Binks, and D. A. Yeowell, *ibid.*, 1964, 86; A. R. Battersby, R. Binks, J. J. Reynolds, and D. A. Yeowell, *J. Chem. Soc.*, 1964, 4257; (b) E. Leete and P. E. Nemeth, *J. Amer. Chem. Soc.*, 1960, **82**, 6055; E. Leete, *ibid.*, 1963, **85**, 3666.

⁶² E. Leete, *Tetrahedron Letters*, 1965, 333.

⁶³ (a) A. I. Scott, H. Guilford, and E. Lee, *J. Amer. Chem. Soc.*, 1971, **93**, 3534; (b) references cited in (a).

⁶⁴ A. I. Scott and K. J. Wiesner, *J.C.S. Chem. Comm.*, 1972, 1075.

The labelling data for colchicine could be accommodated within a plausible biosynthetic pathway (Scheme 11).⁵⁹ The product of union of the C₆-C₃ precursor from phenylalanine and the C₆-C₁ precursor from tyrosine was suggested to be (67). The subsequent steps proposed were phenol-coupling to give the

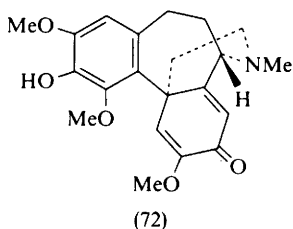
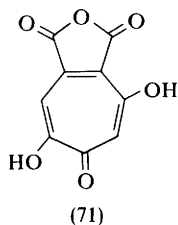


Scheme 11

dienone (68) and then homoallylic ring-expansion,⁶⁵ possibly *via* the *O*-phosphate, to give colchicine (70). The scheme was shown to be incorrect in regard to detail when tritiated (67) failed to label colchicine in *C. autumnale*.⁵⁹

Great interest was generated therefore when a dienone, androcymbine, was isolated from *Androcymbium melanthioides*, a close relative of *Colchicum autumnale*. The structure of androcymbine, which was quickly established as (72),

⁶⁵ Cf. O. Chapman and P. Fitton, *J. Amer. Chem. Soc.*, 1963, **85**, 41.



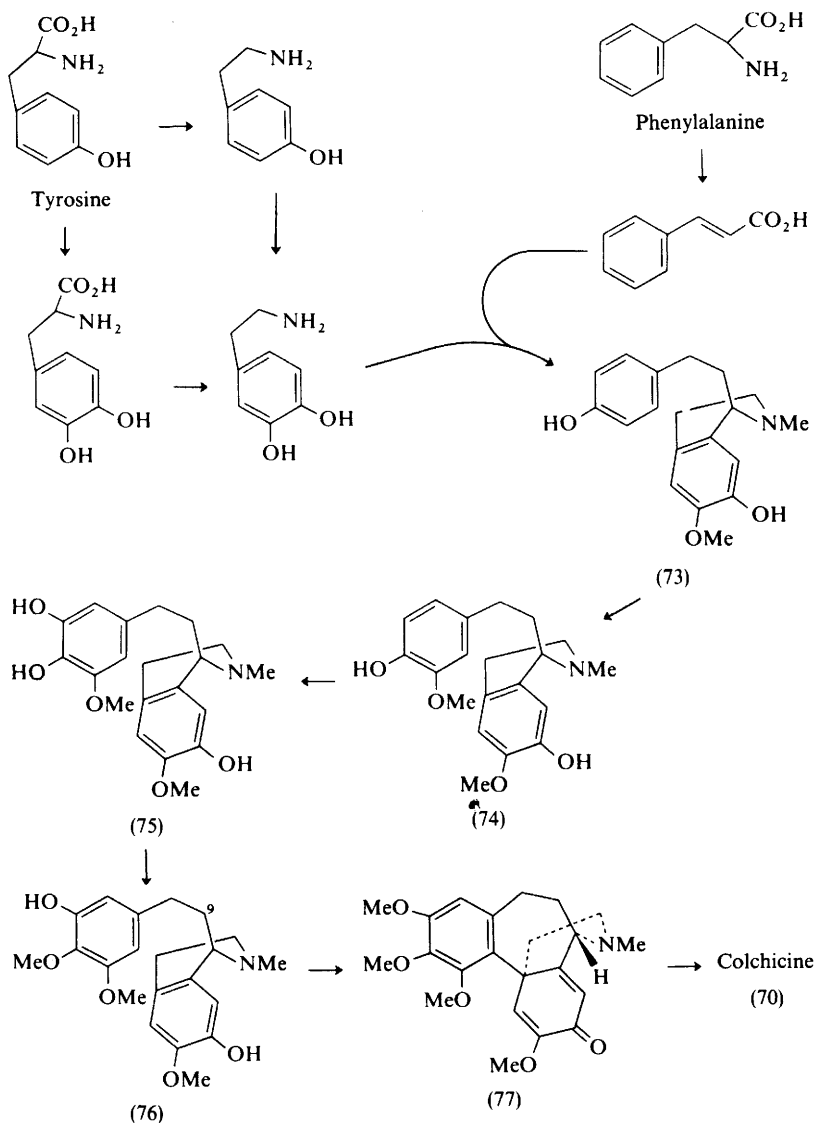
proved to be of singular significance.⁵⁸ Manifestly it appeared to be the product of phenol-coupling of the phenethylisoquinoline (76). Furthermore, a close relationship between androcymbine (72) and the dienone (68) could be seen, and so the earlier hypothetical route to colchicine could be tentatively modified to (76) \rightarrow (77) \rightarrow (70). Hydroxylation of (77) could provide the starting point for ring expansion.

A crucial test of these ideas was made when tritiated *O*-methylandrocymbine [as (77)] was administered to *C. autumnale* and *C. byzantinum*. A remarkably high and specific incorporation into colchicine (70) was observed, thus validating at least part of the pathway.⁶⁰ [¹⁵N]Tyrosine was also incorporated into the alkaloid in accord with the expected derivation of the amino-function of colchicine from that of tyrosine.

The role of the phenethylisoquinoline (76), called autumnaline, in colchicine biosynthesis was next examined.⁶⁰ (*RS*)-[9-¹⁴C]Autumnaline [as (76)] was efficiently and specifically incorporated into colchicine. The pathway (76) \rightarrow (77) \rightarrow (70) is thus established and it turns out that colchicine (70) is simply a modified phenethylisoquinoline. This apparently unusual alkaloid is brought then into the large family of alkaloids derived from 1-substituted isoquinolines.

Tritiated samples of the phenethylisoquinolines (78) and (79) were but poorly utilized in the formation of colchicine (70) and demecolcine, thus strengthening the position of autumnaline (76) as a true precursor for colchicine. The sequence of steps of hydroxylation and methylation which lead from the phenethylisoquinoline formed initially from tyrosine and phenylalanine was explored with phenethylisoquinolines variously substituted with methoxy- and hydroxy-groups. The steps which lie between the two amino-acids and the phenethylisoquinolines was also examined. Cinnamic acid was already established as a colchicine precursor but none of the substituted cinnamic acids (80)–(83) was incorporated and thus some other reaction, perhaps reduction, occurs prior to hydroxylation. From the results a pathway to colchicine could be delineated (Scheme 12) in which *N*-methylation must occur at an early stage; the incorporation recorded for (75) was unexpectedly low but this may be the result of its sensitivity to oxidation. The mechanism of the remarkable ring-expansion which generates the tropolone ring has not yet been established.

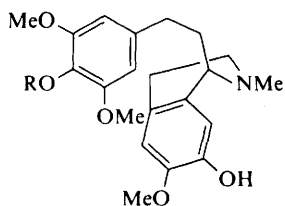
At the time that the structure of androcymbine was deduced, it seemed likely that other alkaloids derived from the 1-phenethylisoquinoline skeleton and which



Scheme 12

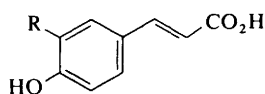
resembled those based on the benzyloquinoline system would be discovered. This has proved to be true and further, the homoaporphines (84)–(86) have been shown to be derived, like colchicine, from autumnaline (76).⁶⁶

⁶⁶ A. R. Battersby, P. Böhler, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1969, 1066; R. B. Herbert, in ref. 14, p. 22.



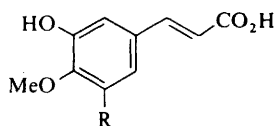
(78) R = Me

(79) R = H



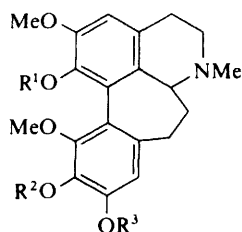
(80) R = H

(81) R = OMe



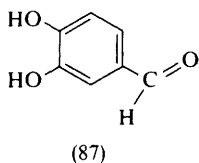
(82) R = H

(83) R = OMe

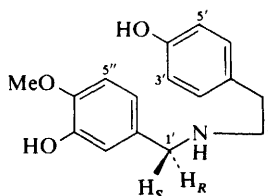
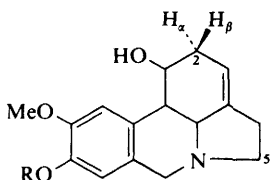
(84) R¹ = R³ = H, R² = Me(85) R¹ = R² = H, R³ = Me(86) R¹ = H, R² = R³ = Me

3 Amaryllidaceae Alkaloids

Lycorenine.—The biological conversion of protocatechualdehyde (87) into lycorenine (91) which proceeds *via* *O*-methylnorbelladine (88) and norpluviine (89) involves first a reduction of the aldehyde carbonyl, and then, in the generation of lycorenine (91), oxidation of this same carbon atom.

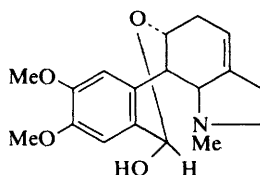


(87)

(88) *O*-Methylnorbelladine

(89) R = H, Norpluviine

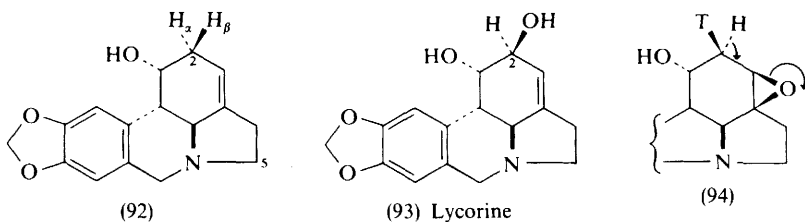
(90) R = Me



(91) Lycorenine

hydrogen addition and removal here are stereospecific and the hydrogen initially introduced is the one later removed.⁶⁷ The absolute stereochemistry of these processes has been elucidated in subsequent experiments.⁶⁸ (1'-R)-[1'-³H, 1-¹⁴C]-O-Methylnorbelladine [as (88)] containing a little of the 1'-S tritio-isomer was incorporated into norpluviine (89) without loss of tritium. This labelled material was then used as a precursor for lycorine (91) in another experiment. The lycorine isolated showed a tritium loss corresponding to the proportion of 1'-R tritium in the O-methylnorbelladine (88) fed; pluviine (90) derived from norpluviine in this experiment showed no tritium loss. The results of all the experiments,^{67,68} taken together, show that for the sequence from protocatchualdehyde (87) *via* (88) and (89) to lycorine (91), hydrogen addition and removal take place on the *re*-face⁶⁹ of the molecules concerned.

Lycorine.—In the conversion of O-methylnorbelladine (88) into lycorine (93), tritium from C-5' of (88) appears at C-2 of norpluviine (89) which is formed as an intermediate; the configuration of the tritium is apparently β .⁷⁰ This tritium is retained in the lycorine (93) subsequently formed, which means that hydroxylation at C-2 proceeds with inversion of configuration.⁷¹ This is of singular interest since biological hydroxylation at saturated carbon normally proceeds with retention of configuration. A reasonable explanation of the results is that the hydroxylation to give lycorine (93) proceeds by a novel mechanism, involving perhaps the epoxide (94). Ring opening, as shown in (94), followed by allylic



rearrangement of the resulting alcohol, would give lycorine (93).⁷¹ Supporting evidence comes from the incorporation of [2 β -³H]caranine [as (92)] into lycorine (93) in *Zephyranthes candida*;⁷² incorporation would not have been observed unless hydroxylation occurred with at least partial inversion of configuration.

In *Clivia miniata*, however, it has been discovered that hydroxylation of caranine occurs with *retention* of configuration,⁷³ following the chance observation that [3',5'-³H₂; O-methyl-¹⁴C]-O-methylnorbelladine [as (88)] was incorporated into lycorine (93) with complete loss of tritium. These results were confirmed when

⁶⁷ C. Fuganti and M. Mazza, *Chem. Comm.*, 1971, 1196; R. B. Herbert, in ref. 2, p. 23.

⁶⁸ C. Fuganti and M. Mazza, *J.C.S. Perkin I*, 1973, 954.

⁶⁹ K. R. Hanson, *J. Amer. Chem. Soc.*, 1966, **88**, 2731.

⁷⁰ G. W. Kirby and H. P. Tiwari, *J. Chem. Soc. (C)*, 1966, 676.

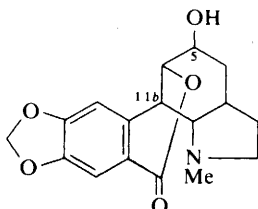
⁷¹ I. T. Bruce and G. W. Kirby, *Chem. Comm.*, 1968, 207; *Chimia (Switz.)*, 1968, **22**, 314.

⁷² W. C. Wildman and N. E. Heimer, *J. Amer. Chem. Soc.*, 1967, **89**, 5265.

⁷³ C. Fuganti and M. Mazza, *J.C.S. Chem. Comm.*, 1972, 936.

[1- ^{14}C]-*O*-methylnorbelladine [as (88)] with equal tritium labelling of positions 3', 5', and 5'' was incorporated into lycorine with retention of the C-5'' tritium label only. Further, [2 α - ^3H ; 5- ^{14}C]caranine [as (92)] was incorporated into lycorine (93) with high retention of tritium and this label was shown to be located at C-2. Thus no 2-oxo-compound can be implicated as an intermediate and the hydroxylation must be stereospecific, proceeding with retention of configuration. The stereospecificity of this reaction follows in part from the observation that tritium from positions 3' and 5' of *O*-methylnorbelladine is completely lost in the formation of lycorine. A non-stereospecific hydroxylation would have led to tritium retention at C-2 by a primary isotope effect. It is also established from these results that protonation of the appropriate *O*-methylnorbelladine derivative to give caranine (92) is also stereospecific.

Further partial substantiation of the above results comes from a feeding experiment with [2 β - ^3H]norpluviine derived biosynthetically from [3',5'- $^3\text{H}_2$]-*O*-methylnorbelladine in daffodils.⁷³ A ^{14}C -label at C-5 served as an internal marker. Surprisingly, incorporation of this material into lycorine in *C. miniata* gave alkaloid with a 20% retention of tritium instead of the expected complete loss; the label was located at C-2. This retention compares with a loss of 8% found for [2 α - ^3H]caranine [as (92)]. Whatever the explanation of this result it would be more convincing if chemically prepared material of high specific activity had been used.



(95)

In the above experiments incorporations were recorded for clivonine (95), the ester component of clivimine, as follows: [3',5',5''- $^3\text{H}_3$; 1- ^{14}C]-*O*-Methylnorbelladine gave clivonine with retention of 32% of tritium; the label was absent from C-5 and C-11b. Clivonine isolated following administration of [2 α - ^3H ; 5- ^{14}C]caranine and [2 β - ^3H ; 5- ^{14}C]norpluviine was inactive.

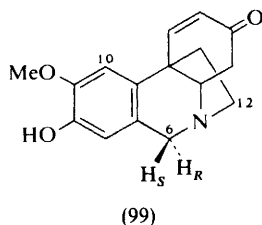
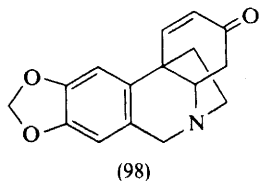
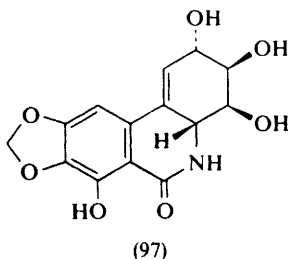
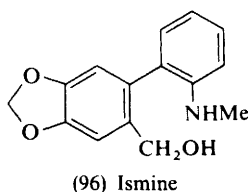
Ismine.—The alkaloid ismine (96) is known⁷⁴ to arise like narciclasine (97)⁷⁵ by a biosynthetic pathway which involves oxocrinine (98). Noroxomaritidine (99) is also implicated in the biosynthesis of narciclasine⁷⁶ and recent experiments⁷⁷

⁷⁴ C. Fuganti and M. Mazza, *Chem. Comm.*, 1970, 1466; J. Staunton, in ref. 31, p. 18.

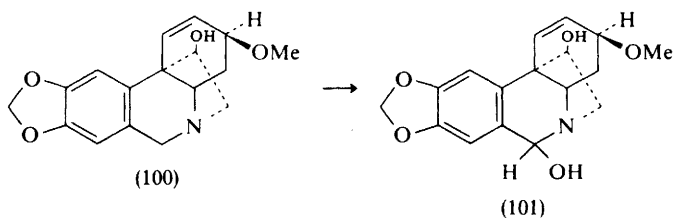
⁷⁵ C. Fuganti, J. Staunton, and A. R. Battersby, *Chem. Comm.*, 1971, 1154; J. Staunton, in ref. 31, p. 16.

⁷⁶ C. Fuganti and M. Mazza, *Chem. Comm.*, 1971, 1388; R. B. Herbert, in ref. 2, p. 21.

⁷⁷ C. Fuganti, *Tetrahedron Letters*, 1973, 1785.



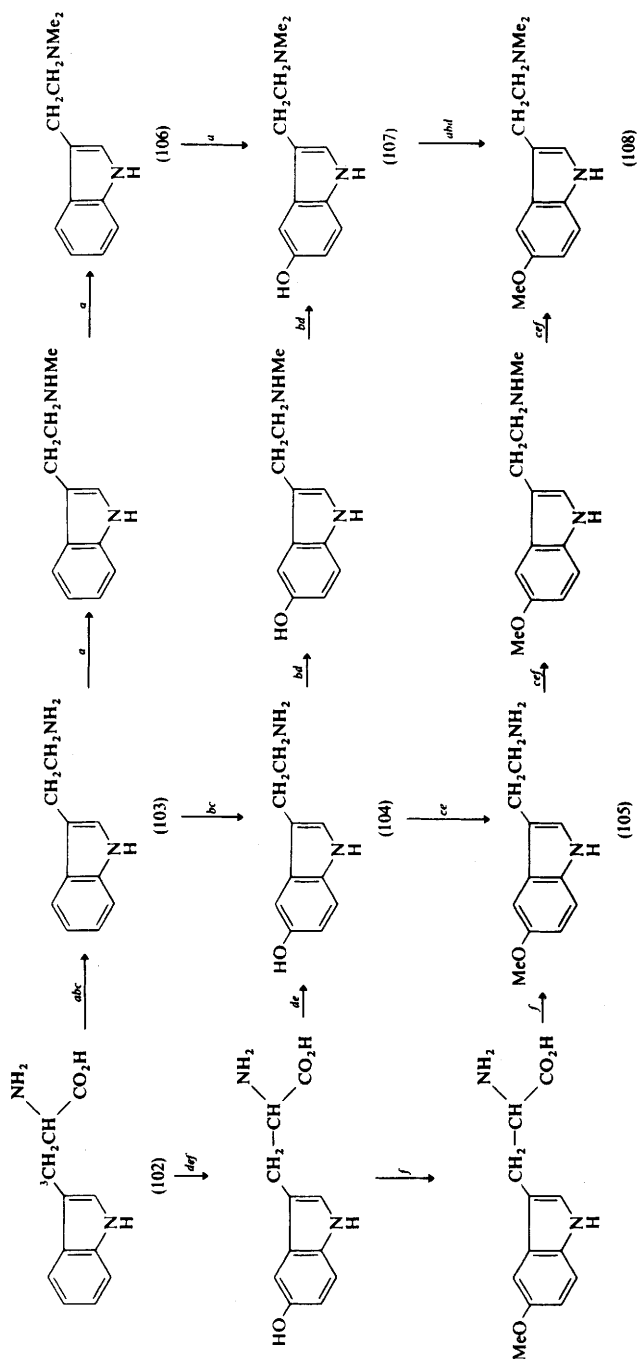
show that it is a precursor for ismine too. $[6,10\text{-}^3\text{H}_2; 12\text{-}^{14}\text{C}]$ Noroxomaritidine was incorporated into ismine (96) in *Sprekelia formosissima* with loss of the ^{14}C label and half the tritium originally present at C-6 which indicates, respectively, that C-12 is not retained as the *N*-methyl group of ismine and that hydrogen removal from C-6 of noroxomaritidine (99) was likely to be stereospecific. Results obtained using optically impure isomers ($>70\%$ pure though) of $(1'R)\text{-}[1'\text{-}^3\text{H}]\text{-O-methylnorbelladine}$ [as (88)] and $(6S)\text{-}[6\text{-}^3\text{H}]\text{noroxomaritidine}$ [as (99)] confirmed, without establishing rigorously, that this hydrogen removal was stereospecific and that, as in the conversion of haemanthamine (100) into haemanthidine (101),⁶⁷ it was the *pro-R* benzylic hydrogen that was lost.



4 Alkaloids Derived from Tryptophan

Dimethyltryptamine Derivatives.—Detailed investigation of the biosynthesis of even quite simple secondary metabolites can reveal complex and devious pathways, as for example in the biosynthesis of the cactus alkaloids.⁷⁸ Multiple

⁷⁸ A. G. Paul, *Lloydia*, 1973, **36**, 36; R. B. Herbert, in ref. 2, p. 16, in ref. 14, p. 16.



Scheme 13

pathways may be revealed as shown for example in a study of the biosynthesis of *NN*-dimethyltryptamine (106) and 5-methoxy-*NN*-dimethyltryptamine (108), the major alkaloids of *Phalaris tuberosa*.⁷⁹ A hypothetical metabolic grid can be constructed for their derivation from tryptophan with twelve intermediates (Scheme 13) if it is assumed that decarboxylation occurs only if a primary amino-function is present. Trace amounts of (102)—(105) and (107) were present in alkaloid extracts but none of the mono-*N*-methyl compounds could be detected, although enzymic evidence⁸⁰ points to *N*-methylation occurring in discrete steps. If it is assumed that the two *N*-methylations are immediately sequential then only six pathways, illustrated for the grid in Scheme 13, need to be considered.

A study of L-[3-¹⁴C]tryptophan [as (102)] and [3-¹⁴C]tryptamine [as (103)] uptake and incorporation into the alkaloids in relation to time showed that both are synthesized and turned over at the same rate. All the hypothetical grid-intermediates except the three mono *N*-methyl compounds were examined where relevant as precursors for (106) and (108) and, apart from *NN*-dimethyltryptamine (106), were found to be incorporated; it appeared that (106) was being transported to the site of alkaloid synthesis at a much lower rate than either (102) or (103). Dilution of activity from [¹⁴C]tryptophan into the alkaloids in the presence of added inactive grid compounds provided further evidence for their role as intermediates. It could be concluded that at least five of the six pathways to (108) could operate but whether these pathways functioned normally in the plant was not clear. Some of the problems, it was hoped, would be solved with cell-free systems; enzymic activity in cell-free systems has been demonstrated for *N*- and *O*-methylation⁸⁰ and for decarboxylation.⁸¹

Pyrrolnitrin.—Following a study with variously labelled tryptophan molecules a pathway for the biosynthesis of pyrrolnitrin (110) has been proposed (path *a*, Scheme 14).⁸² In this scheme entry of both chlorine atoms was assumed to occur at a late stage. This meant that chlorination of the pyrrole ring would have to take place in the 3-position rather than in the more electronically favourable 2- or 5-position. An alternative pathway (path *b*, Scheme 14) which obviates this difficulty was suggested.⁸³ This involves a 1,2-aryl shift in the conversion of (109) into pyrrolnitrin (110). However, examination of the ¹³C n.m.r. spectrum of pyrrolnitrin, after administration of DL-[3-¹³C]tryptophan, showed that C-3 of pyrrolnitrin originates from C-3 of the tryptophan side-chain.⁸³ The results of degradations of pyrrolnitrin derived from [3-¹⁴C]- and [3-¹⁴C, 2-³H]-tryptophan confirmed this conclusion. Thus no rearrangement of the tryptophan skeleton occurs during its biological transformation to pyrrolnitrin.

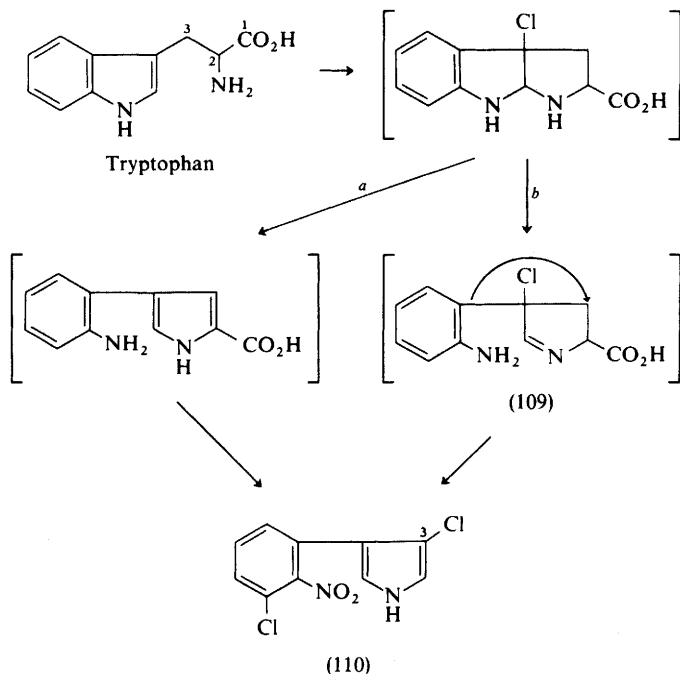
⁷⁹ C. Baxter and M. Slaytor, *Phytochemistry*, 1972, **11**, 2767.

⁸⁰ J. P. G. Mack and M. Slaytor, unpublished results.

⁸¹ C. R. Baxter and M. Slaytor, *Phytochemistry*, 1972, **11**, 2763.

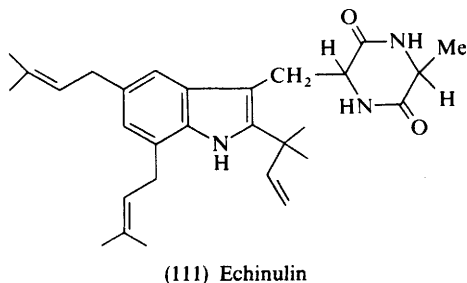
⁸² M. Gorman and D. H. Lively, in 'Antibiotics', ed. D. Gottlieb and P. D. Shaw, Springer-Verlag, Heidelberg, 1967, Vol. 2, p. 433; H. G. Floss, P. E. Manni, R. L. Hamill, and J. A. Mabe, *Biochem. Biophys. Res. Comm.*, 1971, **45**, 781; R. B. Herbert, in ref. 2, p. 13.

⁸³ L. L. Martin, C.-J. Chang, H. G. Floss, J. A. Mabe, E. W. Hagaman, and E. Wenkert, *J. Amer. Chem. Soc.*, 1972, **94**, 8942.



Scheme 14

Echinulin.—Echinulin (111) is derived in *Aspergillus amstelodami* from L-tryptophan,⁸⁴ alanine,⁸⁵ and mevalonic acid,⁸⁵ and the tryptophan derivative, *cyclo*-L-alanyl-L-tryptophanyl (112), serves as a more immediate precursor for echinulin than does tryptophan.⁸⁶ An enzyme, isolated from this fungus and partially purified, has been found to catalyse the transfer of the isoprene unit

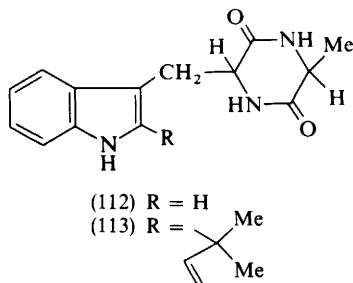


⁸⁴ J. C. MacDonald and G. P. Slater, *Canad. J. Microbiol.*, 1966, **12**, 455; A. J. Birch and K. R. Farrar, *J. Chem. Soc.*, 1963, 4277.

⁸⁵ A. J. Birch, G. E. Blance, S. David, and H. Smith, *J. Chem. Soc.*, 1961, 3128.

⁸⁶ G. P. Slater, J. C. MacDonald, and R. Nakashima, *Biochemistry*, 1970, **9**, 2886.

from 3-methyl-2-butenyl-1-pyrophosphate to *cyclo*-L-alanyl-L-tryptophanyl (112) to form a monoisoprenylated derivative tentatively identified as (113).⁸⁷ Formation of (113) in this way does not establish it as an intermediate in echinulin biosynthesis. However, when material labelled in the two side-chains was



administered to *A. amstelodami* it was incorporated into echinulin with high efficiency and without change in isotope ratio.⁸⁸ The enzymic product (113) is thus clearly implicated in echinulin biosynthesis.

Strychnine.—Although it has been established⁸⁹ that strychnine (117) is biosynthesized from geraniol and tryptophan along the pathway common to other indole alkaloids, and that the 2-carbon bridge (C-22, C-23) derives specifically from acetate, the later stages have remained obscure owing to difficulties in obtaining the correct conditions for significant incorporation of complex substrates like geissoschizine (114), the Wieland–Gumlich aldehyde (118), and diabolone (120). Successful incorporations of (114) and (118) have now been recorded⁹⁰ by growing young seedlings of *Strychnos nux vomica* for ca. 100 days after administration of the precursors, before terminating the experiments.

The incorporation of geissoschizine (114) suggests that the biosynthesis of strychnine closely parallels that of akuammicine (121):⁹¹ in the biosynthesis of this alkaloid in *Vinca rosea* it is the methoxycarbonyl group which is retained but it was felt, though not established, that here it may be the aldehyde function which remains. Although geissoschizal (115) could be isolated from *S. nux vomica* it was not incorporated into strychnine. This suggests that loss of the C₁ unit from geissoschizine (114) occurs after rearrangement of the *Corynanthé* to *Strychnos* skeleton and that dehydropreakuammicine (116) may be an intermediate on the pathway to strychnine (117).

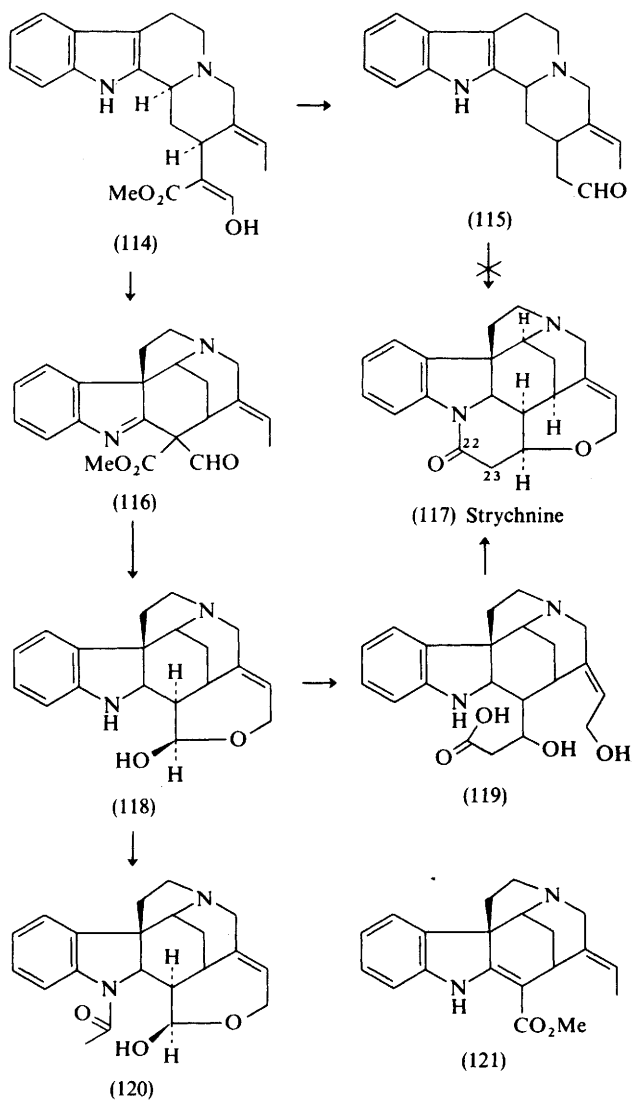
⁸⁷ C. M. Allen, jun., *Biochemistry*, 1972, **11**, 2154.

⁸⁸ C. M. Allen, jun., *J. Amer. Chem. Soc.*, 1973, **95**, 2386.

⁸⁹ Ch. Schlatter, E. E. Waldner, H. Schmid, W. Maier, and D. Gröger, *Helv. Chim. Acta*, 1969, **52**, 776.

⁹⁰ S. I. Heimberger and A. I. Scott, *J.C.S. Chem. Comm.*, 1973, 217.

⁹¹ A. R. Battersby and E. S. Hall, *Chem. Comm.*, 1969, 793; A. I. Scott, P. C. Cherry, and A. A. Qureshi, *J. Amer. Chem. Soc.*, 1969, **91**, 4932; A. I. Scott, *Accounts Chem. Res.*, 1970, **3**, 151; A. R. Battersby, in ref. 14, p. 43.



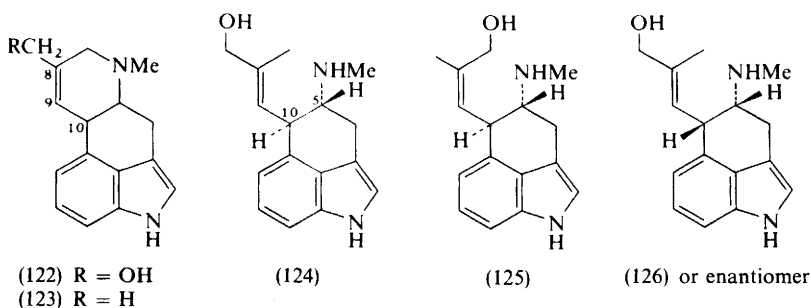
Although the incorporation of the Wieland–Gumlich aldehyde (118) confirms the pioneering ideas on strychnine biosynthesis,^{92,93} diaboline (120) does not lie on the pathway: it was not incorporated into strychnine and its presence in radioactive form was not apparent in an examination of *S. nux vomica* seedlings

⁹² R. B. Woodward, *Nature*, 1948, **162**, 155.

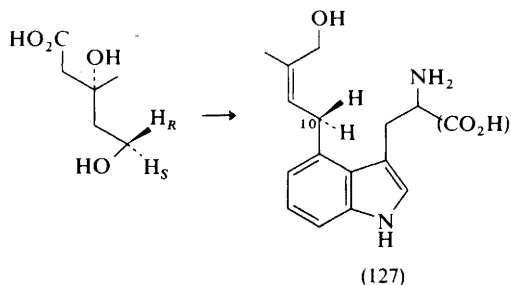
⁹³ R. Robinson, 'The Structural Relations of Natural Products', Oxford University Press, 1955, p. 112.

after administration of DL-[3-¹⁴C]tryptophan. This suggests that the 2-carbon bridge (C-22, C-23) of strychnine may be built in *via* (119). In support of this, an amino-acid was isolated from the plant which was converted into strychnine on treatment with dilute acid and to which the plausible structure (119) was thus assigned; it was more heavily labelled after administration of sodium [2-¹⁴C]-acetate than strychnine itself, which is in keeping with a product-precursor relationship between the two alkaloids.

Ergot.—The results of feeding experiments to *Claviceps* of (3*R*,5*R*)- and (3*R*,5*S*)-[5-³H]mevalonate are that elymoclavine (122), agroclavine (123), chanoclavine-I (124), isochanoclavine-I (125), and (–)-chanoclavine-II (126) are formed with retention of the *pro*-5*S* and loss of the *pro*-5*R* hydrogen.⁹⁴ This has meant abandonment of a unifying hypothesis for the biosynthesis of these alkaloids,

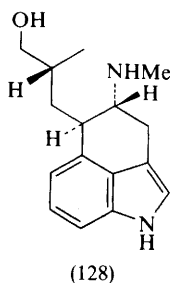


which in essence was that the stereochemistry of the alkaloids at C-5 and C-10 [as (124)] was defined in part by the stereochemistry of C-10 hydroxylation of an intermediate (127).⁹⁴



Dihydrochanoclavine-I (128), a metabolite of *Claviceps paspali*, has been shown by experiments with tritiated material to be convertible into chanoclavine-I (124) and other ergot alkaloids but the incorporation was so low that normally it is

⁹⁴ C. I. Abou-Chaar, H. F. Guenther, M. F. Manuel, J. E. Robbers, and H. G. Floss, *Lloydia*, 1972, **35**, 272; see also: M. Seiler, W. Acklin, and D. Arigoni, *Chem. Comm.*, 1970, 1394; M. Seiler, W. Acklin, and D. Arigoni, *Chimia (Switz.)*, 1970, **24**, 449.



probably a product of, rather than an intermediate in, ergot-alkaloid biosynthesis.⁹⁵

The transformation of chanoclavine-I (124) to elymoclavine (122) has been achieved with a cell-free extract of *Claviceps*⁹⁶ and a similar enzymic conversion of chanoclavine-I (124) into agroclavine (123) has also been effected.⁹⁷

Further feeding experiments⁹⁸ support the earlier conclusion⁹⁹ that isochanoclavine-I (125) is not an intermediate in ergot-alkaloid biosynthesis.

Experiments which have been directed towards elucidating the pathway between lysergic acid (129) and ergocryptine (132) have been inconclusive in *Claviceps* cultures.¹⁰⁰ The results with a cell-free system prepared from a strain of *Elymus*-type ergot fungus have been more definitive.¹⁰¹ Tritiated D-lysergyl-L-valine (130) and L-leucyl-L-proline lactam (131) were incorporated intact into the diastereoisomers ergocryptine/ergocryptinine (132). DL-[1-¹⁴C]Valine was also utilized, if less well, in the presence of elymoclavine (122) as a source of lysergic acid, and unlabelled D-lysergyl-L-valine methyl ester was found to suppress effectively the incorporation of [¹⁴C]elymoclavine into (132). These results clearly indicate that L-valine is built into ergocryptine/ergocryptinine *via* D-lysergyl-L-valine (130) in the cell-free system, and the pathway to ergocryptine/ergocryptinine (132) is from (129) *via* (130).

Simple clavine alkaloids, particularly agroclavine (123) and elymoclavine (122), are progenitors of the lysergic acid (129) moiety of more complex amide and peptide type ergot alkaloids.¹⁰¹⁻¹⁰³ Further results indicate that shift of the 8,9-double bond into the 9,10-position is not a first step.¹⁰³ The $\Delta^{8,9}$ -derivative

⁹⁵ S. Johnne, D. Gröger, P. Zier, and R. Voigt, *Pharmazie*, 1972, **27**, 801.

⁹⁶ E. O. Ogunlana, B. J. Wilson, V. E. Tyler, and E. Ramstad, *Chem. Comm.*, 1970, 775; R. B. Herbert, in ref. 14, p. 28.

⁹⁷ D. Gröger and P. Sajdl, *Pharmazie*, 1972, **27**, 188; R. Voigt and P. Zier, *ibid.*, p. 186.

⁹⁸ R. Voigt and P. Zier, *Pharmazie*, 1972, **27**, 773.

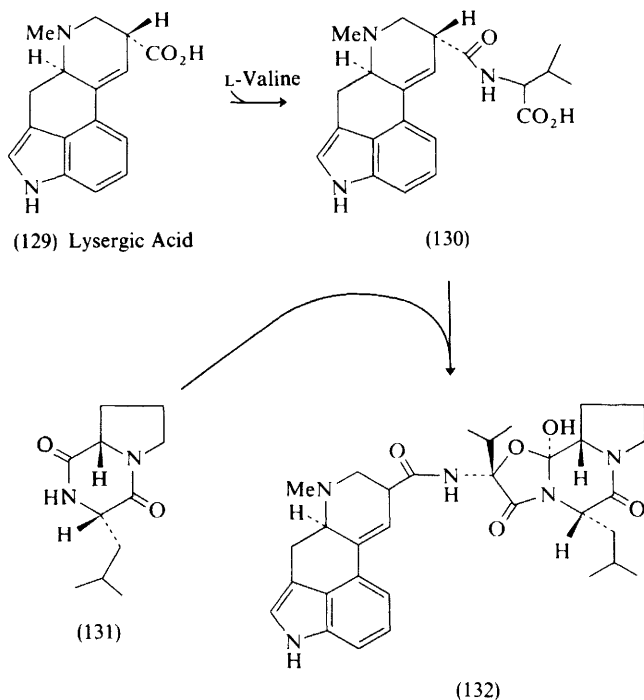
⁹⁹ T. Fehr, W. Acklin, and D. Arigoni, *Chem. Comm.*, 1966, 801; H. G. Floss, U. Horne-mann, N. Schilling, D. Gröger, and D. Erge, *Chem. Comm.*, 1967, 105.

¹⁰⁰ H. G. Floss, G. P. Basmadjian, M. Tcheng, D. Gröger, and D. Erge, *Lloydia*, 1971, **34**, 446; R. B. Herbert, in ref. 2, p. 7.

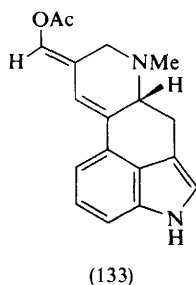
¹⁰¹ T. Ohashi, H. Takahashi, and M. Abe, *Nippon Nôgei Kagaku Kaishi*, 1972, **46**, 535.

¹⁰² K. Mothes, K. Winkler, D. Gröger, H. G. Floss, U. Mothes, and F. Weygand, *Tetra-hedron Letters*, 1962, 933; R. Voigt, M. Bornschein, and G. Rabitzsch, *Pharmazie*, 1967, **22**, 326.

¹⁰³ S. Agurell and M. Johansson, *Acta Chem. Scand.*, 1964, **18**, 2285; H. G. Floss, H. Günther, D. Gröger, and D. Erge, *Z. Naturforsch.*, 1966, **21b**, 128.



of lysergic acid is incorporated into lysergic acid amides but it is a less efficient precursor than lysergic acid (129) and the double bond isomerization also occurs spontaneously. In an attempt to establish the relevance of this incorporation and the point at which double-bond isomerization takes place, feeding experiments with $\Delta^{8,9}$ - and/or $\Delta^{9,10}$ -lysergylaldehyde were planned.¹⁰⁴ The preparation of these compounds got no further than (133), however. As the ergot fungus is



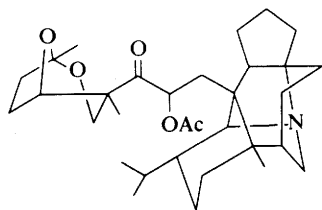
¹⁰⁴ C.-C. L. Lin, G. E. Blair, J. M. Cassady, D. Gröger, W. Maier, and H. G. Floss, *J. Org. Chem.*, 1973, **38**, 2249.

apparently able to cleave acetates, it was thought that $\Delta^{8,9}$ -lysergylaldehyde might be generated from (133) *in vivo*. In the event, incorporation of tritiated material was about as efficient as that of elymoclavine (122). It is likely then that double-bond isomerization takes place at or after the lysergylaldehyde stage.

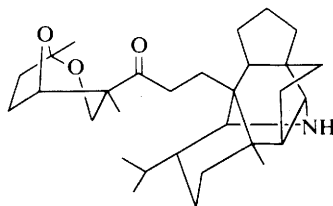
5 Terpenoid and Steroidal Alkaloids

Daphniphyllum Alkaloids.—Investigation of the biosynthesis of the *Daphniphyllum* alkaloids appears forbidding from an experimental viewpoint because of their complex structures and sparse functionality. However, by using the α -acetoxyketone function in a simple degradation of the daphniphylline (134), isolated after administration of suitably labelled mevalonic acid samples to *Daphniphyllum macropodum*, the number of mevalonic acid units involved could be determined and insight gained into the method of assemblage.¹⁰⁵

[2-¹⁴C]Mevalonic acid and [5-¹⁴C]mevalonic acid were incorporated into daphniphylline (134). Periodate cleavage of deacetoxydaphniphylline gave two fragments, the relative radioactivities of which were 4:2 from [2-¹⁴C]mevalonate and 5:1 from [5-¹⁴C]mevalonate; in each case the lower activity corresponds to



(134)



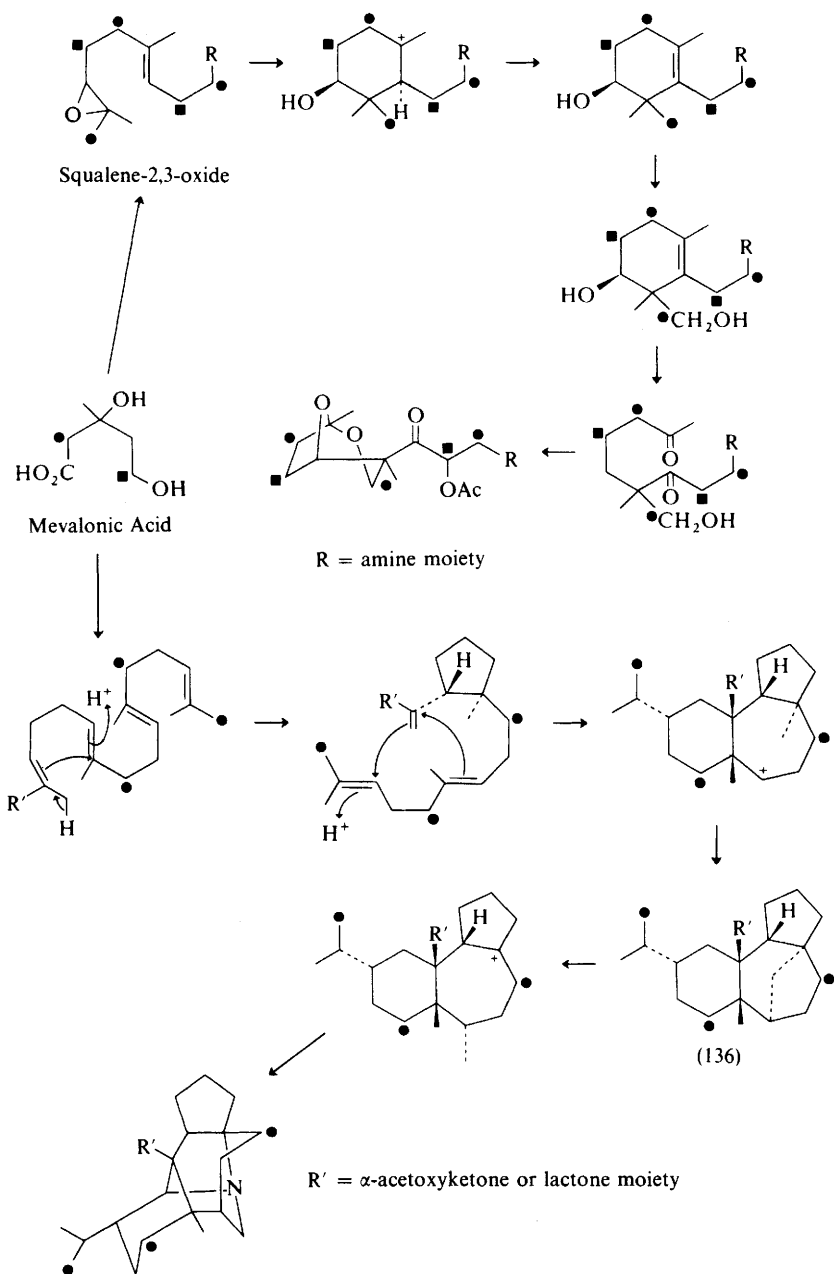
(135)

the moiety containing the lactol function. It is clear that six mevalonate units are involved in daphniphylline biosynthesis and a possible mode of biosynthesis was advanced consistent with the results and taking account of the structures of other daphniphylline alkaloids, *e.g.* secodaphniphylline (135) (Scheme 15).

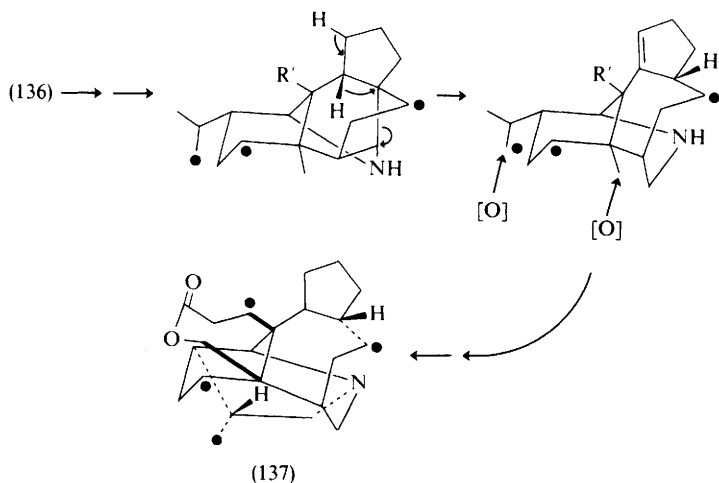
The biosynthesis of C_{22} triterpenoid alkaloids like daphnilactone-B (137) proceeds plausibly *via* C_{30} intermediates such as secodaphniphylline (135). This has been tested for with daphnilactone-B in *D. teijsmanni* by use of RS-[2-¹⁴C] mevalonic acid.¹⁰⁶ A partial degradation of the derived alkaloid indicated that a quarter of the activity was located at the secondary methyl group of (137), from which it can be concluded that four mevalonic acid units are incorporated into daphnilactone-B. A tentative pathway *via* secodaphniphylline was proposed (see Scheme 16).

¹⁰⁵ K. T. Suzuki, S. Okuda, H. Niwa, M. Toda, Y. Hirata, and S. Yamamura, *Tetrahedron Letters*, 1973, 799.

¹⁰⁶ H. Niwa, Y. Hirata, K. Suzuki, and S. Yamamura, *Tetrahedron Letters*, 1973, 2129.

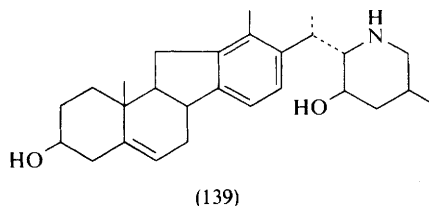
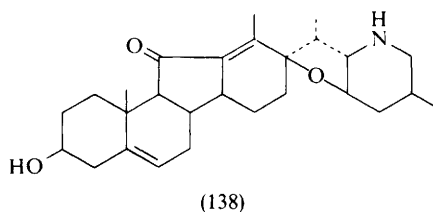


Scheme 15



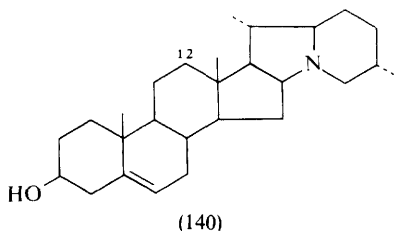
Scheme 16

Steroidal Alkaloids.—Previously presented evidence has indicated that the C-nor-D-homosteroidal alkaloids, e.g. jervine (138), derive biologically from a C_{27} precursor with a normal steroid skeleton.¹⁰⁷ It was suggested^{107,108} that an important intermediate in the formation of C-nor-D-homo-steroidal alkaloids could be solanidine (140) derivative with an equatorial hydroxy-group at C-12 which could serve as an initiation point for rearrangement. Accordingly the role of solanidine (140) as a precursor for veratramine (139) and jervine (138) has been



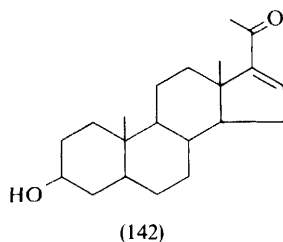
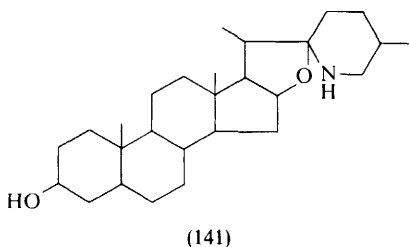
¹⁰⁷ K. Kaneko, H. Mitsuhashi, K. Hirayama, and N. Yoshida, *Phytochemistry*, 1970, 9, 2489; R. B. Herbert, in ref. 2, p. 41.

¹⁰⁸ C. R. Narayanan, *Fortschr. Chem. org. Naturstoffe*, 1962, 20, 298.



examined.¹⁰⁹ When mature *Veratrum grandiflorum* plants were fed with [1-¹⁴C]-acetate in the dark, radioactive solanidine glycoside accumulated in the leaves and disappeared when the plants were subsequently illuminated. The radioactivity appeared then in jervine (138) and veratramine (139). A clear precursor-product relationship between solanidine (140) and the C-nor-D-homo-steroidal bases, (138) and (139), is indicated, albeit under artificial conditions. A similar experiment was carried out with etiolated plants at the budding stage and here a less rapid conversion was observed. However, a new radioactive compound was isolated which was thought to be a hydroxy-solanidine.

Tomatine, the glycoside of tomatidine (141), has been shown to be synthesized mainly in the leaves of tomato plants and to be degraded in the ripening fruits.¹¹⁰ The main product of catabolism has been shown to be an allopregnenolone (142)



derivative, probably the glycoside.¹¹¹ Experiments with cultured tomato roots have shown that there is a close quantitative relationship between the amount of alkaloid and root growth.¹¹²

6 Miscellaneous Aliphatic Bases

Betalaines.—Tyrosine (143) and dopa (144) are sequential precursors for the betalaines, e.g. betanine (145). It has been shown¹¹³ that incorporation of dopa

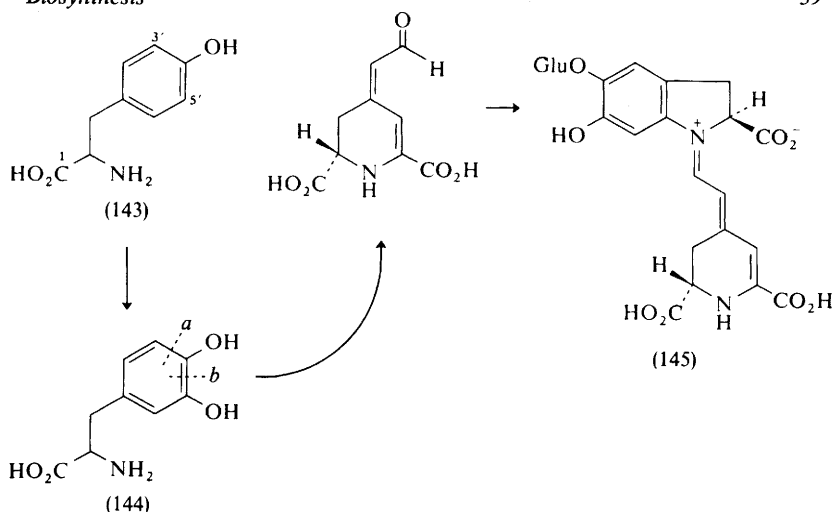
¹⁰⁹ K. Kaneko, M. Watanabe, S. Taira, and H. Mitsuhashi, *Phytochemistry*, 1972, **11**, 3199.

¹¹⁰ H. Sander, *Planta*, 1956, **47**, 374.

¹¹¹ E. Heftmann and S. Schwimmer, *Phytochemistry*, 1972, **11**, 2783.

¹¹² J. G. Roddick and D. N. Butcher, *Phytochemistry*, 1972, **11**, 2991.

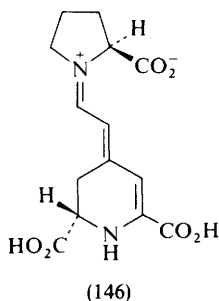
¹¹³ N. Fischer and A. S. Dreiding, *Helv. Chim. Acta*, 1972, **55**, 649; R. B. Herbert, in ref. 2, p. 8.



Scheme 17

into betanine (145) involves cleavage of the aromatic ring, as indicated in Scheme 17, by dotted line *a*. This pathway should result in retention of exactly half the tritium originally present in a sample of [$1\text{-}^{14}\text{C}$; $3',5'\text{-}^3\text{H}_2$]tyrosine [as (143)] whilst cleavage along dotted line *b* should result in complete loss of tritium. As more than half the tritium was lost into betanine (145), however, operation of cleavage mode *b* in addition to *a* could not be excluded.

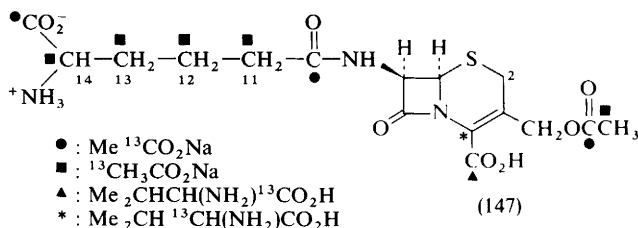
A more recent study¹¹⁴ on the incorporation of [$1\text{-}^{14}\text{C}$; $3',5'\text{-}^3\text{H}_2$]tyrosine, this time with indicaxanthin (146) in *Opuntia ficus indica*, has concluded that almost



exactly half the tritium originally present in the tyrosine is retained in this betalaine. Convincing evidence is thus provided for a single mode of cleavage of dopa leading to the betalaines: fission along dotted line *a* in (144).

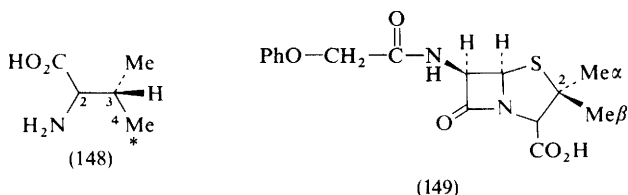
¹¹⁴ G. Impellizzeri and M. Piattelli, *Phytochemistry*, 1972, **11**, 2499.

Cephalosporin C.—Construction of the cephalosporin skeleton from simple units has been examined using ^{13}C -labelled precursors. The first results obtained were with $[1-^{13}\text{C}]$ - and $[2-^{13}\text{C}]$ -acetate, and DL- $[1-^{13}\text{C}]$ - and DL- $[2-^{13}\text{C}]$ -valine, see Scheme 18;¹¹⁵ they confirm and extend those obtained earlier with ^{14}C -labelled materials.¹¹⁶ The higher degree of labelling with $[2-^{13}\text{C}]$ acetate of C-14 compared with C-11, C-12, and C-13, which were similar, suggested that the α -amino adipoyl side-chain of cephalosporin C (147) was constructed from α -ketoglutaric acid and acetylcoenzyme A.



Scheme 18

More recently, valine with a chiral ^{13}C label at C-4 has been used to determine the fate of the isopropyl group during formation of the cephalosporin nucleus.¹¹⁷ (2*RS*, 3*R*)- $[4-^{13}\text{C}]$ Valine (148) was administered to *Cephalosporium acremonium*. The ^{13}C n.m.r. spectrum of the isolated cephalosporin showed that the label was located exclusively at C-2. (2*RS*, 3*R*)- $[4-^{13}\text{C}]$ Valine was also incorporated into penicillin V (149) in *Penicillium chrysogenum* with specific labelling of the β -methyl group at C-2.¹¹⁸



Mitomycins.—The mitomycins, *e.g.* mitomycin A (150), are a group of anti-tumour antibiotics produced by several *Streptomyces* strains. Early work on the

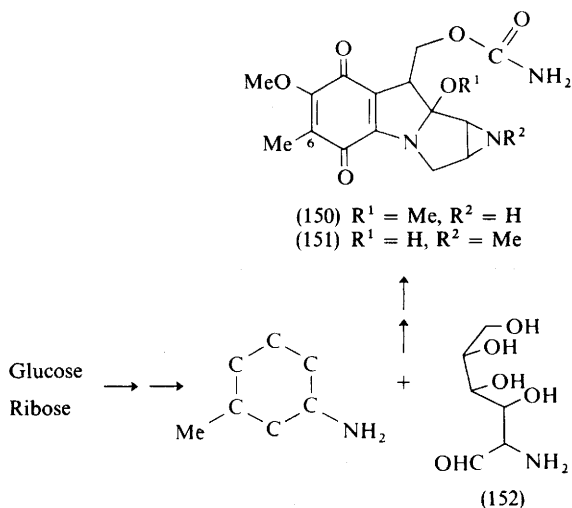
¹¹⁵ N. Neuss, C. H. Nash, P. A. Lemke, and J. B. Grutzner, *J. Amer. Chem. Soc.*, 1971, **93**, 2337; N. Neuss, C. H. Nash, P. A. Lemke, and J. B. Grutzner, *Proc. Roy. Soc.*, 1971, **B179**, 335.

¹¹⁶ P. W. Trown, B. Smith, and E. P. Abraham, *Biochem. J.*, 1963, **86**, 284; P. W. Trown, E. P. Abraham, G. G. F. Newton, C. W. Hale, and G. A. Miller, *Biochem. J.*, 1962, **84**, 157.

¹¹⁷ N. Neuss, C. H. Nash, J. E. Baldwin, P. A. Lemke, and J. B. Grutzner, *J. Amer. Chem. Soc.*, 1973, **95**, 3797.

¹¹⁸ P. A. Lemke, C. H. Nash, and S. W. Pieper, *J. Gen. Microbiol.*, in the press; quoted in ref. 117.

elaboration of these metabolites by *S. verticillatus* had established: (i) radioactive methionine labelled the *O*-methyl groups but not the *C*-methyl group;^{119,120} (ii) label was efficiently incorporated into the carbamoyl function following administration of L-[guanido-¹⁴C]arginine;¹²⁰ (iii) tryptophan, phenylalanine, and shikimic acid, although taken up by the mycelium, were not incorporated into the mitomycins, thus excluding aromatic precursors; (iv) mevalonate, acetate, propionate, D-arabinose, D-xylose, and various C₁ units were not utilized; (v) D-[1-¹⁴C]glucosamine [as (152)] was efficiently incorporated into mitomycin A (150); a Kuhn–Roth oxidation gave inactive acetic acid. High tritium retentions were observed with [¹⁴C,³H]-labelled glucosamine samples: 1-¹⁴C,6-³H: 91%; 1-¹⁴C,1-³H: 78%. [*U*-¹⁴C]Ribose was slightly less well incorporated than glucosamine, as was similarly labelled glucose. Kuhn–Roth oxidation of the mitomycin A isolated after the ribose feed gave acetic acid with 13% of the label in the derived acetic acid [calculated 20% or 40% for intact incorporation into a C₇ unit (Scheme 19)]. Hydrolytic studies showed that the glucose label was confined to the carbon skeleton. The pathway shown in Scheme 19 could then be adduced.¹²⁰



Scheme 19

Recent work has allowed clearer delineation of the role of glucosamine [as (152)] in mitomycin biosynthesis.¹²¹ The D-isomer was found to be more efficiently incorporated than the related hexosamines, D-galactosamine and D-mannosamine, whereas L-glucosamine was incorporated to an insignificant

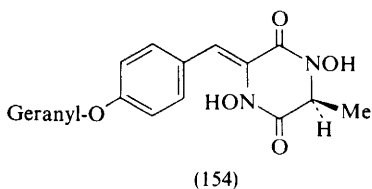
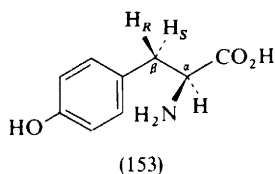
¹¹⁹ E. J. Kirsch and J. D. Korshalla, *J. Bacteriol.*, 1964, **87**, 247.

¹²⁰ U. Hornemann and J. C. Cloyd, *Chem. Comm.*, 1971, 301.

¹²¹ U. Hornemann and M. J. Aikman, *J.C.S. Chem. Comm.*, 1973, 88.

extent, although taken up by the mycelium. The incorporations of galactosamine and mannosamine were rationalized as proceeding *via* D-glucosamine. D-[1- ^{14}C , ^{15}N]Glucosamine was converted into mitomycin B (151) with little loss of ^{15}N label and with as much as 77% of it located at the aziridine nitrogen. Further support is provided therefore for the route outlined in Scheme 19. The preferential incorporation of the D-isomer of glucosamine into the mitomycins is interesting, for D-glucosamine occurs in a variety of other antibiotics.¹²²

Mycelianamide.—The conversion of tyrosine (153) into the mould product mycelianamide (154) involves the formal desaturation of this precursor molecule. The steric course of this reaction has been studied¹²³ as part of a general investigation of the stereochemistry of this and similar reactions in the metabolism of aromatic amino-acids.¹²⁴ Various samples of tyrosine tritiated on the β -methylene carbon in admixture with [U - ^{14}C]- and [α - ^{14}C]-tyrosine were administered to *Penicillium griseofulvum* and the derived mycelianamide (154) was



assayed for radioactivity. Retention of almost half the tritium in the conversion of (β -*R,S*)-[β - ^3H]tyrosine [as (153)] into mycelianamide (154) indicated that the reaction was stereospecific and, from the complete loss of activity from (β -*S*)-[β - ^3H]tyrosine [as (153)] in contrast to a high retention of tritium in the (β -*R*)-isomer, the reaction could be regarded formally as requiring *cis* removal of hydrogen from the L-form of tyrosine; it was clear from the $^{14}\text{C}/^3\text{H}$ values obtained that tyrosine was built into mycelianamide in its entirety.

The observed partial loss of (β -*R*)-tritium may, it was suggested, arise by an exchange process similar to that observed with phenylalanine in *Trichoderma viride*. [The previously reported results¹²⁵ are incorrect: it is the (*pro-R*)- and not the (*pro-S*)- β -methylene hydrogen which undergoes exchange.]

7 Miscellaneous Aromatic Bases

Dolichotheline.—Dolichotheline (155) isolated from the cactus *Dolichothele sphaerica* arises by the union of histamine and isovaleric acid, the latter being

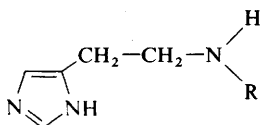
¹²² 'Index of Antibiotics from Actinomycetes', ed. H. Umezawa, University Park Press, State College, Pennsylvania, 1967.

¹²³ G. W. Kirby and S. Nayaranaswami, *J.C.S. Chem. Comm.*, 1973, 322.

¹²⁴ G. W. Kirby and J. Michael, *J.C.S. Perkin I*, 1973, 115.

¹²⁵ J. D. Bu'Lock, A. P. Ryles, N. Johns, and G. W. Kirby, *J.C.S. Chem. Comm.*, 1972, 100; R. B. Herbert, in ref. 2, p. 13.

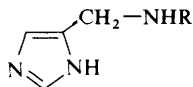
involved plausibly *via* its CoA derivative.¹²⁶ The potential of this plant to synthesize dolichotheline derivatives from unnatural precursors has been tested¹²⁷ with the same motives as those discussed above under morphine. The substrates tested were isobutyric acid, isocaproic acid, benzoic acid, 4(5)-aminomethylimidazole (158), and *N*-isopropylhistamine (156). They were administered with radioactive labelling and in each case where products were obtained the conversions were established to have taken place without scrambling of label.



(155) R = Me₂CHCH₂CO—

(156) R = Me₂CH—

(157) R = Me₂CHCH₂CH₂CO—

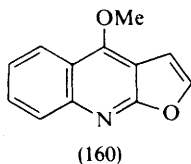


(158) R = H

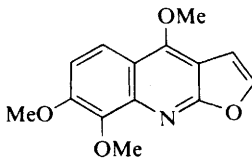
(159) R = Me₂CHCH₂CO—

Of the five compounds tested only two, isocaproic acid and 4(5)-aminomethylimidazole, were transformed into unnatural alkaloids, (157) and (159), respectively, for which similar yields were recorded. The plant enzymes are thus able to utilize substrates with one more or one less methylene group than the natural progenitors of dolichotheline in the synthesis of unnatural analogues. It was suggested that the failure of isobutyric acid to be converted into a dolichotheline analogue may have been due to diversion into normal metabolism *via* isobutyryl-CoA.

Quinoline Alkaloids.—The simplest hypothesis for the biosynthesis of the hydroxylated furanoquinoline alkaloids is that they arise after formation of the furanoquinoline skeleton, *e.g.* that skimmianine (161) arises by hydroxylation of dictamnine (160). Evidence to support this view, however, has not been convincing.¹²⁸ *e.g.*, the incorporation of dictamnine into skimmianine in *Skimmia japonica* is low.¹²⁹ When, however, this conversion was examined in *Choisya ternata* and a *Skimmia* variety which, in contrast to *S. japonica*, contains



(160)



(161)

¹²⁶ H. Rosenberg and A. G. Paul, *Lloydia*, 1971, **34**, 372; R. B. Herbert, in ref. 2, p. 17.

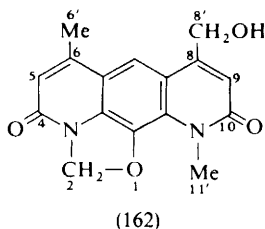
¹²⁷ H. Rosenberg and A. G. Paul, *J. Pharm. Sci.*, 1973, **62**, 403.

¹²⁸ R. B. Herbert, in ref. 2, p. 34.

¹²⁹ J. F. Collins and M. F. Grundon, *Chem. Comm.*, 1969, 621; R. B. Herbert, in ref. 14, p. 12.

skimmianine as a major alkaloid and dictamnine as a minor one, efficient incorporations were obtained.¹³⁰ A major pathway to skimmianine (161) is thus demonstrated as involving the hydroxylation of dictamnine (160).

Nybomycin.—Nybomycin, a metabolite of a *Streptomyces* species, has the unique structure (162). Its biosynthesis has been investigated using ¹⁴C- and ¹³C-labelled precursors, the latter providing information that was not obtainable by degradation in the classical manner.¹³¹ Thus whilst it could be shown that carbons 6' and 8' originated from label in [2-¹⁴C]acetic acid and those at C-6



and C-8 were labelled by [1-¹⁴C]acetic acid, little further information could be adduced. Sodium [1-¹³C]acetate was also incorporated into nybomycin. In the ¹³C n.m.r. spectrum of nybomycin butyrate the separate signals for C-4, C-6, C-8, and C-10 were of approximately equal intensity. Thus the exterior carbon atoms of both pyridone rings are each derived *equally* from identical C₄ acetate-derived units. It was further clear from the ¹³C n.m.r. spectrum that the central ring is not acetate-derived.

Degradation after administration of [methyl-¹⁴C]methionine showed not unexpectedly that C-2 and C-11' only were derived from methionine.

Benzoxazinones.—1,4-Benzoxazin-3-ones have been isolated from maize, wheat, and rye.¹³² One member of this family, 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (euphonically abbreviated to DIMBOA) (163), is a feeding deterrent for the European corn borer¹³³ and is active also against a pathogenic fungus.¹³⁴

DIMBOA (163) has been deduced to be built up from an aromatic unit derived from shikimic acid and a C₂ unit derived from ribose, carbons 2 and 3 of the oxazine ring arising respectively from carbons 2 and 1 of ribose.¹³⁵ Recent experiments¹³⁶ have been directed towards identifying intermediates between

¹³⁰ J. F. Collins, W. J. Donnelly, M. F. Grundon, D. M. Harrison, and C. G. Spyropoulos, *J.C.S. Chem. Comm.*, 1972, 1029.

¹³¹ W. M. J. Knöll, R. J. Huxtable, and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1973, **95**, 2703.

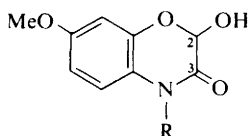
¹³² O. Wahlroos and A. I. Virtanen, *Acta Chem. Scand.*, 1959, **13**, 1906; A. I. Virtanen and P. K. Hietala, *Acta Chem. Scand.*, 1960, **14**, 499, 502.

¹³³ J. A. Klun, C. L. Tipton, and T. A. Brindley, *J. Econ. Entomol.*, 1967, **60**, 1529.

¹³⁴ R. M. Couture, D. G. Routley, and G. M. Dunn, *Physiol. Plant Path.*, 1971, **1**, 515.

¹³⁵ J. E. Reimann and R. U. Byerrum, *Biochemistry*, 1964, **3**, 847.

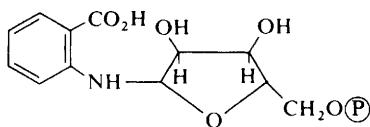
¹³⁶ C. L. Tipton, M.-C. Wang, F. H.-C. Tsao, C.-C. L. Tu, and R. R. Husted, *Phytochemistry*, 1973, **12**, 347.



(163) R = OH

(164) R = H

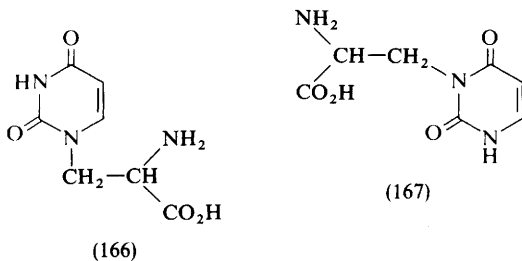
shikimic acid and the benzoxazinones. The results are that whereas both [^{15}N]- and [$1\text{-}^{14}\text{C}$]-anthranilic acids are efficient precursors (low dilution of isotope), [^3H]-3-hydroxyanthranilic acid and [^{14}C]-*o*-aminophenol were not incorporated even when inhibitors for breakdown of *o*-aminophenol were present. Thus anthranilic acid appears to be an immediate precursor and the next intermediate may be *N*-(5'-phosphoribosyl)anthranilate (165), also an intermediate in tryptophan biosynthesis.



(165)

A study of the relationships of the benzoxazinones [as (163)] and *N*-hydroxybenzoxazinones [as (164)] has shown that they are interconvertible and the reactions probably proceed *via* the glucosides.¹³⁶

Pyrimidines.—The plant pyrimidinyl amino-acids willardiine (166) and isowillardiine (167) have been found to arise from serine and uracil.¹³⁷ [$3\text{-}^{14}\text{C}$]Serine was incorporated into the side-chains whereas [$6\text{-}^{14}\text{C}$]orotic acid and [$2\text{-}^{14}\text{C}$]uracil served as precursors for the pyrimidine nuclei. This is in contrast to lathyrine (168) which is derived intact biologically from acyclic precursors, homoarginine (169) and 4-hydroxyhomoarginine (170);¹³⁸ DL-[*guanido*- ^{14}C]-*trans*-4,5-dehydrohomoarginine is not a precursor.¹³⁹



(166)

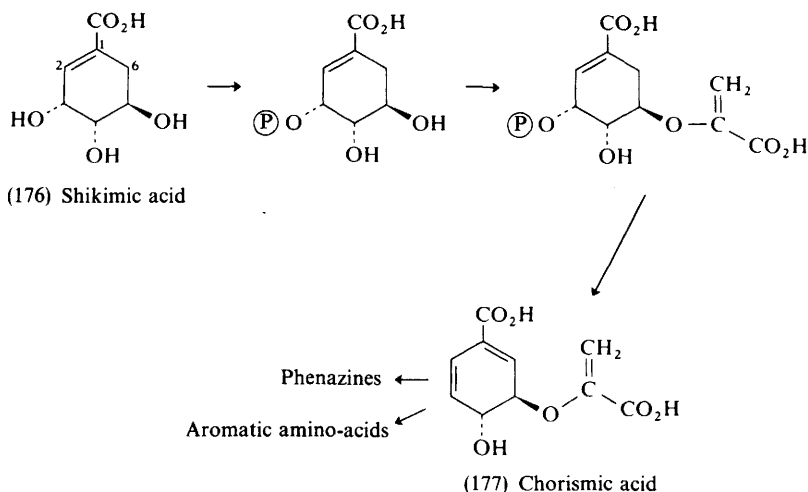
(167)

¹³⁷ T. S. Ashworth, E. G. Brown, and F. M. Roberts, *Biochem. J.*, 1972, **129**, 897.

¹³⁸ E. A. Bell, *Nature*, 1963, **199**, 70; E. A. Bell and J. Przybylska, *Biochem. J.*, 1965, **94**, 35P.

¹³⁹ R. C. Hider and D. I. John, *Phytochemistry*, 1973, **12**, 119.

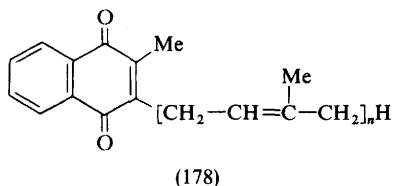
aromatic amino-acids between shikimic acid (176) and chorismic acid (177) inclusive, and most probably it is chorismic acid which is the last metabolic intermediate common to aromatic amino-acid and phenazine biosynthesis (Scheme 20). The previously obtained results indicating that chorismic acid (177)



Scheme 20

was not a pyocyanin precursor^{142,143} are seen to be due to the failure of this compound to be transported across the cell wall.¹⁴⁵ It is notable that in the biosynthesis of naphthoquinones derived from shikimic acid,¹⁴⁶ e.g. vitamin K₂ (178), the branch-point is also at chorismic acid.¹⁴⁷

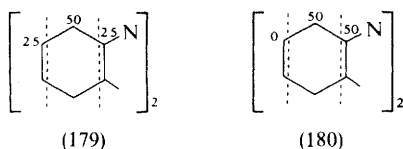
Administration of [1,6-¹⁴C₂]shikimic acid [as (176)] to *Brevibacterium iodinum* gave iodinin (173), in which the carbon skeleton was labelled as shown in (179).¹⁴¹ Results which differed from these were obtained for pyocyanin (175) and phenazine-1-carboxylic acid (174) from similarly labelled shikimic acid.¹⁴⁴ The distribution of activity was shown to be as in (180). A detailed analysis of the possible modes of linking the two shikimic acid units¹⁴⁸ to give a common intermediate



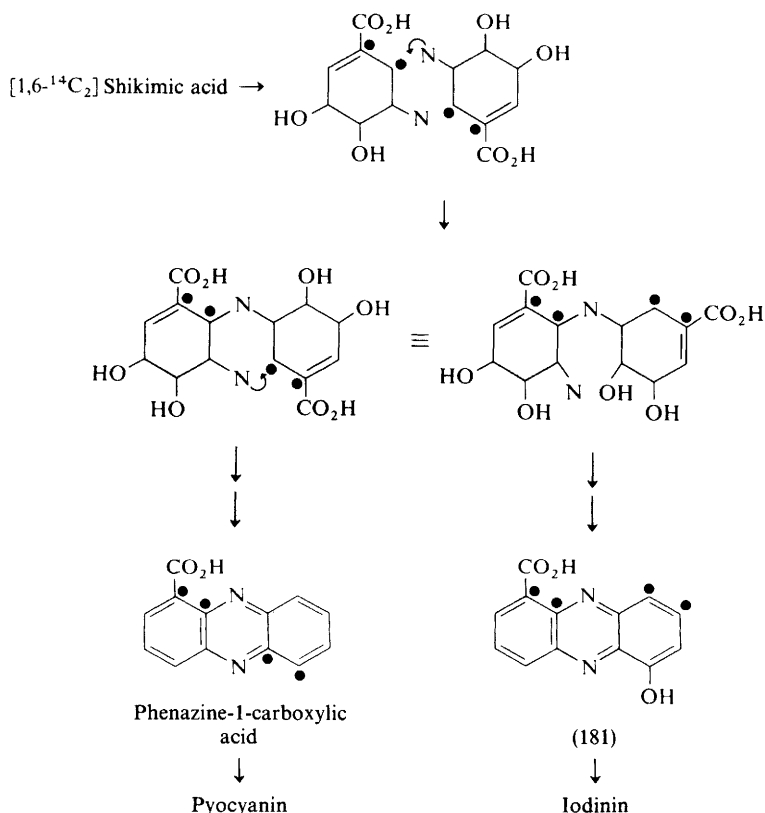
¹⁴⁶ M. H. Zenk and E. Leistner, *Lloydia*, 1968, **31**, 275.

¹⁴⁷ P. Dansette and R. Azerad, *Biochem. Biophys. Res. Comm.*, 1970, **40**, 1090.

¹⁴⁸ F. G. Holliman, unpublished work. Quoted in ref. 144.



for iodinin (173) on the one hand, and pyocyanin (175) and (174) on the other, can be made. If it is assumed that the phenazine ring system is formed from two identical nitrogen-containing units, and the results suggest that they are identical for iodinin at least, then only one arrangement is possible, illustrated in Scheme 21;¹⁴⁴ the proposed pathway takes into account the known intermediacy of 6-hydroxyphenazine-1-carboxylic acid (181) in iodinin (173)^{143,149} biosynthesis



Scheme 21

¹⁴⁹ R. B. Herbert, F. G. Holliman, and P. N. Ibberson, *J.C.S. Chem. Comm.*, 1972, 355.

and of phenazine-1-carboxylic acid (174) in pyocyanin biosynthesis.^{143,150} There are several unusual features in this scheme and its validity needs to be tested in further experiments. In particular, those with suitable singly labelled shikimic acid precursors could prove definitive.

¹⁵⁰ M. E. Flood, R. B. Herbert, and F. G. Holliman, *J.C.S. Perkin I*, 1972, 622.

A review of the general area of alkaloid isolation work with implications for the future contains information relevant to these structure types.¹

1 Pyrrolidine Alkaloids

The roots of nine *Datura* species have been re-examined and the presence of cuscohygrine (1) in all of them has been confirmed.² The inclusion of this genus in the tribe Datureae is supported on the basis of phytochemical correlation. Cuscohygrine has also been isolated from the roots of *Convolvulus erinacius*,³ *Cyphomandra betacea*,⁴ and *Scopolia tangutica*.⁵

Bracken (*Pteridium aquilinum*) has yielded pterolactam (2), which was characterized by spectral data.⁶ It has not been established whether or not pterolactam is responsible for the known carcinogenic properties of this plant.

The identity of desdaine (3) (*Streptomyces caelestis* and *S. desdanus*), pyracrimycin A (*S. eridani*), and cyclamidomycin (an undefined *Streptomyces* strain) has been established.⁷ The name desdaine is now proposed for future use when referring to this antimicrobial agent. Two other antibiotics, kikumycin A (4; R = H) and B (4; R = Me), have been isolated from *S. phaeochromogenes*.⁸ These compounds are additional examples of the 'pyrrole-amidine' type and their structures have been determined by chemical and spectral means. In particular, the amino-acid sequence may be established from the sequential fragmentation of CO—NH bond cleavage observed in the mass spectrum.

Double-resonance n.m.r. studies have been used to assign the stereochemistry of codonopsine (5; R = OMe) and codonopsinine (5; R = H).⁹

¹ H.-L. Li and J. J. Willaman, *Econ. Botany*, 1972, **26**, 61.

² W. C. Evans, A. Ghani, and V. A. Woolley, *Phytochemistry*, 1972, **11**, 2527.

³ S. F. Aripova, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, 401 (*Chem. Abs.*, 1972, **77**, 162 010v).

⁴ W. C. Evans, A. Ghani, and V. A. Woolley, *J.C.S. Perkin I*, 1972, 2017.

⁵ S. A. Minina and I. Barene, *Biol. Aktiv. Veshchestva Flory Fauny Dal'n. Vost. Tikhogo Okeana*, 1971, 22 (*Chem. Abs.*, 1972, **77**, 111 461k).

⁶ K. Takatori, S. Nakano, S. Nagata, K. Okumura, I. Hirono, and M. Shimizu, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1087.

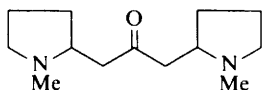
⁷ A. D. Argoudelis, H. Hoeksema, and H. A. Whaley, *J. Antibiotics*, 1972, **25**, 432.

⁸ T. Takaishi, Y. Sugawara, and M. Suzuki, *Tetrahedron Letters*, 1972, 1873.

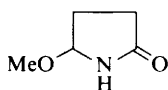
⁹ M. R. Yagudaev, S. F. Matkhalikova, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 495 (*Chem. Abs.*, 1972, **77**, 164 902m).

Trichonine (6) has been synthesized using a Wittig reaction as the key step.¹⁰

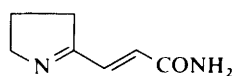
The pharmacology of cuscohygrine (1)⁵ and codonopsine (5; R = OMe)¹¹ has been studied.



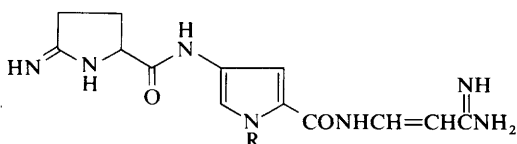
(1)



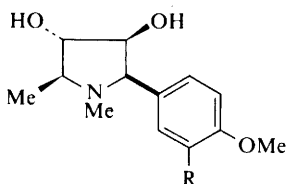
(2)



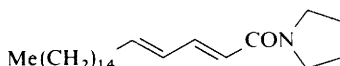
(3)



(4)



(5)



(6)

2 Piperidine Alkaloids

A review dealing with phytochemical and biosynthetic studies of alkaloids of *Conium maculatum* offers the suggestion that these compounds function as part of coenzymes in redox processes analogous to those of nicotinic acid during active growth of the plant.¹² A review describes the application of solution and solid-state i.r. spectroscopy in the Bohlmann band region to conformational problems.¹³ Heats of combustion and formation of coniine are given in a review of thermodynamic properties of a variety of organic compounds.¹⁴

Apart from sedamine [7; R¹ = H, R² = Me, R³ = CH₂CH(OH)Ph], sedridine [7; R¹ = R² = H, R³ = CH₂CH(OH)Ph], and sedinine [7; R¹ = R³ = CH₂CH(OH)Ph, R² = Me, 3,4-double bond] obtained from *Sedum acre*,¹⁵ some interesting structural variations from the norm have been discovered

¹⁰ B. Vig and A. C. Mahajan, *Indian J. Chem.*, 1972, **10**, 564.

¹¹ M. T. Khanov, M. B. Sultanov, and T. A. Egorova, *Farmakol. Alkaloidov Serdech. Glikoyidov*, 1971, 210 (*Chem. Abs.*, 1972, **77**, 135 091r).

¹² J. W. Fairbairn, *Biol. Chem. Umbelliferae, Internat. Symposium*, 1970, ed. V. H. Heywood, Academic Press, London, 1971, p. 361.

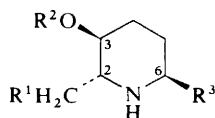
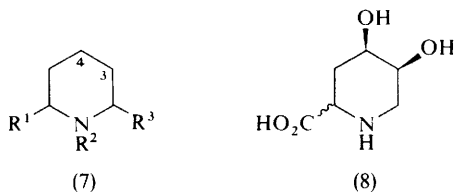
¹³ T. K. Yunusov, A. P. Matveeva, V. B. Leont'ev, F. G. Kamaev, Kh. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1972, 200 (*Chem. Abs.*, 1972, **77**, 19 842n).

¹⁴ E. S. Domalski, *J. Phys. Chem. Ref. Data*, 1972, **1**, 221.

¹⁵ As. Z. Gulubov and Il. Zl. Bozhkova, *Nauch. Tr., Plovdivski Univ., Mat., Fiz., Khim., Biol.* 1972, **10**, 101 (*Chem. Abs.*, 1973, **78**, 13 761j).

during the past year. 4,5-Dihydroxy-L-pipecolic acid (8) has been isolated from *Calliandra haematocephala*.¹⁶ The gross structure (8) rests on spectral data, chemical degradation, and synthesis, the last being effected by osmium tetroxide hydroxylation of L-baikaine (7; $R^1 = \text{CO}_2\text{H}$, $R^2 = R^3 = \text{H}$, 3,4-double bond) which gave a mixture of two isomers one of which was identical with the natural product. The absolute configuration of (8) is being determined by X-ray analysis. During biosynthetic studies on hemlock (*Conium maculatum*), a new alkaloid (\pm)-conhydrinone (7; $R^1 = R^2 = \text{H}$, $R^3 = \text{CH}_2\text{COMe}$) was isolated and its structure was established by synthesis.¹⁷

Full accounts of the structure and stereochemistry of prosopine (9a) and prosopinine (9b), as well as of the new alkaloids isoprosopinine A (9c), isoprosopinine B (9d), prosophylline (9e), prosufrine (9f), and prosufrinine (9g) isolated from *Prosopis africana*, have now appeared.¹⁸ The skeletal structure and substitution pattern of prosopinine (9b) was revealed by dehydrogenation, which yielded the 3-hydroxypyridine derivative (10).^{18a} Wolff-Kishner reduction of (9b) gave deoxoprosopinine (9h) which, when subjected to periodate oxidation, yielded the pyrrolidine (11a) and formaldehyde. Compound (11a) behaved like an N-formylpyrrolidine, giving the N-methyl derivative (11b) upon reduction with lithium aluminium hydride, and, like an open-chain amido-aldehyde, yielding an alcohol amide system with potassium borohydride. Examination of



- (9) a; $R^1 = \text{OH}$, $R^2 = \text{H}$, $R^3 = (\text{CH}_2)_{10}\text{CH}(\text{OH})\text{Me}$
 b; $R^1 = \text{OH}$, $R^2 = \text{H}$, $R^3 = (\text{CH}_2)_9\text{COCH}_2\text{Me}$
 c; $R^1 = \text{OH}$, $R^2 = \text{H}$, $R^3 = (\text{CH}_2)_6\text{CO}(\text{CH}_2)_4\text{Me}$
 d; $R^1 = \text{OH}$, $R^2 = \text{H}$, $R^3 = (\text{CH}_2)_7\text{CO}(\text{CH}_2)_3\text{Me}$
 e; $R^1 = \text{OH}$, $R^2 = \text{H}$, $R^3 = (\text{CH}_2)_9\text{COCH}_2\text{Me}$
 f; $R^1 = R^2 = \text{H}$, $R^3 = (\text{CH}_2)_9\text{CH}(\text{OH})\text{CH}_2\text{Me}$
 g; $R^1 = R^2 = \text{H}$, $R^3 = (\text{CH}_2)_9\text{COCH}_2\text{Me}$
 h; $R^1 = \text{OH}$, $R^2 = \text{H}$, $R^3 = (\text{CH}_2)_{11}\text{Me}$
 i; $R^1 = \text{OH}$, $R^2 = \text{H}$, $R^3 = (\text{CH}_2)_{10}\text{COMe}$
 j; $R^1 = R^2 = \text{H}$, $R^3 = (\text{CH}_2)_3\text{CH}(\text{OH})(\text{CH}_2)_{10}\text{CH}(\text{OH})\text{Me}$

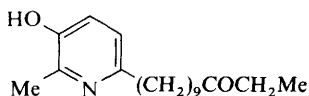
¹⁶ M. Marlier, G. A. Dardenne, and J. Casimir, *Phytochemistry*, 1972, **11**, 2597.

¹⁷ E. Leete and J. O. Olson, *J. Amer. Chem. Soc.*, 1972, **94**, 5472.

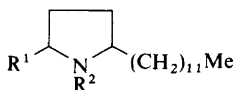
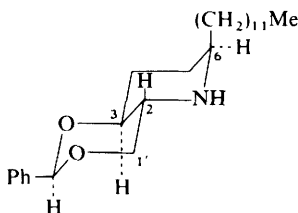
¹⁸ (a) Q. Khuong-Huu, G. Ratle, X. Monseur, and R. Goutarel, *Bull. Soc. chim. belges*, 1972, **81**, 425; (b) Q. Khuong-Huu, G. Ratle, X. Monseur, and R. Goutarel, *ibid.*, p. 443.

the n.m.r. spectrum of *OO'*-benzylidene deoxoprosopinine (12) yielded the relative configuration of prosopinine (9b). Protons at C-2 and C-3 appeared as sextuplets at δ 2.88 ($J_{2,3} = 10$ Hz, $J_{2,1'a} = 10$ Hz, $J_{2,1'e} = 5$ Hz) and δ 3.30 ($J_{3,2} = 10$ Hz, $J_{3,4a} = 10$ Hz, $J_{3,4e} = 5$ Hz), respectively, in strong support for the *trans* ring-juncture and a double-chair conformation. The equatorial orientation of H-6 was assigned on the basis of the half-width height = 18 Hz of a broad multiplet at δ 2.78. The relative configuration of prosopinine is thus as indicated in structure (9b) and its absolute configuration was determined to be 2*R*,3*S*,6*R* by application of Horeau's method to the C-3OH function.^{18b}

That prosopine possesses the structure and absolute stereochemistry (9a) was shown by its conversion by successive Oppenauer oxidation and Wolff-Kishner reduction into deoxoprosopinine (9h).^{18a} Application of Horeau's method to *OO'*-benzylidene derivatives of prosopine and *N*-methylprosopine allowed the assignment of *S* absolute configuration to the C-6 side-chain secondary hydroxy-function in (9a).^{18b} The other structures and absolute stereochemistry (with exception of some side-chain alcohol functions) of alkaloids (9c—g) were defined by application of similar chemical and spectral methods.^{18b} An interesting aspect of this work is the determination of the position of the side-chain alcohol or keto-functions in all alkaloids by examination of the mass spectral fragmentation patterns of the corresponding amines obtained by reduction of oxime derivatives. Two related alkaloids, prosopinone (9i) and alkaloid D (9j) have been isolated from *Cassia carnaval*.¹⁹ Only gross structures have been proposed and structure (9j) especially is a tentative one. It is likely that prosopinone (9i) could be correlated with deoxoprosopinine (9h) of known absolute configuration.



(10)

(11) a; R¹ = OH, R² = CHO
b; R¹ = H, R² = Me

(12)

¹⁹ D. Lythgoe, A. Busch, N. Schwarzberg, and M. J. Vernengo, *Anales Asoc. Quim. Argentina*, 1972, **60**, 317 (*Chem. Abs.*, 1972, **77**, 164 901k).

Haloxylon salicornicum has yielded a number of alkaloids which on the basis of preliminary data appear to possess unusual structures.²⁰ A definitive paper on the alkaloids of this species would be welcome.²¹

A full report is now available on the X-ray crystal structure of bromolythranine hydrobromide (*not* bromolythranidine hydrobromide as previously designated, *cf.* Vol. 2 of this Series), from which the absolute configuration of lythranine (13a; $R^1 = \text{Me}$, $R^2 = R^3 = R^4 = R^6 = \text{H}$, $R^5 = \text{Ac}$) can be deduced.²² The absolute configuration and conformation of lythrancines I–IV (14a–d) and lythrancepines I–III (14e–g), whose structural elucidation has been discussed in Vol. 2 of this Series, has now been assigned.²³ In the n.m.r. spectrum of lythrancine IV (14d), the proton at C-1 was observed at δ 4.17 as a double doublet ($J = 11$ and 4 Hz) suggesting that it was axially oriented, assuming the chair–chair conformation of the quinolizidine ring. The C-3 proton was observed as an octet at δ 5.15 ($J = 3, 6$, and 11.5 Hz) indicating an axial orientation, while the C-4 proton appeared as a triplet at δ 4.91 ($J = 3$ Hz) implying an equatorial position. This information together with previous chemical data (*cf.* Vol. 2) established the *cis* relationship of the hydrogen atoms at C-1, C-3, and C-4. The *trans* relationship of the hydrogens at C-5 and C-9 had been also chemically established earlier. The *cis* quinolizidine ring-juncture was indicated by the chemical shift of the C-1 proton at δ 4.17, which was in close agreement with absorption of this type of proton in model systems and was supported by the absence of Bohlmann bands in the i.r. spectrum of (14d). Jones oxidation of lythrancepine II (14f) gave the expected ketone, which was subjected to successive retro-Michael reaction and catalytic hydrogenation to give (13b) together with an isomeric ketone resulting from the predictable alternative retro-Michael reaction. Sodium borohydride reduction of (13b) took place stereoselectively to yield the diol (13c) which, without purification, was formylated with formic acid and acetic anhydride to yield the crystalline *NOO*-triformate (13d). This compound was shown to be identical with the *NOO*-triformate (13e) obtained by diazomethane methylation and formylation of lythranidine (13f) with the exception of rotations which were of opposite sign but same absolute value. Examination of the o.r.d. and c.d. spectra of (13d) and (13e) proved that the compounds possess an antipodal relationship. Since the absolute configuration of lythranidine (13f) was known, the absolute configurations of lythrancepine II (14f) at C-5, C-9, and C-11 were established as *S*, *S*, and *R*, respectively. Previous chemical interrelationships allow for this absolute configuration assignment for lythrancines I–IV (14a–d) and lythrancepines I (14e) and III (14g) as well. These results, when analysed in conjunction with the relative stereochemistry at C-1, C-3, and C-4, allow only two possible conformational representations for these alkaloids,

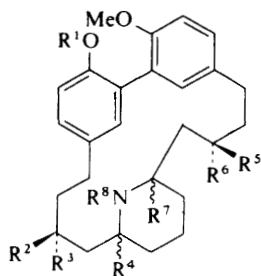
²⁰ F. Sandberg, *Biochem. Physiol. Alkaloide*, Fourth Internat. Symposium, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 177.

²¹ For previous reports on alkaloids of unknown structure, see R. H. F. Manske in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, vol. X, p. 565 and vol. XII, p. 480.

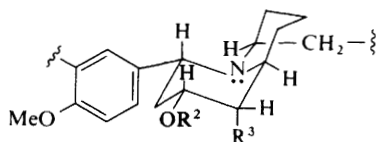
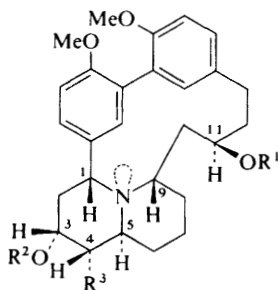
²² R. J. McClure, jun. and G. A. Sim, *J.C.S. Perkin II*, 1972, 2073.

²³ E. Fujita and Y. Saeki, *J.C.S. Perkin I*, 1973, 297.

one of which (14') is preferred on the basis of model examination. That this in fact is the correct conformational and absolute stereochemical representation was shown by the X-ray crystallographic analysis (yet unpublished) of *O*-brosylate of lythrancine II (14b; $R^3 = \text{OSO}_2\text{C}_6\text{H}_4\text{-}p\text{-Br}$). The presence of the two structural types (13) and (14) possessing an antipodal relationship in the same plant is of biosynthetic interest.



- (13) a; $R^1 = R^3 = R^5 = R^8 = \text{H}$, $R^2 = \text{OH}$, $R^4 = \beta\text{-H}$, $R^6 = \text{OAc}$, $R^7 = \alpha\text{-H}$
 b; $R^1 = \text{Me}$, $R^5 = R^8 = \text{H}$, $R^2 + R^3 = \text{O}$, $R^4 = \alpha\text{-H}$, $R^6 = \text{OAc}$, $R^7 = \beta\text{-H}$
 c; $R^1 = \text{Me}$, $R^2 = R^6 = R^8 = \text{H}$, $R^3 = R^5 = \text{OH}$, $R^4 = \alpha\text{-H}$, $R^7 = \beta\text{-H}$
 d; $R^1 = \text{Me}$, $R^2 = R^6 = \text{H}$, $R^3 = R^5 = \text{OCHO}$, $R^4 = \alpha\text{-H}$, $R^7 = \beta\text{-H}$, $R^8 = \text{CHO}$
 e; $R^1 = \text{Me}$, $R^2 = R^6 = \text{OCHO}$, $R^3 = R^5 = \text{H}$, $R^4 = \beta\text{-H}$, $R^7 = \alpha\text{-H}$, $R^8 = \text{CHO}$
 f; $R^1 = R^3 = R^5 = R^8 = \text{H}$, $R^2 = R^6 = \text{OH}$, $R^4 = \beta\text{-H}$, $R^7 = \alpha\text{-H}$

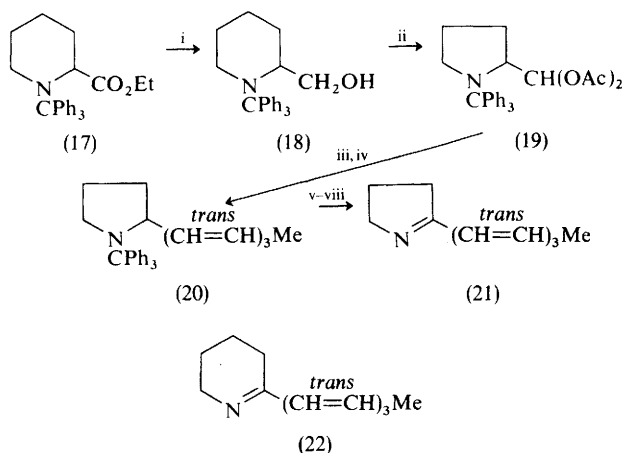


(14')

- (14) a; $R^1 = R^2 = \text{H}$, $R^3 = \text{OH}$
 b; $R^1 = \text{Ac}$, $R^2 = \text{H}$, $R^3 = \text{OH}$
 c; $R^1 = R^2 = \text{Ac}$, $R^3 = \text{OH}$
 d; $R^1 = R^2 = \text{Ac}$, $R^3 = \text{OAc}$
 e; $R^1 = R^2 = R^3 = \text{H}$
 f; $R^1 = \text{Ac}$, $R^2 = R^3 = \text{H}$
 g; $R^1 = R^2 = \text{Ac}$, $R^3 = \text{H}$
 h; $R^1 = R^2 = \text{Ac}$, $R^3 = \text{OAc}$
 i; $R^1 = \text{H}$, $R^2 = \text{Ac}$, $R^3 = \text{OAc}$
 j; $R^1 = R^2 = \text{Ac}$, $R^3 = \text{OH}$ } C-3 epimer

²⁷ J. M. Brand, M. S. Blum, and H. H. Ross, *Insect Biochem.*, 1973, 3, 45.

Some interesting synthetic results have been published in the past year. Details are now available of the methodology for 2,6-dialkyl-3-piperidol preparation²⁸ and of a biomimetic-type synthesis of (\pm)-pseudoconhydrine (16)²⁹ which has been described in Vol. 3 of this Report. One of these reports²⁸ gives a brief review of alkaloids possessing 2,6-dialkyl-3-piperidol structures (*e.g.* prosopine and related alkaloids¹⁷⁻¹⁹)* for which the described general synthesis may find applicability. The pyrroline analogue (21) of nigrifactin (22) has been synthesized (Scheme 1).³⁰ Metal hydride reduction of ethyl *N*-tritylpipecolate (17) gave the alcohol (18) which upon lead tetra-acetate oxidation provided the pyrrolidine (19) in 68 % yield. The mechanism of this intriguing new reaction is unknown although a speculative scheme is discussed which draws analogy to the oxidation of enamines and amines with thallic and mercuric acetate, respectively. A relationship with the rearrangement (9h \rightarrow 11a) may be noted. The diacetate (19) was readily converted into the corresponding aldehyde by base treatment and the latter was subjected to the Horner-Wittig reaction with an appropriate phosphonate ester to yield the triene (20). Treatment of (20) under acidic conditions followed by base treatment furnished the corresponding detritylated compound which was converted into (21) *via* the unstable *N*-chloro-derivative.



Reagents: i, LiAlH_4 or $\text{NaAl(OCH}_2\text{CH}_2\text{OMe)}_2\text{H}_2$; ii, Pb(OAc)_4 , C_6H_6 ; iii, 10 % NaOH ; iv, NaNH_2 , $\text{Me(CH=CH)}_2\text{CH}_2\text{CH}_2\text{PO(OEt)}_2$, THF; v, 10 % HCl , EtOH , 50 $^\circ\text{C}$; vi, Amberlite IRA-400 (OH^-); vii, NCS , Et_2O ; viii, KOH , MeOH .

Scheme 1

* For synthetic work which shows potential for the preparation of these systems, see Section 3.

²⁸ E. Brown and R. Dhal, *Bull. Soc. chim. France*, 1972, 4292.

²⁹ E. Brown, J. Lavoue, and R. Dhal, *Tetrahedron*, 1973, **29**, 455.

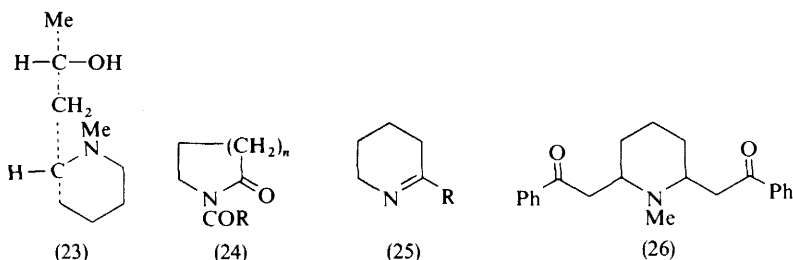
³⁰ H. De Koning, A. Springer-Fidder, M. J. Moolenaar, and H. O. Huisman, *Rec. Trav. chim.*, 1973, **92**, 237.

The four possible isomers of 2-(2-hydroxypropyl)-1-methylpiperidine have been prepared by a conventional route, and *N*-methyl-*allo*-sedridine (from *Sedum sarmentosum*) has been shown to possess the (2*R*,2*S*) absolute configuration (23) by o.r.d. studies and chemical correlation.³¹

The transformation [(24; *n* = 2) → (25; *R* = Prⁿ)], which is simply and reasonably efficient effected with calcium oxide in a melt, shows potential for alkaloid synthesis.³²

Large-scale isolation of lobeline (26) using ion-exchange resins is apparently more efficient than extraction methods.³³ *Lobelia puberula*, *L. cardinalis*, and *L. nicotianaefolia* have been found to be very rich in lobeline.^{34,35}

The antibacterial properties of the fire ant venom alkaloids *trans*-(15*a*–*c*) have been investigated.³⁶



3 Pyridine Alkaloids

A general-interest review on alkaloid isolation work from terrestrial sources deals in part with the *Nicotiana* type.¹ Perhaps it is premature to expand the meaning of 'alkaloid' to include compounds isolated from marine sources. However, the timely and excellent review on this subject clearly shows the large number of N-containing compounds isolated from the sea, among which are homarine (*N*-methylpicolinic acid betaine) and trigonelline (*N*-methylnicotinic acid betaine).³⁷ A very interesting review dealing with non-nutrient natural products which contaminate the food chain contains a section on nicotine and describes its teratogenic effects.³⁸

³¹ H. C. Beyerman, B. S. L. Bordes, L. Maat, and F. M. Warnaar, *Rec. Trav. chim.*, 1972, **91**, 1441.

³² B. P. Mundy and B. R. Larsen, *Synthetic Comm.*, 1972, **2**, 197.

³³ Yu. V. Shostenko, S. Kh. Mushinskaya, I. S. Simon, and E. S. Vysotskaya, *Postep Dziedzinnie Leku Rosl.*, *Pr. Ref. Dosw. Wygloszone Symp.* 1970, ed. F. Kaczmarek, Inst. Przem. Zielarskiego, Poznan, Poland, 1972, p. 122 (*Chem. Abs.*, 1973, **78**, 101 929a); Yu. V. Shostenko and I. S. Simon, *Trudy Voronezh. Gos. Univ.*, 1969, **72**, 213 (*Chem. Abs.*, 1972, **77**, 156 308g).

³⁴ A. Krochmal, L. Wilken, and M. Chien, *Lloydia*, 1972, **35**, 303.

³⁵ C. S. Shah, J. S. Qadry, and M. G. Bhatt, *Phytochemistry*, 1972, **11**, 2884.

³⁶ D. P. Jouvenaz, M. S. Blum, and J. G. MacConnell, *Antimicrob. Agents Chemother.*, 1972, **2**, 291 (*Chem. Abs.*, 1973, **78**, 92 973f).

³⁷ E. Premuzic, *Fortschr. Chem. org. Naturstoffe*, 1971, **29**, 417.

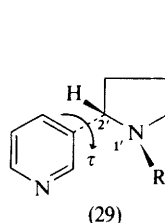
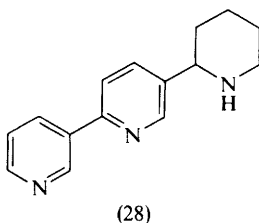
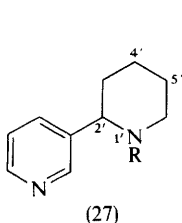
³⁸ L. Fishbein, *Sci. Total Environ.*, 1972, **1**, 211.

Several examples of 2-pyridone and nicotine types are discussed in a review on the application of mass spectrometry to alkaloid structural elucidation.³⁹

A review on amidine cyclizations as they apply to the synthesis of pyridine derivatives has appeared.⁴⁰

Known alkaloids have been isolated from the following sources: *Anabasis aphylla* [anabasine (27; R = H), anabasamine (28)],⁴¹ *Dipsacus azureus* [cantaleine (C₁₁H₁₃O₃N, m.p. 130–131 °C)],⁴² and *Sedum acre* [nicotine (29; R = Me), determined spectrophotometrically only].⁴³ Alkaloid content during the course of ontogeny in *Nicotiana glutinosa*, *N. tabacum* (Havana), and *N. sylvestris* and their reciprocal hybrids has been investigated.⁴⁴ Nicotine was found to be the main alkaloid in all plants. The content of nornicotine (29; R = H) was found to increase during flowering of some of the species while anatabine (27; R = H, 4',5'-double bond) was present in the reciprocal hybrids but not in the parent plants. The aim of these studies is the potential development of hybrid species with low alkaloid content.

New variants of nicotine isolated from *Nicotiana tabacum* have been shown, with one exception, to possess pyrrolidine ring *N*-acylated structures (29; R = CHO, Ac, CON-C₅H₁₁, CON-C₇H₁₅).^{45,46} The exception is 5-methyl-2,3'-bipyridyl (30), whose structure has been confirmed by synthesis.⁴⁶ In the case of (29; R = CHO and Ac) appropriate experiments were carried out to show that these compounds are not artifacts.⁴⁶ Although compounds obtained from cigarette smoke condensate cannot be called alkaloids, it may be noted that anabasine, 2,2'-bipyridyl, *N*-methylanabasine, myosmine (29; 1',2'-double bond), nicotinamide, and β -nicotyrine (31) have been isolated from this source and fully characterized by spectroscopic studies.⁴⁷



³⁹ S. D. Sastry, 'Biochemical Applications of Mass Spectrometry,' ed. G. R. Waller, Wiley-Interscience, New York, 1972, p. 655.

⁴⁰ M. Mioque, C. Fauran, and A. Y. Le Cloarec, *Ann. Chim. (France)*, 1972, 7, 89.

⁴¹ Kh. A. Aslanov, A. I. Ishbaev, K. Inoyatova, Sh. Yusupov, A. S. Sadykov, and V. P. Zakharov, *Khim. prirod. Soedinenii*, 1972, 324 (*Chem. Abs.*, 1972, 77, 161 743z).

⁴² T. U. Rakhmatullayev and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, 400 (*Chem. Abs.*, 1972, 77, 162 011w).

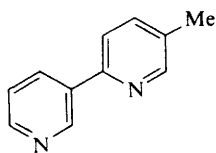
⁴³ As. Z. Gulubov and Il. Z. Bozhkova, *Nauch. Tr., Plovdivski Univ., Mat., Fiz., Khim., Biol.*, 1972, 10, 105 (*Chem. Abs.*, 1973, 78, 13 763m).

⁴⁴ G. S. Il'in, B. Gyorf, M. Ya. Lovkova, and N. S. Minozhedinova, *Izvest. Akad. Nauk S.S.S.R., Ser. biol.* 1972, 756 (*Chem. Abs.*, 1972, 77, 162 093z); M. Ya. Lovkova, B. Gyorf, G. S. Il'in, and N. S. Minozhedinova, *ibid.*, 1973, 115 (*Chem. Abs.*, 1973, 78, 121 566h).

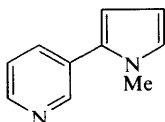
⁴⁵ A. J. N. Bolt, *Phytochemistry*, 1972, 11, 2341.

⁴⁶ A. H. Warfield, W. D. Galloway, and A. G. Kallianos, *Phytochemistry*, 1972, 11, 3371.

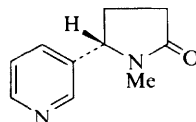
⁴⁷ E. V. Brown and I. Ahmad, *Phytochemistry*, 1972, 11, 3485.



(30)

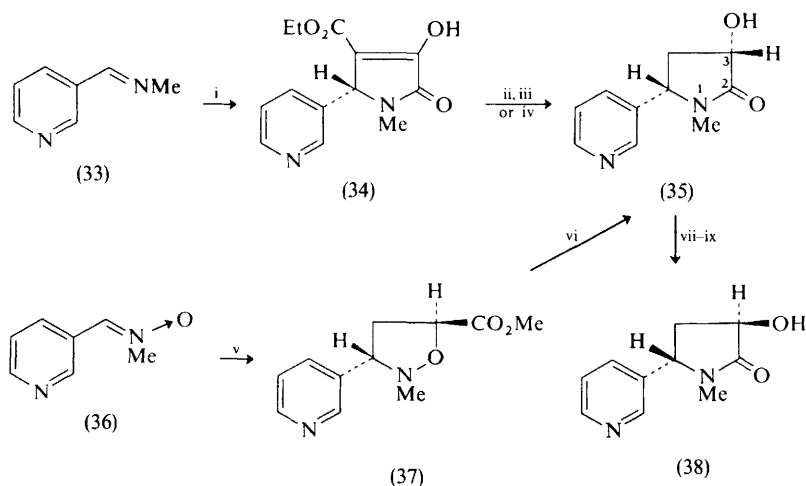


(31)



(32)

The major metabolic routes taken by nicotine in mammalian species involve oxidation of the pyrrolidine ring to the more polar and pharmacologically less active compound cotinine (32). Two new results in this area are of interest. Hydroxycotinine (38) has been shown to be a nicotine metabolite isolated from the urine of smokers, on the basis of spectroscopic data and synthesis by two alternative routes (Scheme 2).⁴⁸ The pyrrolidone (34) was obtained by condensation of Schiff base (33) with diethyl oxalacetate (see Vol. 3 of this Report for a previous application of this reaction). Acid-catalysed hydrolysis of (34) followed directly by a hydrolysis-decarboxylation-reduction sequence yielded synthetic hydroxycotinine (35), which on the basis of its n.m.r. spectrum was shown to be the C-3 epimer of the metabolic product. The alternative approach which also led to (35) was based on the 1,3-dipolar addition reaction of nitrones with $\alpha\beta$ -unsaturated esters to give isoxazolidine derivatives, which upon hydrogenolysis give 3-hydroxy-2-pyrrolidinones. Condensation of the pyridylnitron (36) with



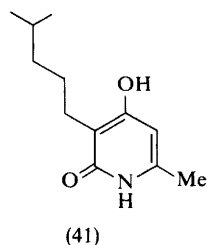
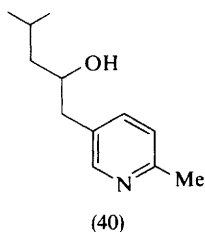
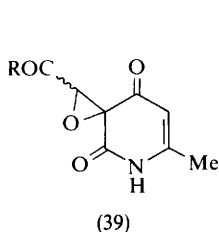
Reagents: i, $\text{EtO}_2\text{CCH}_2\text{COCO}_2\text{Et}$, reflux; ii, 2N-HCl , reflux; iii, NaBH_4 , H_2O ; iv, 47 % HI , HOAc , NaH_2PO_3 , H_2O , reflux; v, $\text{CH}_2=\text{CHCO}_2\text{Me}$, reflux; vi, Raney Ni , H_2 , EtOH ; vii, MeSO_2Cl , $\text{C}_5\text{H}_5\text{N}$; viii, NaOAc , HOAc , reflux; ix, 5 % NaOH , 80°C .

Scheme 2

⁴⁸ E. Dagne and N. Castagnoli, jun., *J. Medicin. Chem.*, 1972, **15**, 356.

methyl acrylate provided the isoxazolidine (37) as the major product with a small amount of the positional isomer with the CO_2Me function at C-4. As expected on the basis of its stereochemistry, compound (37) was also converted into synthetic hydroxycotinine (35) under hydrogenolysis conditions. Epimerization of (35) to the metabolic hydroxycotinine (38) was accomplished by an $\text{S}_{\text{N}}2$ sequence. Stereochemical assignments were established by reference to n.m.r. and mass spectra of phenyl analogues of (35) and (38). An additional metabolite isolated from the urine of rhesus monkeys has been shown to be the *N*-oxide of cotinine (32) on the basis of spectroscopic evidence and synthesis from (*S*)-(-)-cotinine by *m*-chloroperbenzoic acid oxidation.⁴⁹

The antibiotic 'glutamicine' isolated from *Aspergillus flavipes*, which was previously assigned the structure 3-acetyl-4-isovaleryl-6-hydroxy-2(1*H*)-pyridone, must now be assigned the interesting spiropyridone structure (39; $\text{R} = \text{CH}_2\text{CHMe}_2$) on the basis of new chemical and spectroscopic evidence. It has been renamed flavipucine.^{50,51} The n.m.r. spectrum of flavipucine gives evidence for a methyloxobutyl side-chain, an $\text{MeC}=\text{CH}-$ arrangement ($J_{\text{Me,H}} = 0.8 \text{ Hz}$, temperature independent), and an NH (exchangeable) proton.⁵⁰ The remaining unaccounted proton appears as a sharp singlet at $\delta 3.80$ which is assigned to the proton on the epoxide bridge. Lithium aluminium hydride reduction gave in low yield the pyridine (40), whose 2,5-substitution pattern *only* was established by n.m.r. comparison of pyridine ring chemical shifts with known derivatives. However, the alternative structure in which the 2,5-substituents are reversed was excluded by synthesis.⁵¹ Treatment of the lithium salt of 2,5-dimethylpyridine with isovaleraldehyde gave a compound which was shown to be different in spectral parameters and t.l.c. behaviour from that obtained by hydride reduction of flavipucine. Finally, complete corroboration of the flavipucine structure (39; $\text{R} = \text{CH}_2\text{CHMe}_2$) was also obtained by synthesis. Modified catalytic reduction of the antibiotic followed by Wolff-Kishner reduction gave (41) which was prepared by the sodium-ethoxide-catalysed condensation of diethyl 4-methylpentylmalonate with ethyl β -aminocrotonate. The stereochemistry of the side-chain of flavipucine remains to be determined. A second compound which easily cocrystallizes with flavipucine during the purification



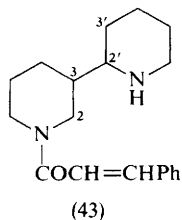
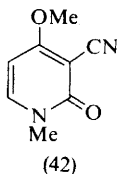
⁴⁹ E. Dagne and N. Castagnoli, jun., *J. Medicin. Chem.*, 1972, **15**, 840.

⁵⁰ J. A. Findlay and L. Radics, *J.C.S. Perkin I*, 1972, 2071.

⁵¹ J. A. Findlay and D. Kwan, *J.C.S. Perkin I*, 1972, 2962.

stage has not been isolated in pure form, but detailed examination of the n.m.r. spectrum of the mixture indicates that it has the isomeric structure [39; R = CH(Me)Et].⁵⁰

The proceedings of a symposium on the biochemistry and physiology of alkaloids held in 1969 contains reviews on the accumulation and translocation of nicotine-type compounds.⁵² In this connection, more recent studies have been published.⁵³⁻⁵⁵ In one of these,⁵⁵ preliminary evidence for a specific physiological or metabolic function of ricinine (42) in *Ricinus communis* has been obtained. The effect of gibberellic acid, indole-3-acetic acid, and kinetin on alkaloid synthesis in some *Nicotiana* species has been studied.^{56,57} Added nicotinic acid decreased the production of trigonelline by *Trigonella foenum-graecum* tissue cultures.⁵⁸



Hückel MO calculations have been carried out on iso-orensine (43; 2',3'-double bond) and compared with those obtained on orensine (43; 2,3-double bond).⁵⁹ An important paper deals with the conformation of chiral nicotine-type alkaloids in aqueous solution as determined by c.d. studies.⁶⁰ The sector rules developed by Snatzke for the L_b band ($\pi \rightarrow \pi^*$ transition) of mono-substituted benzenes were successfully applied to predicting the sign of the Cotton effect of the optically active pyridine derivatives, thus indicating that the effect of the nitrogen atom on the $\pi \rightarrow \pi^*$ transition can be neglected to the first approximation. C.d. measurements showed negative Cotton effects for the pyridine L_b band of (S)-(-)-nicotine (29; R = Me), (S)-(-)-nornicotine (29; R = H), (S)-(-)-anabesine (27; R = H), and (S)-(-)-methylanabesine (27; R = Me) in their neutral and monoprotonated forms, and (S)-(-)-cotinine (32)

⁵² K. Mothes, *Biochem. Physiol. Alkaloide*, Fourth Internat. Symposium, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, E. Germany, 1972, pp. 59, 213, 268.

⁵³ E. Mueller, A. Nelles, and D. Neumann, *Mekh. Pogloshcheniya Veshchestv Rast. Kletkoi, Tr. Simp.* 1970, ed. R. K. Salyaev, *Akad. Nauk S.S.S.R., Sib. Otd., Sib. Inst. Fiziol. Biokhim. Rast. Irkutsk, U.S.S.R.*, 1971, p. 66 (*Chem. Abs.*, 1973, **78**, 106 492n).

⁵⁴ E. K. Nowacki and G. R. Waller, *Z. Pflanzenphysiol.*, 1973, **69**, 228 (*Chem. Abs.*, 1973, **78**, 121 601r).

⁵⁵ G. R. Waller and L. Skursky, *Plant Physiol.*, 1972, **50**, 622.

⁵⁶ K. K. Gupta and S. K. Chatterjee, *Bull. Bot. Soc. Bengal*, 1971, **25**, 103 (*Chem. Abs.*, 1973, **78**, 120 141d).

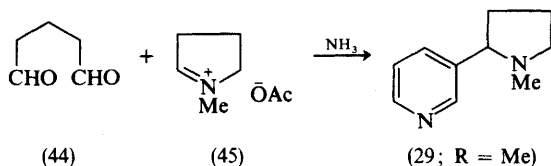
⁵⁷ M. Tabata, N. Hiraoka, H. Yamamoto, Y. Marumoto, and M. Konoshima, *Saibo Seibutsugaku Shimpoijumu*, 1971, **22**, 81 (*Chem. Abs.*, 1973, **78**, 25 192n).

⁵⁸ P. Khanna and S. C. Jain, *Indian J. Exp. Biol.*, 1972, **10**, 248 (*Chem. Abs.*, 1972, **77**, 136 193n).

⁵⁹ L. Carballeira, M. A. Herraiz, and M. A. Rios, *Acta Cient. Compostelana*, 1971, **8**, 65 (*Chem. Abs.*, 1972, **77**, 164 917v).

⁶⁰ B. Testa and P. Jenner, *Mol. Pharmacol.*, 1973, **9**, 10.

in its neutral form. Using conformational analysis and the definition of the torsional angle τ as indicated in structure (29), the observed negative Cotton effects were correlated with two regions of $\tau = 120\text{--}140^\circ$ and $300\text{--}320^\circ$ corresponding to preferred conformations for the alkaloids. MO calculations and X-ray analysis yielded $\tau = 120^\circ$ and 300° and $\tau = 118^\circ$, in good agreement with the c.d. results. This work has interesting implications in drug molecule–receptor site interaction studies. The conformation of an N-substituted anabasine derivative (27; R = CH₂CH₂OH) as studied by i.r. and n.m.r. spectroscopy has been shown to be one in which both substituents take up equatorial positions with respect to the piperidine ring with hydrogen bonding between the hydroxy-group and the pyridine nitrogen.⁶¹



Scheme 3

Synthetic results this year are highlighted by routes involving biogenetic considerations and potentially general new approaches. A biomimetic synthesis of nicotine patterned after Wenkert's suggestion (subsequently supported by biosynthetic evidence) involving condensation of 1,4-dihyronicotinic acid with 1-methyl- Δ^1 -pyrrolinium acetate (45) has been achieved (Scheme 3).⁶² When glutaraldehyde (44), ammonia, and [2-¹⁴C]-(45) were mixed at room temperature at alkaline pH without the exclusion of air, nicotine (29; R = Me) was obtained in best radiochemical yield of 21.3% (pH 10.3). The readily prepared acyl carbanion equivalent (46) has been used for facile syntheses of myosmine (29; R = H, 1',2'-double bond) and nornicotine (29; R = H) in 67% overall yield from pyridine-3-aldehyde (Scheme 4).⁶³ Simple but mechanistically intriguing syntheses of myosmine as well as anabaseine (27; R = H, 1',2'-double bond) by pyrolysis of the acyl lactams (24; R = 3-pyridyl, $n = 1$) and (24; R = 3-pyridyl, $n = 2$), respectively, in the presence of calcium oxide have been described.³²

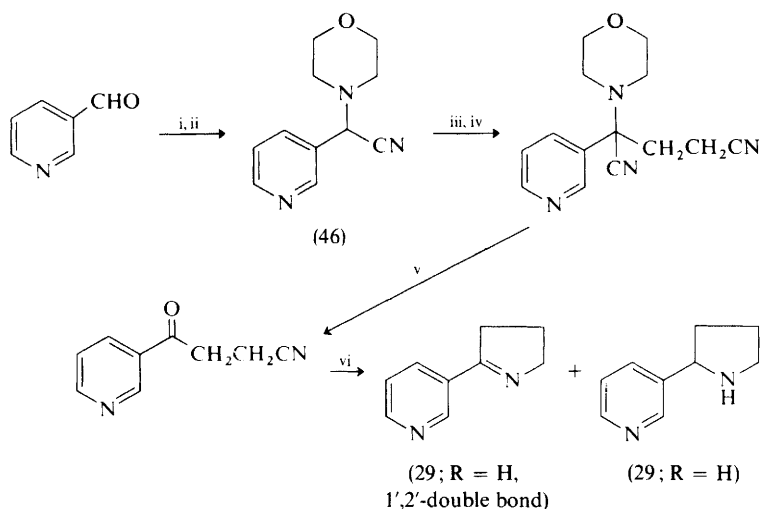
Methods available for the synthesis of carpyrinic acid (50), a logical intermediate for total synthesis of piperidine alkaloids possessing long aliphatic side-chains of the structural type (9) have been reviewed and a new, more efficient route has been described in detail.⁶⁴ The latter (Scheme 5) is initiated by Friedel–Crafts acylation of furan to yield the ketone ester (47) in an optimum 50% yield. Hydrolysis, Huang–Minlon reduction, and re-esterification gave the saturated ester (48). Direct alkylation of furan under Friedel–Crafts conditions was not attempted

⁶¹ M. Karimov, A. S. Sadykov, Kh. A. Aslanov, V. B. Leont'ev, F. G. Kamaev, and T. K. Yunusov, *Khim. prirod. Soedinenii*, 1972, 207 (*Chem. Abs.*, 1972, 77, 48 677t).

⁶² E. Leete, *J.C.S. Chem. Comm.*, 1972, 1091.

⁶³ E. Leete, M. R. Chedekel, and G. B. Bodem, *J. Org. Chem.*, 1972, 37, 4465.

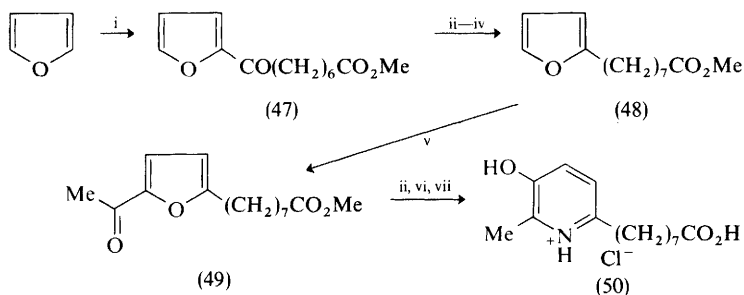
⁶⁴ G. Fodor, J. P. Fumeaux, and V. Sankaran, *Synthesis*, 1972, 464.



Reagents: i, morpholine perchlorate, morpholine, 80 °C; ii, KCN, H₂O, 100 °C; iii, 30% KOH, MeOH, Bu'OH; iv, CH₂=CHCN, Bu'OH, r.t.; v, HOAc, H₂O, THF, 50 °C; vi, Raney Ni, 3 atm NH₃, EtOH.

Scheme 4

because of the unsuccessful history of such reactions. Acylation of (48) to give compound (49) was extensively explored before the conditions indicated were achieved. Application of conditions known to effect the rearrangement of a 2-acylfuran into a 3-hydroxypyridine then yielded carpyrinic acid hydrochloride (50) in an overall 9% yield. Two different routes (together with experimental details for one of them) have also been described by the same group of workers for the synthesis of dehydroprosopine (54), a potential precursor of prosopine (9a, Section 2) (Scheme 6).⁶⁴ The pyridine (51) was converted into a benzylidene or ditetrahydropyranyl derivative (52) which, upon treatment with phenyllithium and 10-undecylenic acid chloride, gave the ketone (53) together with other ketonic products resulting from lack of selectivity in the abstraction of benzylic protons by the strong base. Although (53) was converted into dehydroprosopine (54) in two steps, a selective and higher yield synthesis was achieved *via* the pyridine derivative (56) which itself was readily available from the inexpensive 3-hydroxypyridine (55). Compound (56) was converted in three steps into the phosphonium salt (57) which, upon Wittig reaction with a blocked C₁₀-aldehyde, gave the olefin (58). Catalytic hydrogenation followed by thermolysis gave the alcohol (59) which, upon hydrolysis, produced dehydroprosopine (54) in an overall 5.3% yield. In addition, an interesting 'intramolecularly' blocked derivative (60) was prepared by partial oxidation of the alcohol (59). Speculation on the conversion of (60) into racemic prosopinone (9i, Section 2) and dehydroprosopine (54) was presented.



Reagents: i, $\text{ClCO}(\text{CH}_2)_6\text{CO}_2\text{Me}$, SnCl_4 , CHCl_3 , -55°C ; ii, 1N-KOH , MeOH ; iii, NH_2NH_2 , H_2O , NaOH , $\text{HOCH}_2\text{CH}_2\text{OH}$; iv, conc. H_2SO_4 , MeOH , C_6H_6 ; v, Ac_2O , SnCl_4 , C_6H_6 , $+6^\circ\text{C}$; vi, aq. NH_4OH , NH_4Cl , 170°C ; vii, aq. 1N-HCl .

Scheme 5

Photochemical syntheses of nicotine (31) (72%) and nornicotine (12%) from 3-iodopyridine and *N*-methylpyrrole and pyrrole, respectively, have been reported.⁶⁵

The synthesis of 2,3,6-trihydroxypyridine, a bacterial degradation product of nicotine, has been described.⁶⁶ The hydrogen peroxide reaction of nicotine to give oxynicotine (?) and nornicotine (29; $\text{R} = \text{H}$) has been investigated as a model for the biosynthetic demethylation.⁶⁷ On the other hand, successive treatment of isonicotine (2,3'-bipyridyl) with hydrogen peroxide in acetic acid and phosphorus trichloride at 80°C apparently gives the 2-pyridyl ring *N*-oxide in 22% yield whereas the same sequence at 60°C provides the 3-pyridyl ring *N*-oxide in 10% yield.⁶⁸ The trimethylsilyl derivative (27; $\text{R} = \text{SiMe}_3$)⁶⁹ and various other acylated and alkylated derivatives⁷⁰ of anabasine have been prepared.

A review of bioassay methods for cigarette smoke condensate has been published.⁷¹ It has been concluded that the mouse skin test is most satisfactory for complete carcinogenic assay. A comprehensive survey of standard procedures for the analysis of alkaloids as well as other chemical components of cigarette smoke has appeared.⁷² Several other reports dealing with analytical

⁶⁵ H.-S. Ryang and H. Sakurai, *J.C.S. Chem. Comm.*, 1972, 594.

⁶⁶ P. E. Holmes, S. C. Rittenberg, and H. J. Knackmuss, *J. Biol. Chem.*, 1972, **247**, 7628.

⁶⁷ K. Blaim and R. Ciszewska, *Biokhimiya*, 1972, **37**, 706 (*Chem. Abs.*, 1973, **78**, 55 472w).

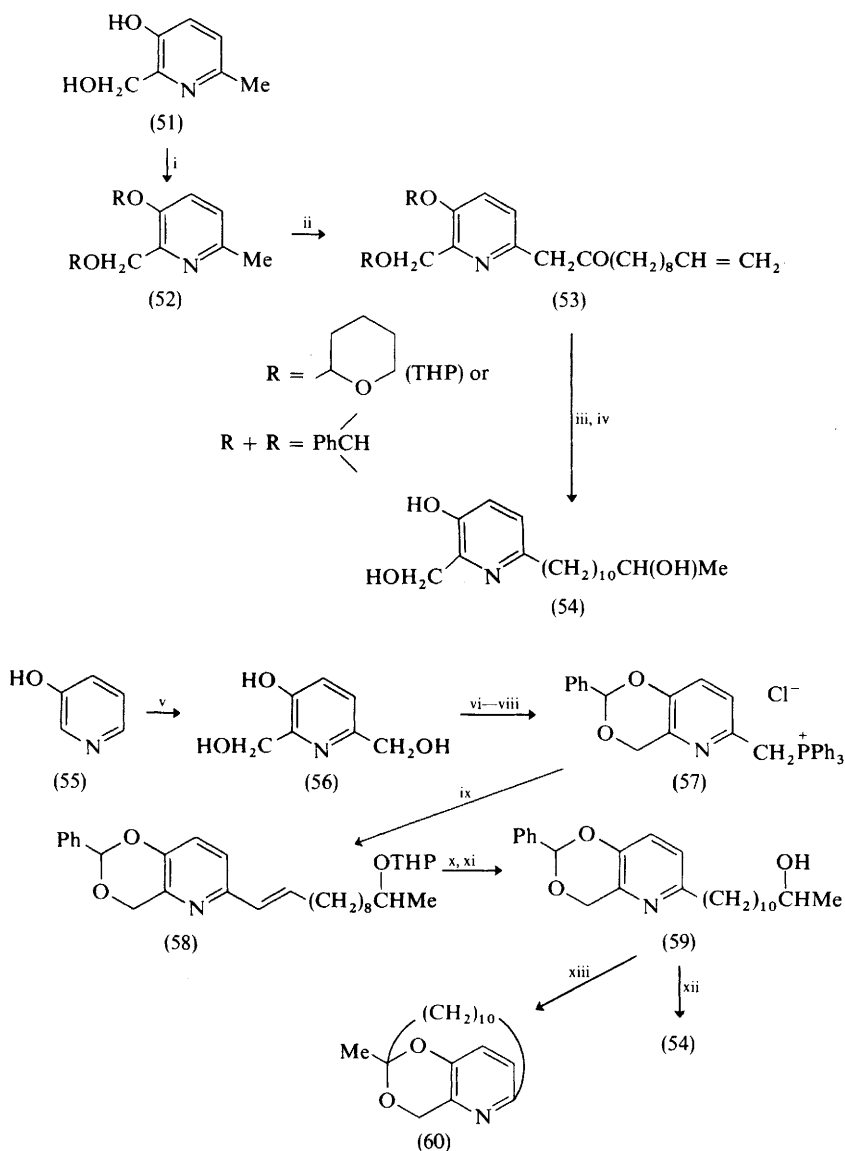
⁶⁸ Yu. V. Kurbatov, Sh. V. Abdullaev, A. S. Kurbatova, O. S. Otroshchenko, and A. S. Sadykov, *Khim. geterotsikl. Soedinenii*, 1973, 378 (*Chem. Abs.*, 1973, **78**, 159 380f).

⁶⁹ Yu. Forostyan, E. I. Efimova, E. P. Kukhta, and I. I. Soroka, *Zhur. obshchei Khim.*, 1972, **42**, 1041 (*Chem. Abs.*, 1972, **77**, 114 628f).

⁷⁰ M. I. Kabachnik, A. S. Sadykov, N. N. Godovikov, Kh. A. Aslanov, A. A. Abdvakhabov, and K. Toremuratov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 952 (*Chem. Abs.*, 1972, **77**, 101 966q); A. A. Abdvakhabov, Kh. A. Aslanov, N. N. Godovikov, M. I. Kabachnik, A. S. Sadykov, and V. U. Rakhmatullina, *ibid.*, 1972, 945 (*Chem. Abs.*, 1972, **77**, 101 967r); L. S. Arutyunyan, E. Yu. Agababyan, and V. A. Mnatsakanyan, *Armenian khim. Zhur.*, 1973, **26**, 59 (*Chem. Abs.*, 1973, **78**, 159 952u).

⁷¹ F. G. Bock, *Chem. Tob. Smoke*, Proc. Symp. 1971, ed I. Schmeltz, Plenum Press, New York, 1972, p. 107.

⁷² K. Rothwell and C. A. Grant, *Tob. Res. Counc., Res. Pap.* 1972, No. 11 (*Chem. Abs.*, 1972, **77**, 137 525j).



Scheme 6

methods for nicotine and related alkaloids may be noted: gas chromatography,⁷³ thermometric titrimetry,⁷⁴ paper electrophoresis,⁷⁵ and u.v. spectroscopy in conjunction with an autoanalyser.⁷⁶ Not surprisingly, efforts are continuing to decrease alkaloid content in tobacco by application of analytical techniques to sift out high-nicotine types,⁷⁷ by different curing methods,⁷⁸ and by selective filtration using cellulose derivatives bearing carboxylic acid functions.⁷⁹ An intriguing study has shown that alkaloid content of cigarette smoke is increased with increasing puff volume and frequency.⁸⁰

A short review on myorelaxant drugs related to the anabasine structure is not readily available.⁸¹ Pharmacological properties of several *p*-substituted *N*-benzoylanabasine derivatives⁸² and the toxicity of pharmaceutical nicotine preparations⁸³ have been investigated.

4 Mono- and Sesqui-terpenoid Alkaloids

Selected information from work on this group during 1970–71 is available.⁸⁴ A review on general trends in alkaloid discovery contains some relevant information on sesquiterpenoid alkaloids in tissue.¹ Mass spectra of the mono-terpenoid alkaloids skytanthine and actinidine are interpreted in a comprehensive review of application of mass spectrometry to alkaloid structural elucidation.³⁹

Activity in the isolation and structural elucidation of new alkaloids has not diminished, as seen from Table 1. Oliveramine (64), isolated from *Gentiana olivieri*, could well be an artifact. The structure of pedicularidine (61; $R^1 = H$, $R^2 = CHO$, $R^3 = Me$) from *Pedicularis olgae* was determined by i.r., u.v., and mass spectroscopy and by successive silver oxide oxidation and esterification to (61; $R^1 = H$, $R^2 = CO_2Me$, $R^3 = Me$). *Tecoma radicans* elaborates boschniakine (61; $R^1 = CHO$, $R^2 = H$, $R^3 = \beta$ -Me), one of the relatively few alkaloids possessing the absolute 8*R*-configuration and found previously only in *Boschniokia rossica* and *Tecoma stans*. The latter species has been shown to produce

⁷³ L. P. Bush, *J. Chromatog.*, 1972, **73**, 243.

⁷⁴ E. J. Greenhow and L. E. Spencer, *Analyst*, 1973, **98**, 98.

⁷⁵ T. Fukuda and K. Mimura, *Eisei Kagaku*, 1972, **18**, 284 (*Chem. Abs.*, 1973, **78**, 67 741w).

⁷⁶ P. Viart and M. Bensoussan, *Ann. Dir. Etud. Equip., SEITA (Serv. Exploit. Ind. Tab. Allumettes)*, Sect. 1, 1971, **9**, 123 (*Chem. Abs.*, 1972, **77**, 111 707v).

⁷⁷ P. Schiltz and J. C. Coussirat, *Ann. Dir. Etud. Equip., SEITA (Serv. Exploit. Ind. Tab. Allumettes)*, Sect. 2, 1971, **8**, 147 (*Chem. Abs.*, 1972, **77**, 137 515f); S. Sugawara, U. Kobashi, S. Eda, and S. Ando, *Nippon Senbai Kosha Chuo Kenkyusho Kenkyu Hokoku*, 1971, No. 113, 89 (*Chem. Abs.*, 1972, **77**, 162 092y); N. Carugno, *J. Nat. Cancer Inst.*, 1972, **48**, 1779 (*Chem. Abs.*, 1972, **77**, 98 890c).

⁷⁸ J. P. Albo, *Ann. Dir. Etud. Equip., SEITA (Serv. Exploit. Ind. Tab. Allumettes)*, Sect. 2, 1971, **8**, 133 (*Chem. Abs.*, 1972, **77**, 137 517h).

⁷⁹ A. Ohnishi, Y. Endo, K. Maeda, and M. Uehara, *Nippon Senbai Kosha Chuo Kenkyusho Kenkyu Hokoku*, 1971, No. 113, 125 (*Chem. Abs.*, 1973, **78**, 2090p).

⁸⁰ L. P. Bush, C. Grunwald, and D. L. Davis, *J. Agric. Food Chem.*, 1972, **20**, 676.

⁸¹ A. A. Abduvakhobov, Kh. A. Aslanov, and A. S. Sadykov, *Khim. Rast. Veshchestv*, 1972, 131 (*Chem. Abs.*, 1973, **78**, 136 470w).

⁸² Kh. A. Aslanov, K. T. Toremuratov, A. A. Abduvakhobov, S. Z. Mukhamedzhanov, and A. S. Sadykov, *Zhur. obshchei Khim.*, 1972, **42**, 2293 (*Chem. Abs.*, 1973, **78**, 72 397t).

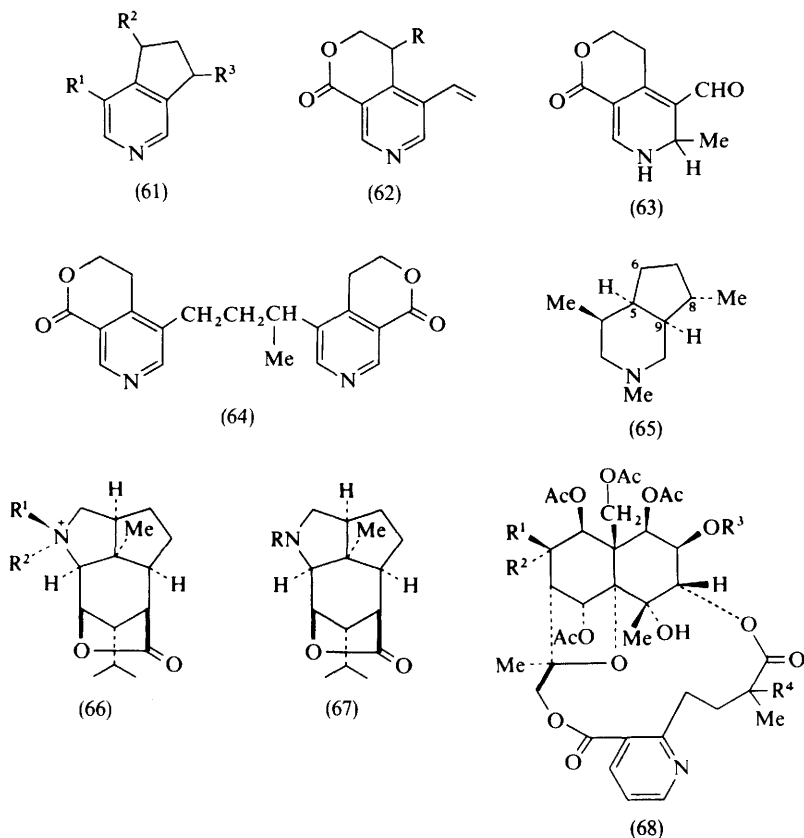
⁸³ P. Driscoll, *Praeventivmedizin*, 1972, **17**, 211 (*Chem. Abs.*, 1973, **78**, 80 490h).

⁸⁴ H. F. Hodson, *Ann. Reports (B)*, 1971, **68**, 493.

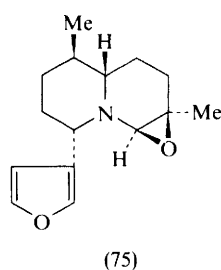
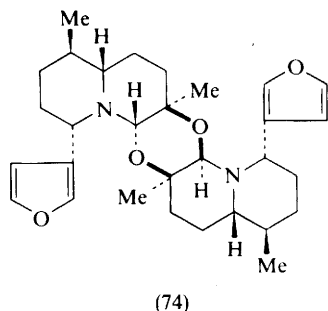
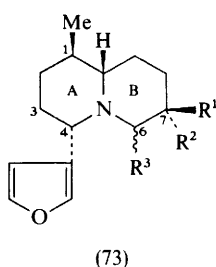
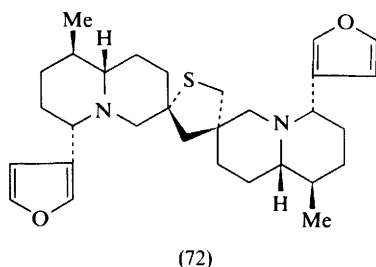
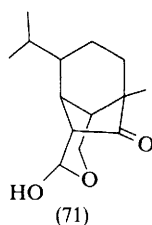
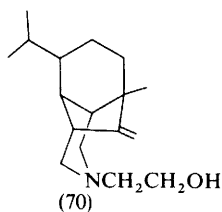
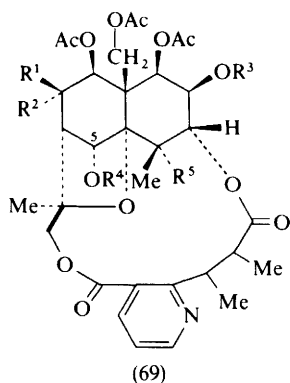
Table 1 Isolation of mono- and sesqui-terpenoid alkaloids

Species	Alkaloid ^a (Structure)	Ref.
	<i>Monoterpenoid Alkaloids</i>	
<i>Actinidia arguta</i>	(-)-Actinidine (61; R ¹ = R ³ = Me, R ² = H)	85
<i>Gentiana olivieri</i>	[Gentianine (62; R = H), Gentianamine (62; R = CH ₂ OH)] ^b	86
	Gentianaine	87
	Gentioflavine (63)	
	Gentiotibetine	86
	Oliveramine (64)	87
	Olivierine	86
	Unnamed, m.p. 235 °C	
<i>Pedicularis olgae</i>	Pedicularidine (61; R ¹ = H, R ² = CHO, R ³ = Me)	88
<i>Plantago arenaria</i>	Unnamed, C ₁₁ H ₁₇ ON ₃ , 'terpenoid behaviour'	89
<i>Tecoma radicans</i>	Boschniakine (61; R ¹ = CHO, R ² = H, R ³ = β-Me)	85
<i>T. stans</i>	Δ ⁵ -Dehydroskytanthine (65; Δ ^{5,6}) } δ-Skytanthine (65)	90
	<i>Sesquiterpenoid Alkaloids</i>	
<i>Dendrobium nobile</i>	Dendrobine N-oxide (66; R ¹ = Me, R ² = O ⁻)	91
	N-Isopentenyl-dendrobium bromide (66; R ¹ = CH ₂ CH=CMe ₂ , R ² = Me) ^b	
	N-Isopentenyl-dendroxinium chloride ^c	
	N-Isopentenyl-6-hydroxy-dendroxinium chloride ^c	
	N-Methyl-dendrobium iodide ^b	
<i>Euonymus alatus</i> f. <i>striatus</i>	Alatamine (68; R ¹ + R ² = O, R ³ = OCPH, R ⁴ = OH)	92
	Euonymine (69; R ¹ = OAc, R ² = H, R ³ = R ⁴ = Ac, R ⁵ = OH)	
	Evonine (69; R ¹ + R ² = O, R ³ = R ⁴ = Ac, R ⁵ = OH)	
	Wilfordine (68; R ¹ = OAc, R ² = H, R ³ = OCPH, R ⁴ = OH)	
<i>E. europaeus</i>	2,5-Bisdeacetylevonine (69; R ¹ + R ² = O, R ³ = R ⁴ = H, R ⁵ = OH)	93
	2-Deacetylevonine (69; R ¹ + R ² = O, R ³ = H, R ⁴ = Ac, R ⁵ = OH)	
	4-Deoxyevonine (69; R ¹ + R ² = O, R ³ = R ⁴ = Ac, R ⁵ = H)	
<i>E. sieboldiana</i>	Euonine (68; R ¹ = OAc, R ² = R ⁴ = H, R ³ = Ac)	95
	Evonimine (68; R ¹ + R ² = O, R ³ = Ac, R ⁴ = H)	
<i>Helminthosporium sativum</i>	Victoxinine (70)	96
<i>Nuphar luteum</i>	Neothiobinupharidine (72)	97
	Neothiobinupharidine sulphoxide (72; S → O)	98
	Nupharolutine (73; R ¹ = OH, R ² = Me, R ³ = H)	99
	Thiobinupharidine (= Thionupholutine-A) (72; isomeric with neothiobinupharidine)	97
<i>N. luteum</i> subsp. <i>macrophyllum</i>	6,7-β-Oxidodeoxynupharidine dimer (74)	100

^a Absence of some structural formulae is due to inaccessibility of original literature.^b Alkaloids previously isolated from this species. ^c Also found in *D. friedricksianum* and *D. hildebrandii*, cf. Vol. 3 of this Report.



- ⁸⁵ D. Gross, W. Berg, and H. R. Schuette, *Phytochemistry*, 1972, **11**, 3082.
- ⁸⁶ T. U. Rakhmatullaev and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 350 (*Chem. Abs.*, 1972, **77**, 162 012x).
- ⁸⁷ T. U. Rakhmatullaev and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, **9**, 64 (*Chem. Abs.*, 1973, **78**, 159 956y).
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- ⁹⁰ D. Gross, W. Berg, and H. R. Schuette, *Phytochemistry*, 1973, **12**, 201.
- ⁹¹ K. Hedman and K. Leander, *Acta Chem. Scand.*, 1972, **26**, 3177.
- ⁹² Y. Shizuri, K. Yamada, and Y. Hirata, *Tetrahedron Letters*, 1973, 741.
- ⁹³ L. Crombie, P. J. Ham, and D. A. Whiting, *Phytochemistry*, 1973, **12**, 703.
- ⁹⁴ H. Budzikiewicz, A. Roemer, and K. Taraz, *Z. Naturforsch.*, 1972, **27b**, 800.
- ⁹⁵ K. Sugiura, K. Yamada, and Y. Hirata, *Tetrahedron Letters*, 1973, 113.
- ⁹⁶ F. Dorn and D. Arigoni, *J.C.S. Chem. Comm.*, 1972, 1342.
- ⁹⁷ R. T. LaLonde and C. F. Wong, *Phytochemistry*, 1972, **11**, 3305.
- ⁹⁸ J. T. Wrobel, A. Iwanow, J. Szychowski, J. Poplawski, C. K. Yu, T. I. Martin, and D. B. MacLean, *Canad. J. Chem.*, 1972, **50**, 1968.
- ⁹⁹ J. T. Wrobel, A. Iwanow, C. Braekman-Danheux, T. I. Martin, and D. B. MacLean, *Canad. J. Chem.*, 1972, **50**, 1831.
- ¹⁰⁰ R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Amer. Chem. Soc.*, 1972, **94**, 8522.



δ -skytanthine (65) (previously obtained only from *Skytanthus acutus*) and Δ^5 -dehydroskytanthine (65; $\Delta^{5,6}$), a new alkaloid which was clearly distinguished from the known Δ^8 -dehydroskytanthine (65; $\Delta^{8,9}$) on the basis of physical properties. It was converted by reduction into δ -skytanthine (65) and the location of its double bond was assigned by n.m.r. spectroscopy.

The configurational assignment at nitrogen in *N*-isopentenyl dendrobium bromide (66; $R^1 = CH_2CH=CMe_2$, $R^2 = Me$) from *Dendrobium nobile* is based on the following reactions: alkylation of dendrobine (67; $R = Me$) with 1-bromo-3-methylbut-2-ene gave compound (66; $R^1 = Me$, $R^2 = CH_2CH=CMe_2$), distinguishable from the natural product on the basis of physical and

spectral data. However, treatment of *N*-isopentenylordendrobine (67; $R = CH_2CH=CMe_2$) with methyl iodide did give (66; $R^1 = CH_2CH=CMe_2$, $R^2 = Me$). Models indicate that the alkylating agent should approach from the less hindered side, *i.e.* the side opposite the lactone bridge, and this argument leads to the configurational assignment. The new alkaloid dendrobine *N*-oxide (66; $R^1 = Me$, $R^2 = O^-$) was synthesized by *m*-chloroperbenzoic acid oxidation of dendrobine and its configuration rests also on the above argument.

Spectroscopic and chemical degradative evidence similar to that previously discussed (Vol. 3 of this Report) has been used in adding new structures to the list of known alkaloids isolated from *Euonymus* species. Some of the early work in this area has been reviewed.¹⁰¹ The new alkaloid, alatamine (68; $R^1 + R^2 = O$, $R^3 = OPh$, $R^4 = OH$) differs from evonine (69; $R^1 + R^2 = O$, $R^3 = R^4 = Ac$, $R^5 = H$) in one of the pyridine side-chains. This can be shown by hydrolysis of alatamine to yield a dicarboxylic acid of a 2,3-disubstituted pyridine corresponding to structure (68). Correlation of alatamine with the known wilfordine (68; $R^1 = OAc$, $R^2 = H$, $R^3 = OPh$, $R^4 = OH$) can be achieved by successive sodium borohydride reduction and acetylation of the former into the latter. Two additional alkaloids of the same structural type (68) were isolated from *E. sieboldiana*.

The report⁹³ describing the isolation and characterization of 2,5-bisdeacetyl-evonine and 2-deacetylevonine from *E. europaeus* provides a method for selective deacetylation with concurrent benzylation at the C-5 oxygen function of evonine (69; $R^1 + R^2 = O$, $R^3 = R^4 = Ac$, $R^5 = OH$). In this manner, C-5 *p*-bromo- and *p*-iodo-benzyl-derivatives were prepared but were found to be unsuitable for X-ray analysis.

The structure and absolute configuration of the *Euonymus* alkaloids evonine (69; $R^1 + R^2 = O$, $R^3 = R^4 = Ac$, $R^5 = OH$) and neoevonine (69; $R^1 + R^2 = O$, $R^3 = Ac$, $R^4 = H$, $R^5 = OH$) has been conclusively established by X-ray analysis of the C-5 bromoacetyl derivative of neoevonine monohydrate.¹⁰²

Victoxinine (70) hydrochloride is a component isolated 15 years ago from victorin, a potent host-specific toxin from *Helminthosporium victoriae*. It has now been obtained from the culture filtrate of *H. sativum* and its structure was proposed on the basis of partial n.m.r. analysis and suspected biogenetic relationship to prehelminthosporal (71) also isolated from *H. sativum*.⁹⁶ Correctness of structure (70) was confirmed by a four-step synthesis from (71).

The rhizomes of *Nuphar luteum* growing in Poland have yielded neothio-binupharidine (72) and a stereoisomer of (72), thionuphlutine-A. Thionuphlutine-A was shown by direct comparison to be identical with thiobinupharidine prepared by metal hydride reduction of 6,6'-dihydroxythionuphlutine-A, a biscarbinolamine alkaloid corresponding to gross structure (72) (*cf.* Vol. 2 of this Report). It is suggested that the name of thiobinupharidine, rather than

¹⁰¹ O. Clauder, L. Hutas, and K. Bojthe-Horvath, *Biochem. Physiol. Alkaloide*, Fourth Internat. Symposium, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 203.

¹⁰² K. Sasaki and Y. Hirata, *J.C.S. Perkin II*, 1972, 1268.

thionuphlutine-A, be retained in the literature. Interestingly, neither neothiobinupharidine nor thiobinupharidine have been detected in *N. luteum* subsp. *macrophyllum* and *N. variegatum* growing in North America. A footnote in this paper⁹⁷ suggests on the basis of a chemical correlation that nuphleine and 6,6'-dihydroxythionuphlutine-A are identical. Neothiobinupharidine sulphoxide (72; $S \rightarrow O$) is the first representative of a *Nuphar* alkaloid possessing a sulphoxide moiety.⁹⁸ Comparison of the mass spectra of (72; $S \rightarrow O$) with neothiobinupharidine (72) was decisive in structural analysis. The two compounds showed many similarities in the lower mass region, the major differences being in the loss of SOH and MeSO fragments for (72; $S \rightarrow O$) compared with the parallel loss of SH and CH₂SH for (72). In addition, an intense peak corresponding to loss of OH was present in neothiobinupharidine sulphoxide. The above information suggested the sulphoxide structure (72; $S \rightarrow O$) for the new alkaloid and this was confirmed by its chemical inter-relationship with neothiobinupharidine (72). The configuration at sulphur remains to be determined.

The monomeric *Nuphar* alkaloid nupharolutine has been shown to possess structure (73; $R^1 = OH$, $R^2 = Me$, $R^3 = H$) on the basis of extensive interpretative comparison of its n.m.r. and high-resolution mass spectra with those of deoxynupharidine (73; $R^1 = R^3 = H$, $R^2 = Me$) and related alkaloids. The presence of a hydroxy-group was indicated by the i.r. spectrum and its tertiary nature was deduced from acetylation studies. The n.m.r. spectrum showed signals at δ 0.92 (d, 3H) and δ 1.21 (s, 3H) which, if compared with the spectrum of deoxynupharidine (73; $R^1 = R^3 = H$, $R^2 = Me$) [δ 0.89 (d, 3H) and δ 1.01 (d, 3H)] supported this assignment. That the OH group is located at the tertiary position in ring B rather than ring A was suggested by the common features of the mass spectra of nupharolutine and castoramine (73; $R^1 = R^3 = H$, $R^2 = CH_2OH$). I.r. (Bohlmann bands, non-hydrogen-bonded OH) and n.m.r. (similarity of chemical shift of the C-4 proton to alkaloids with established equatorial furan arrangement) data allowed the stereochemical assignments indicated with the exception of the configuration of the Me function at C-1. However, nupharolutine was converted into deoxynupharidine (t.l.c. and g.l.c. evidence) and therefore may be assigned the structure (73; $R^1 = OH$, $R^2 = Me$, $R^3 = H$).

The unusual alkaloid (74), isolated from *N. luteum* subsp. *macrophyllum*, may be considered to be a dimer of (75), a compound possessing the relatively rare 2-amino-oxiran unit. Various spectral data established the presence of a deoxynupharidine (73; $R^1 = R^3 = H$, $R^2 = Me$) skeleton with oxygenated carbons at C-6 and C-7. The dimeric nature was evident from the n.m.r. spectrum (two overlapping quartets for C-4 and C-4' hydrogens, two singlets (1:1) for the C-6 and C-6' hydrogens) and was demonstrated by high-resolution mass spectral and molecular weight determinations. Final confirmation of structure and part stereochemistry was achieved by synthesis. Osmium tetroxide oxidation of Δ^6 -dehydrodeoxynupharidine gave the diol (73; $R^1 = R^3 = OH$, $R^2 = Me$) which on standing dehydrated to the dimer (74). The same diol was also isolated from the plant and was shown to be converted into the dimer (74). The *trans*-fused, chair-chair conformation of the quinolizidine ring was established by

examination of solvent-induced shift behaviour of the C-7 and C-1 methyl groups in the n.m.r. spectrum of (74) in comparison with those observed for simple *Nuphar* alkaloids. The remaining question, that of the configurations of C-6 and C-6', was deduced from molecular models, taking into account the chemical-shift non-equivalence of the C-4 and C-4', and C-6 and C-6' protons. From the three possible stereoisomeric dimers differing in configuration at C-6 and C-6', it may be seen that (74), which exhibits two *trans*, chair-chair quinolizidines hooked into a chair 1,4-dioxan ring, is energetically the most favourable and satisfies the molecular symmetry point group (C_1), giving non-equivalence of the C-4 and C-4', and C-6 and C-6' protons. Aerial oxidation of Δ^6 -dehydrodeoxynupharidine followed by borohydride reduction of the crude mixture produced compounds (73; $R^1 = OH$, $R^2 = Me$, $R^3 = H$) and (73; $R^1 = Me$, $R^2 = OH$, $R^3 = H$) thus providing evidence for the formation of the two diols (73; $R^1 = R^3 = OH$, $R^2 = Me$) and (73; $R^1 = Me$, $R^2 = R^3 = OH$), respectively, in the oxidation. Since both diols were also obtained from plant material, the question as to whether or not these are true metabolites or are formed from the Δ^6 -enamine during the isolation procedure remains to be answered. On the basis of examination of reported physical and spectral data, it would appear that the alcohol (73; $R^1 = OH$, $R^2 = Me$, $R^3 = H$) is identical with nupharolutine (*vide supra*).⁹⁹

Alkaloid accumulation studies in leaves, stalks, and flowers of *Nuphar luteum* and *Nymphaea candida* have been carried out.¹⁰³

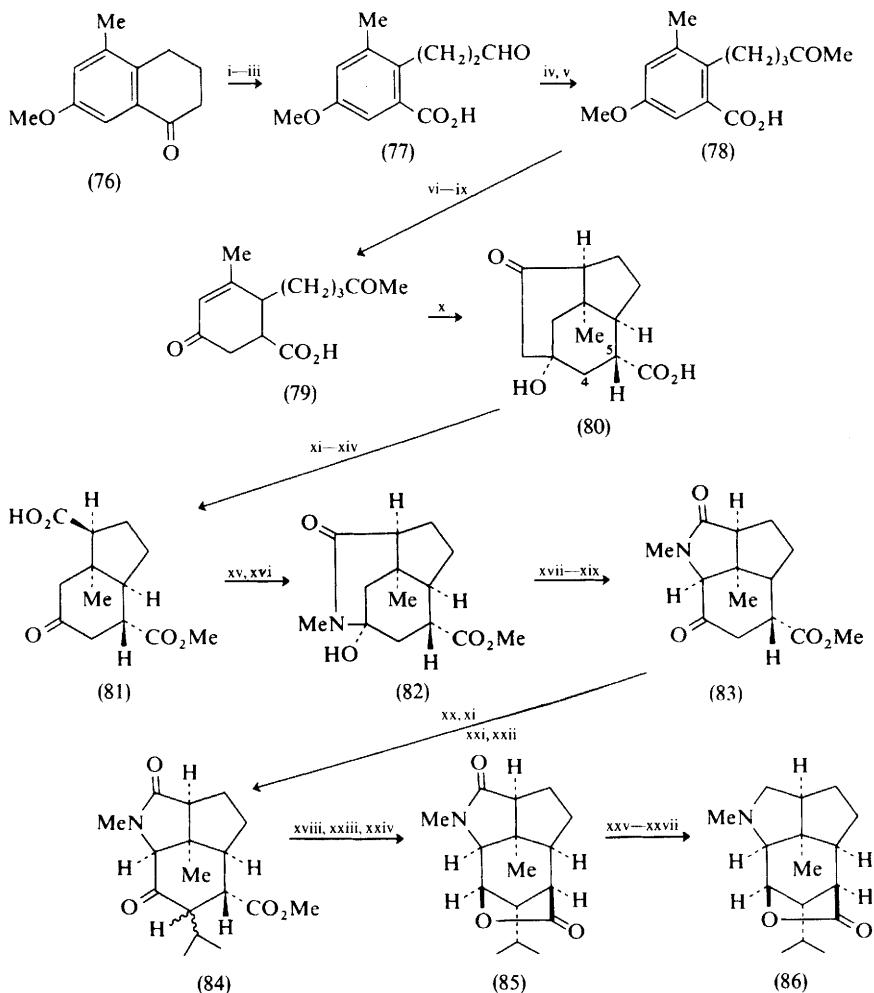
Synthetic work is highlighted this year by two reports of total synthesis by Japanese groups (Schemes 7 and 8).^{104,105} In one report¹⁰⁴ (Scheme 7) which parallels in part previous work (*cf.* Vol. 3 of this Report), the ketone (76) was converted into the acid aldehyde (77) which, *via* a Wittig synthesis followed by hydrolysis, gave the keto-acid (78). Compound (78) was transformed into the key intermediate (79) by a five-step sequence. A combination Michael-aldol stereoselective cyclization of (79) to give the *cis*-hydrindane (80) (and the C-5 epimeric acid, 8:1) was partially based on previous work by W. S. Johnson and co-workers. The stereochemical assignments for (80) and its C-5 epimer were deduced by spectral and chemical means and were reported separately.¹⁰⁶ The ketol acid (80) was converted into an enol acetate ester which was subjected to ozonolysis to give compound (81). Activation of the carboxylic acid function with *NN'*-carbonyldi-imidazole followed by treatment with methylamine gave the lactam (82). Advantage was taken of the masked ketone in (82) to convert it into the α -bromo-derivative and the latter was rearranged by sodium hydride to the pyrrolidone (83). The establishment of stereochemistry of the last three compounds was also reported separately.¹⁰⁶ The isopropyl function was intro-

¹⁰³ L. V. Prosvirova, *Vopr. Obshch. Khim. Biokhim.* 1970, 31 (*Chem. Abs.*, 1972, 77, 111 518j).

¹⁰⁴ K. Yamada, M. Suzuki, Y. Hayakawa, K. Aoki, H. Nakamura, H. Nagase, and Y. Hirata, *J. Amer. Chem. Soc.*, 1972, **94**, 8278.

¹⁰⁵ Y. Inubushi, T. Kikuchi, T. Ibuka, K. Tanaka, I. Saji, and K. Tokane, *J.C.S. Chem. Comm.*, 1972, 1252.

¹⁰⁶ M. Suzuki, Y. Hayakawa, K. Aoki, H. Nagase, H. Nakamura, and K. Yamada, *Tetrahedron Letters*, 1973, 331.

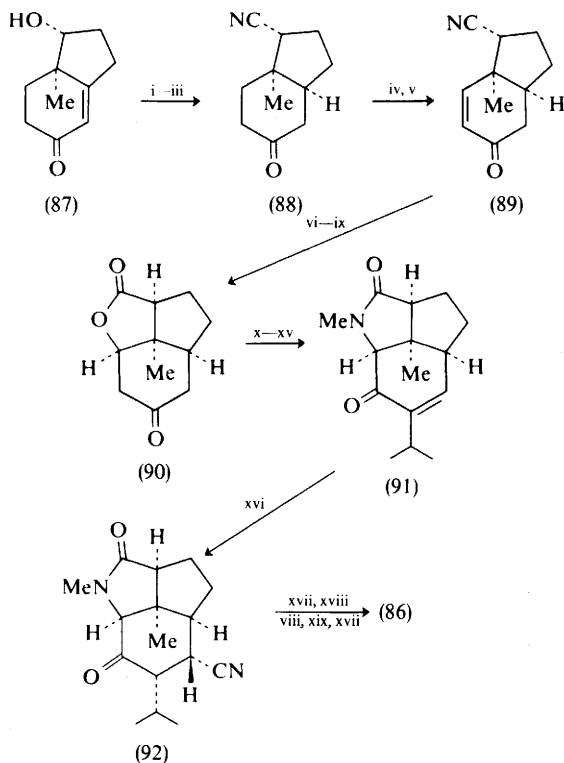


Reagents: i, Ac_2O , TsOH , reflux; ii, O_3 , MeOH , Me_2S , -75°C ; iii, OH^- ; iv, $\text{Ph}_3\text{PCH}_2^-\text{CH(OMe)Me Cl}^-$, MeSOCH_2 , DMSO , glyme, -40°C ; v, H_2O , (CO_2H) ; vi, H^+ , $\text{HOCH}_2\text{CH}_2\text{OH}$; vii, Li , NH_3 , Bu^tOH , THF , -33°C ; viii, H_2O , $(\text{CO}_2\text{H})_2$; ix, 0.4N-HCl , EtOH ; x, Bu^tOK , Bu^tOH , r.t.; xi, CH_2N_2 ; xii, Ac_2O , $10\text{-camphorsulphonic acid}$, 105°C , 24 h ; xiii, O_3 , EtOAc , HOAc , 0°C ; xiv, H_2O ; xv, NN' -carbonyldi-imidazole, 80°C , neat; xvi, 40% aq. MeNH_2 , glyme; xvii, pyridinium bromide perbromide, THF ; xviii, NaH , glyme, reflux; xix, anhydr. $(\text{CO}_2\text{H})_2$; xx, HCO_2Me , NaOMe , C_6H_6 ; xxi, Bu^tSH , $10\text{-camphorsulphonic acid}$, C_6H_6 ; xxii, LiCuMe_2 , Et_2O , -25°C ; xxiii, NaBH_4 , EtOH ; xxiv, H_3O^+ ; xxv, $\text{Et}_3\text{O}^+\text{BF}_4^-$, CH_2Cl_2 ; xxvi, NaBH_4 , glyme; xxvii, anionic Amberlite IR-4A.

Scheme 7

duced into the six-membered ring of (83) by a combination of old and new synthetic methodology. The resulting compound (84) was partially equilibrated with base to give the desired stereochemistry at C-4 and C-5, and this reaction was followed by two simple steps to afford the known oxodendrobine (85). The final stage of the synthesis of (\pm)-dendrobine (86), the reduction of the lactam, was effected by the Borch procedure (but not without a complication).

A key *cis*-hydrindane intermediate was also used in the alternative reported synthesis of (\pm)-dendrobine (Scheme 8).¹⁰⁵ The known ketol (87) was readily converted into the saturated ketonitrile (88) which, upon a bromination–dehydrobromination sequence, gave the enone (89) together with (87) in a ratio of 1:3–4. Compound (89) was converted into the lactone (90) in a lengthy series of

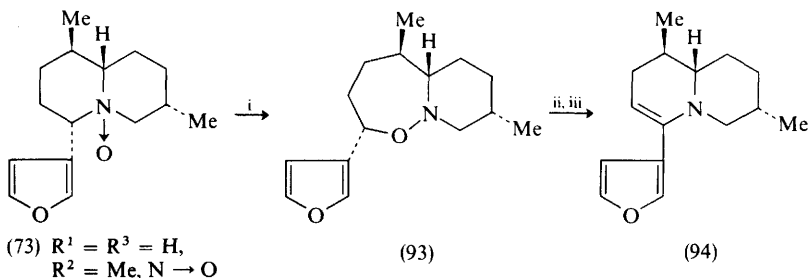


Reagents: i, TsCl, C_5H_5N ; ii, NaCN, DMSO; iii, Pd–SrCO₃, H₂; iv, Br₂; v, HBr, conds. not given; vi, H⁺, HOCH₂CH₂OH; vii, KOH, HOCH₂CH₂OH, H₂O; viii, dil. HCl; ix, 25% H₂SO₄, HOCH₂CH₂OH; x, MeNH₂, HCl, H₂O; xi, Pr⁺MgBr; xii, KHSO₄; xiii, I₂, AcOAg, HOAc, H₂O; xiv, KOH, H₂O, MeOH; xv, CrO₃, C_5H_5N ; xvi, Et₃AlCN; xvii, NaBH₄; xviii, aq. KOH; xix, Et₃O⁺BF₄[–].

Scheme 8

reactions but in >55% overall yield. Some (90) is formed in the potassium hydroxide reaction (step vii); the remaining acid was epimerized and lactonized by the sulphuric acid treatment (step ix). Lactone (90) was treated with methylamine and the resulting lactam was transformed into compound (91) in 10% yield using a Grignard reaction followed by allylic functionalization with Prévost's reagent and subsequent hydrolysis and oxidation. The isomeric enone resulting from allylic rearrangement was produced in 20% yield. Hydrocyanation of (91) gave three isomeric cyano-ketones, one of which (92) (18% yield) was reduced and hydrolysed to oxodendrobine (85). As in the synthesis of Scheme 7, Borch's method was used for the reduction of (85) to (\pm)-dendrobine (86).

In continuing the search for selective introduction of functionality into rings A or B of *Nuphar* alkaloids, LaLonde and co-workers have now reported a neat transformation of (+)-nupharidine (73; $R^1 = R^3 = H$, $R^2 = Me$, $N \rightarrow O$) into the corresponding Δ^3 -enamine (94) (Scheme 9).¹⁰⁷ Meisenheimer rearrangement



Reagents: i, $MeCONMe_2$, reflux; ii, Zn , $HOAc$, H_2O ; iii, MnO_2 .

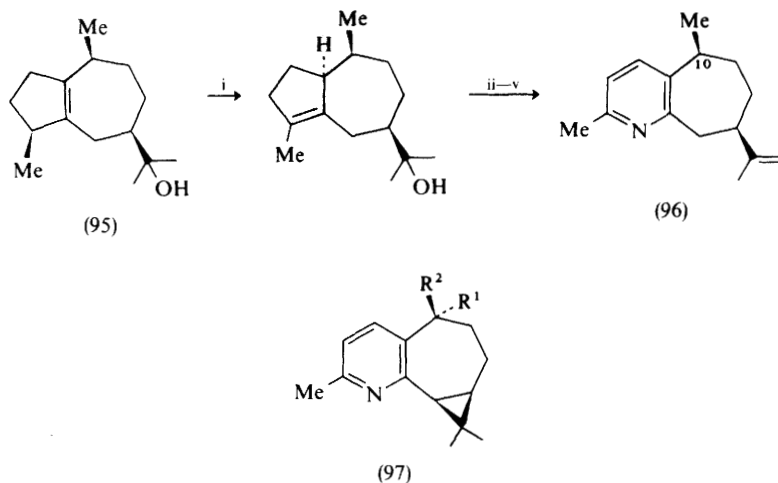
Scheme 9

of (+)-nupharidine gave, regioselectively, the hexahydro-1,2-oxazepine (93) which in two steps provided the unstable enamine (94) which could be reduced with sodium borohydride or borodeuteride in ethanol to give (–)-deoxy-nupharidine (73; $R^1 = R^3 = H$, $R^2 = Me$) and the deoxy-[4β - 2H]nupharidine, respectively. Mass spectra of deoxy-[4β - 2H]- and -[$6\beta,7\beta$ - 2H_2]-nupharidine were also reported in this paper.¹⁰⁷

The alkaloid isolated from *Pogostemon patchouli* originally assigned a C-10 epimeric structure has been shown to possess structure (96) by synthesis from guaiol (95) (Scheme 10).¹⁰⁸ The C-10 epimer of (96) was also prepared from a sesquiterpenoid for comparison purposes. The C-10 configuration in these compounds was determined by comparison of their C-10 Me chemical shifts with those in the conformationally rigid tricyclic compounds (97; $R^1 = H$, $R^2 = Me$) and (97; $R^1 = Me$, $R^2 = H$) which were obtained in small quantities from the above syntheses.

¹⁰⁷ R. T. LaLonde, J. T. Woolever, E. Auer, and C. F. Wong, *Tetrahedron Letters*, 1972, 1503.

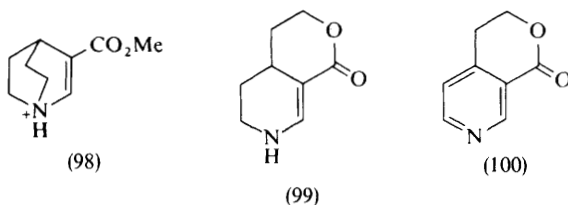
¹⁰⁸ A. Van der Gen, L. M. Van der Linde, and J. G. Witteveen, *Rec. Trav. chim.*, 1972, 91, 1433.



Reagents: i, Pd-C, H₂, EtOAc; ii, O₃, EtOAc, -30 °C; iii, NaHSO₃; iv, NH₂OH.HCl, EtOH; v, SOCl₂, C₅H₅N.

Scheme 10

Details of the synthesis of gentianadine (100) involving the interesting rearrangement [(98) → (99)] (*cf.* Vol. 3 of this Report) have been reported.¹⁰⁹



Anti-inflammatory,¹¹⁰ sedative,¹¹¹ ataractic,¹¹² and other pharmacological activities¹¹³ of gentianine (62; R = H) and related alkaloids have been studied.

¹⁰⁹ J. Dolby, K. H. Hasselgren, S. Castensson, and J. L. G. Nilsson, *Acta Chem. Scand.*, 1972, **26**, 2469.

¹¹⁰ F. Sadritdinov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 146 (*Chem. Abs.*, 1973, **78**, 79 634b).

¹¹¹ N. Tulyaganov, B. L. Danilevskii, and F. S. Sadritdinov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 148 (*Chem. Abs.*, 1973, **78**, 66 918x).

¹¹² B. L. Danilevskii, N. T. Tulyaganov, and F. S. Sadritdinov, *Doklady Akad. Nauk Uzbek. S.S.R.*, 1972, **29**, 37 (*Chem. Abs.*, 1973, **78**, 38 001z).

¹¹³ A. S. C. Wan, E. Macko, and B. Douglas, *Asian J. Med.* 1972, **8**, 334 (*Chem. Abs.*, 1973, **78**, 11 686q).

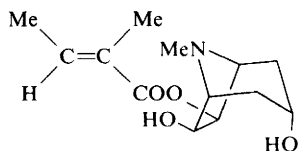
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Tropane Alkaloids

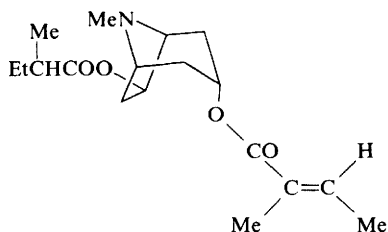
BY J. E. SAXTON

The distribution of alkaloids in the arborescent *Datura suaveolens* H. and B. ex Willd. appears to be somewhat different from that observed in the other *Datura* species. In further investigations¹ on this plant it has been shown that the aerial parts contain apohyoscyne, 3 α ,6 β -ditigloyloxytropan-7 β -ol, hyoscyne, norhyoscyne, meteloidine, atropine, noratropine, (-)- and (\pm)-3 α -tigloyloxytropan-6 β -ol (not previously shown conclusively to be a normal constituent of plant material), and a new alkaloid, 6 β -tigloyloxytropane-3 α ,7 β -diol, m.p. 157—159 °C (1). A synthetic sample of this last base, m.p. 173—176 °C, exhibited similar spectra but, possibly owing to impurities in the small sample of natural alkaloid available, differed in melting point and also gave a crystalline picrate.

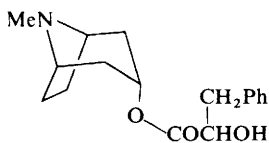
The roots of this plant were also extracted and, in line with observations on the other *Datura* species, were found to contain atropine, hyoscyne, 3 α ,6 β -ditigloyloxytropan-7 β -ol, meteloidine, cuscohygrine, and tropine; the presence of littorine was also claimed. Other alkaloids isolated included 3 α -acetoxytropane, (\pm)-3 α -tigloyloxytropan-6 β -ol, and three new bases, which exhibited the characteristics of diesters of tropane-3 α ,6 β -diol. One of these was identified as 6 β -(α -methylbutyryloxy)-3 α -tigloyloxytropane (2). The variety of tigloyl esters found in this species is thus greater than that found in other tree *Daturae*.¹



(1)



(2)



(3) Littorine

¹ W. C. Evans and J. F. Lampard, *Phytochemistry*, 1972, **11**, 3293.

In further investigations on the occurrence of the solanaceous alkaloids, the distribution of littorine [$(-)-3\alpha-(2\text{-hydroxy-3-phenylpropionyloxy})\text{tropane}$ (3)] and other alkaloids in the roots of nine *Datura* species has been examined.² Both littorine and cuscohygrine occur widely, and were shown to be present in all nine species extracted, viz., *D. stramonium* L., *D. ferox* L., *D. innoxia* Mill., *D. meteloides* DC. ex Dun., *D. metel* L. var. *fastuosa* (Bernh.) Danert, *D. leichhardtii* Muell. ex Benth., *D. cornigera* Hook., *D. candida* (Persoon) Safford, and *D. sanguinea* R. and P. In addition to these and other alkaloids isolated in previous investigations the following new occurrences have also been reported: tropine and ψ -tropine in *D. stramonium*, 3α -tigloyloxytropine in *D. meteloides*, tigloidine in *D. metel* L. var. *fastuosa*, *D. cornigera*, and *D. candida*, and hyoscyamine (or atropine) and hyoscyne in *D. leichhardtii*. It would thus appear that littorine and cuscohygrine, together with tropyl esters, tropine, ψ -tropine and their tigloyl esters, characterize the Datureae tribe of the family Solanaceae, and justify the inclusion in this tribe of both the *Datura* and *Solandra* genera.²

The alkaloid composition of two interspecific *Scopolia* hybrids has been examined. An F_1 hybrid from *S. sinensis* and *S. tangutica* contains scopolamine^{3,4} as principal alkaloid, whereas in the parent forms hyoscyamine is stated to be the main alkaloid.³ Both this hybrid and one from *S. sinensis* x *S. stramonifolia* apparently contain a higher proportion of alkaloids than the parent species, particularly in the budding phase.⁴

The botanical source of the *Mandragora* roots used medicinally for centuries is usually stated to be *M. officinalis* Mill. (\equiv *M. officinarum* L.), but this in turn appears to comprise two species, *M. autumnalis* Bertol. and *M. vernalis* Bertol. These two species, whose roots are structurally similar, have now been extracted individually, but the results show that the plants cannot be differentiated on the basis of their alkaloid content.⁵ Both species contain hyoscyamine, hyoscyne, atropine, cuscohygrine, and belladonnine, in confirmation of a previous report⁶ of their presence in the commercial *Mandragora* drug. In addition, 3α -tigloyloxytropine and 3,6-ditigloyloxytropine were isolated; this is the first time that tigloyl esters have been shown to occur in *Mandragora*.⁵

Another solanaceous plant extracted for the first time is *Physochlaina dubia* Pasch., the roots of which contain hyoscyamine, 6-hydroxyhyoscyamine (4), and 6-hydroxyhyoscyamine diacetate.⁷

The tree tomato, *Cyphomandra betacea* Sendt., which is cultivated for its edible fruits, has been shown to contain tropane alkaloids in its roots.⁸ The principal alkaloid, however, is solamine (5), which has not previously been encountered

² W. C. Evans, A. Ghani, and V. A. Woolley, *Phytochemistry*, 1972, **11**, 2527.

³ I. B. Sandina, *Rast. Resur.*, 1972, **8**, 524 (*Chem. Abs.*, 1973, **78**, 82 095).

⁴ E. A. Rezvaya and S. A. Minina, *Rast. Resur.*, 1973, **9**, 48 (*Chem. Abs.*, 1973, **78**, 121 281).

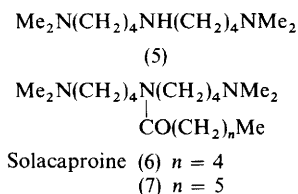
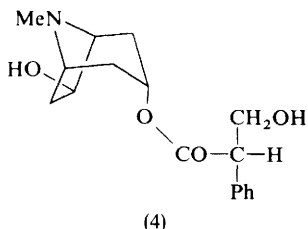
⁵ B. P. Jackson and M. I. Berry, *Phytochemistry*, 1973, **12**, 1165.

⁶ H. Staub, *Helv. Chim. Acta*, 1962, **45**, 2297.

⁷ R. T. Mirzamatov, V. M. Malikov, K. L. Lutfullin, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 493 (*Chem. Abs.*, 1973, **78**, 13 742).

⁸ W. C. Evans, A. Ghani, and V. A. Woolley, *J.C.S. Perkin I*, 1972, 2017.

naturally as the free base. Normally it occurs as its amide derivatives and indeed here also it is accompanied by its caproyl derivative, solacaproine (6), possibly contaminated by the homologue (7). Small amounts of tropinone and cuscohygrine were isolated from the roots, and the presence of atropine, tropine, ψ -tropine, and tigloidine was also detected.



New analytical procedures for the tropane alkaloids include one⁹ based on the use of Mayer's reagent labelled with ^{131}I , an improved colorimetric determination of atropine,¹⁰ and a refined method based on a simple extraction-titration procedure.¹¹ The methods recommended in the German, Belgian, Swiss, and French pharmacopoeias for the determination of belladonna alkaloids have also been compared.¹² An improved procedure for the separation of belladonna alkaloids by t.l.c., and their detection by Dragendorff's reagent followed by sodium nitrite, has been described.¹³

Several investigations have been directed towards increasing the total yield of belladonna alkaloids synthesized by the plant. When gibberellic acid was administered to plants of *Atropa belladonna* at the fourth or fifth leaf stage an increase in stem length, number of leaves, and number of branches was observed.¹⁴ There was also a pronounced increase in the alkaloid content in the plants, particularly at the flowering stage. *Datura stramonium* seeds treated with *N*-nitrosoethylurea or ethyleneimine yielded second generation mutants with different alkaloid content and morphological characteristics from those of the parent plants. One mutant induced by *N*-nitrosoethylurea produced more alkaloids than the other plants.¹⁵ The effect of feeding *NN*-dimethyl(2-chloroethyl)hydrazonium chloride (CMH), a growth regulator, to seedlings of *Datura metel* was to increase significantly the content of hyoscyne and hyoscyamine in the leaves and stems, but to decrease the content in the roots. It is suggested that

⁹ A. M. Nour, A. A. Saleh, A. E. M. Habib, N. Hamad, and A. F. Shalaby, *Isotopenpraxis*, 1972, **8**, 274 (*Chem. Abs.*, 1973, **78**, 23 812).

¹⁰ W. Wisniewski and S. Gwiazdzinska, *Acta Pol. Pharm.*, 1972, **29**, 347 (*Chem. Abs.*, 1972, **77**, 137 031).

¹¹ M. Dorer and M. Lubej, *Arch. Pharm. Ber. Deut. Pharm. Ges.*, 1972, **305**, 273 (*Chem. Abs.*, 1972, **77**, 39 316).

¹² A. Puech, M. Jacob, J. Dupy, and J. Grevoul, *J. Pharm. Belg.*, 1971, **26**, 520 (*Chem. Abs.*, 1972, **77**, 39 326).

¹³ A. Puech, M. Jacob, and D. Gaudy, *J. Chromatog.*, 1972, **68**, 161.

¹⁴ F. Reda and S. A. Baker, *J. Pharm. Sci.*, 1972, **61**, 1970.

¹⁵ P. M. Botnarenko, *Izvest. Akad. Nauk Mold. S.S.R., Ser. biol. khim. Nauk*, 1972, 16 (*Chem. Abs.*, 1973, **78**, 132 298).

alkaloid formation occurs in the roots, and is stimulated by CMH; and that migration of the alkaloids from the roots to the aerial portions of the plant is also accelerated by CMH.¹⁶ The yield of alkaloids in *Atropa caucasica* and *Datura godronii* was also increased significantly if the plants were irradiated with u.v. light three days before being harvested; the increased alkaloid content appears to be mainly due to atropine.¹⁷ The alkaloid content of solanaceous plants is also affected by belladonna mosaic or stolbur infection.¹⁸ In the *Datura*, *Atropa*, and *Scopolia* species studied the alkaloid content in the leaves was increased by mosaic infection; in the roots, however, stolbur infection increased the alkaloid content in *Scopolia tangutica* but decreased it in *S. stramonifolia*. The alkaloid content of *Datura innoxia*,¹⁹ *D. tatula*,²⁰ and *Hyoscyamus desertorum*²¹ during the various vegetative phases has been examined; in this last plant the major alkaloids are scopalamine and hyoscyamine.

It has been observed²² that tissue cultures of *Datura* produce different alkaloids from the intact plants. In the tissue cultures neither hyoscyamine nor hyoscyne could be detected. When hyoscyamine was administered to the tissue cultures no hyoscyne was produced, although the hyoscyamine content gradually diminished. This can be contrasted with the established conversion of hyoscyamine into hyoscyne in intact plants.

Details of the *in vitro* conversion of L-phenylalanine into S-(–)-tropic acid, previously reported in brief,²³ have now been published.²⁴

In seeking new methods for the synthesis of (–)-scopolamine (8) Khuong-Huu and her collaborators²⁵ have investigated possible methods for the introduction of an oxygen function into position 6 in derivatives of tropine. Oxidation of *N*-acetylnortropine (9) by means of lead tetra-acetate afforded mainly (60%) *N*-acetyldeoxynorscopoline (10), which was deacetylated by lithium in ethylamine to give deoxynorscopoline and thence, by Eschweiler–Clarke methylation, to deoxyscopoline (11). An alternative and more direct preparation of deoxyscopoline was afforded by the lead tetra-acetate oxidation of *N*-ethoxycarbonylnortropine (12), which gave an almost quantitative yield of *N*-ethoxycarbonyldeoxynorscopoline (13), reduction (LiAlH_4) of which gave deoxyscopoline (11). It should be noted that this last product has already been used in a synthesis of scopolamine.²⁶

¹⁶ E. N. Abou-Zied, *Experientia*, 1972, **28**, 662.

¹⁷ I. Yankulov, *Rastenievud Nauki*, 1972, **9**, 15 (*Chem. Abs.*, 1973, **78**, 94867).

¹⁸ M. Yankulova and I. Yankulov, *Doklady Akad. Sel'skokhoz. Nauk. Bolg.*, 1971, **4**, 299 (*Chem. Abs.*, 1972, **77**, 45657).

¹⁹ R. Zielinska-Sowicka and K. Szepczyńska, *Diss. Pharm. Pharmacol.*, 1972, **24**, 307.

²⁰ S. M. Aslanov, *Rast. Resur.*, 1972, **8**, 373 (*Chem. Abs.*, 1972, **77**, 111527).

²¹ N. N. Sabri, S. El-Masry, and S. M. Khafagy, *Planta Med.*, 1973, **23**, 4 (*Chem. Abs.*, 1973, **78**, 94789).

²² A. Romeike and H. Koblitze, *Kulturpflanze*, 1970, **18**, 169 (*Chem. Abs.*, 1972, **77**, 58764).

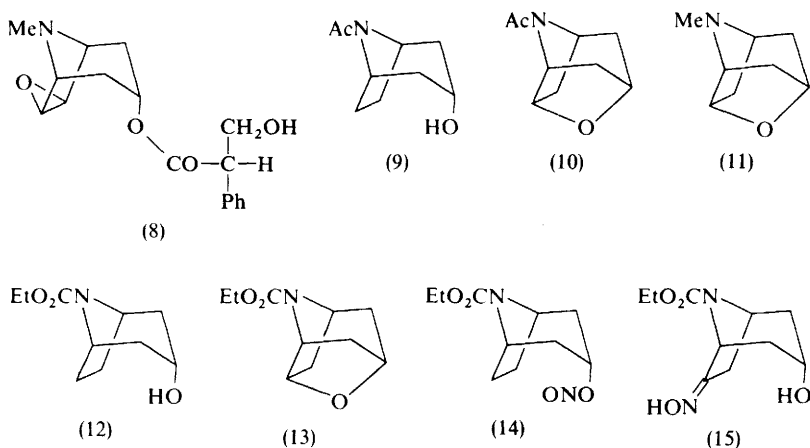
²³ K. Koga, C. C. Wu, and S. Yamada, *Tetrahedron Letters*, 1971, 2287.

²⁴ K. Koga, C. C. Wu, and S. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1282.

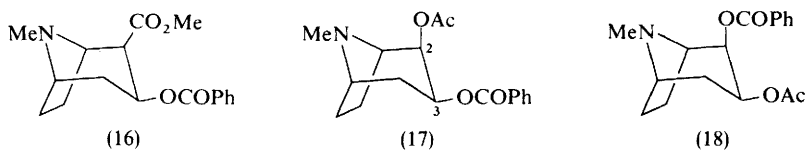
²⁵ F. Khuong-Huu, C. R. Bennett, P. E. Fouche, and R. Goutarel, *Compt. rend.*, 1972, **275**, C, 499.

²⁶ A. Stoll, A. Lindenmann, and E. Jucker, *Helv. Chim. Acta*, 1953, **36**, 1500; A. Stoll, E. Jucker, and A. Lindenmann, *ibid.*, 1954, **37**, 495, 649; G. Fodor, S. Kiss, and J. Rákóczi, *Chimie et Industrie*, 1963, **90**, 225.

In another experiment, irradiation of the nitrite ester (14) of *N*-ethoxycarbonylnortropine gave rise to 6-oximino-*N*-ethoxycarbonylnortropine (15); this has obvious potential as an alternative intermediate to (13).



In an attempt to develop further useful drugs of the cocaine (16) type the reverse esters (17) and (18) have been prepared;²⁷ of these (17) was not a stimulant, but no comment was made about (18). Benzoylation of tropane-2 β ,3 β -diol in pyridine, followed by the usual workup, gave mainly the 3-benzoate, from which (17) was obtained. However, when the benzoylation and acetylation were carried out without isolation of the intermediate benzoate the major product was the ester (18), indicating that the kinetically favoured benzoylation product of the diol is the 2-benzoate, which then isomerizes to the thermodynamically favoured 3-benzoate. In accordance with this it was shown that the 2-benzoate in [²H₆]-acetone or deuteriochloroform, when treated with one drop of D₂O for 15 h, gave an equilibrium mixture containing 75% of the 3-benzoate.²⁷

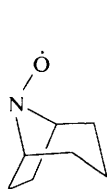


In connection with the study of stable dialkyl nitroxide radicals, Mendenhall and Ingold²⁸ have prepared nortropene-*N*-oxyl (19). This radical was observed to give, reversibly, a diamagnetic dimer (dimer R), but it also underwent an

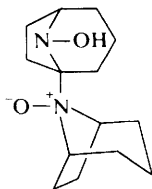
²⁷ S. J. Daum, C. M. Martini, R. K. Kullnig, and R. L. Clarke, *J. Org. Chem.*, 1972, **37**, 1665.

²⁸ G. D. Mendenhall and K. U. Ingold, *J. Amer. Chem. Soc.*, 1972, **94**, 7166.

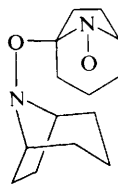
irreversible dimerization in the solid state, and in some solvents, to give a diamagnetic dimer (dimer J), which was shown by X-ray crystallography to have structure (20). In the course of attempting to establish the constitution of dimer J by chemical means, traces of the related hydroxylamine contaminating the nitroxide (19) were removed by reaction with silver oxide. Fractional sublimation of the product gave a residue of dimer J, some unchanged (19), and dark red crystals of a dimeric nitroxide radical, which was not identical with the product obtained by oxidizing dimer J (20) with silver oxide, and was in fact shown by the X-ray method to have the structure (21).



(19)



(20)



(21)

The mass spectra of further tropane and tropidine derivatives have been discussed,²⁹ as also have the n.m.r. spectra of some bifunctional tropanes in the presence of the europium paramagnetic shift reagent.³⁰

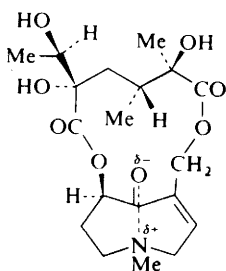
²⁹ J. E. Dewhurst, J. J. Kaminski, and J. H. Supple, *J. Heterocyclic Chem.*, 1972, **9**, 507.

³⁰ G. S. Chappell, B. F. Grabowski, R. A. Sandmann, and D. M. Yourtee, *J. Pharm. Sci.*, 1973, **62**, 414.

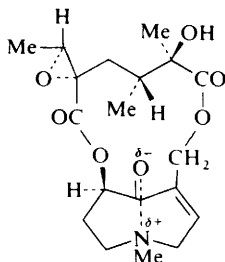
1 General

In last year's Report reference was made to an extensive survey and discussion of the c.d. spectra of seventeen representative pyrrolizidine alkaloids and their component necine bases and necic acids.¹ The conclusions of these workers have been confirmed and amplified by an equally extensive, independent investigation² along the same lines, in which some additional useful correlations and conclusions are made. For example, in neutral (ethanol) solution onetine (1) exhibits a broad c.d. band with a shoulder at approximately 260 nm which indicates the presence of a small amount of the amino-ketone form in equilibrium with the zwitterionic form (1). A similar curve is exhibited by otosenine (2); however, in methylcyclohexane the band owing to the aminoketone form is clearly discernible as a maximum at 285 nm, and in fact is stronger than the band at shorter wavelengths. Since no distinct band owing to the carbonyl group could be detected in the u.v. spectrum in ethanol, and in methylcyclohexane the shoulder exhibited is only weak, it is clear that the c.d. technique is a more sensitive probe for detecting such tautomers in small concentration than the u.v. spectrum.

The influence of the molecular conformation on the c.d. spectrum is well illustrated by madurensine (3), which is known to contain a macrocyclic dicarboxylic ester function attached to positions 1 and 6 of the pyrrolizidine ring.



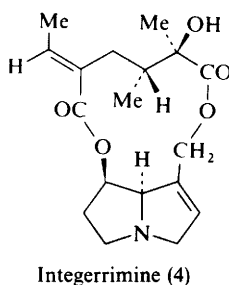
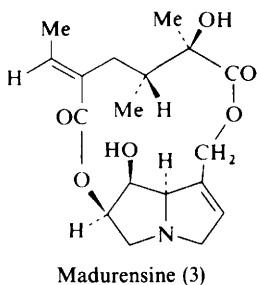
Onetine (1)



Otosenine (2)

¹ C. C. J. Culvenor, D. H. G. Crout, W. Klyne, W. P. Mose, J. D. Renwick, and P. M. Scopes, *J. Chem. Soc. (C)*, 1971, 3653.

² J. Hrbek, L. Hruban, A. Klásek, N. K. Kochetkov, A. M. Likhoshervostov, F. Šantavý, and G. Snatzke, *Coll. Czech. Chem. Comm.*, 1972, 37, 3918.

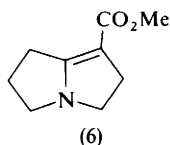
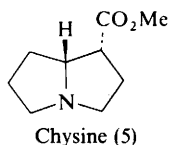


The c.d. spectrum of madurensine is of enantiomorphic type compared with those of related 1,7-diesters, e.g. integerrimine (4), indicating that in (3) the conformation of the diester ring system must be changed drastically.

2 The Ester Alkaloids

The large *Crotalaria* genus comprises more than 300 species, of which approximately 70 are indigenous to the Indian sub-continent. So far, 22 species have been investigated, and the chemistry of the alkaloids isolated from these species has been reviewed by Atal and Sawhney.³

The anomalous absorption reported at 290 nm (in hexane) or 302 nm (in ethanol) for chysine (5) has now been shown⁴ unequivocally to be due to contamination by the corresponding 1,8-dehydro-ester (6), formed by dehydrogenation of (5) during preparative g.l.c.



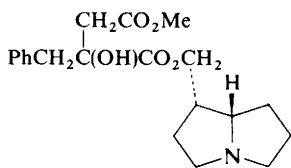
In a survey of the alkaloidal constituents of fourteen *Phalaenopsis* species not previously examined, Brandänge *et al.*⁵ have isolated a new alkaloid, phalaenopsine Is (7), from *Ph. equestris* Rchb. f. In common with the alkaloids phalaenopsine La and phalaenopsine T, phalaenopsine Is is an ester of monomethyl 2-benzylmalate of unknown configuration, the amino-alcohol component here being isoretronecanol. In a second extraction of this plant a mixture of phalaenopsine Is with its diastereoisomer phalaenopsine T (8), was obtained. A mixture of diastereoisomeric alkaloids was also obtained from *Ph. sanderiana* Rchb. f. and *Ph. stuartiana* Rchb. f.; here the constituents were phalaenopsine T (8) and phalaenopsine La (9). Phalaenopsine La was also shown to be present in *Ph.*

³ C. K. Atal and R. S. Sawhney, *Indian J. Pharm.*, 1973, **35**, 1.

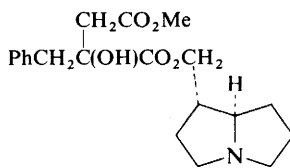
⁴ S. Brandänge, B. Lünig, and C. Lundin, *Acta Chem. Scand.*, 1973, **27**, 433.

⁵ S. Brandänge, B. Lünig, C. Moberg, and E. Sjöstrand, *Acta Chem. Scand.*, 1972, **26**, 2558.

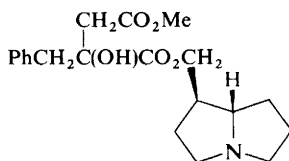
amboinensis, *Ph. schilleriana* and *Ph. sumatrana*, while phalaenopsine T also occurs in *Ph. aphrodite* and *Ph. fimbriata*. One or both of these alkaloids have also been detected in *Ph. hieroglyphica*, *Ph. lueddemanniana*, *Ph. violacea*, and *Ph. esmeralda* (\equiv *Doritis pulcherrima*). Two further species investigated, *Ph. gigantea* and *Ph. lindenii*, appeared not to contain alkaloids in the single extraction so far completed.⁵



Phalaenopsine Is (7)

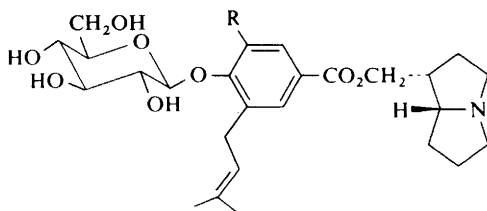


Phalaenopsine La (9)

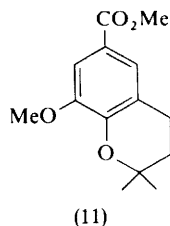


Phalaenopsine T (8)

The structure of hammarbine (10), the minor alkaloid of *Hammarbya paludosa* (L.) O.K., has now been elucidated.⁶ This alkaloid, obtained as an amorphous solid, gave lindelofidine and 2,2-dimethyl-6-methoxycarbonyl-8-methoxychroman (11) on acid-catalysed methanolysis, together with a small amount of methyl 4-hydroxy-3-methoxy-5-(3-methoxy-3-methylbutyl)benzoate (12). Acid hydrolysis of hammarbine gave glucose, which was shown by standard methods to be attached to the remainder of the molecule by its anomeric centre. Since the rotation of hammarbine is similar to that of its congener, paludosine (13), it is also assumed to contain a β -D-glucopyranosidic linkage, as shown in (10).

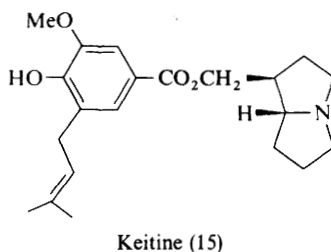
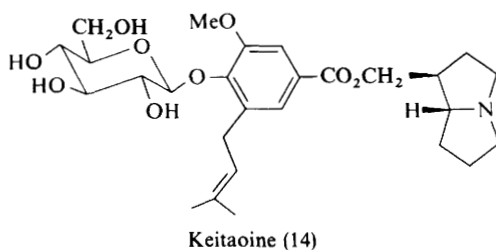
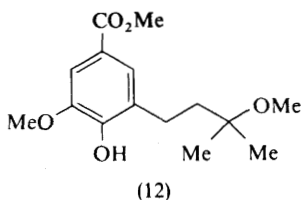


Hammarbine (10) R = OMe

Paludosine (13) R = CH₂CH=CMc₂

(11)

⁶ B. Lindström and B. Lünig, *Acta Chem. Scand.*, 1972, **26**, 2963.



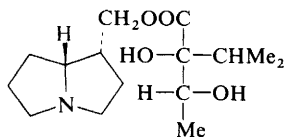
Two related alkaloids have also been isolated from *Liparis keitaoensis* Hay. The structure of keitaoine (14) follows from its acid-catalysed methanolysis to laburnine, the chroman derivative (11), and the ester (12), and from the production of glucose on acid hydrolysis. Conventional methods established the presence of a β -D-glucopyranoside ring in keitaoine, which therefore has the constitution (14).

The second alkaloid, keitine, contains neither glucose nor any other sugar residue, and since it affords laburnine and the compounds (11) and (12) on acid-catalysed methanolysis it must contain a free phenolic group, as shown in (15). When subjected to the same reaction conditions as obtained during the isolation of the alkaloids from the plant, keitaoine did not afford keitine, so the latter may well exist in the plant; however, *post mortem* enzymic hydrolysis of (14) to (15) has not yet been definitely excluded.⁶

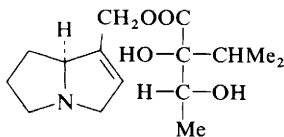
The roots of *Eupatorium stoechadosmum* Hance, used as a diuretic and as a source of incense in Japan, contain lindelofine (16) and supinine (17).⁷

⁷ T. Furuya and M. Hikichi, *Phytochemistry*, 1973, **12**, 225.

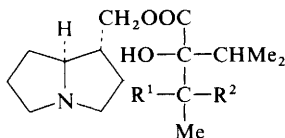
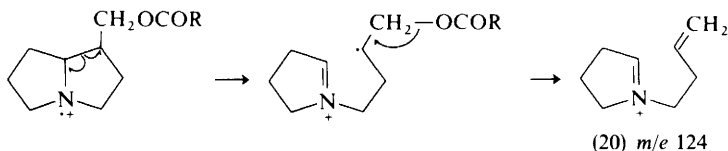
Pictumine, $C_{14}H_{23}NO_4$, is a new ester alkaloid isolated from the aerial parts of *Cynoglossum pictum* Ait.⁸ Its structure has not been clarified, but it is reported to contain a heliotridane nucleus, an $\alpha\beta$ -unsaturated ester group, and a tertiary hydroxy-group.



Lindelofine (16)



Supinine (17)

Viridiflorine (18) $R^1 = OH, R^2 = H$ Trachelanthamine (19) $R^1 = H, R^2 = OH$ (20) m/e 124

The mass spectra of viridiflorine (18) and its acetonide, trachelanthamine (19) and its acetate, and lindelofine (16) have been recorded.⁹ As expected, the isomers (16), (18), and (19) gave very similar spectra, although there were some differences in peak intensities. The base peak in all five spectra is due to the fragment (20) at m/e 124.

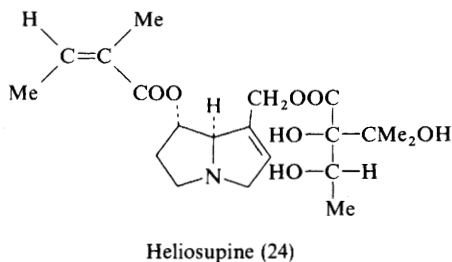
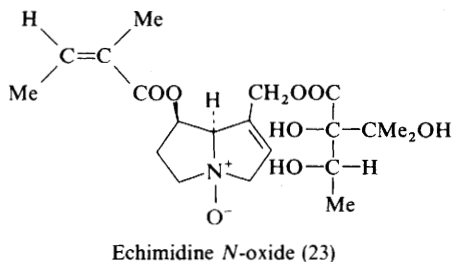
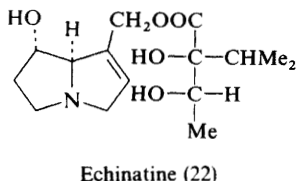
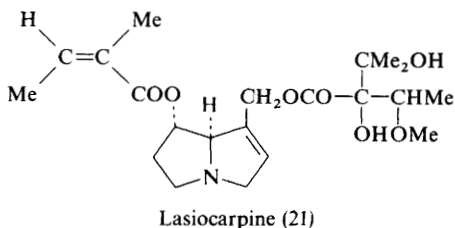
The alkaloid content of *Symphytum caucasicum* during its vegetative development in different localities has been studied.¹⁰ The maximum alkaloid content was observed in the roots of Tashkent plants. Eight alkaloids were detected, of which asperumine, lasiocarpine (21), echinatine (22) and echimidine *N*-oxide (23) were identified. In a similar study¹¹ of the constituents of *Paracynoglossum imeretinum* heliosupine (24), echinatine and their *N*-oxides were shown to be present in all phases of plant growth during a two-year period. Heliosupine and

⁸ I. V. Man'ko and L. G. Marchenko, *Khim. prirod. Soedinenii*, 1972, **8**, 655 (*Chem. Abs.*, 1973, **78**, 84 611).

⁹ U. A. Abdullaev, Y. V. Rashkes, K. Shakhidoyatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 634 (*Chem. Abs.*, 1973, **78**, 84 612).

¹⁰ I. V. Man'ko, Z. V. Mel'kumova, and V. F. Malysheva, *Rast. Resur.*, 1972, **8**, 538 (*Chem. Abs.*, 1973, **78**, 82 085).

¹¹ I. V. Man'ko, L. G. Marchenko, and O. Ya. Peshkova, *Rast. Resur.*, 1972, **8**, 371 (*Chem. Abs.*, 1972, **77**, 111 526).



its *N*-oxide have also been shown to occur in *Cynoglossum pictum* roots.¹² *Senecio sylvaticus* L, the wood groundsel, a European species naturalized in New Zealand, contains sarracine *N*-oxide (25).¹³ Extraction of the plant material and evaporation at low temperature gave solely sarracine *N*-oxide. However, prolonged boiling during Soxhlet extraction gave non-crystalline benzene-soluble material which afforded sarracine *N*-oxide on oxidation with hydrogen peroxide. Hydrolysis of the crude alkaloid gave angelic acid contaminated with some tiglic acid. It is suggested that both the reduction of the *N*-oxide to sarracine, and the isomerization of angelic to tiglic ester are possibly free-radical processes initiated by iron ions present in the plant material. The alkaloid silvasenecine, obtained by Müller¹⁴ in the only previous extraction of this plant, may well be a

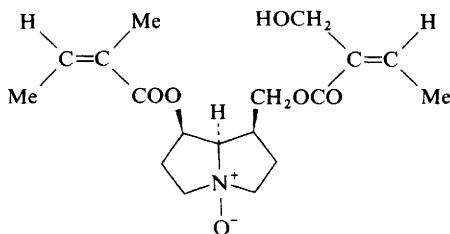
¹² I. V. Man'ko and L. G. Marchenko, *Khim. prirod. Soedinenii*, 1972, **8**, 812 (*Chem. Abs.*, 1973, **78**, 94812).

¹³ E. P. White and F. L. Warren, *Anales de Quim. (B)*, 1972, **68**, 723.

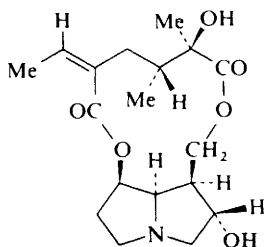
¹⁴ A. Müller, *Heil-u. Gewurz-Pflanzen*, 1924, 7 (from J. J. Blackie, *Pharm. J.*, 1937, **138**, 102). (*Chem. Zentr.*, 1925, II, 1049).

mixture of sarracine and its *N*-oxide contaminated with the corresponding tiglate esters.¹³

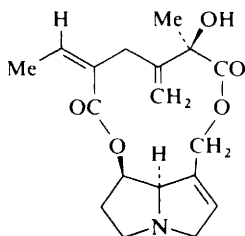
Echium italicum var. *biebersteinii* contains six alkaloids, of which one is stated to be related to echiumine, while two others are probably retronecine and heliotridine diesters.¹⁵ *Echium diffusum* apparently contains the same three alkaloids. It should be noted that *Echium italicum* L. proper contains echimidine, but full details of this work are not available.¹⁶



Sarracine *N*-oxide (25)



Rosmarinine (26)



Seneciophylline (27)

In the large group of macrocyclic diester alkaloids some new sources of known alkaloids have been reported, some new alkaloids have been isolated, and their structures elucidated. Thus, *Senecio taiwanensis* contains rosmarinine (26), and *S. morrisonensis* contains integerrimine (4).¹⁷ Three *Senecio* species of Azerbaijan origin, *S. propinquus* Schisch., *S. platyphyllus* M.B. and DC., and *S. lampsanoides* DC., have been studied, with particular reference to their suitability for the pharmaceutical industry.¹⁸ The rhizomes and roots of *S. propinquus* contain seneciophylline (27), which accounts for ~87% of the total alkaloid

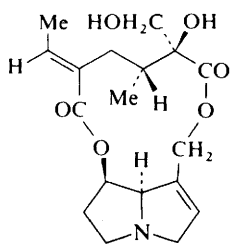
¹⁵ H. Amal and O. Ates, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1971, 7, 85 (*Chem. Abs.*, 1972, 77, 72 582).

¹⁶ C. C. J. Culvenor and L. W. Smith, unpublished work, quoted in L. B. Bull, C. C. J. Culvenor, and A. T. Dick, 'The Pyrrolizidine Alkaloids', North Holland Publishing Co., Amsterdam, 1968, p. 237.

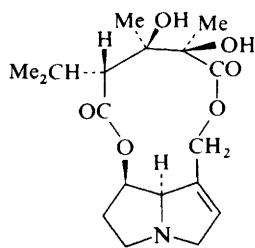
¹⁷ S. T. Lu, C. N. Lin, T. S. Wu, and D. C. Shieh, *J. Chinese Chem. Soc. (Taipei)*, 1972, 19, 127 (*Chem. Abs.*, 1972, 77, 161 936).

¹⁸ D. S. Khalilov, *Izvest Akad. Nauk Azerb. S.S.R., Ser. Biol. Nauk*, 1971, 122 (*Chem. Abs.*, 1972, 77, 123 781).

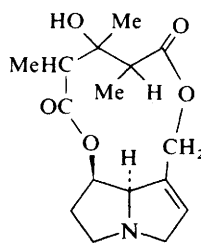
content.¹⁹ Three other alkaloids are also present, but these have not so far been identified. Both the aerial and the underground parts of *S. platyphyllus* M.B. and DC. [*S. rhombifolius* (Willd.) Sch. Bip.] contain^{19a} platyphylline, seneciophylline, and neoplatyphylline, in agreement with previous observations, the extraction process adopted yielding the alkaloids mainly as their *N*-oxides. The alkaloids of *S. lamsanoides*, which appear not to have previously been investigated, have not yet been identified. The aerial and underground parts of *S. kubensis*, also investigated for the first time, contain mainly seneciophylline.^{19a}



Usaramine (28)



Trichodesmine (29)



(30)

Integerrimine (4) is the major alkaloid of *Cacalia hastata* L. subsp. *orientalis* Kitamura, a reputedly edible wild plant of northern Japan.²⁰ It also occurs, together with usaramine (28), in *Crotalaria intermedia* Kotschy,²¹ and in association with trichodesmine (29) in *C. tetragona* Roxb.²² Two further retronecine diesters, crispatine (30) and its stereoisomer fulvine, occur in *C. madurensis* R. Wight.²³ Crobarbatine (31) is a new retronecine derivative which has been isolated from the seeds of *C. barbata* R. Graham.²⁴ The presence of the functional groups implied in (31) was deduced from the i.r. and n.m.r. spectra, and its formulation as an α -hydroxy-ester was also supported by its mass spectrum, which showed an important peak at *m/e* 251, owing to loss of carbon dioxide from the molecular ion [(31a) \rightarrow (32)]; the product (32) of this fragmentation then loses the acetyl group to give an ion at *m/e* 208. The necic acid component, crobarbatic acid, has not hitherto been encountered in the pyrrolizidine alkaloid series, and was obtained from the hydrolysis of crobarbatine as a monobasic acid, $C_7H_{10}O_4$, which did not respond to the ferric chloride test for α -hydroxyacids. Since it exhibited absorption at 1757 cm^{-1} it is formulated as the γ -lactone carboxylic acid (33).²⁴

¹⁹ D. S. Khalilov, I. A. Damirov, and M. V. Telezhenetskaya, *Khim. prirod. Soedinenii*, 1972, **8**, 656 (*Chem. Abs.*, 1973, **78**, 108 214).

^{19a} D. S. Khalilov and M. V. Telezhenetskaya, *Khim. prirod. Soedinenii*, 1973, **9**, 128 (*Chem. Abs.*, 1973, **78**, 156 643).

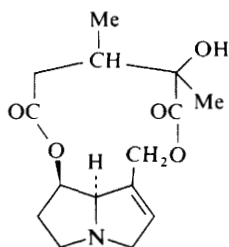
²⁰ K. Hayashi, A. Natorigawa, and H. Mitsuhashi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 201.

²¹ R. S. Sawhney and C. K. Atal, unpublished work, reported in ref. 3.

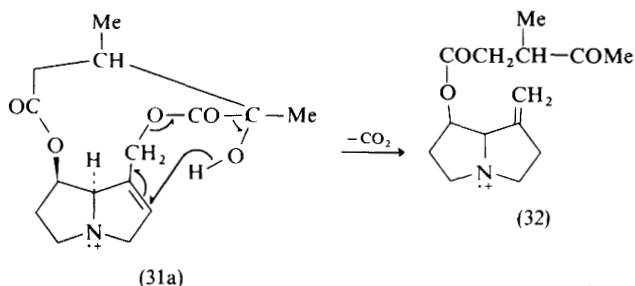
²² C. K. Atal, unpublished work, reported in ref. 3.

²³ A. E. M. Habib, M. R. I. Saleh, and M. A. Farag, *Lloydia*, 1971, **34**, 455.

²⁴ S. C. Puri, R. S. Sawhney, and C. K. Atal, *Experientia*, 1973, **29**, 390.

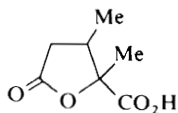


Crobarbatine (31)



(31a)

(32)



Crobarbatic acid (33)

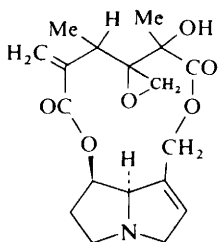
Further structural work has been reported on swazine, isoline, and erucifoline, three more alkaloids based on retronecine. Swazine, from *Senecio swaziensis*, was earlier²⁵ shown to be an ester of retronecine with a new dicarboxylic acid. A definitive determination of the structure of swazine methiodide by the X-ray method has now shown²⁶ the correct structure of swazine to be (34); this differs from the structure previously proposed in that the mode of attachment of the dicarboxylic acid unit to the retronecine nucleus is reversed. The conformation of the molecule is such that the methylene group and adjacent carbonyl group are oriented approximately *cis* with a dihedral angle of 54° between them; this accounts for u.v. absorption at a distinctly shorter wavelength than that expected for an acrylic ester chromophore.

The structure and absolute configuration of isoline (35) have now been clarified.²⁷ Isolinecic acid, the acid component of isoline, affords a dilactone

²⁵ C. G. Gordon-Gray, R. B. Wells, N. Hallak, M. B. Hursthouse, S. Neidle, and T. P. Toube, *Tetrahedron Letters*, 1972, 707.

²⁶ M. Laing and P. Sommerville, *Tetrahedron Letters*, 1972, 5183.

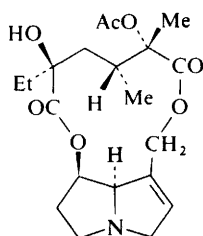
²⁷ E. D. Coucourakis, C. G. Gordon-Gray, and C. G. Whiteley, *J.C.S. Perkin I*, 1972, 2339.



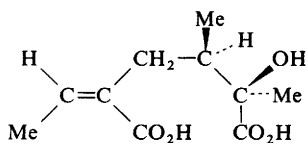
Swazine (34)

which was shown to be diastereoisomeric with a dilactone prepared previously²⁸ from senecic acid (36). Since senecic acid has the (2*R*,3*R*) absolute configuration its dilactone must be (2*R*,3*R*,5*R*) as it is impossible to form the dilactone if C-5 has the opposite configuration to C-2. The lactone from isolinecic acid must therefore have either the (2*S*,3*R*,5*S*) or the (2*R*,3*S*,5*R*) configuration; a choice between the two can obviously be made if the stereochemistry at C-3 can be determined. This was achieved by degradation of both senecic acid and isolinecic acid to the dione (37). Since both acids gave the same dione, C-3 in isolinecic acid must have the *R* configuration, and the dilactone has the configuration (2*S*,3*R*,5*S*).

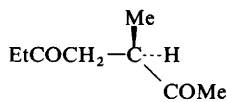
It was earlier²⁹ proposed, but without supporting evidence, that the acetoxy-group in isoline is situated at C-5 in the acid moiety. However, the fact that it is the C-2 hydroxy-group which is acetylated is shown by the n.m.r. spectrum of



Isoline (35)



Senecic acid (36)



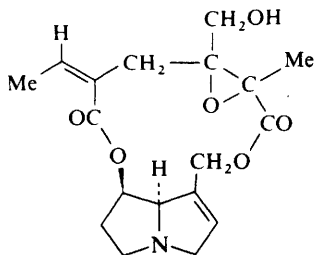
(37)

²⁸ N. I. Koretskaya, A. V. Danilova, and L. M. Utkin, *Zhur. obshchei Khim.*, 1962, 32, 3823 (*Chem. Abs.*, 1963, 58, 12 504).

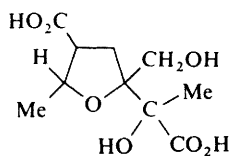
²⁹ E. D. Coucourakis and C. G. Gordon-Gray, *J. Chem. Soc. (C)*, 1970, 2312.

owing to loss from the molecular ion of the appropriate unit derived from the grouping: $\text{Me}-\text{C}(\text{OH})\text{CO}_2\text{H}$.

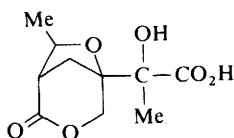
In contrast to the monolactone of erucifolinecic acid the dilactone still contains the ethylidene group; there are consequently two possible structures (43) and (44) for this dilactone, both of which are consistent with the n.m.r. data. Of these, (43) is preferred on the basis of the i.r. spectrum.³³



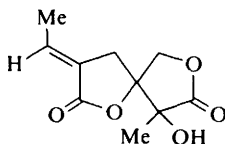
Erucifoline (40)



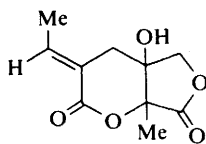
Erucifolinecic acid (41)



(42)

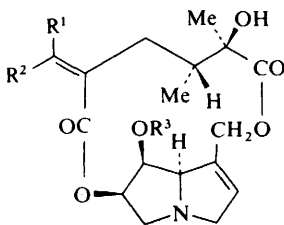


(43)



(44)

In an earlier communication³⁴ the presence of madurensine (3), 7-acetyl-madurensine (45), and 6-acetylanacrotine (46) in the leaves and stems of *Crotalaria agatiflora* Schweinf., which is cultivated as a garden species in Australia, was briefly mentioned. The full account of this investigation³⁵ reveals that these esters are accompanied in the plant by anacrotine (47), 7-acetyl-*cis*-madurensine (48), 6-acetyl-*trans*-anacrotine (49), and two other alkaloids, which are almost



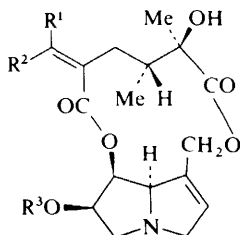
Madurensine (3) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{H}$

7-Acetylmadurensine (45) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ac}$

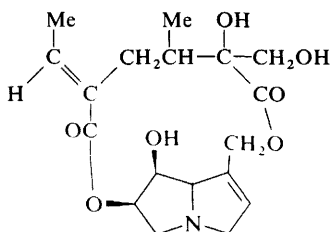
7-Acetyl-*cis*-madurensine (48) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Ac}$

³⁴ C. C. J. Culvenor and L. W. Smith, cited in C. C. J. Culvenor, L. W. Smith, and R. I. Willing, *Chem. Comm.*, 1970, 65.

³⁵ C. C. J. Culvenor and L. W. Smith, *Anales de Quim.*, 1972, **68**, 883.



- 6-Acetylanacrotine (46) $R^1 = H, R^2 = Me, R^3 = Ac$
 Anacrotine (47) $R^1 = R^3 = H, R^2 = Me$
 6-Acetyl-*trans*-anacrotine (49) $R^1 = Me, R^2 = H, R^3 = Ac$
 (51) $R^1 = Me, R^2 = H, R^3 = CO-C(=CHMe)Me$

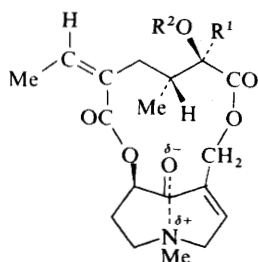


Crotaflorine (50)

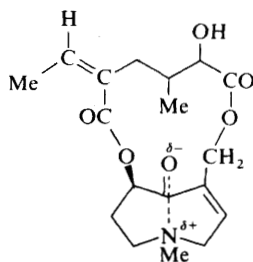
certainly the diester of retronecic acid with crotanecine [crotaflorine, (50)] and the angeloyl ester (51) of *trans*-anacrotine. These eight esters of crotanecine are so far the only ones that have been encountered naturally.

Anacrotine (47) and madurensine (3) are also found in *C. laburnifolia* L. subsp. *eldomae* (Bak. f.) Polhill, which is indigenous to Kenya and Tanzania.³⁶ These two alkaloids have previously been isolated from *C. laburnifolia* proper, of Indian origin; to date, however, no other alkaloids have been reported. In contrast, the subspecies *eldomae* has been shown to contain three further alkaloids, which have been identified as senkirkine [renardine, (52)], hydroxysenkirkine (53), and crotafoline (54); the last is a new alkaloid.³⁶ The structure of hydroxysenkirkine was deduced from its n.m.r. spectrum and confirmed, except for the mode of attachment of the necic acid component to otonecine, by the isolation of isatinecic acid (55), following hydrolysis. The mode of attachment of isatinecic acid follows from a comparison of the mass spectra of senkirkine and hydroxysenkirkine. Senkirkine suffers fission at the allylic ester linkage followed by loss of CO_2 to give an ion at m/e 321, depicted as (56). Further fragmentation (at *a*) gives an ion at m/e 250. Hydroxysenkirkine, by an analogous process, gives an ion at m/e 337 (57), and an ion at m/e 250 (fission at *a*), presumably identical with the ion from senkirkine.

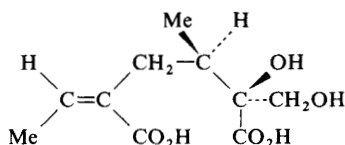
³⁶ D. H. G. Crout, *J.C.S. Perkin I*, 1972, 1602.



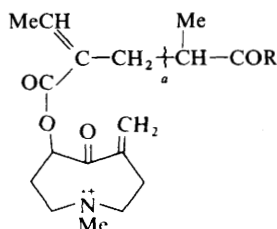
Senkirkine (52) $R^1 = \text{Me}$, $R^2 = \text{H}$
 Hydroxysenkirkine (53) $R^1 = \text{CH}_2\text{OH}$, $R^2 = \text{H}$
 O-Acetylsenkirkine (61) $R^1 = \text{Me}$, $R^2 = \text{Ac}$



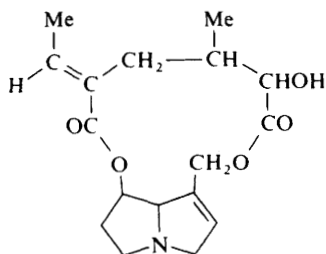
Crotafoline (54)



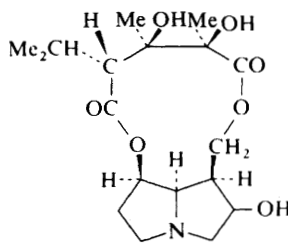
Isatinic acid (55)



(56) $R = \text{Me}$
 (57) $R = \text{CH}_2\text{OH}$
 (59) $R = \text{H}$



Nilgirine (58)



Croalbidine (60)

The presence of an otonecine component in crotafoline was apparent from its characteristic mass spectrum, and the overall structure (54) was deduced from its n.m.r. spectrum. The presence of the geometrically isomeric necic acid in another pyrrolizidine alkaloid, nilgirine (58),^{37,38} was also considered to lend vicarious support to this structure. Again the mode of attachment of the necic

³⁷ C. K. Atal, C. C. J. Culvenor, R. S. Sawhney, and L. W. Smith, *Tetrahedron Letters*, 1968, 5605.

³⁸ R. S. Sawhney and C. K. Atal, *Planta Med.*, 1972, 21, 435 (*Chem. Abs.*, 1972, 77, 34 741).

acid component follows from the mass spectrum of crotafoline, which exhibits ions at m/e 307 (59) and m/e 250 (fission at a). The geometry about the double bond in the necic acid is indicated by the position of the n.m.r. resonance of the olefinic proton, which occurs at a higher field than the corresponding resonance in its geometrical isomer, in which the proton is deshielded by the ester carbonyl group.³⁶

The alkaloid crotastratine, isolated by Gandhi *et al.*³⁹ from the seeds of *C. striata* (\equiv *C. mucronata* Desv.), appears to be nilgirine.³

Croalbidine, $C_{18}H_{29}NO_7$, m.p. 208–209 °C, is a new base isolated from *C. albida* Heyne ex Roth (\equiv *C. montana*), the roots of which have been used as a purgative.⁴⁰ Acid hydrolysis of croalbidine affords (+)-trichodesmic acid and croalbinecine, whose structure appears to be 2,7-dihydroxy-1-hydroxymethylpyrrolizidine. Croalbidine is thus formulated as (60), and this is the first reported occurrence of an alkaloid derived from a necine base of the croalbinecine type in the *Crotalaria* genus.

Full details have now been published of the X-ray determination of the structure and absolute configuration of clivorine.⁴¹ In a second report on the new alkaloid emiline, from *Emilia flammea*, the isolation of otonecine from the alkaline hydrolysis is recorded.⁴² During their survey of the constituents of Indian *Crotalaria* species, Sawhney *et al.*⁴³ have observed the presence of *O*-acetylsenkirkine (61) and isosenkirkine in *C. walkeri* Arnott. The close similarity of the mass spectra of senkirkine and isosenkirkine reveals that they are very probably stereoisomers, although the detailed stereochemistry of the new base has not been determined.

3 Pharmacological Aspects

The pharmacology and hepatotoxicity of the pyrrolizidine alkaloids continue to attract considerable attention, and further general reviews of this area have been published.^{44–46} Monocrotaline has perhaps been studied more intensively than any other pyrrolizidine alkaloid from this point of view, and recent investigations include a study of the pathological changes induced in monkeys following administration of monocrotaline at different ages,⁴⁷ and the suppression, by

³⁹ R. N. Gandhi, T. R. Rajagopalan, and T. R. Seshadri, *Current Sci.*, 1968, **37**, 285.

⁴⁰ R. S. Sawhney and C. K. Atal, *Indian J. Chem.*, 1973, **11**, 88.

⁴¹ K. B. Birnbaum, *Acta Cryst.*, 1972, **B28**, 2825.

⁴² H. Tomczyk and S. Kohlmuenger, *Herba Pol.*, 1971, **17**, 226 (*Chem. Abs.*, 1972, **77**, 19848).

⁴³ R. S. Sawhney, M. S. Bhatia, and C. K. Atal, unpublished work, reported in ref. 3.

⁴⁴ A. R. Pomeroy and C. Raper, *Arch. Internat. Pharmacodyn. Therap.*, 1972, **199**, 5 (*Chem. Abs.*, 1973, **78**, 24073).

⁴⁵ A. R. Mattocks, Phytochemistry Ecology, Proceedings Phytochemistry Society Symposium, 1971, 179 (*Chem. Abs.*, 1973, **78**, 80417).

⁴⁶ R. Schoental, *Oncology, Proceedings International Cancer Congress*, 1970, **5**, 203 (*Chem. Abs.*, 1973, **78**, 39 062).

⁴⁷ J. R. Allen and C. F. Chesney, *Experimental Mol. Pathol.*, 1972, **17**, 220 (*Chem. Abs.*, 1973, **78**, 12445).

monocrotaline and the related pyrrole, of DNA synthesis in rat liver.^{48,49} Other reports are concerned with the effect of monocrotaline and monocrotaline pyrrole on lung tissue.^{50,51} The modification of monocrotaline toxicity by phenobarbital and chloramphenicol has also been studied.⁵² Apparently the prior stimulation of microsomal enzymes in rats by means of phenobarbital results in an enhanced toxicity of monocrotaline. Conversely the acute toxic effects of monocrotaline are diminished by the prior administration of the enzyme inhibitor chloramphenicol.

Other pyrrolizidine alkaloids that cause necrosis of liver cells or malignant tumours are retrorsine,⁵³⁻⁵⁵ isatidine, riddelliine,⁵³ trichodesmine, incanine,⁵⁶ lasiocarpine,^{55,57,58} senkirkine, hydroxysenkirkine,⁴⁶ and heliotrine.^{59,60} Lasiocarpine and retrorsine are toxic to human embryo liver cells but not to lung cells, possibly because lung cells do not metabolize these alkaloids to their toxic pyrrole analogues. Retronecine pyrrole, in contrast, is toxic to both kinds of cell.⁵⁵ In mice and rats, however, retrorsine, isatidine, riddelliine, and monocrotaline, are reported to cause lung edema as well as liver damage.⁵³ Pyrrolizidine alkaloids have also been shown to cause tumours of the central nervous system; thus, spinal cord tumours were observed in rats fed with *Heliotropium ramosissimum*, retronecine, and hydroxysenkirkine.⁶¹

⁴⁸ I. C. Hsu, C. F. Chesney, and J. R. Allen, *Proc. Soc. Exp. Biol. Med.*, 1973, **142**, 1133 (*Chem. Abs.*, 1973, **78**, 132 448).

⁴⁹ I. N. H. White and A. R. Mattocks, *Biochem. J.*, 1972, **128**, 291.

⁵⁰ M. Umeda and M. Saito, *Acta Pathol. (Japan)*, 1971, **21**, 507 (*Chem. Abs.*, 1972, **77**, 136 064).

⁵¹ R. Plestina and H. B. Stoner, *J. Pathol.*, 1972, **106**, 235.

⁵² J. R. Allen, C. F. Chesney, and W. J. Frazee, *Toxicol. Appl. Pharmacol.*, 1972, **23**, 470.

⁵³ R. Schoental and B. D. Pullinger, *E. African Med. J.*, 1972, **49**, 436 (*Chem. Abs.*, 1973, **78**, 92 550).

⁵⁴ A. R. Mattocks and I. N. H. White, *Chem. Biol. Interactions*, 1973, **6**, 297.

⁵⁵ S. J. Armstrong and A. J. Zuckerman, *Brit. J. Exp. Pathol.*, 1972, **53**, 138 (*Chem. Abs.*, 1972, **77**, 97 499).

⁵⁶ V. F. Smirnov, *Vop. Med. Khim. Biokhim. Gorm., Deistviya Fiziol. Aktiv. Veshchestv. Radiats.* 1970, **52** (*Chem. Abs.*, 1972, **77**, 122 796).

⁵⁷ S. J. Armstrong, R. G. Bird, and A. J. Zuckerman, *Brit. J. Exp. Pathol.*, 1972, **53**, 145 (*Chem. Abs.*, 1972, **77**, 97 500).

⁵⁸ D. J. Svoboda and J. K. Reddy, *Cancer Res.*, 1972, **32**, 908.

⁵⁹ V. E. Nazyrova and G. S. Alimova, *Med. Zhur. Uzbek.*, 1972, **3**, 40 (*Chem. Abs.*, 1972, **77**, 57 346).

⁶⁰ C. I. Burshtein, *Med. Zhur. Uzbek.*, 1972, **3**, 53 (*Chem. Abs.*, 1972, **77**, 57 347).

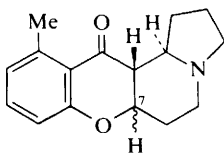
⁶¹ R. Schoental and J. B. Cavanagh, *J. Nat. Cancer Inst.*, 1972, **49**, 665 (*Chem. Abs.*, 1973, **78**, 67 942).

Very little new work in this small sub-group of alkaloids has been reported during the year under review.

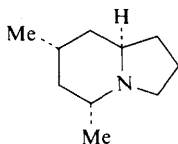
Full details have been published¹ of the synthesis of (\pm)-elaecarpine (1) and (\pm)-isoelaecarpine (2) by Tanaka and Iijima.²

Although the alkaloids of *Dendrobium* species are discussed elsewhere in this Report it is relevant to note here that dendroprimine,³ a simple indolizidine constituent of *Dendrobium primulinum* Lindl., has the absolute configuration shown in (3).⁴ Successive Hofmann degradation and reduction sequences ultimately afforded *S*-(+)-4-methylnonane (4) of established absolute configuration; dendroprimine is thus (5*R*,7*S*,9*R*)-5,7-dimethyloctahydroindolizine (3).

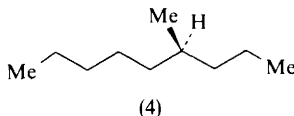
It has already been pointed out⁵ that the structure (5) proposed⁶ for tylophorinidine is unacceptable, and it is therefore of some interest to note that a



Elaecarpine (1) α -H at C-7
Isoelaecarpine (2) β -H at C-7



Dendroprimine (3)



(4)

¹ T. Tanaka and I. Iijima, *Tetrahedron*, 1973, **29**, 1285.

² T. Tanaka and I. Iijima, *Tetrahedron Letters*, 1970, 3963.

³ B. L ning and K. Leander, *Acta Chem. Scand.*, 1965, **19**, 1607.

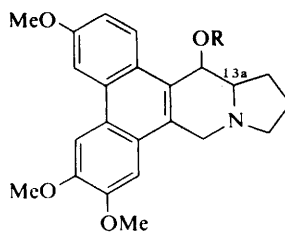
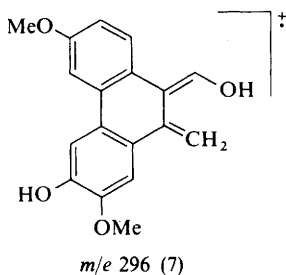
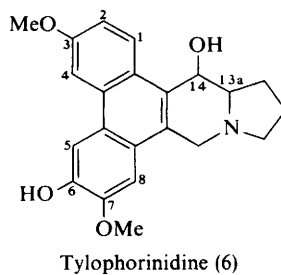
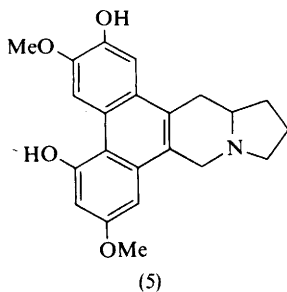
⁴ L. Blomqvist, K. Leander, B. L ning, and J. Rosenblom, *Acta Chem. Scand.*, 1972, **26**, 3203.

⁵ J. E. Saxton, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1972, Vol. 2, p. 76.

⁶ N. B. Mulchandani, S. S. Iyer, and L. P. Badheka, *Chem. and Ind.*, 1971, 505.

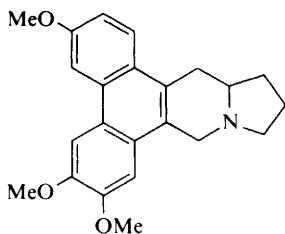
re-investigation of this alkaloid has resulted in the revised structure (6).⁷ Tylophorinidine, $C_{22}H_{23}NO_4$, m.p. 216–218 °C, $[\alpha]_D^{25} + 105^\circ$ ($CHCl_3$), exhibits a u.v. spectrum closely similar to that of tylophorinine and is, in consequence, probably a 2,3,6-trioxygenated phenanthrene derivative. It contains one phenolic hydroxy-group ($FeCl_3$ reaction and u.v. spectrum in alkali) and, in contrast to the previous report, gives rise to a monomethyl ether which contains one free alcoholic hydroxy-group. The i.r. absorption of tylophorinidine diacetate at 1760 (phenolic acetate) and 1730 cm^{-1} (alcoholic acetate) is thus explained.

The mass spectrum of tylophorinidine exhibits a base peak at m/e 296 owing to the ion (7) formed by retro-Diels–Alder loss of the pyrrolidine ring. The ready loss of carbon monoxide from this ion to give a fragment ion at m/e 268 provides evidence for the location of the alcoholic hydroxy-group at position 14. In accordance with this the n.m.r. spectrum of *O*-acetyl-*O*-methyltylophorinidine is virtually identical with that of acetyltylophorinine (8); also the alcoholic hydroxy-group in tylophorinidine itself can be removed by hydrogenolysis in the presence of perchloric acid. The free hydroxy-group in *O*-methyltylophorinidine can be removed similarly, or by treatment with perchloric acid followed by reduction with sodium borohydride. The product of these hydrogenolyses was identified firmly as (\pm)-deoxytylophorinine (9); consequently *O*-methyltylophorinidine is (10) and *O*-acetyl-*O*-methyltylophorinidine is (11).

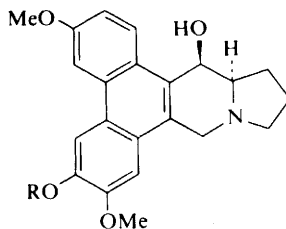
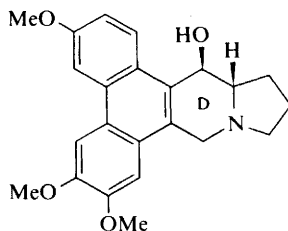


O-Methyltylophorinidine (10) R = H
O-Acetyl-*O*-methyltylophorinidine (11) R = Ac

⁷ T. R. Govindachari, N. Viswanathan, J. Radhakrishnan, B. R. Pai, S. Natarajan, and P. S. Subramanian, *Tetrahedron*, 1973, **29**, 891.



Deoxytylophorinine (9)

(12a) R = Me
Tylophorinidine (12c) R = H

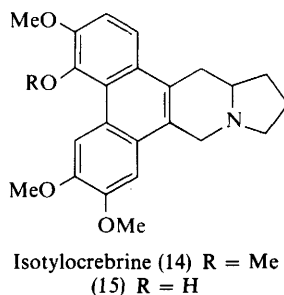
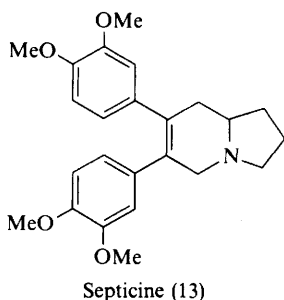
(12b)

Tylophorinine and *O*-methyltylophorinidine thus have the same gross structure (10) and since they are not enantiomers they must be diastereoisomers. The facile loss of the benzylic hydroxy-group from *O*-methyltylophorinidine by hydrogenolysis under acidic conditions to give a *racemic* product is best interpreted as dehydration followed by reduction, which suggests a *trans* diaxial disposition of hydroxy-group at C-14 and hydrogen at C-13a, as shown in (12a). This is also consistent with the n.m.r. data for tylophorinidine and its derivatives in different solvents, which indicate dimer formation by hydrogen-bonding between an axial hydroxy-group of one molecule and the nitrogen atom of the other. In tylophorinine the hydroxy-group and the C-13a hydrogen must be *cis* oriented, and the production on hydrogenolysis of an optically pure, laevorotatory deoxy-compound is presumably the result of direct displacement of the hydroxy-group. The n.m.r. data and pK_a value for tylophorinine are interpreted tentatively as indicating an axial hydroxy-group in this molecule also, with C-13a hydrogen equatorially oriented with respect to ring D (12b).

The position of the free phenolic hydroxy-group in tylophorinidine may be deduced from the n.m.r. spectra of its diacetate and its *O*-acetyl-*O*-methyl derivative (8). In the spectra of these two compounds the signals owing to protons at C-1, C-2, C-4, and C-8 are found at approximately the same positions, but the signal owing to the C-5 hydrogen is deshielded in the spectrum of diacetyltylophorinidine, presumably by an acetoxy-group situated at C-6. Hence tylophorinidine has the structure (12c; R = H).⁷ Recently, this alkaloid has been shown to occur in a different genus, *Pergularia pallida* (fam. Asclepiadaceae).⁸

⁸ N. B. Mulchandani and S. R. Venkatachalam, 8th International Symposium on the Chemistry of Natural Products, New Delhi, 1972.

Rao's Alkaloid C, extracted like tylophorinidine from *T. asthmatica*,⁹ was earlier postulated to be an isomer of tylophorinidine, since it was claimed to give tylophorinine on methylation. From a consideration of the available data, Govindachari *et al.*⁷ suggest that it is at least possible that Alkaloid C is in fact a solvated form of tylophorinidine, and that Rao's 'tylophorinine', obtained by methylation, is the diastereoisomeric *O*-methyltylophorinidine.



Two further minor alkaloids of *T. asthmatica* were identified⁷ as (+)-septicine (13) and (+)-isotylocrebrine (14), the latter in all probability identical with the product obtained by methylation of Alkaloid B (15), isolated by Rao¹⁰ from *T. crebriflora*.

Tylophora hirsuta Wight has been reported to contain alkaloids, but to date none appears to have been identified.¹¹ Two reviews of this group of phenanthroindolizidine alkaloids have also been published.^{12,13}

⁹ K. V. Rao, R. A. Wilson, and B. Cummings, *J. Pharm. Sci.*, 1971, **60**, 1725.

¹⁰ K. V. Rao, R. A. Wilson, and B. Cummings, *J. Pharm. Sci.*, 1970, **59**, 1501; K. V. Rao, *ibid.*, p. 1608.

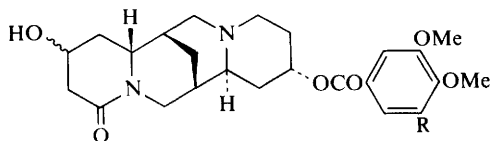
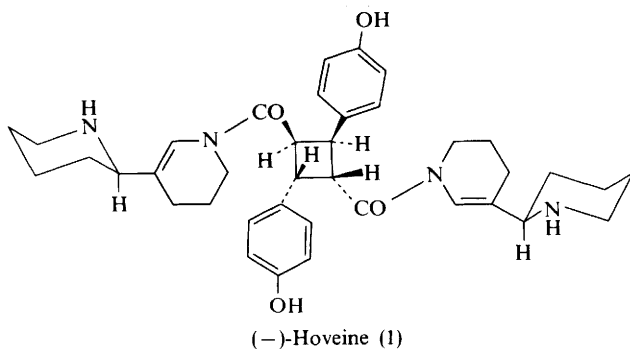
¹¹ H. H. S. Fong, M. Trojánek, J. Trojánek, and N. R. Farnsworth, *Lloydia*, 1972, **35**, 117.

¹² W. Wiegand, *Pharm. Ztg.*, 1972, **117**, 1509 (*Chem. Abs.*, 1973, **78**, 43 801).

¹³ T. R. Govindachari, *J. Indian Chem. Soc.*, 1973, **50**, 1.

1 The Cytisine-Lupanine-Sparteine-Matrine Group

Occurrence, and Isolation of New Alkaloids.—The Australian genus *Hovea* (fam. Leguminosae) has not hitherto been widely studied. Aside from the isolation of (+)-sparteine from *H. longifolia* R.Br. and *H. acutifolia* A. Cunn.,¹ the only recorded investigation of this genus has been contributed by Cannon, Joshi, and Williams,² who isolated (+)-sparteine, (–)-lupanine, (–)-anagryne, and (–)-cytisine from *H. elliptica* (Sm.) DC. *Hovea longipes* Benth. has now been shown to contain ~1% alkaloids, of which the major component is (–)-cytisine. A relatively minor component is (–)-baptifoline, but the most interesting and pharmacologically useful constituent is not a quinolizidine alkaloid but a dimeric piperidine base, (–)-hoveine (1), which is reported to exhibit marked hypotensive activity.³



Catalauverine (2) R = H

Catalaudesmine (3) R = OMe

¹ J. H. Morrison and K. G. Neill, *Austral. J. Sci. Res.*, 1949, **2A**, 427.

² J. R. Cannon, K. R. Joshi, and J. R. Williams, *Austral. J. Chem.*, 1971, **24**, 1537.

³ J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, A. H. Redcliffe, A. A. Sioumis, and H. Soares, *Anales de Quim.*, 1972, **68**, 737.

In earlier investigations a new alkaloid, catalauverine, was isolated⁴ from the branches of *Sarothamnus catalaunicus* Webb [*S. arboreus* (Desf.) Webb subsp. *catalaunicus* C. Vic. \equiv *Cytisus malacitanus* Boiss. subsp. *catalaunicus* Heywood]. Extraction of the leaves has now yielded another new alkaloid, catalaudesmine.^{5,6} Hydrolysis of catalauverine yields veratric acid, whereas catalaudesmine yields 3,4,5-trimethoxybenzoic acid; the basic component of these two alkaloids appears to be a new derivative of 13-hydroxylupanine, probably the 4-hydroxy-derivative. Catalauverine and catalaudesmine are thus tentatively formulated as (2) and (3), respectively.⁶

Details of the extraction⁷ of the branches of *Sarothamnus patens* (L.) Webb [*Cytisus striatus* (Hill) Rothm.] have now been published.⁸ Aside from the new alkaloid isocinevanine this plant also contains (–)-sparteine, lupanine, cineverine, 13-hydroxylupanine, and sarodesmine.

Four samples of *Cytisus canariensis* L. have been investigated, and anagryne, *N*-methylcytisine, cytisine, and aphylline (10-oxosparteine) have been isolated.⁹ The only previously known source of aphylline was *Anabasis aphylla* (fam. Chenopodiaceae). In two samples of *C. canariensis* aphylline proved to be the major alkaloid; in the other two samples, which were actually of the variety *ramosissimus*, *N*-methylcytisine was the principal alkaloid, and in one sample aphylline could not be detected.

Several *Thermopsis* species have also been investigated.¹⁰ In general the stems and leaves before flowering of the plant appeared to constitute the richest source of alkaloids; after flowering the alkaloid content decreased. Sparteine and cytisine were found in all the species studied, i.e. *T. dolichocarpa* Nikitin, *T. fabacea* DC., *T. mollis* Curt., *T. montana* Nutt., *T. caroliniana* Curt., and *T. lanceolata* R.Br. Lupanine was also found in the first four of these species, and thermopsine in *T. dolichocarpa* and *T. montana*. The main base of *T. caroliniana* remains unidentified.¹⁰ The new dimeric alkaloid dimethamine, found in the green parts of *Thermopsis alterniflora* in association with argentine and argentamine, is apparently 3-(3,4-dihydro-12-methyl-5-cytisyl)-12-methylcytisine (4).¹¹ Argentine, first isolated from *Ammodendron argenteum*, has the structure (5), and has been synthesized* from cytisine and phosgene.¹²

⁴ G. Faugeras and M. Paris, *Ann. pharm. fran.*, 1968, **26**, 265.

⁵ G. Faugeras and R. R. Paris, 6th Symposium Flora Europaea, in *Boissiera*, 1971, **19**, 201.

⁶ G. Faugeras and R. R. Paris, *Anales de Quim.*, 1972, **68**, 811.

⁷ G. Faugeras, R. R. Paris, and E. Valdes-Bermejo, *Compt. rend.*, 1971, **273**, C, 1372.

⁸ G. Faugeras, R. R. Paris, and E. Valdes-Bermejo, *Ann. pharm. franç.*, 1972, **30**, 527.

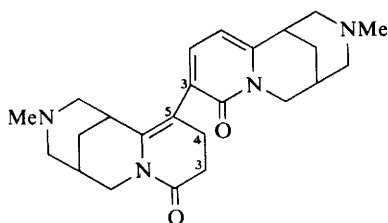
⁹ E. Steinegger and E. V. Hornstein, *Anales de Quim.*, 1972, **68**, 893.

¹⁰ E. Balcar-Skrzydłowska and B. Borkowski, *Biochem. Physiol. Alkaloide*, Fourth Internat. Symposium, 1969, 493 (*Chem. Abs.*, 1972, **77**, 123 881).

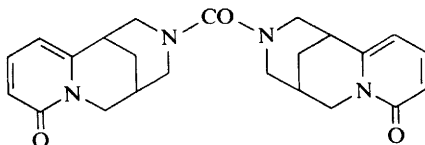
¹¹ S. Iskandarov, V. I. Vinogradova, R. A. Shaimardanov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 218 (*Chem. Abs.*, 1972, **77**, 58 788).

¹² K. A. Aslanov, Y. K. Kushmuradov, and A. S. Sadykov, *Biochem. Physiol. Alkaloide*, Fourth Internat. Symposium, 1969, 463 (*Chem. Abs.*, 1972, **77**, 140 388).

* Since cytisine is one of the alkaloids of this species, and since chloroform was used in the extraction process, the status of argentine as an alkaloid, rather than an artifact, is open to question.



Dimethamine (4)



Argentine (5)

As noted last year *Lupinus hispanicus* var. *bicolor* has been extracted, apparently for the first time.^{13a} (+)-Epilupinine, (–)-lupinine, and gramine were isolated, together with Alkaloid Y, which was not identified.^{13a,13b} In the course of a survey of Egyptian medicinal flora *Retama raetam* has been re-investigated. The seven alkaloids isolated were identified as retamine, sparteine, anagryne, thermopsine, cytisine, sophoramine, and sophochrysine.¹⁴

Much of the recent work on the constituents of the *Leontice* and *Sophora* genera, which form the principal sources of the matrine group of alkaloids, stems from Eastern Europe, and full details are not readily accessible. Tubers of *Leontice leontopetalum* contain¹⁵ α -isolupanine, leontiformidine, [3-(2-piperidiny)quinolizidine], (+)-lupanine, leontiformine, palmatine, and tetrahydro-palmatine. This co-occurrence of quinolizidine and benzyloquinoline bases in the tubers is reminiscent of the alkaloid content of the leaves, from which (+)-lupanine, leontiformine, and (–)-stylopine were earlier isolated.¹⁶ The tubers of another *Leontice* species, *L. smirnowii*, were earlier¹⁷ shown to contain lupanine, (+)-argemonine, and taspine. A more recent investigation by the same group or workers¹⁸ has revealed the presence of sophocarpine and a new alkaloid

¹³ (a) I. Ribas-Marques and M. Regueiro-Garcia, *Anales de Quim.*, 1971, **67**, 93 (*Chem. Abs.*, 1971, **75**, 31, 280); (b) M. Regueiro-Garcia, *Acta Cient. Compostelana*, 1970, **7**, 165 (*Chem. Abs.*, 1972, **77**, 2777).

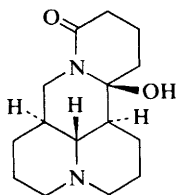
¹⁴ Z. F. Ahmed, A. M. Rizk, and F. M. Hammouda, Postep Dziedzinie Leku Rosl., Pr. Ref. Dosw. Wygloszone Symp., 1970, 20 (*Chem. Abs.*, 1973, **78**, 94 856).

¹⁵ P. P. Panov, L. N. Panova, and N. M. Mollov, *Doklady Bolg. Akad. Nauk*, 1972, **25**, 55 (*Chem. Abs.*, 1972, **77**, 72 554).

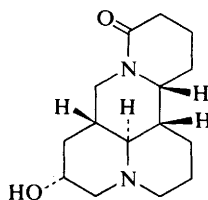
¹⁶ P. P. Panov, N. M. Mollov, and L. Panova, *Compt. rend. Acad. bulg. Sci.*, in press, cited in N. M. Mollov and I. C. Ivanov, *Tetrahedron*, 1970, **26**, 3805.

¹⁷ E. G. Tkeshelashvili, S. Iskandarov, K. S. Mudzhiri, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 539 (*Chem. Abs.*, 1971, **75**, 137 536); *Soobshch. Akad. Nauk Gruz. S.S.R.*, 1971, **64**, 461 (*Chem. Abs.*, 1972, **76**, 70 044).

¹⁸ E. G. Tkeshelashvili, S. Iskandarov, K. S. Mudzhiri, and S. Yu. Yunusov, *Soobshch. Akad. Nauk. Gruz. S.S.R.*, 1973, **69**, 357 (*Chem. Abs.*, 1973, **78**, 156 646).



Leontismine (6)

3 α -Hydroxysophoridine (7)

leontismine, which proves to be 11-hydroxyleontine (6), since dehydration is stated to yield isosophoramine, and reduction (LiAlH_4) gives leontane.

In the *Sophora* genus it has been shown¹⁹ that the dried seeds of *S. japonica* L. contain cytisine, *N*-methylcytisine, sophocarpine, and matrine, together with four unidentified alkaloids. Following their earlier extraction of the upper parts of *S. griffithii*,²⁰ Primukhamedov *et al.*²¹ have now extracted the roots, from which cytisine, *N*-methylcytisine, matrine, and an unidentified alkaloid were isolated. Apparently (+)-sparteine and sophoramine, present in the aerial parts, were not detected in the roots. The constituents of the aerial parts of *S. alopecuroides* have again been investigated;²² the alkaloids isolated included cytisine, *N*-(2-hydroxyethyl)cytisine, baptifoline, sophoridine, and 3 α -hydroxysophoridine (7), which has not previously been encountered. *S. linearifolia* Griseb., of *S.* American origin, contains (+)-matrine, its *N*-oxide, and (+)-sparteine.²³ Finally, an investigation of *S. prodanii* E. Anders. has shown that the highest concentration of alkaloids is found in the seeds. The leaves, fruits, roots, and stems contain decreasing amounts of alkaloids. To date, however, none of the alkaloids appears to have been identified.²⁴

Structural, Spectroscopic, and Chemical Studies.—The alkaloid albertine was first isolated in 1967 from the aerial parts of *Leontice alberti*.²⁵ In a subsequent communication²⁶ it was suggested that albertine is a 13-hydroxy-7,11-dehydromatrine (8), on the basis of its transformation products, and its conversion by dehydration into sophoramine (9). Very recently,²⁷ this structure for albertine

¹⁹ B. A. Abdusalomov, K. A. Aslanov, A. S. Sadykov, and O. A. Khoroshkova, *Khim. prirod. Soedinenii*, 1972, **8**, 658 (*Chem. Abs.*, 1973, **78**, 108 230).

²⁰ I. Primukhamedov, K. A. Aslanov, and A. S. Sadykov, *Nauch. Tr., Tashkent Gos. Univ.*, 1968, No. 341, 128 (*Chem. Abs.*, 1970, **72**, 79 280).

²¹ I. Primukhamedov, K. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1972, **8**, 398 (*Chem. Abs.*, 1972, **77**, 162 009).

²² T. E. Monakhova, N. F. Proskurnina, O. N. Tolkachev, V. S. Kabanov, and M. E. Perel'son, *Khim. prirod. Soedinenii*, 1973, **9**, 59 (*Chem. Abs.*, 1973, **78**, 159 960).

²³ R. A. Corral, O. O. Orazi, and M. T. Pizzorno, *Anales Asoc. quim. argentina*, 1972, **60**, 37 (*Chem. Abs.*, 1972, **77**, 34 744).

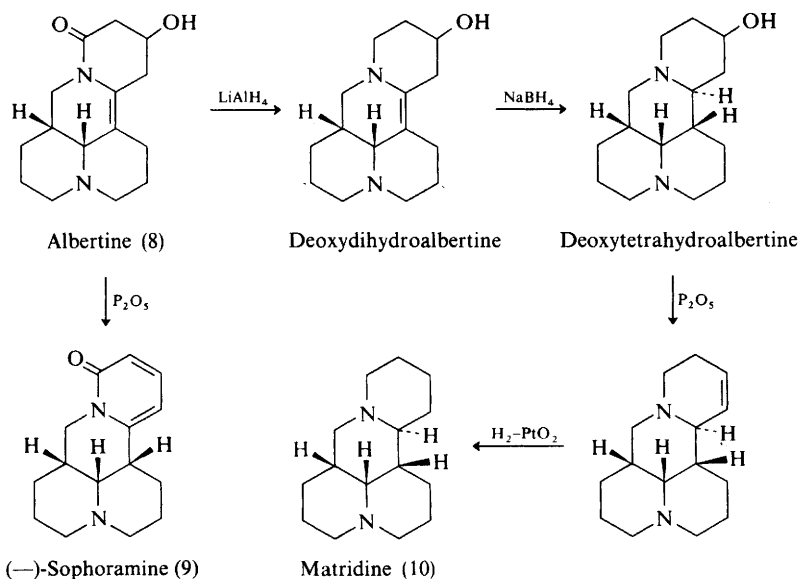
²⁴ N. Pislarasu, M. Palade, and A. Badauta-Tocan, *Farmacia (Bucharest)*, 1972, **20**, 41 (*Chem. Abs.*, 1972, **77**, 58 807).

²⁵ S. Iskandarov, R. N. Nuriddinov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1967, **3**, 26 (*Chem. Abs.*, 1967, **67**, 100 294).

²⁶ I. Iskandarov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 137 (*Chem. Abs.*, 1968, **69**, 77 567).

²⁷ S. Iskandarov, D. D. Kamalitinov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 628 (*Chem. Abs.*, 1973, **78**, 84 616).

has received confirmation, and some new reactions have been reported, principally its conversion into matridine (10) by the route shown in the accompanying Scheme.



Scheme 1

Much attention continues to be paid to the spectrographic properties of the quinolizidine alkaloids, primarily with a view to elucidating their conformations. The INDOR ^1H n.m.r. spectra of three alkaloids, sparteine, lupanine, and 13-hydroxylupanine, have been closely examined,²⁸ and the results confirm the earlier conclusion²⁹ that in solution the preferred conformations of these alkaloids are those shown in structures (11)–(13), in which ring C assumes the boat conformation.* In other communications the i.r. spectra of 22 alkaloids in the $2800\text{--}2500\text{ cm}^{-1}$ region have been recorded,³⁰ the mass spectra of eleven alkaloids have been discussed,³¹ and the same group of workers have recorded

* The conformational diagram (11) represents the absolute configuration of (-)-sparteine, and is given here for convenient comparison with (+)-lupanine (12) and hydroxylupanine (13). In fact the actual base studied in ref. 28 was (+)-sparteine (pachycarpine); which lupanine enantiomer was used was not specified.

²⁸ A. S. Sadykov, F. G. Kamayev, V. A. Korenevsky, V. B. Leont'ev, and Yu. A. Ustynyuk, *Org. Magn. Resonance*, 1972, **4**, 837.

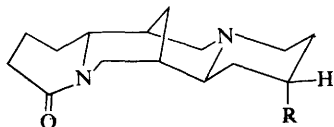
²⁹ M. Wiewiórowski, O. E. Edwards, and M. D. Bratek-Wiewiórowska, *Canad. J. Chem.*, 1967, **45**, 1447.

³⁰ T. K. Yunusov, A. P. Matwejeva, V. B. Leont'ev, F. G. Kamayev, K. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1972, **8**, 200 (*Chem. Abs.*, 1972, **77**, 19 842).

³¹ E. K. Timbekov, F. S. Eshvaev, K. A. Aslanov, A. I. Ishbaev, and T. K. Kasymov, *Khim. prirod. Soedinenii*, 1972, **8**, 194 (*Chem. Abs.*, 1972, **77**, 26 159).

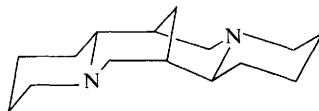
the o.r.d. spectra of a number of quinolizidine alkaloids containing a lactam function.³²

The microbiological oxidation of (–)-sparteine by means of *Trametes gibbosa*, a micro-organism of the Basidiomycetes family, gives rise to a 17-hydroxy-sparteine (14).³³ Attempts to obtain (14) in a pure, crystalline state were unsuccessful, but it was characterized by means of the trichloromethyl derivative (14; OH → CCl₃), and by potassium ferricyanide oxidation, which afforded crystalline 17-oxosparteine. From the yield of 17-oxosparteine obtained, the microbial oxidation of sparteine was calculated to proceed in 38% yield.³³

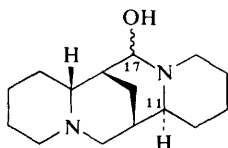


(+)-Lupanine (12) R = H

(+)-13-Hydroxylupanine (13) R = OH



(–)-Sparteine (11)



17-Hydroxysparteine (14)

In previous studies³⁴ the behaviour of α -isosparteine *N*-oxide and sparteine *N*-oxide on protonation has been described. α -Isosparteine *N*-oxide (15) readily forms a monocation which gives rise to a dication (16) only stable as the diperchlorate in the solid state or in strongly acidic solutions. In contrast, sparteine *N*-16-oxide monocation (17) is readily protonated but instead of a dication a stable sesquiperchlorate is formed, which has been shown by X-ray analysis to have structure (18).³⁵ It is presumed that steric factors prevent the formation of a stable hydrogen-bonded sesqui-salt from the monocation from (15). It has now been shown³⁶ that lithium can replace the central hydrogen-bonded proton in (18), with formation of a stable sesquiperchlorate: [sparteine *N*-oxide HClO₄]₂ · LiClO₄ (19). This accords with recent reports that lithium bonds, analogous to hydrogen bonds, can be formed in appropriate circumstances.³⁷

³² A. I. Ishbaev, K. A. Aslanov, A. S. Sadykov, and M. A. Ramazanova, *Khim. prirod. Soedinenii*, 1972, 8, 328 (*Chem. Abs.*, 1972, 77, 152 414).

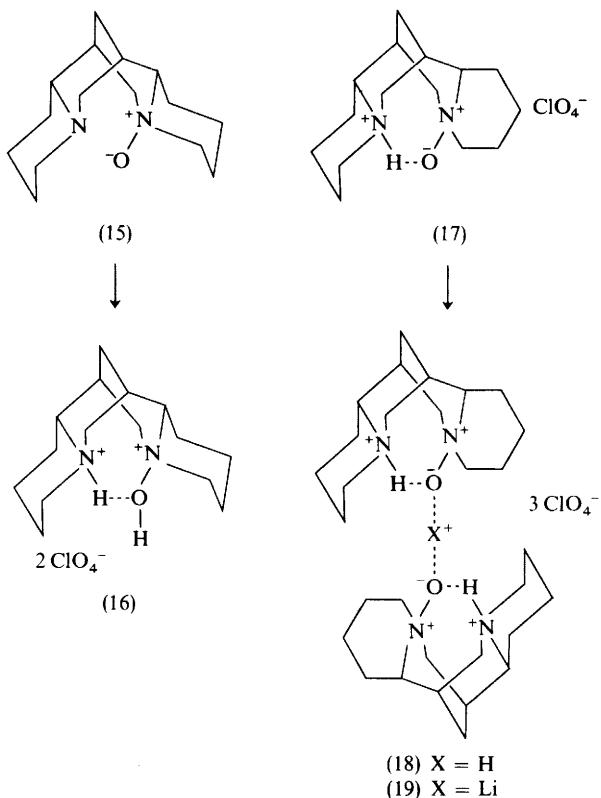
³³ K. Furuya, K. Aida, Y. Koiso, and S. Okuda, *Chem. and Pharm. Bull. Japan*, 1973, 21, 231.

³⁴ P. Baranowski, J. Skolik, and M. Wiewiórowski, *Tetrahedron*, 1964, 20, 2383.

³⁵ S. N. Srivastava and M. Przybylska, *Acta Cryst.*, 1969, B25, 1651.

³⁶ J. Skolik, K. Langowska, and M. Wiewiórowski, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1972, 20, 383.

³⁷ P. A. Kollman, J. F. Liebman, and L. C. Allen, *J. Amer. Chem. Soc.*, 1970, 92, 1142.



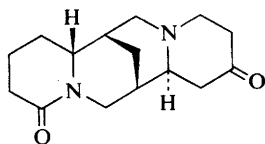
The behaviour of hydroxylupanine on oxidation has been studied further.³⁸ Earlier attempts to achieve a selective oxidation to 13-oxolupanine (20) failed, owing to facile oxidation at position 17; oxidation by *N*-bromosuccinimide, for example, yielded 13,17-dihydroxylupanine, and oxidation by chromic acid in pyridine or glacial acetic acid gave 13,17-dioxolupanine. Oppenauer oxidation with cyclohexanone, xylene, and aluminium phenoxide results in concomitant isomerization of the C-D ring-junction with formation of 13-oxo- α -isolupanine (21),³⁹ although use of fluorenone and potassium *t*-butoxide in benzene is said to afford the desired 13-oxolupanine.⁴⁰ It has now been shown³⁸ that oxidation of 13-hydroxylupanine by means of chromic acid in 90% acetic acid containing 5% perchloric acid affords a good yield of 13-oxolupanine. Oppenauer oxidation with aluminium phenoxide and cyclohexanone affords 13-oxolupanine under comparatively mild conditions (160 °C, 20 min), but under more vigorous conditions (180 °C, 2 h) 13-oxo- α -isolupanine is formed, by isomerization of the

³⁸ W. Wysocka and M. Wiewiórowski, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1973, **21**, 29.

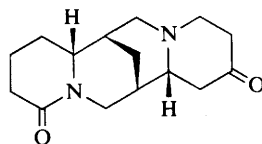
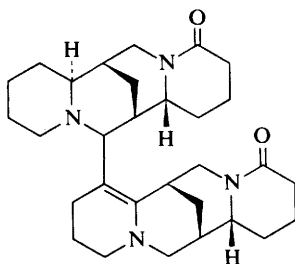
³⁹ F. Bohlmann, E. Winterfeldt, O. Schmidt, and W. Renschke, *Chem. Ber.*, 1961, **94**, 1767.

⁴⁰ A. Goosen, E. R. Kaplan, and M. A. Osry, *J.S. African Chem. Inst.*, 1966, **19**, 57.

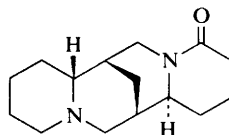
initially formed 13-oxolupanine. In accordance with this it was shown that 13-oxolupanine can be isomerized to (21) with aluminium phenoxide in boiling xylene; other bases (sodium methoxide and sodium butoxide) proved ineffective.³⁸



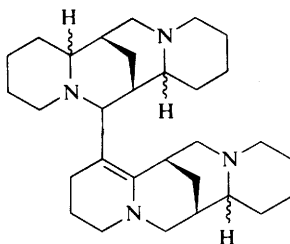
13-Oxolupanine (20)

13-Oxo- α -isolupanine (21)

(22)



Isolupanine (23)



(24)

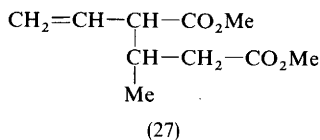
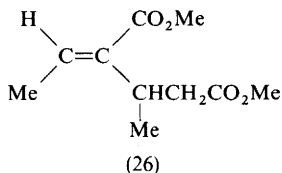
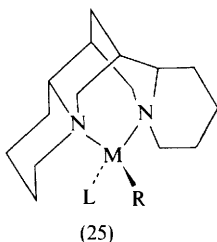
The photo-oxidation of lupanine with oxygen in the presence of methylene blue as sensitizer affords a diplospartyrine for which structure (22) is proposed.⁴¹ Sparteine, under similar reaction conditions, yields isolupanine (23) and a diplospartyrine (24), together with a small amount of lupanine.

The possibility of achieving partial asymmetric syntheses using organometallic reagents in the presence of sparteine has been examined further.⁴² It was shown that the rate of 1,4-addition of Grignard reagent to conjugated enones is drastically reduced in the presence of (–)-sparteine, and the less reactive enones could be recovered from attempted reaction at room temperature, although some reaction

⁴¹ D. Herlem, Y. Hubert-Brierre, F. Khuong-Huu, and R. Goutarel, *Tetrahedron*, 1973, **29**, 2195.

⁴² R. A. Kretchmer, *J. Org. Chem.*, 1972, **37**, 2744.

was observed in one case (1,3-diphenyl-2-propen-1-one + MeMgI) after prolonged reflux in benzene. However, in other cases, competing side-reactions resulted in neither recovery of starting material nor desired product. Addition of cuprous chloride (but not cuprous iodide or lithium chloride) to the reacting system gave much improved results, although the yields of conjugate addition products were never high. The highest yield observed (64%) was found in the 1,4-addition of methylmagnesium iodide–cuprous chloride to 1,3-diphenyl-2-propen-1-one in the presence of sparteine. Here the optical purity of the product, 1,3-diphenyl-3-methyl-propan-1-one, was shown to be 5%; in other reactions of this kind values in the range 3–6% were obtained.⁴² These results suggest that the reagent in these reactions is a complex (25) formed from sparteine chelated with metal M (Mg or Cu), and that L represents a ligand such as the chloride ion. Such a complex would doubtless offer some steric hindrance to approach by a reagent, and also exert some steric control if reaction were permitted.



The dimerization of methyl crotonate when catalysed by an aluminium alkyl–sparteine complex results not only in a partial asymmetric synthesis but also in a new type of dimer.⁴³ With an equimolar amount of aluminium isobutyl–sparteine complex methyl crotonate gave a mixture of the dimers (26) and (27), with a small amount of a third isomer which may well be a diastereoisomer of (27). When the sparteine complexes of aluminium triethyl and aluminium trimethyl were used as catalyst the dimer (27) was the sole product, and it is noteworthy that this is also the only product of the dimerization when catalytic amounts of complex were used, regardless of the nature of the alkyl group. In all cases the dimer exhibited a small dextrorotation, but the optical purity of the product was not estimated. The formation of dimer (27) has not

⁴³ M. Ikeda, T. Hirano, and T. Tsuruta, *Tetrahedron Letters*, 1972, 4477.

previously been observed; in an earlier investigation it was shown⁴⁴ that dimerization of methyl crotonate in the presence of the Cu_2O -isocyanide system resulted in the formation of dimer (26) and its geometrical isomer. It was postulated that these were formed *via* (27), but the presence of (27) was not detected in the reaction mixture.

The ability of sparteine to act as a bidentate chelating ligand is thus well established, although aside from the magnesium derivative none of the sparteine complexes has hitherto been closely investigated. Recently, however, it has been shown that comparatively stable complexes of stoichiometry $\text{M}(\text{sp})\text{X}_2$ are formed from halides of first-row transition elements such as nickel, cobalt, copper, and zinc, which are stable in ethanol and chloroform. Analogous ones of the form $\text{M}(\text{sp})\text{Cl}_3$ can be prepared from iron(III) and manganese(III), but these are only stable in the solid state.⁴⁵ The magnetic moments and electronic spectra of the nickel and cobalt complexes have been measured, and so has the circular dichroism of the nickel chloride-sparteine complex. All the results obtained so far are consistent with a tetrahedral structure for these complexes.

An analytical procedure for the evaluation of quinolizidine and other groups of alkaloids uses a densitometric method following separation of the alkaloids by t.l.c. or electrophoresis.⁴⁶

2 *Ormosia* Alkaloids

In further work⁴⁷ on the alkaloids of *Ormosia semicastrata* the presence of (\pm)-piptanthine and (–)-18-epiormosanine has been confirmed. Ormosanine, previously stated⁴⁸ to be racemic, has now been shown to be laevorotatory, and the fourth alkaloid, now named (–)-ormocastrine, has been shown to have the structure (28) (relative configuration only). The doubt previously expressed concerning the position of the double bond in (28) has been dispelled by examination of the 220 MHz n.m.r. spectrum, which shows that the proton to which the olefinic proton is strongly coupled is responsible for a multiplet at τ 8.00; irradiation here causes the olefinic signal at τ 4.35 to collapse to a slightly broadened singlet, while irradiation of the olefinic proton causes the signal at τ 8.00 to sharpen. Although still an unresolved multiplet the coupling constants of this signal at τ 8.00 are clearly smaller than the coupling observed with the olefinic proton, and it is considered extremely unlikely that a geminal coupling is involved. Consequently there is only one proton on the carbon atom adjacent to the olefinic proton.

The stereochemistry of ormocastrine was established by reaction with urea, which gave homoxyormocastrine (29). Hydrogenation of (29) gave three products the most important of which was identified as homoxyormosanine. The second reduction product is presumably homoxy-16-epiormosanine, while the third

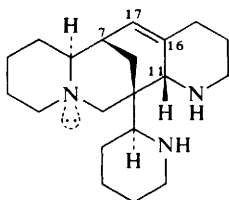
⁴⁴ T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *J. Org. Chem.*, 1970, 35, 670.

⁴⁵ S. F. Mason and R. D. Peacock, *J.C.S. Dalton*, 1973, 226.

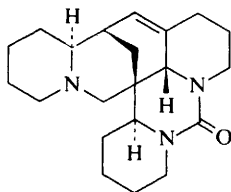
⁴⁶ G. Faugeras and M. Paris, *Bull. Soc. chim. France*, 1973, 109.

⁴⁷ S. McLean, M. L. Roy, H. J. Liu, and D. T. Chu, *Canad. J. Chem.*, 1972, 50, 1639.

⁴⁸ S. McLean, P. K. Lau, S. K. Cheng, and D. G. Murray, *Canad. J. Chem.*, 1971, 49, 1976.



Ormocastrine (28)
Podopetaline (28)



Homoxyormocastrine (29)

product, an isomer of the starting material, most probably has the double bond in the 11,16-position. In consonance with this structure (28) for ormocastrine, reduction gave two products, ormosanine and (presumably) 16-epiormosanine; the latter, as expected, gave a homoxy-derivative identical with the second reduction product of homoxyormocastrine.⁴⁷

The C_{20} -pentacyclic alkaloids characteristic of the *Ormosia* and *Piptanthus* genera are not confined exclusively to these genera. Thus, podopetaline (28), a major component of the complex mixture of alkaloids contained in *Podopetalum ormondii* F. Muell., is an optically active base whose structure and absolute configuration have been determined by the *X*-ray method;⁴⁹ in fact this is the first determination of the absolute configuration of any member of this group of alkaloids, and will no doubt prove to be a most useful reference point.

This structure for podopetaline, m.p. 77.5–79 °C, $[\alpha]_D - 48^\circ$ (MeOH), is thus the same as that deduced above, on chemical and spectroscopic grounds, for (–)-ormocastrine, for which m.p. 263 °C, $[\alpha]_D - 29^\circ$ (MeOH) was reported.⁴⁸ In fact the physical constants for podopetaline hydrobromide, m.p. 253–256 °C, $[\alpha]_D - 37^\circ$ (MeOH), are much closer to those reported for ormocastrine base. However, the dichotomy here has not yet been resolved.

Several alkaloids have been isolated from *Ormosia amazonica* Ducke; these include ormosanine, dasycarpine, piptanthine, ormosajine, and three isomers, $C_{20}H_{33}N_3$, in minute amounts.⁵⁰

3 Alkaloids of Coccinellidae

As reported in Volume 3 of this Report, the structure of coccinellin (30), the defensive *N*-oxide alkaloid of the ladybird, *Coccinella septempunctata*, has been established by the *X*-ray crystal structure analysis of its hemihydrochloride.⁵¹ This work makes it clear that the A–C and B–C ring-junctions in the molecule are *cis*, and the correct conformation is as given in (31).

In further investigations into the basic constituents of ladybirds, two new alkaloids, hippodamine and convergine, have been isolated from the American

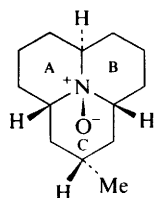
⁴⁹ N. K. Hart, S. R. Johns, J. A. Lamberton, M. F. Mackay, A. McL. Mathieson, and L. Satzke, *Tetrahedron Letters*, 1972, 5333.

⁵⁰ D. T. W. Chu, *Diss. Abs.*, 1972, **33B**, 1429.

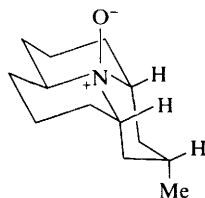
⁵¹ R. Karlsson and D. Losman, *J.C.S. Chem. Comm.*, 1972, 626.

species, *Hippodamia convergens*.⁵² The n.m.r. and mass spectra of hippodamine indicate that it is a stereoisomer of precoccinellin and since it is optically inactive it may be either a symmetrical isomer or a racemate. The first of these possibilities is excluded by the ¹³C n.m.r. spectrum, which although similar to that of precoccinellin, gives evidence for an unsymmetrical structure. Hippodamine is consequently regarded as racemic 2-methyl-*trans,cis,cis*-perhydro-9b-azaphenylene (32).⁵²

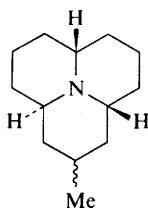
Converginine, C₁₃H₂₃NO, contains one oxygen atom in the form of a hydrogen-bonded carbonyl group (ν_{\max} 1680 cm⁻¹). It also behaves as a secondary base, and gives rise to an *N*-acetyl derivative. Since converginine hydrochloride is devoid of carbonyl groups it is evident that in the free base there is a strong transannular interaction between the carbonyl group and the amino-group and that in acidic solution a methanolamine salt arises. Reduction of converginine with lithium aluminium hydride gives hippodamine; hence converginine must be a hydroxyhippodamine with the hydroxy-group present on a carbon atom adjacent to nitrogen, *i.e.* racemic 3-methyl-13-azabicyclo[7,3,1]tridecan-5-one (33), or 11-methyl-13-azabicyclo[7,3,1]tridecan-5-one (34), without, as yet, stereochemical implication.⁵² Although not formally a quinolizidine derivative, adaline (35), isolated from the European ladybird, *Adalia bipunctata* L., and also from the varieties *quadrimaculata* Scopoli and *pantherina* L., is almost certainly related biogenetically to precoccinellin (36), from which it may hypothetically be derived *via* fission of rings A and C, followed by recyclization [arrows in (36) and (37)].⁵³



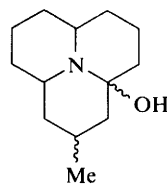
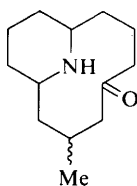
Coccinellin (30)



(31)



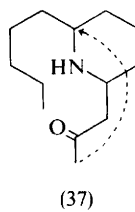
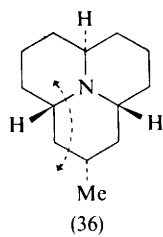
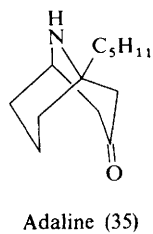
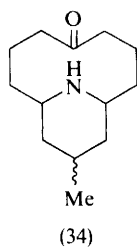
(32)



(33)

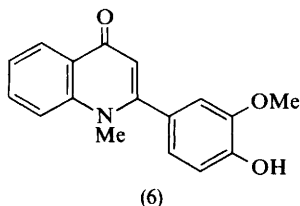
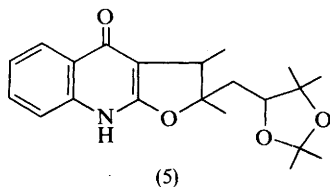
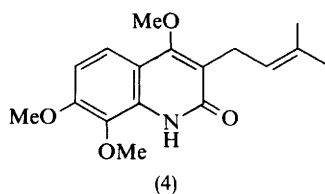
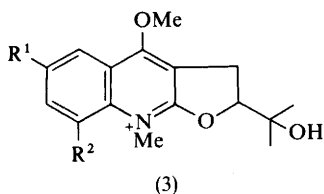
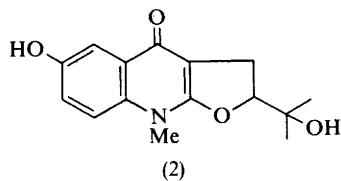
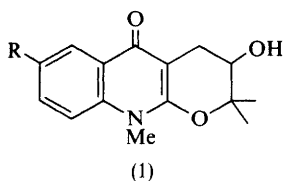
⁵² B. Tursch, D. Dalozé, J. M. Pasteels, A. Cravador, J. C. Braekman, C. Hootele, and D. Zimmermann, *Bull. Soc. chim. belges*, 1972, **81**, 649.

⁵³ B. Tursch, J. C. Braekman, D. Dalozé, C. Hootele, D. Losman, R. Karlsson, and J. M. Pasteels, *Tetrahedron Letters*, 1973, 201.

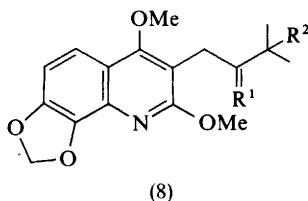
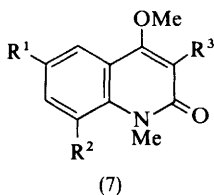


1 Quinoline Alkaloids

Alkaloid isolation studies are summarized in the Table. Details on the isolation, correlation, and synthesis of alkaloids from *Balfourodendron riedelianum* are now available.¹ The structures of (\pm)-ribalinine (1; R = H) and ribalinidine (1; R = OH) were deduced from spectral studies and the former was also synthesized by adaptation of an established route. Ribalinidine as well as ribaline (2) were readily correlated with *O*-methylribalinium chloride (3; R¹ = OMe, R² = H). Application of Horeau's method to the phenolic *O*-methyl ether of ribalinidine (2) led to the assignment of (*S*)-configuration.



¹ R. A. Corral, O. O. Orazi, and I. A. Benages, *Tetrahedron*, 1973, **29**, 205.

**Table** Isolation of quinoline and furoquinoline alkaloids

Species	Alkaloid (structure)	Ref.
<i>Balfourodendron riedelianum</i>	(±)-Ribalinine (1; R = H)	1
	(-)-Ribalinidine (1; R = OH)	
	(±)- and (+)-Ribaline (2)	
<i>Choisya ternata</i>	O-Methylbalfourodinium salt (3; R ¹ = H, R ² = OMe) ^a	2
<i>Dictamnus albus</i>	Preskimmianine (4)	3
<i>Fagara chalybea</i>	Skimmianine ^a	4
<i>Haplophyllum bucharicum</i>	(Bucharine, dictamnine, γ-fagarine, haplopine, robustine, skimmianine) ^a	5
	Bucharamine (5)	
<i>H. foliosum</i>	Folimidine (6)	6
	Folimine (7; R ¹ = R ³ = H, R ² = OMe)	7
	Foliosine ^a	
	N-Methyl-2-phenyl-2-quinolinone ^a	
<i>H. hispanicum</i>	Skimmianine ^a	8
	Evoxine ^a	
	Evoxine monoacetate	
<i>H. obtusifolium</i>	(Evoxine, skimmianine) ^a	5
<i>H. pedicellatum</i>	Haplopine ^a	
	Robustine ^a	
<i>Helietta parvifolia</i>	Flindersiamine (?)	9
<i>Orixa japonica</i>	Japonine ^a	10
	Kokusagine ^a	
	O-Methylbalfourodinium salt ^a	
<i>Ptelea trifoliata</i>	Orixinone (8; R ¹ = O, R ² = H)	11
	Unnamed (?)	

^a Known alkaloids. Most of the structural representations may be found in previous volumes of this series.

² R. Garestier and M. Rideau, *Compt. rend.*, 1972, **274**, D, 3541.

³ R. Storer and D. W. Young, *Tetrahedron Letters*, 1972, 2199.

⁴ F. Fish and P. G. Waterman, *Phytochemistry*, 1972, **11**, 1866.

⁵ K. Ubaidullaev, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 343 (*Chem. Abs.*, 1973, **78**, 2010n).

⁶ D. M. Razzakova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 755 (*Chem. Abs.*, 1973, **78**, 84 605x).

⁷ D. M. Razzakova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 133 (*Chem. Abs.*, 1972, **77**, 72 563x).

⁸ A. G. Gonzalez, R. Moreno Ordóñez, and F. Rodriguez Luis, *Anales de Quim.*, 1972, **68**, 1133 (*Chem. Abs.*, 1973, **78**, 82 069b).

⁹ X. A. Dominguez and A. Merjianian, *Rev. Latinoamer. Quim.*, 1972, **3**, 31 (*Chem. Abs.*, 1972, **77**, 137 357f).

¹⁰ W. J. Donnelly and M. F. Grundon, *J.C.S. Perkin I*, 1972, 2116.

¹¹ R. Garestier and M. Rideau, *Compt. rend.*, 1972, **274**, D, 2651.

The structure of preskimmianine (4) has been confirmed by conventional synthesis.³ It is suggested that (4) is a biogenetic precursor of skimmianine; other comments on the biosynthesis of these alkaloids are offered.

N.m.r. evidence was used to assign the structure of bucharamine (5) from *Haplophyllum bucharicum* although several alternative structures could not be completely eliminated.⁵ Its mass spectrum is discussed elsewhere.¹²

Orixinone (8; $R^1 = O$, $R^2 = H$) was isolated from *Orixa japonica* in an attempt to detect epoxides as biogenetic intermediates.¹⁰ Its structure rests on spectral data and synthesis from orixine (8; $R^1 = H$, OH , $R^2 = OH$). Neither orixine nor its corresponding epoxide was detected by t.l.c. examination of leaf and stem extracts.

Two alkaloids appear to be plant-growth inhibitors.^{2,11} The structure of one of these, *O*-methylbalfourodinium salt (3; $R^1 = H$, $R^2 = OMe$) from *Choisya ternata*, has been definitely established,² whereas the other alkaloid from *Ptelea trifoliata* is considered to be related to pteleoline [7; $R^1 = R^2 = OMe$, $R^3 = CH(OH)C(Me)=CH_2$] on the basis of u.v. spectral data.¹¹

Dictamnine, γ -fagarine, kokusaginine, and skimmianine have been isolated from the roots of *Ruta graveolens* grown in a sterile nutrient medium.¹³

The mass spectra of the acetones of bucharine, dihydrobucharine, evoxine, and foliosidine have been discussed.¹²

Details concerning the determination of the absolute (*R*)-configuration of platydesminium metho-salt (3; $R^1 = R^2 = H$), by ozonolysis to (*R*)-3-hydroxy-4,4-dimethyl- γ -butyrolactone, have appeared.¹⁴ This method may have general utility for establishing absolute configuration of compounds possessing oxygenated isoprenyl groups attached directly to aromatic systems (see also below).

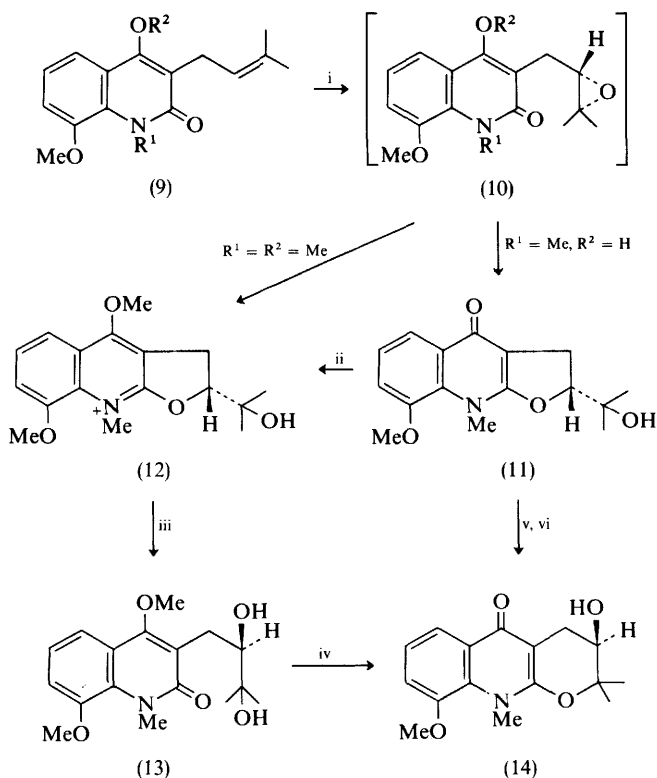
A number of significant synthetic contributions have appeared. Asymmetric synthesis of balfourodine (11), *O*-methylbalfourodinium perchlorate (12), and isobalfourodine (14) has been effected using previously developed methodology (Scheme 1).¹⁵ Treatment of the quinoline (9; $R^1 = Me$, $R^2 = H$) with (+)-peroxycamphoric acid gave (+)-balfourodine (11) (9.3% optical induction), presumably *via* the elusive epoxide (10; $R^1 = Me$, $R^2 = H$). A number of other chiral peroxy-acids were also investigated. *O*-Methylbalfourodinium salt (12) was prepared from the quinoline (9; $R^1 = R^2 = Me$) under similar conditions or by methylation of balfourodine (11) with methyl iodide. The optical activity of (12) was indicated by mild alkaline hydrolysis to (–)-balfourolone (13). (+)-Isobalfourodine (14) was obtained by acid-catalysed cyclization of (13) and by a two-step rearrangement of (+)-balfourodine (11). The (*R*)-configuration of (+)-balfourodine (11), (+)-isobalfourodine (14), and (–)-balfourolone (13) (also an alkaloid isolated from *Balfourdendron riedelianum* and obtained by mild hydrolysis of chiral *O*-methylbalfourodinium salt) as shown in the structural

¹² Ya. V. Rashkes, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, 8, 336.

¹³ I. V. Kuzovkina and K. Szendrei, *Izvest. Akad. Nauk S.S.S.R., Ser. biol.*, 1973, 275 (*Chem. Abs.*, 1973, 78, 156 641f).

¹⁴ J. F. Collins and M. F. Grundon, *J.C.S. Perkin I*, 1973, 161.

¹⁵ R. M. Bowman, J. F. Collins, and M. F. Grundon, *J.C.S. Perkin I*, 1973, 626.



Reagents: i, (+)-peroxycamphoric acid, CHCl_3 , 0°C ; ii, MeI, reflux; iii, 2N-NaOH, 25°C ; iv, 20% HCl, reflux; v, Ac_2O ; vi, OH^- .

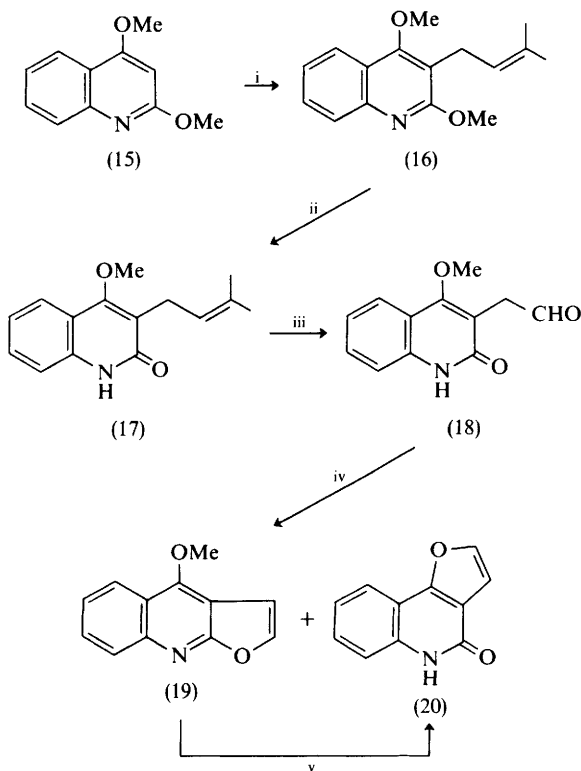
Scheme 1

formulae was determined by ozonolysis to (+)-(*R*)-3-hydroxy-4,4-dimethyl- γ -butyrolactone. The (*R*)-configuration shown for (+)-*O*-methylbalfourodinium salt (12) is assumed since it can be obtained from (+)-balfourodine (11) under mild conditions. The stereochemical result observed in the rearrangement of (+)-balfourodine (11) to (+)-isobalfourodine (14) contrasts with an early observation and requires a mechanistic rationale involving partial retention of configuration. The mechanism of the asymmetric epoxidation and the biosynthesis of these alkaloids and similar pyrano- and furo-coumarins were also discussed.¹⁵

The necessity to synthesize ^{14}C -labelled alkaloids resulted in the development of new efficient routes (48–66% yields) for dictamnine, γ -fagarine, and skimmianine.^{16,17} For example, dictamnine (19) was prepared according to Scheme 2.

¹⁶ J. F. Collins, W. J. Donnelly, M. F. Grundon, D. M. Harrison, and C. G. Spyropoulos, *J.C.S. Chem. Comm.*, 1972, 1029.

¹⁷ J. F. Collins, G. A. Gray, M. F. Grundon, D. M. Harrison, and C. G. Spyropoulos, *J.C.S. Perkin I*, 1973, 94.



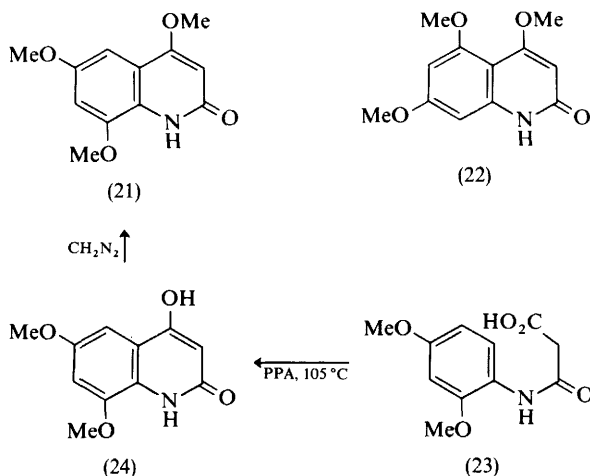
Reagents: i, BuⁿLi, BrCH₂CH=CMe₂, THF; ii, dry HCl, Et₂O; iii, O₃, MeOH or O₃O₄, NaIO₄, H₂O, dioxan; iv, PPA, 150 °C; v, PPA, 180 °C.

Scheme 2

Treatment of 2,4-dimethoxyquinoline (15) with 3,3-dimethylallyl bromide according to a general method developed by Narasimhan (see Vol. 3, p. 110) furnished compound (16) in 81 % yield which, under acidic conditions, provided the 2-quinolone (17). Ozonolysis or osmium tetroxide-periodate oxidation yielded the aldehyde (18) (>90 %) which, by polyphosphoric acid treatment, gave dictamnine (19) (72 %). The thermodynamically more stable angular isomer (20) was also isolated in 5 % yield from the cyclization reaction. In fact, dictamnine (19) was partially converted into the unnatural system (20); mechanistic considerations for this reaction were presented.¹⁷

The revised structures (21) and (22) were proposed for halfordamine, an alkaloid isolated from *Halfordia scleroxyla*, on the basis of u.v. spectroscopic evidence.¹⁸ Verification that halfordamine is represented by (21) was obtained by

¹⁸ R. Storer and D. W. Young, *Tetrahedron Letters*, 1972, 1555.



Scheme 3

two syntheses,^{18,19} one of which is shown in Scheme 3.¹⁹ Treatment of 2,4-dimethoxyaniline with malonic acid gave the acid anilide (23) which, when subjected to careful heating with polyphosphoric acid, provided the quinolone (24). Methylation gave the *O*-methyl derivative (21), which showed an n.m.r. spectrum identical with that reported for the natural product.

Masculosidine (25; R¹ = R³ = OMe, R² = H), pteleine (25; R¹ = OMe, R² = R³ = H), evolitrine (25; R¹ = R³ = H, R² = OMe), and γ -fagarine (25; R¹ = R² = H, R³ = OMe) have been synthesized by a conventional route.²⁰ A new preparation of furo[2,3-*b*]quinoline (27; R = H) whose potential for alkaloid synthesis has not been tested has been described.²¹ Bromination of (26) followed by dehydrobromination gave the derivative (27; R = CO₂Et) which upon hydrolysis and decarboxylation (copper bronze in refluxing diphenyl ether) gave compound (27; R = H) in good overall yield.

The preparation of a number of 2,3-dihydrofuro[3,2-*d*]quinoline (28),²² 2*H*-pyrano[2,3-*b*]quinoline (29),²³ and cinchoninic acid (30)²⁴ derivatives may be of general interest.

T.l.c. profiles of extracts from *Ptelea trifoliata* have been obtained for an area encompassing Southern U.S. and Mexico.²⁵ Kokusaginine, ptelefoline, and

¹⁹ P. Venturella, A. Bellino, and F. Piozzi, *Chem. and Ind.*, 1972, 887.

²⁰ T. Sekiba, *Bull. Chem. Soc. Japan*, 1973, **46**, 577.

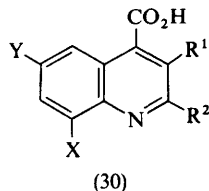
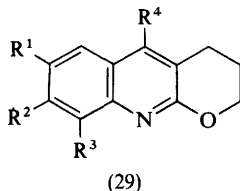
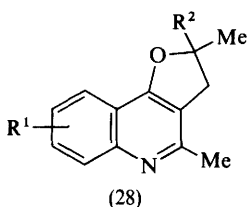
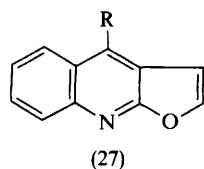
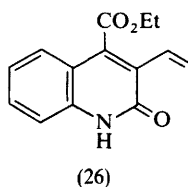
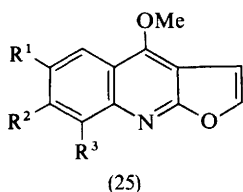
²¹ P. Shanmugam and P. Lakshminarayana, *Z. Naturforsch.*, 1972, **27b**, 474.

²² L. V. Gyl'budagyan and Sh. A. Sagatelyan, *Khim. geterotsikl. Soedineniya*, 1973, **84** (*Chem. Abs.*, 1973, **78**, 111 168r).

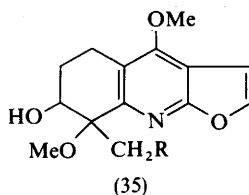
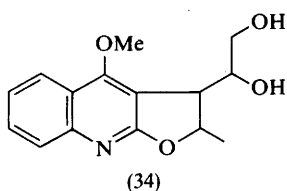
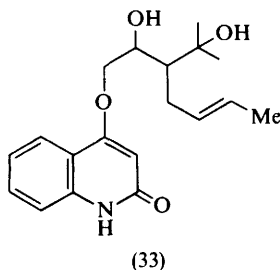
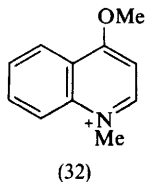
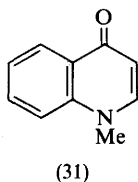
²³ P. Shanmugam and V. T. Ramakrishnan, *Proc. Indian Acad. Sci. (A)*, 1972, **75**, 96 (*Chem. Abs.*, 1972, **77**, 139 848r).

²⁴ G. Y. Sarkis, *J. Chem. and Eng. Data*, 1972, **17**, 388.

²⁵ H. E. Bailey, J. D. Mookken, and V. L. Bailey, *Herba Hung.*, 1971, **10**, 49 (*Chem. Abs.*, 1973, **78**, 156 598x).



skimmianine were identified and three unknown alkaloids were detected. A u.v. spectroscopic method for the determination of echinopsine (31) applicable to tablet analysis has been reported.²⁶



The physiology and biosynthesis of echinorine (32) have been discussed.²⁷ Russian workers have described certain pharmacological properties of a number of alkaloids: bucharaine (33) (suppression of aggressive response),²⁸ dubinidine

²⁶ N. Nin'o, *Trudy Nauchnoizsled. Khim.-Farm. Inst.*, 1972, 7, 411 (*Chem. Abs.*, 1973, 78, 164 151m).

²⁷ P. Schroeder, *Biochem. Physiol. Alkaloide*, Fourth Internat. Symposium, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 519.

²⁸ N. P. Polievtsev, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 164 (*Chem. Abs.*, 1973, 78, 119 188t).

(34) (sedative, hypothermic, and antimicrobial effects),^{29,30} evoxine (antimicrobial),³⁰ skimmianine (25; $R^1 = H$, $R^2 = R^3 = OMe$) and skimmianine-iron complex (antimicrobial, sedative, hypothermic, and antidiuretic properties),³⁰⁻³² haplphyllidine (35; $R = CH=CMe_2$), and performine [35; $R = CH_2C(OH)Me_2$] (ataractic and sedative effects).³³⁻³⁵

2 Quinazoline Alkaloids

Cyclizations of amidines to quinazolines and other heterocyclic systems have been reviewed.³⁶

The (2'S,3'R) absolute configuration has been assigned to febrifugine (36) on the basis of extensive n.m.r. spectral studies on the alkaloid and numerous model systems.^{37,38} The facile thermal isomerization of (37), a key intermediate in the synthesis of febrifugine, to the *trans*-isomer (38)³⁷ prompted re-investigation of the *cis* stereochemistry originally assigned to the piperidine ring of the alkaloid. Synthetic *cis*- and *trans*-febrifugines were synthesized from the corresponding piperidine derivatives (37) and (38) according to published procedures.³⁸ The *trans*-isomer (36) and the natural product were found to have identical i.r. spectra in arsenic trichloride solution. Furthermore, the 100 MHz n.m.r. spectra of the *O*-acetates were identical and showed a quartet at δ 3.98 ($J = 7$ Hz) which collapsed to a doublet ($J = 7$ Hz) upon irradiation of the side-chain methylene signal and therefore could be assigned to the C-2'-H. The C-3'-H appeared as a multiplet at δ 5.0 ($J = 4-5, 7$, and $9-10$ Hz). The couplings are most compatible with a *trans*-diaxial hydrogen arrangement. Attempts to repeat old synthetic work in order to resolve the difference in stereochemical assignments was beset by difficulties. However, one intermediate (39) was prepared and its configuration was assigned on the basis of n.m.r. analysis and application of dihedral angle estimation by ratio method (DAERM).³⁸ The (2'S,3'R) absolute configuration for febrifugine (36) is thus based on the degradative experiments of Hill and Edwards,³⁹ who assigned the C-2' absolute configuration, and the present work.

²⁹ N. P. Polievtsev, N. I. Evdokimova, and M. B. Sultanov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 171 (*Chem. Abs.*, 1973, **78**, 119 191p).

³⁰ I. Isamukhamedov, *Farmakol. Alkaloidov. Serdechnykh Glikozidov*, 1971, 224 (*Chem. Abs.*, 1973, **78**, 92 966f).

³¹ N. I. Evdokimova, N. P. Polievtsev, and M. B. Sultanov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 167 (*Chem. Abs.*, 1973, **78**, 119 189u).

³² N. I. Evdokimova and A. G. Kurmykov, *Med. Zhur. Uzbek.*, 1972, 61.

³³ N. P. Polievtsev, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 170 (*Chem. Abs.*, 1973, **78**, 119 190n).

³⁴ B. L. Danilevskii, N. T. Tulyaganov, and F. S. Sadritdinov, *Doklady Akad. Nauk. Uzbek. S.S.R.*, 1972, **29**, 37 (*Chem. Abs.*, 1973, **78**, 38 001z).

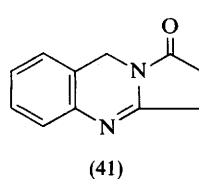
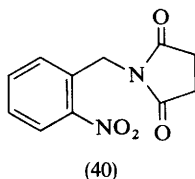
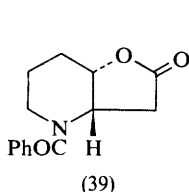
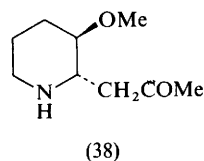
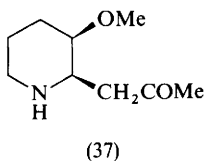
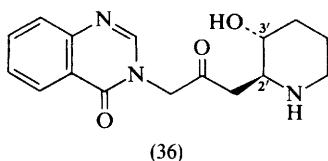
³⁵ N. P. Polievtsev, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 161 (*Chem. Abs.*, 1973, **78**, 79 635c).

³⁶ M. Miocque, C. Fauran, and A. Y. Le Cloarec, *Ann. Chim. (France)*, 1972, **7**, 89.

³⁷ D. F. Barringer, jun., G. Berkelhammer, S. D. Carter, L. Goldman, and A. E. Lanzilotti, *J. Org. Chem.*, 1973, **38**, 1933.

³⁸ D. F. Barringer, jun., G. Berkelhammer, and R. S. Wayne, *J. Org. Chem.*, 1973, **38**, 1937.

³⁹ R. K. Hill and A. G. Edwards, *Chem. and Ind.*, 1962, 858.



The absolute configuration of the C-3'-OH groups is the same as that in δ -hydroxylysine, an attractive biogenetic precursor of febrifugine.

Treatment of the succinimide (40) with triethyl phosphite has been shown to give a 5.3% yield of 1-oxo-3-deoxyvasicine (41).⁴⁰ Reports on the preparation of 4-quinazolinones not directly related to alkaloidal structures may nevertheless be of interest.⁴¹⁻⁴³ One of these⁴³ describes some quinazolinone derivatives which possess hypnotic activity.

3 Acridone and Related Alkaloids

A comprehensive review on the acridine group of alkaloids has been published.⁴⁴ Summaries of recent work on acridones from *Ruta graveolens*⁴⁵ and on benzodiazepine (e.g. cyclophenin) and quinoline alkaloids from *Penicillium cyclopium* and *P. viridicatum*⁴⁶ are available in the proceedings of a symposium held in 1969. T.l.c. patterns of 24 alkaloids have been charted in a manner which is useful for identification of any particular alkaloid in this group.⁴⁷ The anti-tumour activity of acronycine (42) is discussed in relation to other structurally diverse alkaloids possessing such properties.⁴⁸

⁴⁰ T. Kametani, K. Nyu, and T. Yamanaka, *Yakugaku Zasshi*, 1972, **92**, 1184 (*Chem. Abs.*, 1973, **78**, 4208g).

⁴¹ M. P. Thakur and S. K. P. Sinha, *J. Indian Chem. Soc.*, 1972, **49**, 1185.

⁴² Yu. V. Kozhevnikov and N. V. Pilat, *Trudy Perm. Sel.-Khoz. Inst.*, 1971, No. 79, 66 (*Chem. Abs.*, 1973, **78**, 16 128u).

⁴³ T. Hisano, M. Ichikawa, G. Kito, and T. Nishi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2575.

⁴⁴ J. E. Saxton, in 'The Acridines', ed. R. M. Acheson, Wiley-Interscience, New York, 2nd edn., 1973, p. 379 (Vol. 9 in 'The Chemistry of Heterocyclic Compounds', General Eds. A. Weissberger and E. C. Taylor).

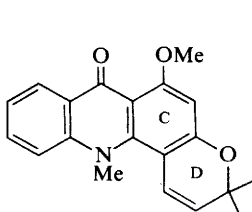
⁴⁵ K. Szendrei, J. Reisch, I. Novak, and E. Minker, *Biochem. Physiol. Alkaloids*, Fourth Internat. Symposium, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 513.

⁴⁶ M. Luckner and L. Nover, *Biochem. Physiol. Alkaloids*, Fourth Internat. Symposium, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 525.

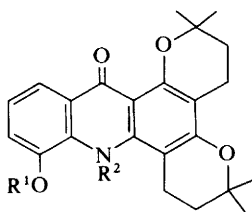
⁴⁷ Zs. Rozsa, K. Szendrei, I. Novak, and J. Reisch, *J. Chromatog.*, 1972, **72**, 421.

⁴⁸ M. E. Wall, *Biochem. Physiol. Alkaloids*, Fourth Internat. Symposium, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 39.

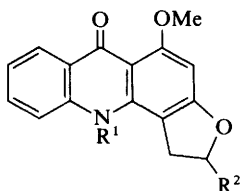
N-Methylbicycloatalaphylline (43; $R^1 = H$, $R^2 = Me$) is the third alkaloid isolated from the root bark of *Atalantia monophylla*.⁴⁹ Its structure rests on spectroscopic evidence and chemical correlation with the *N*-methyl derivative of the known *O*-methylbicycloatalaphylline (43; $R^1 = Me$, $R^2 = H$). Rutacridone [44; $R^1 = H$, $R^2 = C(Me)=CH_2$] and the acridone derivatives (45; $R = H$) and (45; $R = OMe$) have been isolated from the callus culture of *Ruta graveolens*.⁵⁰ Four other alkaloids of the anellated dihydrofuran ring type (44) have been obtained from the same source by other workers.^{51,52} These are gravacridondiol [44; $R^1 = Me$, $R^2 = C(OH)(Me)CH_2OH$] and gravacridondiol monomethyl ether [44; $R^1 = Me$, $R^2 = C(OH)(Me)CH_2OMe$],⁵¹ and gravacridonchlorine [44; $R^1 = Me$, $R^2 = C(Cl)(Me)CH_2OH$] and gravacridonolchlorine [44; $R^1 = Me$, $R^2 = C(Cl)(CH_2OH)CH_2OH$].⁵² The chlorine-containing alkaloids are not artifacts.



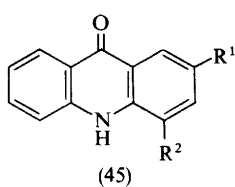
(42)



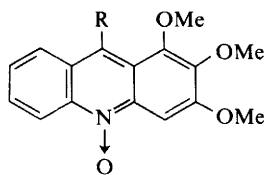
(43)



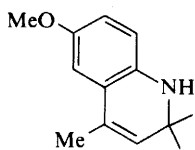
(44)



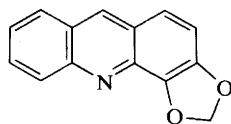
(45)



(46)



(47)



(48)

⁴⁹ D. Basu and S. C. Basa, *J. Org. Chem.*, 1972, **37**, 3035.

⁵⁰ W. Scharlemann, *Z. Naturforsch.*, 1972, **27b**, 806.

⁵¹ J. Reisch, Zs. Rozsa, K. Szendrei, I. Novak, and E. Minker, *Phytochemistry*, 1972, **11**, 2121.

⁵² J. Reisch, K. Szendrei, Zs. Rozsa, I. Novak, and E. Minker, *Phytochemistry*, 1972, **11**, 2359.

Oxidative coupling reactions for 2-aminobenzophenones provide low-yield syntheses of acridones.⁵³ For example, treatment of 2-amino-3'-hydroxybenzophenone with $K_2S_2O_8$ or $Mn(OAc)_2$ furnishes a mixture of 2- and 4-hydroxy-9-acridones (45; $R^1 = OH$, $R^2 = H$) and (45; $R^1 = H$, $R^2 = H$), respectively, in 1–8% yield. A number of 1,2,3-trimethoxyacridine *N*-oxides (46; $R = Cl, SH$, or $NHNHSO_2C_6H_4Me$) have been prepared.⁵⁴ The ring CD N-containing analogue (47) of acronycine (42) has been synthesized and found to possess antitumour activity.⁵⁵

Dubamine (48) has been shown to possess broad antimicrobial properties.³⁰

⁵³ I. H. Bowen, P. Gupta, M. S. Khan, and J. R. Lewis, *J.C.S. Perkin I*, 1972, 2524.

⁵⁴ M. Ionescu, M. Vlassa, and I. Gola, *J. prakt. Chem.*, 1972, **314**, 441.

⁵⁵ K. J. Liska, *J. Medicin. Chem.*, 1972, **15**, 1177.

1 General

The first comprehensive treatise on the chemistry and pharmacology of isoquinoline alkaloids, which will no doubt soon be found on the bookshelves of all practising chemists in this area, has been published.¹

An extensive review on the pharmacology of Papaveraceae alkaloids excluding morphine and codeine is not readily available.² The significance of the contributions to benzyloisoquinoline alkaloid chemistry carried out at the Olomouc Institute in Czechoslovakia may be appreciated from a recent review.³ Another short review concerned principally with the chemistry of isoquinoline alkaloids is available.^{3a}

A proposal of a systematic nomenclature for alkaloids which is based on a IUPAC system should be of general interest.⁴

Synthesis of a variety of benzyloisoquinoline alkaloids by photochemical and phenolic oxidative coupling reactions has been the major research activity of Kametani and his co-workers. Reviews on these topics are now available.^{5,6}

Electron-addition mass spectra of simple isoquinoline, 1-benzyloisoquinoline, and morphine alkaloids may be used to provide information on molecular weight and constitution.⁷ Extensive studies on correlation of methylenedioxy and methoxy substituents on aromatic and heteroaromatic rings with u.v. spectra are of interest in the isoquinoline alkaloid field.⁸

The quaternary salt-carbinolamine equilibria of a number of benzyloisoquinoline alkaloids and simple isoquinolines have been studied.⁹

¹ M. Shamma, 'The Isoquinoline Alkaloids: Chemistry and Pharmacology', Academic Press, New York, 1972.

² V. Preininger, *Acta Univ. Palacki. Olomouc., Fac. Med.*, 1972, **61**, 213 (*Chem. Abs.*, 1972, **77**, 159 956c).

³ A. Nemeckova, *Khim. Rast. Veshchestv*, 1972, 35 (*Chem. Abs.*, 1973, **78**, 145 161y).

^{3a} T. R. Govindachari and N. Viswanathan, *J. Sci. Ind. Res.*, 1972, **31**, 244.

⁴ F. Kuffner, *Biochem. Physiol. Alkaloide, Int. Symp.*, 4th 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 33.

⁵ T. Kametani and K. Fukumoto, *Accounts Chem. Res.*, 1972, **5**, 212.

⁶ T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657.

⁷ T. Tuemmler and K. Schreiber, *Biochem. Physiol. Alkaloide, Int. Symp.*, 4th 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 313.

⁸ F. Santavy, *Khim. Rast. Veshchestv*, 1972, 86 (*Chem. Abs.*, 1973, **78**, 136 477d).

⁹ V. Simanek, *Khim. Rast. Veshchestv*, 1972, 95 (*Chem. Abs.*, 1973, **78**, 136 478e).

The Emmert reaction and dimerization-dehydrogenation of alkaloids have been reviewed.¹⁰ Russian authors have also provided a review on cleavage of N—C bonds in saturated heterocyclic systems.¹¹

A technique used for the transfer of *Rauwolfia* alkaloids from t.l.c. plates directly to KBr discs for i.r. spectral examination should find general application.¹²

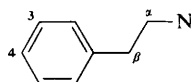
2 β -Phenethylamines

A review on the chemistry and pharmacology of nutmeg which includes a discussion of the hallucinogenic activity of amphetamines has appeared.¹³ An expert review concerning the synthesis of mescaline and other hallucinogens may also be of general interest.¹⁴ A combination gas chromatography-mass spectroscopy investigation of alkaloids from *Carnegia gigantea*, including 3-methoxytyramine, has been discussed in a lecture.¹⁵

A report on official methods of alkaloid analysis devotes a section to the determination of ephedrine.¹⁶

Results of isolation and structural elucidation work are recorded in Table 1.¹⁷⁻²⁹

Table 1 Isolation of β -phenethylamine alkaloids



Species	Alkaloid	Ref.
<i>Cannabis sativa</i>	Cannabamine C, C ₁₄ H ₂₁ N ₃ O ₃	17
<i>Coryphantha</i>	<i>NN</i> -Dimethyltyramine (Hordenine)	18
<i>cornifera</i>	4-Methoxy- β -hydroxy- β -phenethylamine	18
<i>var. echinus</i>	<i>N</i> -Methyl-3,4-dimethoxy- β -phenethylamine	18
	<i>N</i> -Methyl-4-methoxy- β -phenethylamine	18
	β - <i>O</i> -Methylsynephrine (<i>N</i> -Methyl-4-hydroxy- β -methoxy- β -phenethylamine)	18
	<i>N</i> -Methyltyramine (<i>N</i> -Methyl-4-hydroxy- β -phenethylamine)	18
<i>C. ramillosa</i> ^a	Hordenine	19
	<i>N</i> -Methyl-4-methoxy- β -phenethylamine	19
	β - <i>O</i> -Methylsynephrine	19
	<i>N</i> -Methyltyramine	19
	Synephrine (<i>N</i> -Methyl-4-hydroxy- β -hydroxy- β -phenethylamine)	19

¹⁰ O. S. Otroshchenko, A. A. Žiyaev, and G. A. Tolkacheva, *Khim. Rast. Veshchestv*, 1972, 120 (*Chem. Abs.*, 1973, **78**, 148 094q).

¹¹ E. I. Levkoeva and L. N. Yakhontov, *Uspekhi Khim.*, 1972, **41**, 1337 (*Chem. Abs.*, 1972, **77**, 151 746p).

¹² W. E. Court and M. S. Habib, *J. Chromatog.*, 1972, **73**, 274.

¹³ D. A. Kalbhen, *Angew. Chem. Internat. Edn.*, 1971, **10**, 370.

¹⁴ A. Hofmann, *Svensk. farm. Tidskr.*, 1971, **75**, 933 (*Chem. Abs.*, 1972, **76**, 149 609g).

¹⁵ S. Agurell, J. G. Bruhn, and K. Sheth, *Biochem. Physiol. Alkaloide, Int. Symp.*, 4th 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 275.

¹⁶ E. Smith, *J. Assoc. Offic. Analyt. Chemists*, 1972, **55**, 248.

Table 1—continued

Species	Alkaloid	Ref.
<i>Desmodium gangeticum</i> ^b	Candicine (NNN-Trimethyl-4-hydroxy- β -phenethylammonium salt)	20
<i>D. tiliaefolium</i> ^c	NN-Dimethyl-3,4-dimethoxy- β -phenethylamine	21
	3,4-Dimethoxy- β -phenethylamine	21
	Hordenine	21
	N-Methyl-3,4-dimethoxy- β -hydroxy- β -phenethylamine	21
	Tyramine (4-Hydroxy- β -phenethylamine)	21
<i>D. triflorum</i>	β -Phenethylamine	22
	Tyramine	22
	Unstable quaternary alkaloid	22
<i>Fagara chalybea</i> ^c	Candicine	23
<i>Lophophora williamsii</i>	3,4-Dihydroxy-5-methoxy- β -phenethylamine	24
	Dopamine (3,4-Dihydroxy- β -phenethylamine)	24
	Epinine (N-Methyldopamine)	24
	4-Hydroxy-3-methoxy- β -phenethylamine	24
<i>Obregonia denegrii</i>	Hordenine	25
	N-Methyltyramine	25
	Tyramine	25
<i>Pelecyphora aselliformis</i>	3-Demethyltrichocereine (NN-Dimethyl-3-hydroxy-4,5-dimethoxy- β -phenethylamine)	26
	3,4-Dimethoxy- β -phenethylamine	26
	Hordenine	26
	Mescaline	26
	N-Methyl-3,4-dimethoxy- β -phenethylamine	26
	N-Methylmescaline	26
		26
<i>Phalaris arundinacea</i>	Hordenine	27
<i>Ungernia trisphaera</i>	Hordenine	28
Uruguayan cactus (?)	Hordenine	29
	N-Methyltyramine	29
	Tyramine	29

^a All listed alkaloids have been isolated from other *Coryphantha* species; ^b Identification of other alkaloids is indicated; original literature not available; ^c Several quaternary alkaloids also detected.

¹⁷ F. K. Klein, H. Rapoport, and H. W. Elliott, *Nature*, 1971, **232**, 258.

¹⁸ K. M. K. Hornemann, J. M. Neal, and J. L. McLaughlin, *J. Pharm. Sci.*, 1972, **61**, 41.

¹⁹ P. T. Sato, J. M. Neal, L. R. Brady, and J. L. McLaughlin, *J. Pharm. Sci.*, 1973, **62**, 411.

²⁰ S. Ghosal and S. K. Bhatfacharya, *Planta Med.*, 1972, **22**, 434.

²¹ S. Ghosal and R. S. Srivastava, *Phytochemistry*, 1973, **12**, 193.

²² S. Ghosal, R. S. Srivastava, P. K. Banerjee, and S. K. Dutta, *Phytochemistry*, 1971, **10**, 3312.

The first indication that *Cannabis sativa* contains alkaloidal components has been reported.¹⁷ Cannabamines A, B, C, and D were isolated only in sufficient amounts for mass spectral analysis; on this basis, cannabamine C appears to be a *β*-phenethylamine derivative. Two new cactus alkaloids, *β*-*O*-methylsynephrine and 4-methoxy-*β*-hydroxy-*β*-phenethylamine, have been isolated from *Coryphantha cornifera* var. *echinus*.¹⁸ The latter compound has not been previously reported as a natural product. Six other *Coryphantha* species were shown to possess *β*-phenethylamine alkaloids; synephrine (*N*-methyl-4-hydroxy-*α*-hydroxy-*β*-phenethylamine) was found to be present in all species. A useful reference list of alkaloids isolated from Cactaceae is also given.¹⁸ There is a rumour that *C. runyonii* is being promoted in California as a 'natural and legal' psychedelic agent; it exhibits about one-fifth the potency of peyote.

In connection with biosynthetic studies in peyote (*Lophophora williamsii*) it was necessary to establish that certain incorporated precursors are in fact elaborated by the plant.²⁴ After extensive trials with various techniques, it was found that the presence of the proposed intermediates listed in Table 1 could be ascertained by the inverse isotope-dilution technique. However, it was not possible to establish the presence of dopa and 3,4,5-trihydroxy-*β*-phenethylamine in peyote using this method. The amount of tyramine hydrochloride (0.003%) isolated from *Obregonia denegrii*, a Mexican cactus commonly called a 'peyote', indicates that this species is quite different from the other peyote cacti (*Lophophora* and *Ariocarpus*), which usually contain only trace amounts (if any) of tyramine.²⁵ The report of alkaloid isolation from *Pelecyphora aselliformis* constitutes the first time these compounds have been found in a cactus other than *Lophophora*.²⁶ (For results of other workers on this species see Vol. 3 of these Reports). Application of g.c.-mass spectral instrumentation was successful in the characterization of hordenine, isolated from the seeds of four varieties of canary grass (*Phalaris arundinacea*).²⁷

An interesting observation has been made in connection with biosynthetic studies in barley.³⁰ The major alkaloid isolated from the seedlings of barley treated with ethylene oxide was found to be *N*-methyltyramine whereas normal plants were shown to produce hordenine and *N*-methyltyrosine in a ratio of 3:1. An increased amount of activity in the study of alkaloids produced from plant tissue culture is to be noted. A recent report describing the effect of tyrosine and L-phenylalanine on the formation of alkaloids in the seed callus tissue of

²³ F. Fish and P. G. Waterman, *Phytochemistry*, 1972, **11**, 3007.

²⁴ J. Lundstrom, *Acta Chem. Scand.*, 1971, **25**, 3489.

²⁵ J. M. Neal, P. T. Sato, and J. L. McLaughlin, *Econ. Bot.*, 1971, **25**, 382.

²⁶ J. M. Neal, P. T. Sato, W. N. Howald, and J. L. McLaughlin, *Science*, 1972, **176**, 1131.

²⁷ M. Williams, R. F. Barnes, and J. M. Cassady, *Crop Sci.*, 1971, **11**, 213.

²⁸ Kh. Allayarov and Kh. A. Abduazimov, *Probl. Osvoeniya Pustyn*, 1970, 83. [From *Ref. Zhur. Khim.*, 1970, Abstr. No. 13F1090 (*Chem. Abs.*, 1971, **75**, 148 488j)].

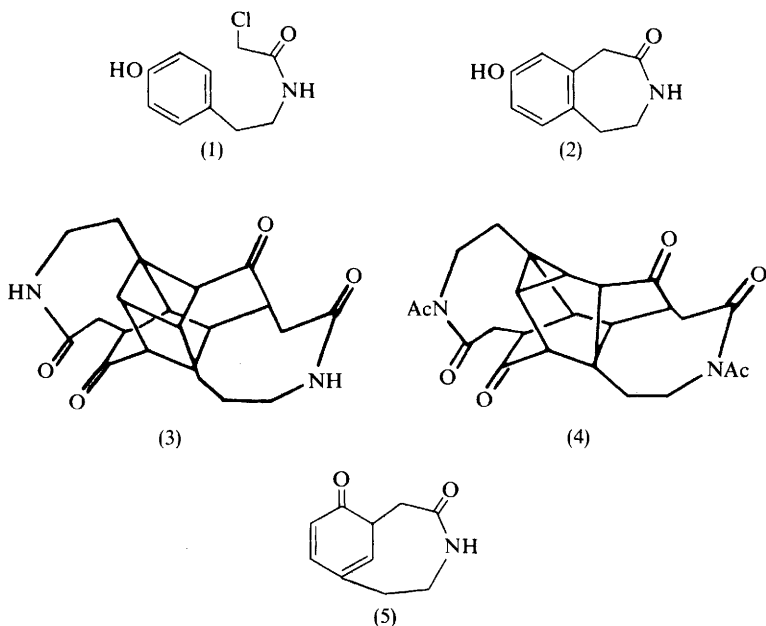
²⁹ J. X. De Vries, P. Moyna, V. Diaz, S. Agurell, and J. G. Bruhn, *Rev. Latinoamer. Quim.*, 1971, **2**, 21 (*Chem. Abs.*, 1971, **75**, 31 357z).

³⁰ E. Leete, R. M. Bowman, and M. F. Manuel, *Phytochemistry*, 1971, **10**, 3029.

Datura stramonium also provides a literature survey of this area.³¹ Total ephedrine content in dried shoots of *Ephedra procera*, *E. intermedia*, and *E. distachya* has been reported.³²

Excellent recovery of L-dopa from the seeds of nine *Mucuna* species has been achieved by ion-exchange followed by dextran column chromatography.³³

Still more bizarre photochemical rearrangements of *N*-chloroacetyl- β -phenethylamine derivatives have been uncovered.³⁴ Photolysis of *N*-chloroacetyl-tyrosine (1) gives, besides the benzazepine (2), the photodimers (3) (40%) and (4) (12%). The structures of the dimers have been established by X-ray crystallographic analysis;³⁴ both appear to be formed *via* the cyclohexadienone (5), which may be detected and trapped by a Diels-Alder reaction.³⁵ The effect of oxygen, silver carbonate, and solvent on these photoreactions has also been studied.³⁶ The Dakin-West reaction of dopa has been investigated.³⁷



³¹ T. V. Sairam and P. Khanna, *Lloydia*, 1971, **34**, 170.

³² G. M. Mamedov and G. M. Nasirova, *Rast. Resur.*, 1973, **9**, 57 (*Chem. Abs.*, 1973, **78**, 121 283p).

³³ M. E. Daxenbichler, C. H. VanEtten, F. R. Earle, and W. H. Tallent, *J. Agric. Food Chem.*, 1972, **20**, 1046.

³⁴ T. Iwakuma, H. Nakai, O. Yonemitsu, D. S. Jones, I. L. Karle, and B. Witkop, *J. Amer. Chem. Soc.*, 1972, **94**, 5136.

³⁵ T. Iwakuma, O. Yonemitsu, N. Kanamaru, K. Kimura, and B. Witkop, *Angew. Chem.*, 1973, **85**, 85.

³⁶ O. Yonemitsu, H. Nakai, Y. Okuno, S. Naruto, K. Hemmi, and B. Witkop, *Photochem. and Photobiol.*, 1972, **15**, 509.

³⁷ C. -Y. Yang, *Hua Hsueh*, 1971, 133 (*Chem. Abs.*, 1972, **77**, 113 986j).

Stereoselective synthesis of tyrosine and phenylalanine derivatives possessing deuterium or tritium at the β -position has been reported.³⁸ Synthesis of β -fluoro-analogues of β -phenethylamine alkaloids has been accomplished.³⁹

The X-ray crystal structure of mescaline hydrochloride has been determined.⁴⁰

A method for the separation of mescaline, *N*-methylephedrine, and several other β -phenethylamines on t.l.c. as their dansyl [1-(dimethylamino)-5-naphthalenesulphonyl] derivatives may have wider application.⁴¹ Cation exchange of ephedrine has been studied in detail.⁴² A colorimetric method for L-ephedrine and D-pseudoephedrine has been reported.⁴³ A new polyamide liquid phase for the g.c. separation and identification of alkaloids has been described.⁴⁴ Other analytical methods using t.l.c.,⁴⁵ t.l.c.-electrophoresis,⁴⁶ and thermogravimetry⁴⁷ have application to alkaloid studies. Finally, the reaction of a mixture of hydrazine and nitrous acid with tyramine derivatives gives stable fluorescent solutions.⁴⁸ The nature of the reaction and the compounds responsible for the fluorescence are unknown; thus the analytical application of this method must be preceded by further investigation of the method itself.

Pharmacological studies of ephedrine⁴⁹ and candicine²⁰ may be noted.

3 Simple Isoquinoline Alkaloids

A reference list of alkaloids found in cacti is available.¹⁸

Ancistrocladisine (6) has been isolated from the roots of *Ancistrocladus heyneanus*.^{50a} Its structure is based on spectral and Hofmann degradative evidence similar to that obtained for the other two novel alkaloids previously isolated from this species (see Vols. 2 and 3 of these Reports), one of which has received corroborative structural evidence.^{50b} Evidence for the structures of carnegine (7; $R^1 = H$, $R^2 = R^3 = Me$), gigantine (7; $R^1 = OH$, $R^2 = R^3 = Me$), and norcarnegine (salsolidine) (7; $R^1 = R^3 = H$, $R^2 = Me$), isolated from

³⁸ G. W. Kirby and J. Michael, *J.C.S. Perkin I*, 1973, 115.

³⁹ G. Aranda, *Chim. Ther.*, 1971, 6, 262 (*Chem. Abs.*, 1972, 76, 25 448j).

⁴⁰ D. Tsoucaris, C. De Rango, G. Tsoucaris, Ch. Zelwer, R. Parthasarathy, and F. E. Cole, *Cryst. Struct. Comm.*, 1973, 2, 193.

⁴¹ J. M. Neal and J. L. McLaughlin, *J. Chromatog.*, 1972, 73, 277.

⁴² A. K. Gurban, L. M. Ovsyanko, and G. L. Starobinets, *Vestnik Beloruss. Univ.*, 1970, 2, 8 (*Chem. Abs.*, 1972, 77, 66 536a).

⁴³ K. Kimura, H. Shimada, S. Nomura, Y. Hisada, and T. Tanaka, *Yakugaku Zasshi*, 1973, 93, 364 (*Chem. Abs.*, 1973, 78, 164 146p).

⁴⁴ D. J. Jenden, M. Roch, and R. Booth, *J. Chromatog. Sci.*, 1972, 10, 151.

⁴⁵ T. Walicka, *Farm. Polon.*, 1971, 27, 169 (*Chem. Abs.*, 1971, 75, 80 346d).

⁴⁶ A. S. C. Wan, *J. Chromatog.*, 1971, 60, 371.

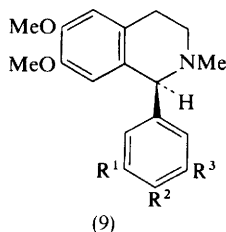
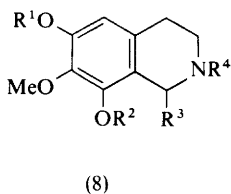
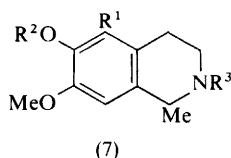
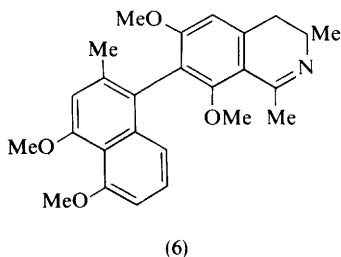
⁴⁷ J. Masse, S. Alberola, J. Rambaud, and F. Sabon, *Trav. Soc. Pharm. Montpellier*, 1970, 30, 283 (*Chem. Abs.*, 1971, 75, 40 342t).

⁴⁸ P. H. Scott, *Biochem. J.*, 1971, 123, 977.

⁴⁹ M. N. Kononov, B. A. Krivut, R. G. Maksimova, N. N. Ostrovskii, and E. A. Edel'shtein, *Otkrytiya, Izobret., Prom. Obratzs, Tovarneye Znaki*, 1972, 49, 16 (*Chem. Abs.*, 1973, 78, 47 828b).

⁵⁰ (a) T. R. Govindachari, P. C. Parthasarathy, and H. K. Desai, *Indian J. Chem.*, 1972, 10, 1117; (b) T. R. Govindachari, P. C. Parthasarathy, and H. K. Desai, *ibid.*, 1971, 9, 931.

Carnegia gigantea, is presented in the proceedings of a recent symposium.¹⁵ Two other alkaloids were detected but their structures were not fully established. Salsolidine as well as salsoline (7; $R^1 = R^2 = R^3 = H$) have been obtained from *Desmodium tiliaefolium* together with β -phenethylamine and tryptamine alkaloids.²¹ This marks the first time that (a) simple isoquinolines have been found in this genus and (b) three different alkaloid types have been encountered in a single legume species. Details of the very careful isolation and identification work of trace alkaloids from peyote (*Lophophora williamsii*) have appeared.⁵¹ Isoanhalamine (8; $R^1 = R^3 = R^4 = H$, $R^2 = Me$), isoanhalidine (8; $R^1 = R^3 = H$, $R^2 = R^4 = Me$), isoanhalonidine (8; $R^1 = R^4 = H$, $R^2 = R^3 = Me$), and isopellotine (8; $R^1 = H$, $R^2 = R^3 = R^4 = Me$) have been characterized by application of the g.l.c.-mass spectral technique, and their biosynthetic relationship to the major cactus alkaloids has been discussed. The occurrence of anhalidine (8; $R^1 = R^4 = Me$, $R^2 = R^3 = H$) in *Pelecyphora aselliformis* has been confirmed and the additional alkaloid pellotine (8; $R^1 = Me$, $R^2 = R^3 = R^4 = H$) has been identified in this species.²⁶ This report is significant in that it describes the first isolation of tetrahydroisoquinoline and β -phenethylamine (see above, p. 129) alkaloids from a North American cactus other than *Lophophora williamsii*. However, the much lower concentration of alkaloids in *P. aselliformis* raises doubt regarding the physiological effects of this species. Small amounts of anhalidine (8; $R^1 = R^4 = Me$, $R^2 = R^3 = H$) and anhalonidine (8; $R^1 = R^3 = Me$, $R^2 = R^4 = H$) have been isolated from *Stetsonia coryne*.⁵²



⁵¹ J. Lundstrom, *Acta Chem. Scand.*, 1972, **26**, 1295.

⁵² S. Agurell, J. G. Bruhn, J. Lundstrom, and U. Svensson, *Lloydia*, 1971, **34**, 183.

Full reports on the absolute configuration of cryptostylin I (9; $R^1 = H$, $R^2 + R^3 = OCH_2O$), II ($R^1 = H$, $R^2 = R^3 = OMe$), and III ($R^1 = R^2 = R^3 = OMe$), determined by X-ray crystallographic and c.d. spectral analysis, have been published.^{53,54} The X-ray crystal structure of the methiodide of cryptostylin I has also been determined.⁵⁵

Peyoxylic acid (10; $R = Me$) and *o*-methylpeyoruvic acid (10; $R = H$) have been synthesized by treatment of mescaline hydrochloride with methyl pyruvate and butyl glyoxylate, respectively.⁵⁶ A conventional synthesis of calycotamine (11; $R^1 = Me$, $R^2 = CH_2OH$) has been reported.⁵⁷ The conversion of corgoine (12; $R = H$) from *Corydalis gortschakovii* into sendaverine (12; $R = Me$) has been described,⁵⁸ and a degradation of the methiodide of the latter alkaloid which should be useful in biosynthetic experiments has been devised.⁵⁹

The implication of tetrahydroisoquinoline alkaloids as elicitors of a number of pharmacological responses in mammalian tissue⁶⁰ has given impetus to an *in vitro* study of the reaction between L-dopa (13; $R^1 = R^2 = H$) derivatives with formaldehyde and acetaldehyde.⁶¹ For example, treatment of L-dopa with acetaldehyde in the presence of 0.5N-sulphuric acid at 50 °C gave a 95:5 mixture of (14; $R^1 = Me$, $R^2 = H$) and (14; $R^1 = H$, $R^2 = Me$). The absolute configuration of the major product (14; $R^1 = Me$, $R^2 = H$) was determined by X-ray analysis of its ethyl ester hydrochloride. The minor component (14; $R^1 = H$, $R^2 = Me$) was also obtained by mercuric acetate oxidation of (14; $R^1 = Me$, $R^2 = H$) followed by sodium borohydride reduction. Interestingly, the 3-*O*-methyl ether (13; $R^1 = Me$, $R^2 = H$), which is a major metabolite of L-dopa in man and accumulates in mammalian tissue, was found to be most resistant to the cyclization reaction with aldehydes. This area will undoubtedly receive impetus from the report that salsolinol (11; $R^1 = H$, $R^2 = Me$) has recently been identified as an *in vivo* metabolite in patients with Parkinson's disease who were being treated orally with L-dopa.⁶² Of interest in this connection is also the study of inhibition of alkaloid formation by cysteine in rat brain homogenates.⁶³

⁵³ J. F. Blount, V. Toome, S. Teitel, and A. Brossi, *Tetrahedron*, 1973, **29**, 31; cf. also T. Kametani, H. Sugi, and S. Shibuya, *ibid.*, 1971, **27**, 2409.

⁵⁴ K. Leander, B. Luning, and L. Westin, *Acta Chem. Scand.*, 1973, **27**, 710.

⁵⁵ L. Westin, *Acta Chem. Scand.*, 1972, **26**, 2305.

⁵⁶ G. J. Kapadia, G. S. Rao, M. H. Hussain, and B. K. Chowdhury, *J. Heterocyclic Chem.*, 1973, **10**, 135.

⁵⁷ J. Kobor and K. Koczka, *Szegedi Tanarkepzo Foiskola Tud. Kozlem.*, 1969, 179 (*Chem. Abs.*, 1973, **78**, 4 389s).

⁵⁸ M. U. Ibragimova, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, 211 (*Chem. Abs.*, 1971, **75**, 36 400t).

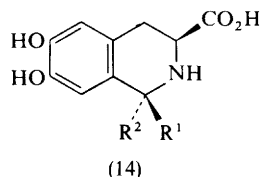
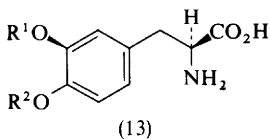
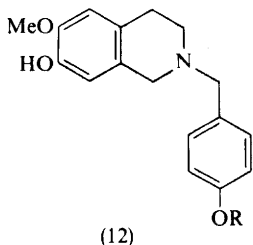
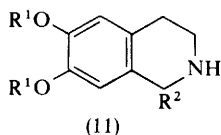
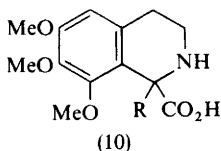
⁵⁹ B. Olesch and H. Boehm, *Arch. Pharm. (Weinheim)*, 1972, **305**, 222.

⁶⁰ For recent references, see G. Cohen, *Biochem. Pharmacol.*, 1971, **20**, 1757; R. Heikkila, G. Cohen, and D. Dembiec, *J. Pharmacol. Exp. Ther.*, 1971, **179**, 250 (*Chem. Abs.*, 1972, **76**, 30 523j).

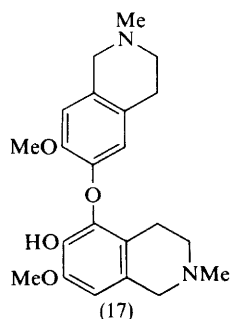
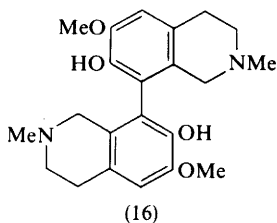
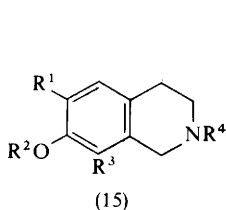
⁶¹ A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, 1972, **55**, 15.

⁶² M. Sandler, S. B. Carter, K. R. Hunter, and G. M. Stern, *Nature*, 1973, **241**, 439.

⁶³ S. G. A. Alivisatos, F. Ungar, O. H. Callaghan, L. P. Levitt, and B. Tabakoff, *Canad. J. Biochem.*, 1973, **51**, 28.

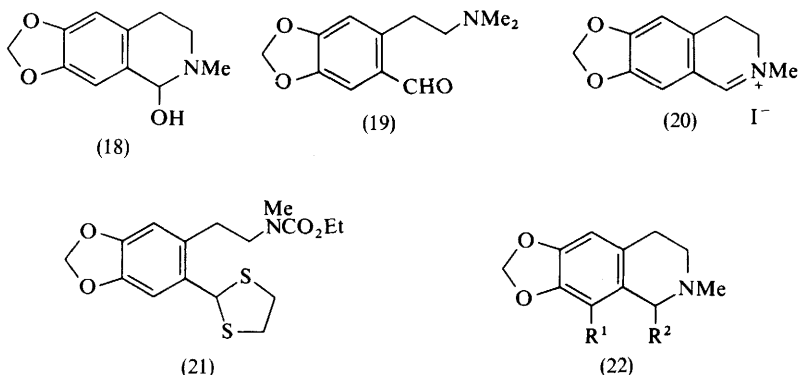


Continuation of studies dealing with electrolytic oxidation of phenolic tetrahydroisoquinolines as biosynthetic models has been reported by Bobbitt and co-workers.⁶⁴ Compounds lacking phenolic hydroxy-groups were found to be stable to the electrolysis conditions. However, a series of compounds (15; $R^1 = \text{OMe}$, $R^2 = R^3 = \text{H}$; $R^1 = \text{OH}$, $R^2 = \text{Me}$, $R^3 = \text{H}$; $R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3 = \text{OH}$; $R^4 = \text{Me}$ or COMe in all cases) yielded mostly crystalline carbon-carbon or carbon-oxygen dimers. The effect of variables such as the nature of anode, the cell design, the solvent, the pH, and the reaction time was investigated and the optimum conditions for phenol coupling were determined. The most interesting results were observed in the oxidation of the sodium salts of (15) in acetonitrile. For example, oxidation of (15; $R^1 = \text{OMe}$, $R^2 = R^3 = \text{H}$, $R^4 = \text{Me}$) gave mainly the carbon-carbon dimer (16), whereas (15; $R^1 = \text{OH}$, $R^2 = R^4 = \text{Me}$, $R^3 = \text{H}$) yielded the carbon-oxygen dimer (17). If the electrolysis is carried out in acid solution or on *N*-acetyl derivatives of (15) only carbon-carbon dimers are obtained. The reason for the unique behaviour of (15; $R^1 = \text{OH}$, $R^2 = R^4 = \text{Me}$, $R^3 = \text{H}$) and (15; $R^1 = \text{H}$, $R^2 = R^4 = \text{Me}$, $R^3 = \text{OH}$) in yielding carbon-oxygen dimers is not clear.



⁶⁴ J. M. Bobbitt, H. Yagi, S. Shibuya, and J. T. Stock, *J. Org. Chem.*, 1971, **36**, 3006.

Not unexpectedly, the reaction of hydrastinine (18) with methyl iodide has been shown to yield a mixture of the methiodide of (19) and (20).⁶⁵ A more interesting reaction sequence involving treatment of (20) with ethyl chloroformate followed by thioacetalation to give (21) was also reported in this paper. Treatment of hydrohydrastinine (22; $R^1 = R^2 = H$) or hydrocotarnine (22; $R^1 = OMe$, $R^2 = H$) with ethyl diazoacetate or diazoacetone yielded the corresponding stable diazo-carbonyl derivatives [22; $R^1 = H$, $R^2 = C(N_2)CO_2Et$] and [22; $R^1 = OMe$, $R^2 = C(N_2)COMe$].⁶⁶ Cotarnine (22; $R^1 = OMe$, $R^2 = OH$) with ethyl diazoacetate in absolute methanol-ether gave [22; $R^1 = OMe$, $R^2 = C(N_2)CO_2Et$], probably *via* the methyl ether (22; $R^1 = R^2 = OMe$).⁶⁷



Sephadex column chromatography has been used to separate cotarnine in alkaloidal mixtures.⁶⁸ Spectrophotometric and titrimetric methods for salsoline (7; $R^1 = R^2 = R^3 = H$) and salsolidine (7; $R^1 = R^3 = H$, $R^2 = Me$) have been developed.⁶⁹⁻⁷¹ Exchange properties of salsoline on cation-exchange resins have been studied.⁴²

4 Benzyloisoquinoline Alkaloids

Table 2 lists new sources of alkaloids. From the chemotaxonomic point of view, isolation of armepavine from *Euonymus europaeus* (Order Celastrales) is not unexpected since this type of alkaloid has been previously found in the related

⁶⁵ M. D. Rozwadowska, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1971, **19**, 673 (*Chem. Abs.*, 1972, **76**, 99 480k).

⁶⁶ B. Goerber, G. Bauer, S. Pfeifer, G. Dube, and G. Engelhardt, *Pharmazie*, 1970, **25**, 790.

⁶⁷ B. Goerber and S. Ganschow, *Pharmazie*, 1973, **28**, 68.

⁶⁸ M. I. Goryaev, N. P. Kamenskii, and P. P. Gladyshev, *Farmatsiya (Moscow)*, 1973, **22**, 39 (*Chem. Abs.*, 1973, **78**, 128 454d).

⁶⁹ U. Dustov, N. Kh. Maksudov, Sh. T. Talipov, and R. Kh. Dzhiyanbaeva, *Zhur. analit. Khim.*, 1972, **27**, 2272 (*Chem. Abs.*, 1973, **78**, 66 687w).

⁷⁰ G. L. Starobinets and E. M. Rakhman'ko, *Vestsi Akad. Navuk Belarusk. S.S.R., Ser. Khim. Navuk*, 1972, **22** (*Chem. Abs.*, 1972, **77**, 39 323x).

⁷¹ E. M. Rakhman'ko and G. L. Starobinets, *Vestsi Akad. Navuk Belarusk. S.S.R., Ser. Khim. Navuk*, 1972, 112 (*Chem. Abs.*, 1973, **78**, 75 920u).

Orders Euphorbiales (Euphorbiaceae) and Rhamnales (Rhamnaceae).⁷³ Since macrocyclic peptide alkaloids have been isolated from *E. europaeus*, a biosynthetic relationship between this class and the benzyloisoquinoline type may be conjectured. L-(+)-Armepavine metho-salt was isolated for the first time from a natural source (*Xanthoxylum inerme*).⁷⁵ The isolation work on the dry ripe seed capsules of *Papaver somniferum* has been stimulated by the fact that this represents a new raw material for the industrial-scale production of a number of alkaloids.⁷⁷

Table 2 Isolation of benzyloisoquinoline alkaloids

Alkaloid (Structure)	Plant source(s)	Ref.
Armepavine (23; R ¹ = R ² = R ⁵ = Me, R ³ = R ⁴ = OH)	<i>Discaria crenata</i>	72
	<i>Euonymus europaeus</i>	73
	<i>Nelumbo nucifera</i>	74
L-(+)-Armepavine metho-salt	<i>Xanthoxylum inerme</i> (<i>Fagara boninensis</i>)	75
Coclaurine (23; R ¹ = Me, R ² = R ⁴ = R ⁵ = H, R ³ = OH)	<i>Retanilla ephedra</i>	75a
(-)-Magnocurarine (23; R ¹ = R ⁵ = Me, R ² = R ⁴ = H, R ³ = OH, metho-salt)	<i>Colletia hystrix</i>	75a
N-Methylcoclaurine (23; R ¹ = R ⁵ = Me, R ² = R ⁴ = H, R ³ = OH)	<i>Discaria crenata</i>	72
	<i>Nelumbo nucifera</i>	74
N-Methylisococlaurine (23; R ¹ = R ⁴ = H, R ² = R ⁵ = Me, R ³ = OH)	<i>N. nucifera</i>	74
N-Norarmepavine (23; R ¹ = R ² = Me, R ³ = OH, R ⁴ = R ⁵ = H)	<i>N. nucifera</i>	76
Papaveraldine (24; R = O)	<i>Papaver somniferum</i> (capsules)	77
Papaverine (24; R = H ₂)	<i>P. somniferum</i>	77
(+)-Reticuline (23; R ¹ = R ⁵ = Me, R ² = H, R ³ = OMe, R ⁴ = OH)	<i>Cinnamomum laubattii</i>	78
	<i>Cryptocarya foveolata</i>	79
	<i>C. odorata</i>	80
	<i>Litsea leefeana</i>	79
Tembetarine (Reticuline metho-salt)	<i>Fagara chalybea</i>	23
Unnamed (23; R ¹ = R ⁵ = Me, R ² = H, R ³ = OH, R ⁴ = OMe)	<i>Erythrina arborescens</i>	81

⁷² P. Pacheco, S. M. Albonico, and M. Silva, *Phytochemistry*, 1973, **12**, 954.

⁷³ D. W. Bishay, Z. Kowalewski, and J. D. Phillipson, *Phytochemistry*, 1973, **12**, 693.

⁷⁴ J. Kunitomo, Y. Yoshikawa, S. Tanaka, Y. Imori, K. Isoi, Y. Masada, K. Hashimoto, and T. Inoue, *Phytochemistry*, 1973, **12**, 699.

⁷⁵ H. Ishi, H. Ohida, and J. Haginiwa, *Yakugaku Zasshi*, 1972, **92**, 118.

^{75a} E. Sanchez and R. Torres, *Anales. Asoc. quim. argentina*, 1971, **59**, 343 (*Chem. Abs.*, 1972, **77**, 85 620q).

⁷⁶ T. -H. Yang, C. -M. Chen, C. -S. Lu, and C. -L. Liao, *J. Chinese Chem. Soc. (Taipei)*, 1972, **19**, 143 (*Chem. Abs.*, 1972, **77**, 161 937r).

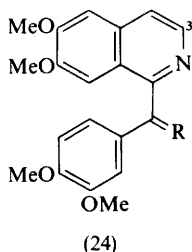
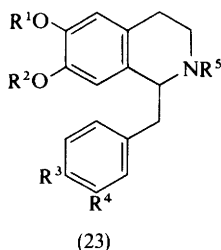
⁷⁷ J. Hodkova, Z. Vesely, Z. Koblicova, J. Holubek, and J. Trojanek, *Lloydia*, 1972, **35**, 61.

⁷⁸ J. Ellis, E. Gellert, and R. E. Summons, *Austral. J. Chem.*, 1972, **25**, 1829.

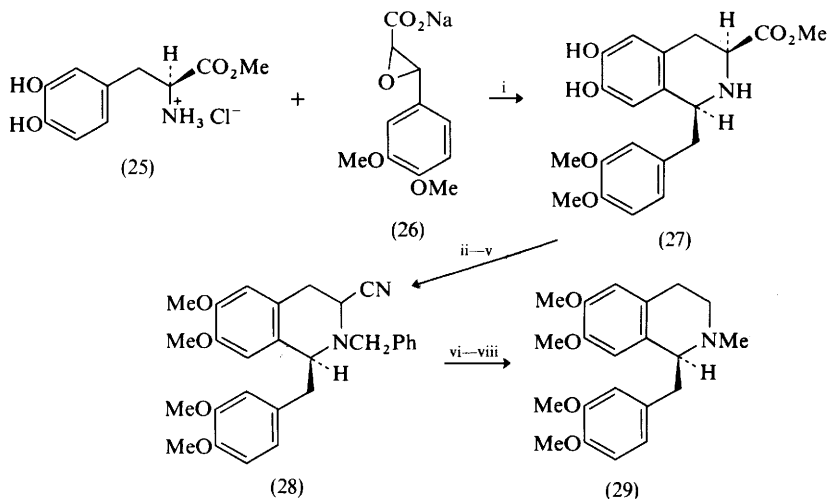
⁷⁹ J. A. Lambertson and V. N. Vashist, *Austral. J. Chem.*, 1972, **25**, 2737.

⁸⁰ I. R. C. Bick, N. W. Preston, and P. Potier, *Bull. Soc. chim. France*, 1972, 4596.

⁸¹ S. Ghosal, A. Chakraborti, and R. S. Srivastava, *Phytochemistry*, 1972, **11**, 2101.



Although solutions of papaverine (24; $R = H_2$) in organic solvents are relatively stable in the dark,⁸² they readily undergo oxidative reactions when exposed to sunlight to give papaveraldine (24; $R = O$), papaverinol (24; $R = H, OH$), papaverine *N*-oxide, and 6,7-dimethoxyisoquinoline *N*-oxide.⁸³



Reagents: i, pH 4, 35°C; ii, CH_2N_2 ; iii, NH_3 , MeOH; iv, $PhCH_2Cl$, K_2CO_3 , EtOH; v, P_2O_5 , C_5H_5N ; vi, $NaBH_4$, EtOH- C_5H_5N ; vii, H_2 , Pd-C, HCl; viii, $NaBH_4$, CH_2O , MeOH.

Scheme 1

A comprehensive review on the syntheses of papaverine (24; $R = H_2$) has appeared which presents comparison of method (or modification) with yield and reaction conditions.⁸⁴ A new biogenetic-type synthesis of (*S*)-(+)-laudanosine (29) has been reported⁸⁵ (Scheme 1). Acid-catalysed condensation of L-(+)-3,4-

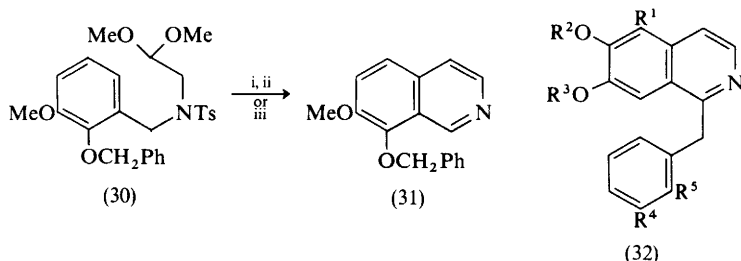
⁸² S. Pfeifer, G. Behnsen, and L. Kuehn, *Pharmazie*, 1972, 27, 639.

⁸³ S. Pfeifer, G. Behnsen, L. Kuehn, and R. Kraft, *Pharmazie*, 1972, 27, 734.

⁸⁴ A. V. Luk'yanov, V. S. Onoprienko, and V. A. Zasosov, *Khim.-Farm. Zhur.*, 1972, 6, 14 (*Chem. Abs.*, 1972, 77, 101 940b).

⁸⁵ S. Yamada, M. Konda, and T. Shioiri, *Tetrahedron Letters*, 1972, 2215.

dihydroxyphenylalanine methyl ester hydrochloride (25) with the sodium glycidate (26) gave in 44% yield a diastereoisomeric mixture of (27) and its C-1-epimer in a ratio of 2.4 : 1. Methylation with diazomethane followed by an ester to nitrile interconversion, involving also intermediate N-protection, gave the α -cyanoamine (28), which in three reductive steps was converted into (S)-(+)-laudanosine (29). Apparently independently of this work, a South American group has obtained (\pm)-isococlaurine (23; $R^1 = R^4 = R^5 = H$, $R^2 = Me$, $R^3 = OH$) from the reaction of the sodium salt of 3-benzyloxyphenylglycidate [refer to (26)] with 3-hydroxy-4-methoxy- β -phenethylamine followed by catalytic hydrogenation.⁸⁶ Details (see Vol. 2 of these Reports) of another route to (\pm)-laudanosine using (2-(3,4-dimethoxyphenylacetyl)-4,5-dimethoxyphenylacetic acid as a key intermediate have appeared.⁸⁷ A recently developed efficient method for isoquinoline synthesis [(30) \rightarrow (31), Scheme 2] has been modified to a one-step process and has been applied to the preparation of escholamine (32; $R^1 = H$, $R^2 + R^3 = CH_2$, $R^4 + R^5 = OCH_2O$) and takatonine (32; $R^1 = R^4 = OMe$, $R^2 = R^3 = Me$, $R^5 = H$).⁸⁸ Tetrahydropapaveroline (23; $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = OH$) has been obtained from norlaudanosine (23; $R^1 = R^2 = Me$, $R^3 = R^4 = OMe$, $R^5 = H$) by treatment with hydrobromic or hydriodic acid.⁸⁹ Interest in tetrahydropapaveroline has been high as a result of its as yet unclear connection with alcoholism⁶³ and Parkinson's disease.⁶²



Reagents: i, HCl, dioxan; ii, $KOBu^t$; iii, 6N-HCl, dioxan, reflux, N_2 .

Scheme 2

The photolysis of papaverine *N*-oxide (33) in acetone solution has been shown to yield the 1,3-benzoxazepine derivative (34) and the isomeric benzofurans (36) and (37) as major products (Scheme 3).⁹⁰ Products of the type (36) and (37) are without precedent in the photochemical rearrangement of simpler isoquinoline *N*-oxides and appear to arise by acid-catalysed rearrangement of the presumed intermediate (35) upon silica gel chromatography. A number

⁸⁶ M. R. Falco, J. X. De Vries, and G. Mann, *Z. Chem.*, 1973, 13, 56.

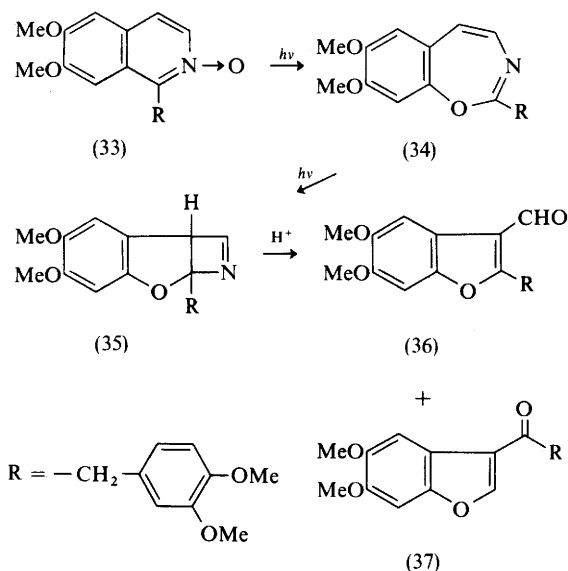
⁸⁷ I. W. Elliott, jun., *J. Heterocyclic Chem.*, 1972, 9, 853.

⁸⁸ A. J. Birch, A. H. Jackson, P. V. R. Shannon, and P. S. P. Varma, *Tetrahedron Letters*, 1972, 4789.

⁸⁹ S. Teitel, J. O'Brien, and A. Brossi, *J. Medicin. Chem.*, 1972, 15, 845.

⁹⁰ J. B. Bremner and P. Wiriyaichitra, *Austral. J. Chem.*, 1973, 26, 437.

of papaverine derivatives with benzylic functionalization, e.g. [24; R = OH, (CH₂)₃NMe₂] and (24; R = H, NHR), have been prepared for biological testing purposes.^{91,92} C-3-Oxygenated analogues of papaverine (24; R = H₂) have been obtained from benzoisopyrylium salts⁹³ using the key dimethoxyphenyl-acetic acid derivative referred to earlier.⁸⁷



Scheme 3

Knabe has reviewed⁹⁴ his interesting work concerning the mechanism of the acid-catalysed rearrangement of 1,2-dihydroisoquinolines, which has also been discussed in Vols. 2 and 3 of these Reports.

In the field of analytical methods, papaverine continues to receive a great deal of attention: new spectrophotometric,^{70,95} titrimetric,^{96,97} and gas-chromatographic⁹⁸ methods for this alkaloid have been developed. In addition,

⁹¹ M. Debaert, A. Lespagnol, M. Devergnies, A. Robelet, and M. Lesenne, *Chim. Ther.*, 1972, 7, 413 (*Chem. Abs.*, 1973, 78, 58 645r).

⁹² M. Debaert, A. Lespagnol, M. Devergnies, and M. Boniface, *Bull. Soc. chim. France*, 1972, 3584.

⁹³ G. N. Dorofeenko and V. G. Korobkova, *Khim. geterotsikl. Soedinenii*, 1971, 7, 1601 (*Chem. Abs.*, 1972, 77, 19 846s).

⁹⁴ J. Knabe, *Biochem. Physiol. Alkaloide, Int. Symp.*, 4th 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 299.

⁹⁵ S. Kh. Mushinskaya, V. A. Danel'yants, and A. M. Sych, *Postep Dziedzinie Leku Rosl., Pr. Ref. Dosw. Wygloszone Symp.*, 1970, 203 (*Chem. Abs.*, 1973, 78, 68 876f).

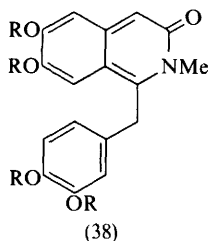
⁹⁶ T. Pelczar, *Acta Polon. Pharm.*, 1972, 29, 465 (*Chem. Abs.*, 1973, 78, 88 640c).

⁹⁷ G. Payen, *Pharm. Hosp. France*, 1971, 105 (*Chem. Abs.*, 1972, 77, 24 836t).

⁹⁸ A. Bechtel, *Chromatographia*, 1972, 5, 404.

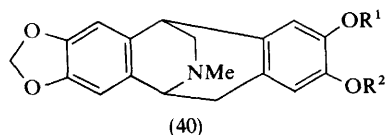
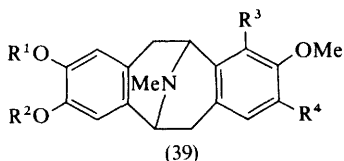
the behaviour of papaverine on cation-exchange resin,⁴² its reaction with a complex inorganic ion,⁹⁹ and the thermogravimetric properties of its reinecke salt¹⁰⁰ have been studied.

The 3(2*H*)-isoquinoline analogues (38) of papaverine (24; R = H₂) have been shown to possess better vasodilator properties than the alkaloid itself.¹⁰¹ Recent synthetic work on these compounds has been published.^{87,93} Hypotensive and spasmolytic activity has been reported for some *N*-acyl- and -alkyl-papaverine salts.¹⁰² The relationship of the spasmolytic effect of papaverine with its inhibition of oxidative phosphorylation by rat liver and heart mitochondria *in vitro* has been studied.¹⁰³ Inhibition of oxygen uptake by *Saccharomyces cerevisiae* (yeast) in the presence of laudanose (23; R¹ = R² = R⁵ = Me, R³ = R⁴ = OMe) has been reported.¹⁰⁴



5 Pavine Alkaloids

The structure of platycerine (39; R¹ = R² = Me, R³ = OH, R⁴ = H), which was slightly in doubt with respect to its positions of hydroxyl and methoxyl functions, has now been confirmed by synthesis using the modified Pomeranz-Fritsch (Scheme 2) and Reissert reactions as key steps.¹⁰⁵ A conventional synthesis of carychine (39; R¹ + R² = CH₂, R³ = H, R⁴ = OH) has appeared.¹⁰⁶



⁹⁹ J. Zsako, D. Opreescu, Cs. Varhelyi, and I. Ganescu, *Zhur. neorg. Khim.*, 1972, 17, 3242 (*Chem. Abs.*, 1973, 78, 48 800y).

¹⁰⁰ J. Masse, J. Rambaud, S. Alberola, and F. Sabon, *Trav. Soc. Pharm. Montpellier*, 1972, 32, 215 (*Chem. Abs.*, 1972, 77, 33 849x).

¹⁰¹ W. E. Kreighbaum, W. F. Kavanaugh, W. T. Comer, and D. Deitchman, *J. Medicin. Chem.*, 1972, 15, 1131.

¹⁰² K. T. Poroshin, Yu. D. Sadykov, K. Kh. Khaidarov, A. L. Vovsi-Kol'shtein, V. A. Degtyarev, and V. K. Burichenko, *Khim. prirod. Soedinenii*, 1972, 8, 83 (*Chem. Abs.*, 1972, 77, 56 640r).

¹⁰³ R. Michel and A. Uzan, *J. Pharmacol.*, 1972, 3, 265.

¹⁰⁴ R. H. Vallejos and O. A. Roveri, *Biochem. Pharmacol.*, 1972, 21, 3179.

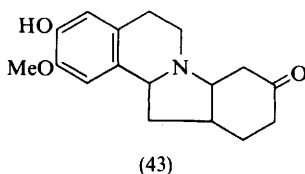
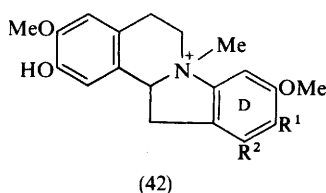
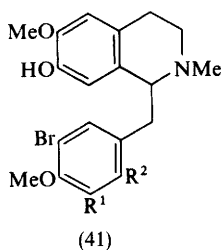
¹⁰⁵ F. R. Stermitz and D. K. Williams, *J. Org. Chem.*, 1973, 38, 1761.

¹⁰⁶ S. Natarajan and B. R. Pai, *Indian J. Chem.*, 1972, 10, 451.

The synthesis of the two isopavine alkaloids (40; $R^1 = H$, $R^2 = Me$) and (40; $R^1 = Me$, $R^2 = H$) has been accomplished¹⁰⁷ by taking advantage of a recently developed method to hydrate a 1,2-dihydroisoquinoline derivative (see Vol. 3 of these Reports). Compound (40; $R^1 = Me$, $R^2 = H$) was found to be identical with amurensine, and thus a total synthesis of this alkaloid has been achieved.

6 Dibenzopyrrocolines

Treatment of the benzyloisoquinoline derivatives (41; $R^1 = OMe$, $R^2 = H$) and (41; $R^1 = H$, $R^2 = OMe$) with sodium amide in liquid ammonia provided (\pm)-cryptaustoline¹⁰⁸ (42; $R^1 = OMe$, $R^2 = H$) and the analogue¹⁰⁹ (42; $R^1 = H$, $R^2 = OMe$), respectively, among other products. Benzyne intermediates are probably involved in these reactions. The ring D non-aromatic analogue (43) of this alkaloid type has been synthesized by a conventional route.¹¹⁰



7 Proaporphine, Aporphine, and Phenanthrene Alkaloids

Table 3¹¹¹⁻¹³¹ shows that isolation and structural elucidation work on these groups has not diminished. In addition to the alkaloids isolated from *Annona glabra* which are listed, norlaureline (44; $R^1 + R^2 = CH_2$, $R^3 = R^5 = R^6 = H$, $R^4 = OMe$), aporphine (44; $R^1 + R^2 = CH_2$, $R^3 = R^5 = R^6 = H$, $R^4 = OH$), and the dienone (49; $R = H$) were indicated from n.m.r. and mass spectral studies of certain preparative t.l.c. fractions.¹¹² The report on alkaloid isolation

¹⁰⁷ S. F. Dyke and A. C. Ellis, *Tetrahedron*, 1972, **28**, 3999.

¹⁰⁸ T. Kametani, K. Fukumoto, and T. Nakano, *J. Heterocyclic Chem.*, 1972, **9**, 1363.

¹⁰⁹ T. Kametani, K. Fukumoto, and T. Nakano, *Tetrahedron*, 1972, **28**, 4667.

¹¹⁰ G. C. Morrison, R. O. Waite, and J. Shavel, jun., *J. Heterocyclic Chem.*, 1972, **9**, 683.

¹¹¹ H. Upreti, D. S. Bhakuni, and M. M. Dhar, *Phytochemistry*, 1972, **11**, 3057.

¹¹² T. -H. Yang, C. -M. Chen, and S. -S. Kuan, *J. Chinese Chem. Soc. (Taipei)*, 1971, **18**, 133 (*Chem. Abs.*, 1972, **77**, 16 567r).

Table 3 Isolation of proaporphine, aporphine, and phenanthrene alkaloids.

Species	Alkaloid (Structure) ^a	Ref.
<i>Actinodaphne obovata</i>	Actinodaphnine ^b (44; R ¹ + R ² = CH ₂ , R ³ = R ⁶ = H, R ⁴ = OMe, R ⁵ = OH)	111
	Laurotetanine	111
	N-Methyl-laurotetanine	111
<i>Annona glabra</i>	(-)-N-Methylactinodaphnine ^b (44; R ¹ + R ² = CH ₂ , R ³ = H, R ⁴ = OMe, R ⁵ = OH, R ⁶ = Me)	112
<i>Aristolochia argentina</i>	Argentinine ^b (45; R ¹ = R ³ = R ⁴ = H, R ² = R ⁵ = Me)	113
<i>Cocculus carolinus</i>	Magnoflorine	114
<i>Cryptocarya odorata</i>	Cryptodrine ^b (44; R ¹ + R ² = R ⁴ + R ⁵ = CH ₂ , R ³ = R ⁶ = H)	80
	Isocorydine	80
	Laurotetanine	80
	N-Methyl-laurotetanine	80
<i>Enantia polycarpa</i>	L-(+)-Isocorydine	115
<i>Fagara lepreurii</i> , <i>F. rubescens</i> , <i>F. viridis</i>	Magnoflorine	23
<i>Glaucium flavum</i>	Glaucine	116
	Glauvine ^b (46)	117
<i>Lindera oldhamii</i>	d-Dicentrine	118
	Dicentrinone ^c	118
	O-Methylbulbocapnine ^b (44; R ¹ + R ² = CH ₂ , R ³ = R ⁴ = OMe, R ⁵ = H, R ⁶ = Me)	118
	N-Methylhernangerine (N-Methylnandigerine)	118
	N-Methylhernovine (N-Methyllovigerine)	118
<i>Liriodendron tulipifera</i>	Lirinine ^b (44; R ¹ = R ⁶ = Me, R ² = R ³ = R ⁴ = H, R ⁵ = OMe)	119

¹¹³ H. A. Priestap, E. A. Ruveda, S. M. Albonico, and V. Deulofeu, *Anales Asoc. quim. argentina*, 1972, **60**, 309 (*Chem. Abs.*, 1972, **77**, 164 898q).

¹¹⁴ D. J. Slatkin, N. J. Doorenbos, J. E. Knapp, and P. L. Schiff, jun., *J. Pharm. Sci.*, 1972, **61**, 1825.

¹¹⁵ M. Leboeuf and A. Cavé, *Plant. Med. Phytother.*, 1972, **6**, 87 (*Chem. Abs.*, 1972, **77**, 98 777w).

¹¹⁶ L. Bubeva-Ivanova, N. Donev, E. Mermerska, B. Avramova, P. Ioncheva, and S. Stefanov, *Postep Dziedzinie Leku Rosl., Pr. Ref. Dosw. Wygloszone Symp.*, 1970, 104 (*Chem. Abs.*, 1973, **78**, 88 550y).

¹¹⁷ L. D. Yakhontova, V. I. Sheichenko, and O. N. Tolkachev, *Khim. prirod. Soedinenii*, 1972, 214 (*Chem. Abs.*, 1972, **77**, 48 675r).

¹¹⁸ S. -T. Lu, S. -J. Wang, P. -H. Lai, C. -M. Lin, and L. -C. Lin, *Yakugaku Zasshi*, 1972, **92**, 910 (*Chem. Abs.*, 1972, **77**, 101 949m).

¹¹⁹ R. Ziyaev, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 67 (*Chem. Abs.*, 1973, **78**, 159 939v).

Table 3—continued

Species	Alkaloid (Structure) ^a	Ref.
<i>Litsea leefeana</i>	Boldine (44; R ¹ = R ³ = H, R ² = R ⁶ = Me, R ⁴ = OMe, R ⁵ = OH)	79
	Lauroilsine	79
<i>L. sebifera</i>	Actinodaphnine	111
	Boldine	111
	Laurotetanine	111
	N-Methyl-laurotetanine	111
<i>L. wightiana</i>	Boldine	111
	Norboldine (44; R ¹ = R ³ = R ⁶ = H, R ² = Me, R ⁴ = OMe, R ⁵ = OH)	111
<i>Merendera raddeana</i>	Merenderine ^b (48; R ¹ = R ⁵ = H, R ² = R ⁴ = Me, R ³ = OMe)	120
<i>Mitrella kentii</i>	Anonaine	121
	Asimilobine	121
	Liriodenine	121
<i>Monodora angolensis</i>	Isoboldine	122
<i>Nelumbo nucifera</i>	N-Nornuciferine	76
	Nuciferine	76
	Oxoushinsunine ^d	76
	Anonaine	74
	Dehydroanonaine ^b (47; R ¹ + R ² = CH ₂ , R ³ = R ⁴ = R ⁵ = H)	74
	Dehydronuciferine ^b (47; R ¹ = R ² = R ⁵ = Me, R ³ = R ⁴ = H)	74
	Dehydroroemerine ^b (47; R ¹ + R ² = CH ₂ , R ³ = R ⁴ = H, R ⁵ = Me)	74
	N-Nornuciferine	74
	Nornuciferine	74
	Nuciferine	74
	Pronuciferine	74
	Roemerine	74
<i>Nemuaron vieillardii</i>	Atheroline	122a
	Laurotetanine	122a
	N-Methyl-laurotetanine	122a
	Norisocorydine	122a

¹²⁰ M. K. Yusupov, A. A. Trozyan, Kh. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1972, 777 (*Chem. Abs.*, 1973, 78, 94 874y).

¹²¹ J. Ellis, E. Gellert, and R. E. Summons, *Austral. J. Chem.*, 1972, 25, 2735.

¹²² M. Leboeuf, J. Parelo, and A. Cavé, *Plant. Med. Phytother.*, 1972, 6, 112 (*Chem. Abs.*, 1972, 77, 111 494y).

^{122a} I. R. C. Bick, H. M. Leow, N. W. Preston, and J. J. Wright, *Austral. J. Chem.*, 1973, 26, 455.

Table 3—continued

Species	Alkaloid (Structure) ^a	Ref.
<i>Ocotea puberula</i>	Dehydro-ocoteine ^b [47; R ¹ + R ² = CH ₂ , R ³ = R ⁴ = OMe, R ⁵ = Me, C(3)-OMe]	123
	Didehydro-ocoteine ^b [Dehydro-ocoteine with C(4)–C(5) double bond]	123
<i>O. variabilis</i>	(+)-Apoglazioline (44; R ¹ = R ⁶ = Me, R ² = R ³ = R ⁵ = H, R ⁴ = OH)	124
	(+)-Glazioline (49; R = Me)	124
	(+)-Nantenine (44; R ¹ = R ² = R ⁶ = Me, R ³ = H, R ⁴ + R ⁵ = OCH ₂ O)	124
	Variabiline ^b [44; R ¹ = R ⁶ = Me, R ² = R ³ = R ⁵ = H, R ⁴ = N(CH ₂ Ph) ₂]	124
<i>Papaver somniferum</i> (callus tissue)	Magnoflorine	125
<i>Schefferomitra</i> <i>subaequalis</i>	Anolobine (44; R ¹ + R ² = CH ₂ , R ³ = R ⁴ = R ⁶ = H, R ⁵ = OH)	126
	Asimilobine	126
	Isoboldine	126
<i>Stephania sasakii</i>	Steporphine ^b [44; R ¹ + R ² = CH ₂ , R ³ = R ⁴ = R ⁵ = H, R ⁶ = Me, C(4)–OH]	127
<i>Thalictrum minus</i>	Preocoteine <i>N</i> -oxide [44; R ¹ = R ⁶ = Me, R ² = R ³ = H, R ⁴ = R ⁵ = OMe, C(4)–OMe, N → O]	128
	Thalicmidine (44; R ¹ = R ⁶ = Me, R ² = R ³ = H, R ⁴ = R ⁵ = OMe)	128
	Thalicmidine <i>N</i> -oxide	128
	Thalicmine	128
	Thalicminine	128
<i>T. minus</i> , race B	Magnoflorine	129
<i>Uvariopsis guineensis</i>	8,9-Dimethoxyliroidenine (50; R ¹ + R ² = CH ₂ , R ³ = R ⁴ = OMe)	130
	Liriodenine	130
	9-Methoxyliroidenine (50; R ¹ + R ² = CH ₂ , R ³ = OMe, R ⁴ = H)	130

¹²³ F. Baralle, N. Schwarzbarg, M. Vernengo, and J. Comin, *Experientia*, 1972, **28**, 875.¹²⁴ M. P. Cava, M. Behforouz, and M. J. Mitchell, *Tetrahedron Letters*, 1972, 4647.¹²⁵ T. Furuya, A. Ikuta, and K. Syono, *Phytochemistry*, 1972, **11**, 3041.¹²⁶ E. Gellert and R. Rudzats, *Austral. J. Chem.*, 1972, **25**, 2477.¹²⁷ J. Kunimoto, Y. Hasegawa, Y. Imori, and E. Yuge, *Yakugaku Zasshi*, 1972, **92**, 1496 (*Chem. Abs.*, 1973, **78**, 58 642n).¹²⁸ V. G. Khozhdaev, S. Kh. Maekh, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, 631 (*Chem. Abs.*, 1973, **78**, 108 183m).¹²⁹ C. W. Geiselman, S. A. Gharbo, J. L. Beal, and R. W. Doskotch, *Lloydia*, 1972, **35**, 296.¹³⁰ M. Leboeuf and A. Cavé, *Phytochemistry*, 1972, **11**, 2833.

Table 3—continued

Species	Alkaloid (Structure) ^a	Ref.
<i>Uvariopsis guineensis</i>	8-Methoxyuvariopsine ^b (45; $R^1 + R^2 = CH_2$, $R^3 = R^4 = OMe$, $R^5 = Me$)	130
	Noruariopsamine ^b (45; $R^1 = R^2 = Me$, $R^3 = R^4 = OMe$, $R^5 = H$)	130
	Uvariopsamine ^b (45; $R^1 = R^2 = R^5 = Me$, $R^3 = R^4 = OMe$)	130
	Uvariopsamine <i>N</i> -oxide ^b	130
	Uvariopsine (45; $R^1 + R^2 = CH_2$, $R^3 = R^4 = OMe$, $R^5 = Me$)	130
<i>U. solheidii</i>	Uvariopsine	131

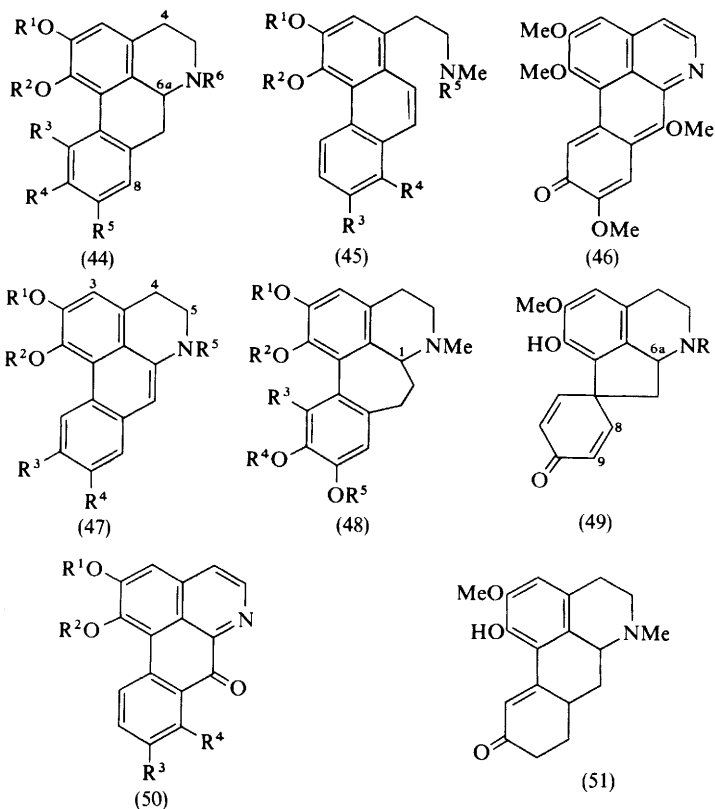
^a Structures of alkaloids for which no formulation appears may be found in the corresponding section of Vol. 2 of these Reports; ^b New alkaloid; ^c Oxoaporphine alkaloid detected but not isolated; ^d Structure not given owing to lack of access to original literature.

from *Fagara* species presents some interesting chemotaxonomic considerations with regard to the three types (benzylisoquinoline, furoquinoline, and acridone) found in this genus.²³ The interesting dienone alkaloid glauvine (46) from *Glaucium flavum* was converted into the aporphine (44; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = OAc$, $R^5 = OMe$, $R^6 = Ac$) by Zn-HCl reduction followed by acetylation.¹¹⁷ Oxoushinsunine isolated from *Nelumbo nucifera* apparently possesses tumour-inhibitory activity.⁷⁶ Variabiline [44; $R^1 = R^6 = Me$, $R^2 = R^3 = R^5 = H$, $R^4 = N(CH_2Ph)_2$] from *Ocotea variabilis* is the first example of an aminoaporphine.¹²⁴ Its structure is based on spectral data and synthesis from (+)-glaziovine (49; $R = Me$) by treatment with dibenzylamine-dibenzylamine hydrochloride at 200 °C. That variabiline is not an artifact was established by the appropriate experiments.

Steporphine [44; $R^1 + R^2 = CH_2$, $R^3 = R^4 = R^5 = H$, $R^6 = Me$, C(4)-OH] from *Stephania sasakii* was the first example of a C(4)-hydroxylated aporphine; its structural elucidation has now been reported in detail.¹²⁷ The (6a-*R*) absolute configuration of steporphine has been established by o.r.d. studies but the C(4)-configuration has yet to be determined. Cataline [44; $R^1 = R^2 = R^6 = Me$, $R^3 = H$, $R^4 = R^5 = OMe$, C(4)-OH], the other known C(4)-hydroxylated aporphine (see Vol. 3 of these Reports), has C(4)- β -OH orientation according to n.m.r. studies.

The description of uvariopsine (45; $R^1 + R^2 = CH_2$, $R^3 = R^4 = OMe$, $R^5 = Me$) from *Uvariopsis solheidii* comprises only a small portion of a monograph dealing with alkaloid detection or identification in 82 species of 28 different families of plants from the Congo.¹³¹

¹³¹ A. Bouquet, *Trav. Doc. ORSTROM*, 1972, vol. 13, 112 pp. (*Chem. Abs.*, 1973, **78**, 121 363q).



Jolantamine possesses the highly reduced aporphine structure (51) on the basis of u.v. and n.m.r. spectral information.¹³²

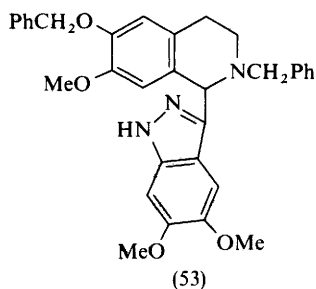
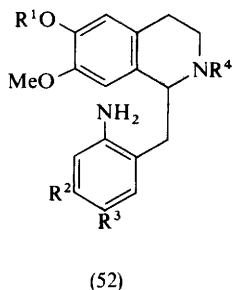
A detailed procedure for the isolation of bulbo-capsarine (44; R¹ + R² = CH₂, R³ = OH, R⁴ = OMe, R⁵ = H, R⁶ = Me) from *Corydalis pallida* nodules has been described.¹³³

The absolute configurations of crotsparine [49; R = H, C(6a)- α -H] and crotsparine [49; R = H, C(8,9)-dihydro, C(6a)- β -H] have been determined by synthesis from the requisite resolved benzyloquinoline alkaloids of established absolute configuration using the phenol oxidative-coupling reaction.¹³⁴ The absolute configuration of sparsiflorine [44; R¹ = Me, R² = R³ = R⁵ = R⁶ = H, R⁴ = OH, C(6a)- α -H] was established by correlating its *N*-methyl derivative with the acid-catalysed rearrangement product of *N*-methylcrotsparine (49; R = Me).

¹³² M. K. Yusupov, D. A. Abdullaeva, Kh. A. Aslanov, and A. S. Sadykov, *Doklady Akad. Nauk. S.S.S.R.*, 1973, **208**, 1123 (*Chem. Abs.*, 1973, **78**, 136 482b).

¹³³ A. F. Polyakova, B. K. Rostotskii, and N. S. Dubinin, *Tr. Alma-At. Med. Inst.*, 1970, 458 (*Chem. Abs.*, 1972, **77**, 85 633w).

¹³⁴ D. S. Bhakuni, S. Satish, and M. M. Dhar, *Tetrahedron*, 1972, **28**, 4579.



Synthetic activity in this area has also been maintained at a high level. Details of the synthesis of (\pm) -bracteoline¹³⁵ (44; $R^1 = R^6 = \text{Me}$, $R^2 = R^3 = \text{H}$, $R^4 = \text{OH}$, $R^5 = \text{OMe}$) and a synthesis of (\pm) -*N*-acetylnornantanine¹³⁶ (44; $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 + R^5 = \text{OCH}_2\text{O}$, $R^6 = \text{Ac}$) have appeared; both approaches use the Pschorr cyclization as the key step. A homoaporphine derivative (48; $R^1 = R^5 = \text{Me}$, $R^2 = R^3 = R^4 = \text{H}$) has been prepared by the photo-Pschorr reaction^{137a} (*Cf.* also Vol. 3 of these Reports) and $(-)$ -kresigine [48; $R^1 = R^4 = R^5 = \text{Me}$, $R^2 = \text{H}$, $R^3 = \text{OMe}$, C(1)- β -H] has been obtained by photocyclization of the requisite brominated 1-phenethyltetrahydroisoquinoline.^{137b} An abnormal result was obtained in an attempt to apply the photo-Pschorr reaction to the diazonium salt of (52; $R^1 = R^4 = \text{CH}_2\text{Ph}$, $R^2 = R^3 = \text{OMe}$) in that the indazole derivative (53) was the sole isolated product.¹³⁸ It is interesting to compare this result from the photochemical reaction with that from the study of the Pschorr cyclization of some model benzyloisoquinolines (52; $R^1 = \text{Me}$, $R^2 = R^3 = \text{H}$, $R^4 = \text{H}$, Me , and CH_2Ph), under normal conditions, which indicates that yields of product increase in the order $\text{H} > \text{Me} > \text{CH}_2\text{Ph}$ of the R^4 substituent.¹³⁹

Two groups have reported independently on an improved method for the preparation of benzyloisoquinolines which may serve as key intermediates in the synthesis of aporphine and dimeric benzyloisoquinoline alkaloids.^{140,141} Scheme 4 illustrates the synthesis of (\pm) -nuciferine (44; $R^1 = R^2 = R^6 = \text{Me}$, $R^3 = R^4 = R^5 = \text{H}$) by this method.¹⁴⁰ Thalimidine, glaucine, and a precursor (44; $R^1 = R^2 = R^6 = \text{Me}$, $R^3 = \text{H}$, $R^4 = \text{OMe}$, $R^5 = 3,4\text{-dimethoxyphenoxy}$) to the dimeric benzyloisoquinoline alkaloid thalicarpine were also synthesized by these general methods.^{140,141}

¹³⁵ P. Kerekes, K. Delenk-Heydenreich, and S. Pfeifer, *Magyar Kém. Folyóirat*, 1972, **78**, 410 (*Chem. Abs.*, 1972, **77**, 140 369s).

¹³⁶ C. R. Ghoshal and S. K. Shah, *Chem. and Ind.*, 1972, 889.

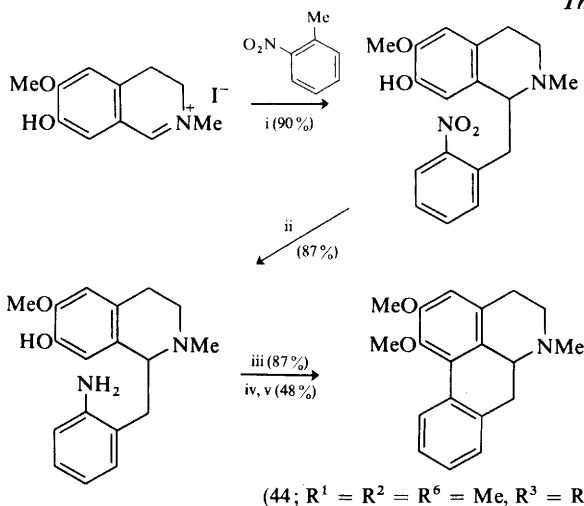
¹³⁷ (a) T. Kametani, T. Nakano, C. Seino, S. Shibuya, K. Fukumoto, T. R. Govindachari, K. Nagarajan, B. R. Pai, and P. S. Subramanian, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1507; (b) T. Kametani, Y. Satoh, and K. Fukumoto, *J.C.S. Perkin I*, 1972, 2160.

¹³⁸ T. Kametani, Y. Aizawa, T. Sugahara, S. Shibuya, M. S. Premila, and B. R. Pai, *Indian J. Chem.*, 1972, **10**, 987.

¹³⁹ D. R. Dalton, and A. A. Abraham, *Synthetic Comm.*, 1972, **2**, 303.

¹⁴⁰ S. M. Kupchan, V. Kameswaran, and J. W. A. Findlay, *J. Org. Chem.*, 1973, **38**, 405.

¹⁴¹ K. D. Paull, R. R. Engle, L. -M. Twanmoh, H. B. Wood, jun., and J. S. Driscoll, *J. Pharm. Sci.*, 1972, **61**, 1481.



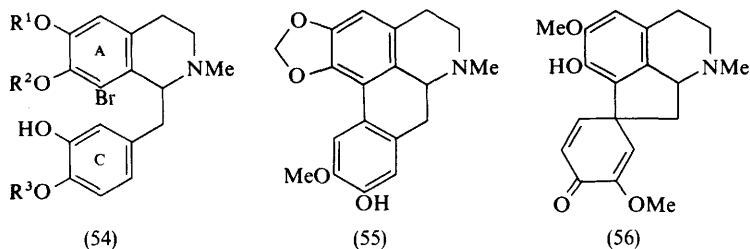
Reagents: i, KOBu^t , DMA; ii, H_2 , Pd-C; iii, NaNO_2 , 1:1 20% H_2SO_4 -HOAc; iv, Cu powder; v, CH_2N_2 .

Scheme 4

Details of the photochemical syntheses of aporphine and proaporphine alkaloids have been reported.¹⁴² For example, irradiation of the brominated tetrahydrobenzylisoquinolines (54; $R^1 + R^2 = \text{CH}_2$, $R^3 = \text{Me}$) and (54; $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$) in the presence of sodium hydroxide gave low yields of (\pm)-cassythicine (55) and (\pm)-orientalinone (56) respectively. Thus only the products which resulted from coupling *para* to the hydroxy-group in ring c of (54) were obtained, and none of the corresponding *ortho*-coupled compounds were detected. Similarly the aporphine alkaloids (\pm)-pukateine (44; $R^1 + R^2 = \text{CH}_2$, $R^3 = \text{OH}$, $R^4 = R^5 = \text{H}$, $R^6 = \text{Me}$) and (\pm)-*N*-methyl-laurotetanine (44; $R^1 = R^2 = R^6 = \text{Me}$, $R^3 = \text{H}$, $R^4 = \text{OMe}$, $R^5 = \text{OH}$) were obtained. It is instructive to compare these results with those obtained by the same group of workers from the photolysis of benzyltetrahydroisoquinolines in which the bromine substituent was appropriately located in ring c rather than ring a, from which only abnormal products were isolated (see Vol. 3 of these Reports). To add to the armoury of photochemical methods for aporphine skeleton synthesis (*cf.* also Vol. 3 of these Reports), it was recently discovered that irradiation of an appropriately substituted *N*-ethoxycarbonyl-1-benzylidene-tetrahydroisoquinoline yields the corresponding aporphine, which upon reduction gives (\pm)-neolitsine (44; $R^1 + R^2 = \text{CH}_2$, $R^3 = \text{H}$, $R^4 + R^5 = \text{OCH}_2\text{O}$, $R^6 = \text{Me}$).¹⁴³ Thus the desired photocyclodehydrogenation reaction may be brought about in precursors without bromine substituents. Presumably, however, this method will suffer somewhat in regioselectivity.

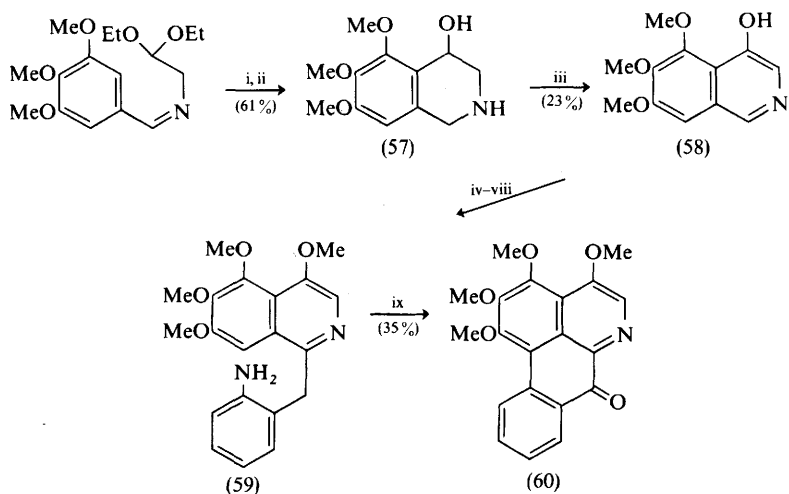
¹⁴² T. Kametani, K. Fukumoto, S. Shibuya, H. Nemoto, T. Nakano, T. Sugahara, T. Takahashi, Y. Aizawa, and M. Toriyama, *J.C.S. Perkin I*, 1972, 1435.

¹⁴³ G. Y. Moltrasio, R. M. Sotelo, and D. Giacomello, *J.C.S. Perkin I*, 1973, 349.



(\pm)-Isoboldine (44; $R^1 = R^6 = \text{Me}$, $R^2 = R^3 = \text{H}$, $R^4 = \text{OMe}$, $R^5 = \text{OH}$) may be obtained in 53% yield from (\pm)-reticuline using VOCl_3 as the oxidizing agent.¹⁴⁴ The utility of VOCl_3 for oxidative coupling reactions deserves further attention.

The synthesis of (\pm)-thaliporphine¹⁰⁸ (44; $R^1 = R^2 = R^6 = \text{Me}$, $R^3 = \text{H}$, $R^4 = R^5 = \text{OMe}$) and the aporphine¹⁰⁹ [44; $R^1 = R^6 = \text{Me}$, $R^3 = R^5 = \text{H}$, $R^2 = \text{H}$, $R^4 = \text{OMe}$, C(8)-OMe] exemplify two further applications of the route mediated by a benzyne intermediate.

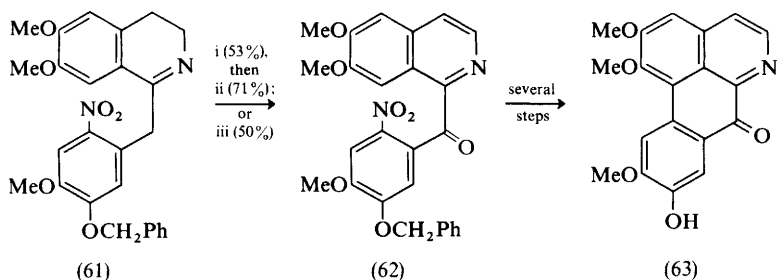


Reagents: i, H_2 , Pt, EtOH; ii, 6N-HCl, EtOH, 0–5°C; iii, 10% Pd-C, *p*-cymene, 140–145°C; iv, CH_2N_2 , MeOH, dioxan, Et_2O ; v, KCN, PhCOCl , CH_2Cl_2 ; vi, NaH, NaI, *o*- $\text{NO}_2\text{-C}_6\text{H}_4\text{CH}_2\text{Cl}$, PhH; vii, Triton B, MeOH; viii, H_2 , Raney Ni, THF; ix, NaNO_2 , 2N- H_2SO_4 , MeOH.

Scheme 5

¹⁴⁴ M. A. Schwartz, *Synthetic Comm.*, 1973, 3, 33.

The first synthesis of a C(4)-oxygenated oxoaporphine alkaloid has been recorded.¹⁴⁵ Imenine (60) was elaborated using mainly a conventional sequence (Scheme 5); however, points of interest include the direct synthesis of 4-hydroxyisoquinoline [(57) \rightarrow (58)], albeit in low yield, the first example of a successful Pschorr cyclization of a 1-(2-aminobenzyl)isoquinoline (59), and the facile aerial oxidation of the C(7)-methylene in the unisolable immediate precursor of imenine (60). The synthesis of a phenolic oxoaporphine, atheroline (63), has been achieved in the same laboratories (Scheme 6).¹⁴⁶ Conventional elaboration of the intermediate (61) was followed by a key oxidation-dehydrogenation which provides the 1-benzoylisoquinoline (63). The survival of the nitro and benzyl functions under the hydrogenolysis reaction conditions [step (ii) in Scheme 6] in the transformation (61) \rightarrow (62) is to be noted. A number of oxoaporphines have been prepared in low yield by the CrO_3 -HOAc oxidation of aporphine derivatives.¹⁴⁷ Furthermore, a detailed investigation of aporphine alkaloid oxidation using iodine and several other mild oxidizing agents has been published (Scheme 7).¹⁴⁸ An example of the behaviour of non-phenolic aporphines is provided by nuciferine (44; $\text{R}^1 = \text{R}^2 = \text{R}^6 = \text{Me}$, $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$), which is oxidized to the dehydroaporphine (47; $\text{R}^1 = \text{R}^2 = \text{R}^5 = \text{Me}$, $\text{R}^3 = \text{R}^4 = \text{H}$) in 87% yield. On the other hand, the noraporphines are oxidized to oxoaporphines under these conditions, e.g., *O*-methylnandigerine (44; $\text{R}^1 + \text{R}^2 = \text{CH}_2$, $\text{R}^3 = \text{R}^4 = \text{OMe}$, $\text{R}^5 = \text{R}^6 = \text{H}$) is converted into compound (64) in about 50% yield. These oxidation conditions appear most suitable for the aporphine to oxoaporphine conversion. Finally, the phenolic aporphines *N*-methylnandigerine (65; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) and bulbocapnine (65; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$) are converted in low yield into the same *ortho*-quinone (66) under mercuric chloride oxidation conditions. Compound (66) was also isolated in 9% yield from the iodine oxidation of (65; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$).



Reagents: i, CrO_3 , HOAc; ii, 10% Pd-C, *p*-cymene; iii, Pd-C, *p*-cymene, O_2 .

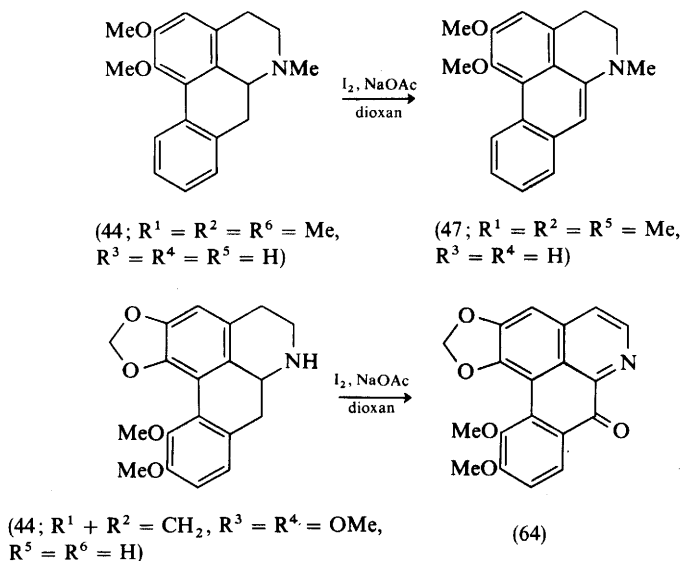
Scheme 6

¹⁴⁵ M. P. Cava and I. Noguchi, *J. Org. Chem.*, 1973, **38**, 60.

¹⁴⁶ M. P. Cava and I. Noguchi, *J. Org. Chem.*, 1972, **37**, 2936.

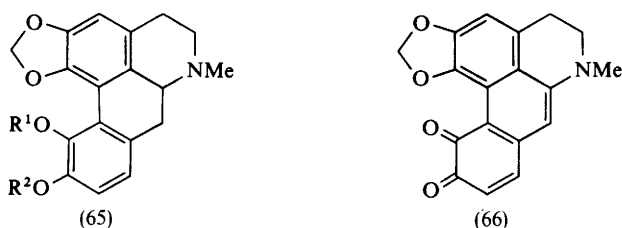
¹⁴⁷ J. G. Cannon, J. C. Kim, and M. A. Aleem, *J. Heterocyclic Chem.*, 1972, **9**, 731.

¹⁴⁸ M. P. Cava, A. Venkateswarlu, M. Srinivasan, and D. L. Edie, *Tetrahedron*, 1972, **28**, 4299.



Scheme 7

Some phenyltetrazolyl ethers of apomorphine have been prepared.¹⁴⁹ The properties of boldine (44; $R^1 = R^3 = \text{H}$, $R^2 = R^6 = \text{Me}$, $R^4 = \text{OMe}$, $R^5 = \text{OH}$) cyanurate have been described.¹⁵⁰



The pharmacological properties of a number of alkaloids and alkaloid-derived compounds have been studied: anonaine,¹⁵¹ optical antipode of apomorphine,¹⁵²

¹⁴⁹ R. Bogнар, Gy. Gaal, P. Kerekes, and E. Debreczeni, *Acta Phys. Chim. Debrecina*, 1971, **17**, 234 (*Chem. Abs.*, 1973, **78**, 43 797t).

¹⁵⁰ H. B. Rodrigues, *Rev. Asoc. bioquim. argentina*, 1972, **37**, 10 (*Chem. Abs.*, 1972, **77**, 152 398p).

¹⁵¹ S. F. Fakhrutdinov and M. B. Sultanov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 207 (*Chem. Abs.*, 1972, **77**, 109 453r).

¹⁵² W. S. Saari, S. W. King, and V. J. Lotti, *J. Medicin. Chem.*, 1973, **16**, 171.

bulbocapnine,¹⁵³ corydine,¹⁵³ corydine methiodide,¹⁵⁴ corytuberine methiodide,¹⁵⁵ *OO*-diacetylmagnoflorine,¹⁵⁵ glaucine,^{116,156,156a} isocorydine,¹⁵³ isocorydine methiodide,¹⁵⁴ isofugapavine,¹⁵¹ magnoflorine,¹⁵⁵ *O*-methylisocorydine methiodide,¹⁵⁴ roemerine,^{151,153} thalicmidine,^{153,156} thalicmidine methiodide,¹⁵⁴ and thalicmine.¹⁵⁶

Respiration of *Saccharomyces cerevisiae* was inhibited by xanthoplanine (laurotetanine methiodide), laurifoline, and *N*-methylglaucine in 30–300 $\mu\text{mol l}^{-1}$ concentrations.¹⁰⁴

8 Morphine and Morphinandienone Alkaloids

Sinoacutine (67; $R^1 = \text{H}$, $R^2 = \text{OH}$) has been isolated from *Cocculus carolinus* (Menispermaceae)¹¹⁴ and *O*-methylflavinantine (67; $R^1 = \text{OMe}$, $R^2 = \text{H}$) has been obtained from *Nemuaron vieillardii* (Monimiaceae).^{122a} A new source of the chlorine-containing alkaloids acutumine (68; $R = \text{Me}$) and acutumidine (68; $R = \text{H}$) is *Pachygone pubescens*.¹⁵⁷ The new hasubanan alkaloids staphabysine (69; $R^1 = \text{H}$, $R^2 + R^3 = \text{O}$), staphaboline (69; $R^1 = R^3 = \text{H}$, $R^2 = \text{OH}$), and prostephabyssine (70) have been obtained from *Stephania abyssinica*.¹⁵⁸ Stephabyssine was correlated with the known metaphanine (69; $R^1 = \text{Me}$, $R^2 + R^3 = \text{O}$) by methylation; sodium borohydride reduction of stephabyssine provided staphaboline, whose C(7)-OH stereochemistry was assigned on the basis of n.m.r. measurements. Aqueous hydrochloric acid treatment of prostephabyssine gave stephabyssine, thus completing the alkaloid interrelationships. Additional alkaloids have been isolated from *S. hernandifolia* and *S. delavayi*.^{159,160} Both plants yield hernandolinol^{159a} (71; $R^1 = \text{H}$, $R^2 = \text{OMe}$, $R^3 = \text{OH}$, $R^4 = \text{H}$, OH , $R^5 = \text{H}_2$) and delavaine^{159a} (72), while *S. delavayi* also provides 16-oxodelavaine^{159b} (71; $R^1 + R^2 = \text{OCH}_2\text{O}$, $R^3 = \text{H}$, $R^4 = R^5 = \text{O}$) and *S. hernandifolia* also yields 3-*O*-demethylhernandifoline (73).¹⁶⁰ All structures are based on extensive spectroscopic information and some chemical degradation. The structural proposal (73) for 3-*O*-dimethylhernandifoline is tentative.

¹⁵³ F. Sadritdinov, M. B. Sultanov, and Z. F. Ismailov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 127 (*Chem. Abs.*, 1973, **78**, 79 630x).

¹⁵⁴ Kh. S. Shamirzaeva and S. F. Fakhruddinov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 141 (*Chem. Abs.*, 1973, **78**, 79 633a).

¹⁵⁵ S. F. Fakhruddinov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 155 (*Chem. Abs.*, 1972, **77**, 122 094u).

¹⁵⁶ S. F. Fakhruddinov and Kh. S. Shamirzaeva, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 137 (*Chem. Abs.*, 1973, **78**, 79 632z).

^{156a} V. V. Berezhinskaya, *Postep Dziedziny Leku Rosl.*, *Pr. Ref. Dosw. Wygloszone Symp.*, 1970, 164 (*Chem. Abs.*, 1973, **78**, 119 087j).

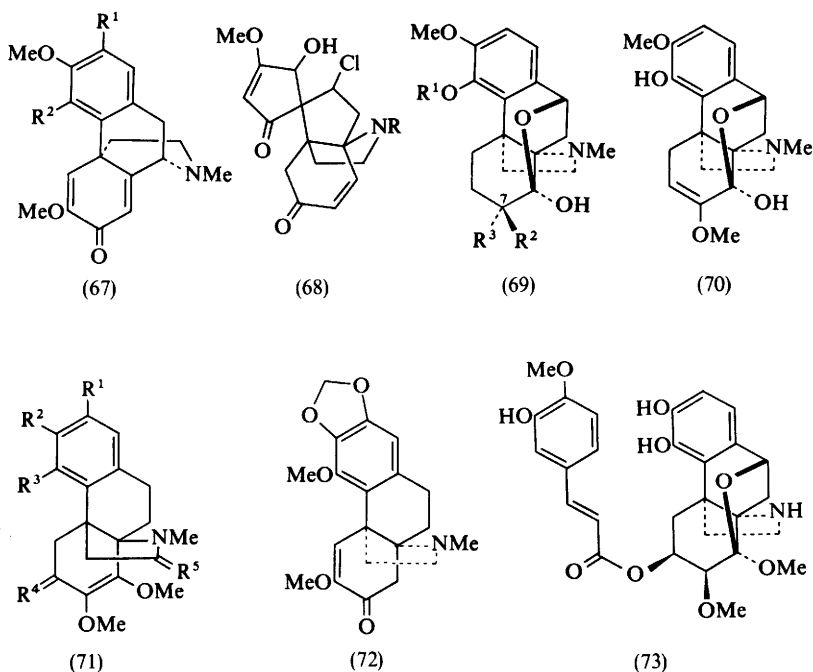
¹⁵⁷ N. K. Hart, S. R. Johns, J. A. Lambertson, and H. Soares, *Austral. J. Chem.*, 1972, **25**, 2289.

¹⁵⁸ S. M. Kupchan, A. J. Liepa, and T. Fujita, *J. Org. Chem.*, 1973, **38**, 151.

¹⁵⁹ (a) T. N. Il'inskaya, I. I. Fadeeva, M. E. Perel'son, and A. D. Kuzovkov, *Postep Dziedziny Leku Rosl.*, *Pr. Ref. Dosw. Wygloszone Symp.*, 1970, 98 (*Chem. Abs.*, 1973, **78**, 58 647t); (b) T. N. Il'inskaya, M. E. Perel'son, I. I. Fadeeva, D. A. Fesenko, and O. N. Tolkachev, *Khim. prirod. Soedinenii*, 1972, 129 (*Chem. Abs.*, 1972, **77**, 98 719d).

¹⁶⁰ I. I. Fadeeva, M. E. Perel'son, O. N. Tolkachev, T. N. Il'inskaya, and D. A. Fesenko, *Khim. prirod. Soedinenii*, 1972, 130 (*Chem. Abs.*, 1972, **77**, 72 561w).

Details of extraction procedures for codeine⁷⁷ and morphine¹⁶¹ from poppy capsules are available. A study concerning the stability of alkaloids in organic solvents such as methanol, acetone, chloroform, and benzene under normal laboratory conditions has been initiated.^{82,162} It was shown that photochemical reactions occur in diffuse sunlight which are strongly dependent on the particular solvent used.



New varieties of poppy plants have been produced by cross-breeding of *Papaver* species which give 0.6–0.9% yields of morphine.^{163,164} Studies on the effect of growth regulators (cytokinins;¹⁶⁵ benzyladenine, indole-3-acetic acid, and gibberellin¹⁶⁶) have been reported.

¹⁶¹ V. Kamedulski, B. Dimov, and Iv. Tonev, *Farmatsiya (Sofia)*, 1972, **22**, 34 (*Chem. Abs.*, 1972, **77**, 130 524z).

¹⁶² S. Pfeifer, G. Behnsen, and L. Kuehn, *Pharmazie*, 1972, **27**, 648.

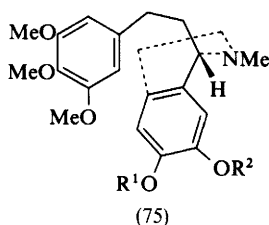
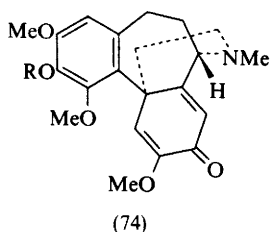
¹⁶³ K. Lorincz and P. Tetenyi, *Postep Dziedzinie Leku Rosl.*, *Pr. Ref. Dosw. Wygloszone Symp.*, 1970, 190 (*Chem. Abs.*, 1973, **78**, 69 264s).

¹⁶⁴ S. Sarkany, B. Danos, and I. Sarkany-Kiss, *Herba Polon.*, 1971, **17**, 410 (*Chem. Abs.*, 1972, **77**, 39 098c).

¹⁶⁵ P. Gracza and G. Verzar-Petri, *Postep Dziedzinie Leku Rosl.*, *Pr. Ref. Dosw. Wygloszone Symp.*, 1970, p. 182 (*Chem. Abs.*, 1973, **78**, 53 889p).

¹⁶⁶ P. Gracza and G. Verzar-Petri, *Biochem. Physiol. Alkaloide, Int. Symp.*, 4th 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 293.

Details concerning the structural elucidation of the homomorphinandienone alkaloid androcymbine (74; $R = H$) have appeared.¹⁶⁷ A key chemical test of the structure was provided by the sodium-liquid ammonia reduction of *O*-methylandrocymbine (74; $R = Me$), which yielded the isoquinoline derivative (75; $R^1 = Me$, $R^2 = H$). An alternative structure (75; $R^1 = H$, $R^2 = Me$) for the reduction product of (74; $R = Me$) was considered and was thought to be insufficiently distinguishable from (75; $R^1 = Me$, $R^2 = H$) to deem it necessary to undertake synthesis of both compounds. The syntheses were carried out by conventional routes and structure (75; $R^1 = Me$, $R^2 = H$) was conclusively established for the degradation product of *O*-methylandrocymbine (74; $R = Me$), thus confirming the structural assignment of the alkaloid as (74; $R = H$). A brief review of these modified 1-phenethylisoquinoline alkaloids is also given in this paper.¹⁶⁷ The *X*-ray crystal structure of the hasubanan derivative (71; $R^1 = H$, $R^2 = OMe$, $R^3 = OSO_2C_6H_4-p-Br$, $R^4 = O$, $R^5 = H_2$) has been determined.¹⁶⁸



Conformational analysis of morphine derivatives has been carried out by i.r. spectroscopy.¹⁶⁹ An extensive n.m.r. study of a number of codeine and isocodeine derivatives has been effected using N.O.E. and double-resonance experiments.¹⁷⁰ Conformational and configurational assignments were confirmed by these studies. A computer-simulated n.m.r. spectral analysis of codeine using a program written in FORTRANIV language has been published.¹⁷¹ The mass-spectral fragmentation patterns of a number of hasubanan derivatives have been interpreted with the aid of the high-resolution technique and deuterium-labelled compounds.¹⁷²

Inubushi has reviewed the recent activity of his research group in the field of hasubanan alkaloid synthesis.¹⁷³ Details concerning the electro-oxidative synthesis of a number of morphinandienone alkaloids from unfunctionalized

¹⁶⁷ A. R. Battersby, R. B. Herbert, L. Pijewska, F. Santavy, and P. Sedmera, *J.C.S. Perkin I*, 1972, 1736.

¹⁶⁸ D. N. J. White, A. T. McPhail, and G. A. Sim, *J.C.S. Perkin II*, 1972, 1280.

¹⁶⁹ Z. Dinya, S. Makleit, S. Szabo, T. Mile, and R. Bognar, *Acta Chim. Acad. Sci. Hung.*, 1973, **75**, 393 (*Chem. Abs.*, 1973, **78**, 159 945u).

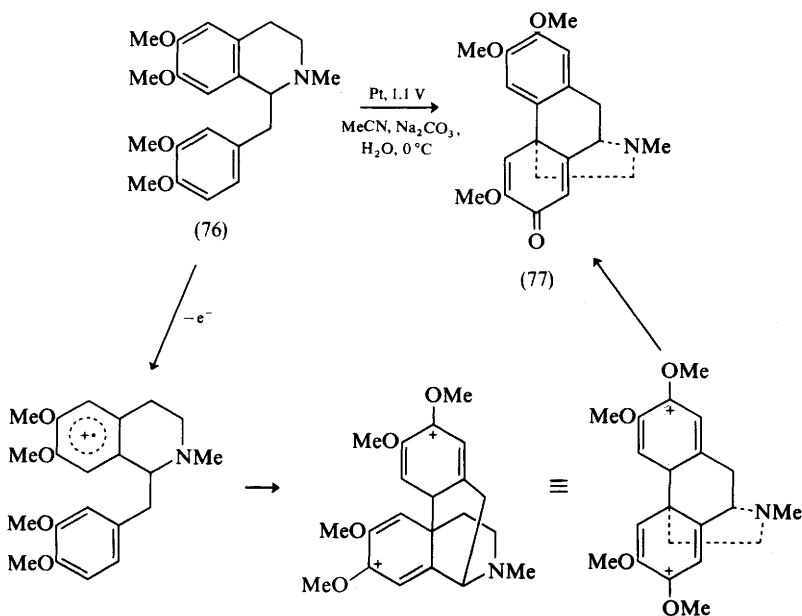
¹⁷⁰ A. E. Jacobson, H. J. C. Yeh, and L. J. Sargent, *Org. Magn. Resonance*, 1972, **4**, 875.

¹⁷¹ S. R. Heller and A. E. Jacobson, *Analyt. Chem.*, 1972, **44**, 2219.

¹⁷² K. Abe, M. Onda, and S. Okuda, *Org. Mass Spectrometry*, 1972, **6**, 715.

¹⁷³ Y. Inubushi, T. Ibuka, and K. Tanaka, *Yuki Gosei Kagaku Kyokai Shi*, 1972, 98 (*Chem. Abs.*, 1973, **78**, 159 942r).

benzyltetrahydroisoquinolines have appeared.¹⁷⁴ This method deserves attention since it overcomes a number of deficiencies (low yield, additional synthetic steps, side reactions) of the widely used Pschorr procedure. For example, (\pm)-laudanosine (76) may be converted into *O*-methylflavinantine (77) in 52% yield at a platinum electrode (Scheme 8). Moreover, the yield of flavinantine was increased to 63% by adding an equal molar concentration of bis(acetonitrile)-palladium(II) chloride. The interesting mechanistic speculation (Scheme 8) is under experimental test. The superiority of the electro-oxidative method to the photochemical cyclization of brominated benzyltetrahydroisoquinolines for the preparation of morphinandienone alkaloids should also be noted. Using the latter method, only low yields of (\pm)-pallidine (67; $R^1 = \text{OH}$, $R^2 = \text{H}$) and (\pm)-salutaridine (67; $R^1 = \text{H}$, $R^2 = \text{OH}$, β -N-containing bridge) have been achieved.¹⁴²

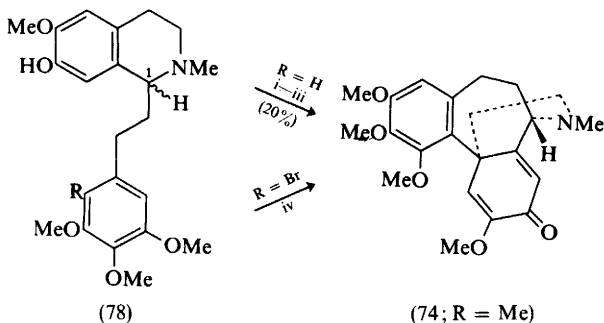
**Scheme 8**

A short synthesis of (\pm)-*O*-methylandrocymbine (74; $R = \text{Me}$) takes advantage of the capability of thallium(III) trifluoroacetate to effect a two-electron intramolecular oxidative coupling reaction (Scheme 9).¹⁷⁵ A further highlight in this synthesis is the use of a borane protective function for the tertiary amine (78;

¹⁷⁴ L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Amer. Chem. Soc.*, 1973, **95**, 2651.

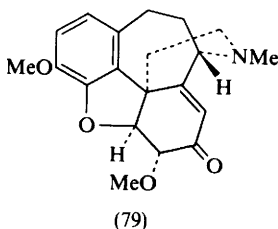
¹⁷⁵ M. A. Schwartz and B. F. Rose, *J. Amer. Chem. Soc.*, 1973, **95**, 612.

R = H). (–)-O-Methylandrocymbine was obtained, albeit in low yield, by photolysis of the brominated chiral (1*S*)-phenethyltetrahydroisoquinoline derivative (78; R = Br).^{137b} Similarly, irradiation of the (1*R*)-isomer of (78; R = Br) gave (+)-O-methylandrocymbine. Using this procedure, a low-yield synthesis of a kreysiginine-type compound (79) has also been achieved.¹⁷⁶



Reagents: i, B₂H₆, CHCl₃-THF; ii, 2–3 mol equiv. Ti(OAc)₃, CH₂Cl₂, room temp., dark; iii, Na₂CO₃, MeOH, reflux; iv, *hν*, 450 W Hanovia (Pyrex), NaOH, EtOH.

Scheme 9

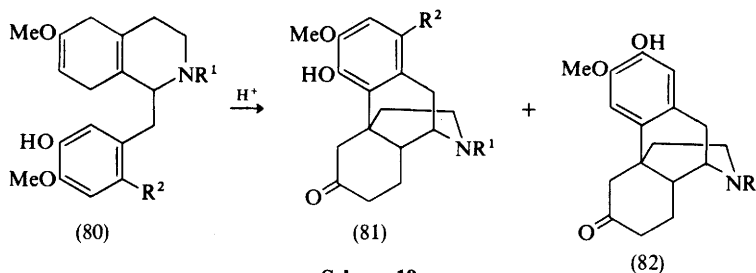


Acid-catalysed cyclization of the 1-benzyl-1,2,3,4,5,8-hexahydroisoquinoline (80; R¹ = Me, R² = H) yields a mixture of (81; R¹ = Me, R² = H) and (82; R = Me) (Scheme 10). Since the former isomer is the minor and low-yield product, economic synthesis of morphine-like compounds cannot be achieved. It has now been found that the undesired isomer may be completely eliminated in the series (80; R¹ = CHO, R² = Me), and a yield of 85% of (81; R¹ = CHO, R² = Me) can be achieved.¹⁷⁷ It is conceivable that if a suitable blocking function at R² may be introduced into (80), a synthesis of morphine paralleling the Gates approach may be achieved. An improvement in the morphine → codeine transformation has been reported.¹⁷⁸

¹⁷⁶ T. Kametani, T. Kohno, R. Charubala, and K. Fukumoto, *Tetrahedron*, 1972, **28**, 3227.

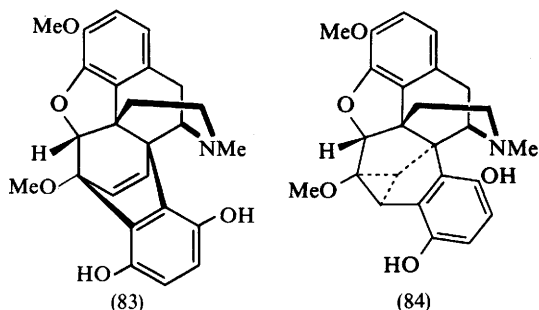
¹⁷⁷ H. C. Beyerman, E. Buurman, and L. Maat, *J.C.S. Chem. Comm.*, 1972, 918.

¹⁷⁸ D. M. Smirnov, E. L. Sigal, K. Ya. Marechek, and V. P. Zakharov, *Khim.-Farm. Zhur.*, 1972, **6**, 31 (*Chem. Abs.*, 1972, **77**, 101 952g).



Scheme 10

A review dealing with chemical and pharmacological evaluation of modified morphine structures has appeared.¹⁷⁹ The solvolysis of 7 β -iodoneopinone dimethyl acetal in the presence of a variety of nucleophiles leads to indolino-codeinone derivatives (*cf.* Vol. 3 of these Reports). Details of this work are now available.¹⁸⁰ The unsensitized photolysis of thebainequinone or thebainehydroquinone (83) gives the intriguing photo-product (84) in up to 65% yield; it presumably arises by a di- π -methane \rightarrow vinylcyclopropane rearrangement.¹⁸¹ The structure was established by an X-ray crystallographic analysis. The acid-catalysed rearrangement of (84) is also reported and is of mechanistic interest. Treatment of thebaine with aqueous sodium bisulphite solution (pH 4) in the presence (but not in the absence) of oxygen gives a good yield of 6-*O*-demethylsalutaridine (85).¹⁸² Partially on the basis of labelling experiments which showed that the C(7)-oxygen function is derived from bisulphite, a mechanism of the transformation was proposed. 6-Methylisocodeine (86) was prepared by treatment of codeinone with dimethylsulphoxonium methylide followed by lithium aluminium hydride reduction.¹⁸³ Analysis of the n.m.r. spectra of (86), the precursor oxiran derivative, and related codeines has been mentioned (*vide supra*).¹⁷⁰



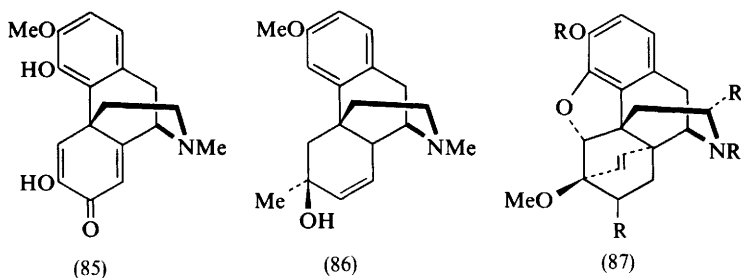
¹⁷⁹ K. Kanematsu, *Yuki Gosei Kagaku Kyokai Shi*, 1972, **30**, 709 (*Chem. Abs.*, 1972, **77**, 164 906r).

¹⁸⁰ R. M. Allen and G. W. Kirby, *J.C.S. Perkin I*, 1973, 363.

¹⁸¹ Z. J. Barneis, R. J. Warnet, D. M. S. Wheeler, M. G. Waite, and G. A. Sim, *Tetrahedron*, 1972, **28**, 4683.

¹⁸² L. F. Bjeldanes and H. Rapoport, *J. Org. Chem.*, 1972, **37**, 1453.

¹⁸³ L. J. Sargent and A. E. Jacobson, *J. Medicin. Chem.*, 1972, **15**, 843.



Detailed reports concerning the displacement reactions of 6-*O*-tosyl- and 6-*O*-mesyl-14-hydroxycodeines leading to azido- and amino-,¹⁸⁴ halogeno-,¹⁸⁵ and isothiocyanato-¹⁸⁶ derivatives have appeared. The continuation of solvolytic studies on 14 β -bromocodeine¹⁸⁷ and 14-bromocodeine dimethyl acetal¹⁸⁸ which provide entries to the indolinocodeinones has been reported. A relatively large number of 6,14-*endo*-ethenotetrahydrothebaine derivatives (87) have been prepared for pharmacological evaluation.^{189–191} Two other reports deal with the preparation of simpler systems related to the morphine skeleton.^{192,193} In connection with studies on the immunogenic properties of a conjugate of morphine hemisuccinate with bovine serum albumin, the structure of morphine monoheemisuccinate was formulated to be one involving succinate to morphine attachment *via* the 6-OH function on the basis of chemical evidence.¹⁹⁴

A review dealing with methods of detection of narcotic agents, including opium, is not readily accessible.¹⁹⁵ A related report describes standardized procedures for analysis of morphine in opium samples.¹⁶ As in a previous year (*cf.* Vol. 2 of these Reports), numerous analytical methods and modifications have been reported, and these are summarized in Table 4. Possibly of some special interest is the report concerning the difficulty of applying official methods of analysis for morphine as a result of the similar colorimetric and polarographic

¹⁸⁴ S. Makleit, L. Radics, R. Bogнар, T. Mile, and E. Olah, *Magyar Kém. Folyóirat*, 1972, **78**, 223 (*Chem. Abs.*, 1972, **77**, 19 841m); S. Makleit, L. Radics, R. Bogнар, T. Mile, and E. Olah, *Acta Chim. Acad. Sci. Hung.*, 1972, **74**, 99 (*Chem. Abs.*, 1972, **77**, 152 404n).

¹⁸⁵ R. Bogнар, S. Makleit, L. Radics, and T. Mile, *Magyar Kém. Folyóirat*, 1972, **78**, 228 (*Chem. Abs.*, 1972, **77**, 19 840k); S. Makleit, L. Radics, R. Bogнар, and T. Mile, *Acta Chim. Acad. Sci. Hung.*, 1972, **74**, 111 (*Chem. Abs.*, 1972, **77**, 152 405p).

¹⁸⁶ R. Bogнар, T. Mile, S. Makleit, and S. Berenyi, *Magyar Kém. Folyóirat*, 1972, **78**, 279 (*Chem. Abs.*, 1972, **77**, 114 619d); R. Bogнар, T. Mile, S. Makleit, and S. Berenyi, *Acta Chim. Acad. Sci. Hung.*, 1973, **75**, 297 (*Chem. Abs.*, 1973, **78**, 111 562q).

¹⁸⁷ K. Abe, M. Onda, and S. Okuda, *J. C. S. Perkin I*, 1973, 316.

¹⁸⁸ W. Fleischhacker, H. Markut, and F. Vieboeck, *Monatsh.*, 1972, **103**, 1066.

¹⁸⁹ J. W. Lewis, P. A. Mayor, and D. I. Haddlesey, *J. Medicin. Chem.*, 1973, **16**, 12.

¹⁹⁰ J. W. Lewis, M. J. Readhead, and A. C. B. Smith, *J. Medicin. Chem.*, 1973, **16**, 9.

¹⁹¹ J. W. Lewis and M. J. Readhead, *J. Medicin. Chem.*, 1973, **16**, 84.

¹⁹² R. R. Wittekind, T. Capiris, and S. Lazarus, *J. Heterocyclic Chem.*, 1972, **9**, 1441.

¹⁹³ N. S. Prostakov and O. G. Kesarev, *Khim. geterotsikl. Soedinenii*, 1972, 1671 (*Chem. Abs.*, 1973, **78**, 71 878p).

¹⁹⁴ B. H. Wainer, F. W. Fitch, R. M. Rothberg, and J. Fried, *Science*, 1972, **178**, 647.

¹⁹⁵ H. Neuninger, *Oesterr. Apoth. Zig.*, 1973, **27**, 91 (*Chem. Abs.*, 1973, **78**, 155 200z).

behaviour of co-occurring alkaloids.¹⁹⁶ The utility of anion-exchange resins in isolation and purification of morphine^{42,197} and codeine¹⁹⁷ has been described. Other reports of possible interest deal with the use of polybuffer solutions in the extraction of morphine,¹⁹⁸ extraction of codeine with fatty acid-organic solvent combinations,¹⁹⁹ and the distribution-constant behaviour of codeine-dye associates in bromoform-water extraction.²⁰⁰

Table 4 *Analysis of morphine alkaloids*

Substance(s) analysed*	Method(s)	Refs.
M, C, T	gas chromatography	98
C	mercurimetric titration	96
M	differential spectrophotometry	a
M, C, T	chromatography-spectrophotometry	95
M	photocolorimetry	b
M	chromatography-titration	c
M	isotope dilution	d
Opium alkaloids	liquid chromatography	e
C	spectrophotometry	f
Opium alkaloids	t.l.c.	g
M	t.l.c.	h
M	titration	i
Normorphine	acetylation → g.l.c. or t.l.c.	j

* M = morphine, C = codeine, T = thebaine; ^aR. V. D. Rondina, A. L. Bandoni, and J. D. Coussio, *J. Pharm. Sci.*, 1973, **62**, 502 (*Chem. Abs.*, 1973, **78**, 11 526t); ^bV. A. Danel'yants and Yu. V. Shostenko, *Farm. Zhur. (Kiev)*, 1972, **27**, 48 (*Chem. Abs.*, 1973, **78**, 75 914v); ^cA. I. El-Sebai and Y. A. Beltagy, *U.A.R. J. Pharm. Sci.*, 1971, **12**, 303; ^dE. Brochmann-Hanssen, *J. Pharm. Sci.*, 1972, **61**, 1118; ^eC.-Y. Wu, S. Siggia, T. Robinson, and R. D. Waskiewicz, *Analyt. Chim. Acta*, 1973, **63**, 393; ^fI. Grecu and S. Barbu, *Farmacia (Bucharest)*, 1972, **20**, 21 (*Chem. Abs.*, 1972, **77**, 39 304s); ^gG. Chams, N. Kheradmandan, I. Yaraghtchi, and V. Chahmanche, *Internat. Crim. Police Rev.*, 1972, **27**, 162 (*Chem. Abs.*, 1973, **78**, 67 745a); A. Viala, J. Catalin, and F. Gouezo, *Bull. Soc. chim. France*, 1973, 97; K. C. Guven and N. Guven, *Eczacilik Bul.*, 1972, **14**, 75 (*Chem. Abs.*, 1973, **78**, 62 218w); M. Sarsunova and B. Kakac, *Cesk. Farm.*, 1972, **21**, 102 (*Chem. Abs.*, 1972, **77**, 92 904p); ^hE. Klug, *Z. analyt. Chem.*, 1972, **260**, 31 (*Chem. Abs.*, 1972, **77**, 105 646h); A. V. Gaevskii and P. M. Loshkarev, *Khim.-Farm. Zhur.*, 1972, **6**, 54 (*Chem. Abs.*, 1972, **77**, 79 578r); J. Paul and F. Conine, *Microchem. J.*, 1973, **18**, 142; ⁱH. Myint and U. Cho, *Union Burma J. Sci. Technol.*, 1970, **3**, 33 (*Chem. Abs.*, 1972, **77**, 92 903n); ^jR. J. Miller, C. Jolles, and H. Rapoport, *Phytochemistry*, 1973, **12**, 597.

A comprehensive review on narcotic analgesics includes a useful section on the opium alkaloids.²⁰¹ A procedure for the preparation of a standard sample of morphine which may be used in the evaluation of pharmacopoeial preparations

¹⁹⁶ V. A. Danel'yants, S. Kh. Mushinskaya, and Yu. V. Shostenko, *Khim.-Farm. Zhur.*, 1973, **7**, 47 (*Chem. Abs.*, 1973, **78**, 164 150k).

¹⁹⁷ S. Kh. Mishinskaya, Yu. V. Shostenko, E. S. Vysotskaya, and N. G. Bozhko, *Khim.-Farm. Zhur.*, 1972, **6**, 34 (*Chem. Abs.*, 1973, **78**, 75 812k).

¹⁹⁸ L. I. Burtko, *Farmatsiya (Moscow)*, 1972, **21**, 17 (*Chem. Abs.*, 1972, **77**, 66 232y).

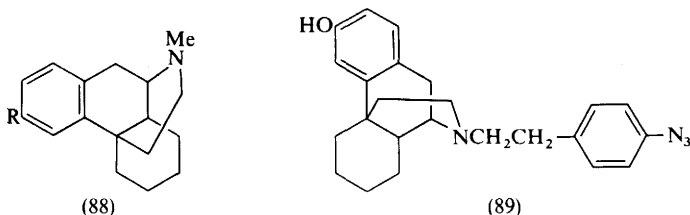
¹⁹⁹ L. Jusiak, *Acta Polon. Pharm.*, 1972, **29**, 277 (*Chem. Abs.*, 1972, **77**, 156 356w).

²⁰⁰ G. L. Starobinets, S. L. Doan, and S. F. Petrashkevich, *Vestsi Akad. Navuk Belarusk. S.S.R., Ser. Khim. Navuk*, 1972, **24** (*Chem. Abs.*, 1973, **78**, 8 413t).

²⁰¹ H. B. Murphree, 'Drill's Pharmacology in Medicine', 4th edn., ed. J. R. Dipalma, McGraw-Hill, New York, 1971, p. 324.

has been described.²⁰² Dependence,²⁰³ tolerance,²⁰⁴ and behavioural effects²⁰⁵ of morphine have been studied in rats. In addition, biochemical studies have been carried out to determine the effect of morphine on the fatty-acid level in plasma²⁰⁶ and the action of codeine on the activity of a number of liver enzymes,²⁰⁷ using the rat as the experimental animal.

The analgesic properties of morphine sulphates²⁰⁸ and 6-methylisocodeine (86)¹⁸³ have been determined. Some new 3-substituted *N*-methylmorphinan derivatives (88) have been synthesized and found to possess promising antitussive activities and low toxicities.^{209,210} Sinoacutine and sinomenine possess neurotropic properties.^{156a}



The synthesis of a tritiated norlevorphanol derivative (89) has been reported.²¹¹ This compound may be useful as a photochemical affinity label for opiate receptor sites.

There is a high incidence of severe dermatitis among workers in the pharmaceutical industry concerned with manipulating opium and its alkaloids.²¹²

9 Colchicine Alkaloids

Two reviews on this group have appeared in the Russian literature.^{213,214}

A new alkaloid, K-13, from *Colchicum kesselringii*, has the structure (90).²¹⁵

²⁰² A. V. Suranova, *Sb. Nauch. Tr., Tsent. Aptech. Nauch.-Issled. Inst.*, 1971, 126 (*Chem. Abs.*, 1973, **78**, 62 219x).

²⁰³ D. M. Katz and H. Steinberg, *Biochem. Pharmacol. Aspects Depend. Rep. Marihuana Res., Symp.*, ed. H. M. Praag, F. Bohn, and N. V. DeErven, Haarlem, Netherlands (*Chem. Abs.*, 1973, **78**, 79 626a).

²⁰⁴ H. A. Tilson, S. Stolman and R. H. Rech, *Res. Comm. Chem. Pathol. Pharmacol.*, 1972, **4**, 581.

²⁰⁵ S. G. Holtzman and R. E. Jewett, *Life Sci.*, 1972, **11**, 1085.

²⁰⁶ S. J. Mule and E. Whitlock, *Biochem. Pharmacol.*, 1972, **21**, 2153.

²⁰⁷ S. Ada, V. Bota, and V. Kovacs, *Rev. Med.*, 1972, **18**, 464 (*Chem. Abs.*, 1973, **78**, 132 067x).

²⁰⁸ M. Mori, K. Oguri, H. Yoshimura, K. Shimomura, O. Kamata, and S. Ueki, *Life Sci.*, 1972, **11**, 525.

²⁰⁹ M. Murakami, N. Inukai, and N. Nagano, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1699.

²¹⁰ M. Murakami, S. Kawahara, N. Inukai, N. Nagano, H. Iwamoto, and H. Ida, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1706.

²¹¹ B. A. Winter and A. Goldstein, *Mol. Pharmacol.*, 1972, **8**, 601.

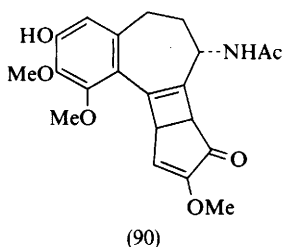
²¹² E. R. Fedotov and G. K. Rakhimova, *Zdravookhr. Kaz.*, 1972, 29 (*Chem. Abs.*, 1973, **78**, 33 506b).

²¹³ F. Santavy, *Khim. Rast. Veshchestv*, 1972, 7 (*Chem. Abs.*, 1973, **78**, 136 471x).

²¹⁴ M. K. Yusupov, *Khim. Rast. Veshchestv*, 1972, 19 (*Chem. Abs.*, 1973, **78**, 148 093p).

²¹⁵ Kh. Turdikulov, M. K. Yusupov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1972, 502 (*Chem. Abs.*, 1973, **78**, 13 747j).

Deacetylcolchicine and deacetylcolchicine are also new alkaloids isolated from *Merendera robusta* whose structures have not been fully established.²¹⁶ Colchicine, colchamine, β -lumicolchicine, colchameine, 2-desmethycolchicine, and 4 new nontropolone bases named MJ-1 (jolantamine), MJ-2, MJ-3, and MJ-4 have been obtained from *M. jolantae*.²¹⁷



Gibberellin-colchicine effects in promotion of growth rate of *Azuki angularis* and *Vigna angularis* have been studied.²¹⁸

Luminescence spectra of colchicine have been measured.²¹⁹

A number of *N*-(halogenoacetyl)-deacetylcolchicines have been prepared which possess 3- and 10-fold antimitotic activity in comparison to colchicine.²²⁰ A series of characteristically coloured metal chelates (e.g. Cu^{II}, Au, Co^{II}, Ru^{III}, U^{VI}, and Os^{VIII}) of colchicine have been studied in solution.²²¹

Optimum conditions for the chromatographic separation of colchicine from the indole alkaloid ajmaline have been reported using criteria based on *R_f* values and shapes of chromatographic spots.²²² Conditions for efficient extraction of colchicine²²³ and colchamine²²⁴ from aqueous solutions and the effect of added electrolytes on the extractability of colchicine²²⁵ have been described. The action of colchicine on *Amoeba proteus* ATPases,²²⁶ separation of membrane functions,²²⁷ inhibition of intestinal fluid production in response to *Vibrio cholera* toxin,²²⁸ and the binding of this alkaloid to brain tubulin²²⁹ have been studied.

²¹⁶ Kh. Turdikulov, M. K. Yusupov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1972, 247 (*Chem. Abs.*, 1972, 77, 58 718w).

²¹⁷ K. M. Zuparova, B. Chommadov, M. K. Yusupov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1972, 487 (*Chem. Abs.*, 1973, 78, 1 989b).

²¹⁸ H. Shibaoka, *Plant Cell Physiol.*, 1972, 13, 461.

²¹⁹ H. Roigt and R. M. Leblanc, *Canad. J. Chem.*, 1972, 50, 1959.

²²⁰ H. Lettre, K. H. Doenges, K. Barthold, and T. J. Fitzgerald, *Annalen*, 1972, 758, 185.

²²¹ I. P. Mittal and K. N. Johri, *Current Sci.*, 1972, 41, 599 (*Chem. Abs.*, 1972, 77, 131 372k).

²²² D. Panova, M. F. Mincheva, and A. D. Minchev, *Doklady Bolg. Akad. Nauk*, 1972, 25, 1245 (*Chem. Abs.*, 1973, 78, 52 338w).

²²³ V. I. Svetlichnaya, *Farm. Zhur. (Kiev)*, 1972, 27, 62 (*Chem. Abs.*, 1972, 77, 105 661j).

²²⁴ V. I. Svetlichnaya, *Farm. Zhur. (Kiev)*, 1972, 27, 54 (*Chem. Abs.*, 1973, 78, 33 973h).

²²⁵ V. I. Svetlichnaya, *Farm. Zhur. (Kiev)*, 1972, 27, 48 (*Chem. Abs.*, 1972, 77, 156 307f).

²²⁶ C. R. Gicquaud and P. Couillard, *Rev. Canad. Biol.*, 1972, 31, 97.

²²⁷ T. E. Ukena and R. D. Berlin, *J. Exp. Med.*, 1972, 136, 1.

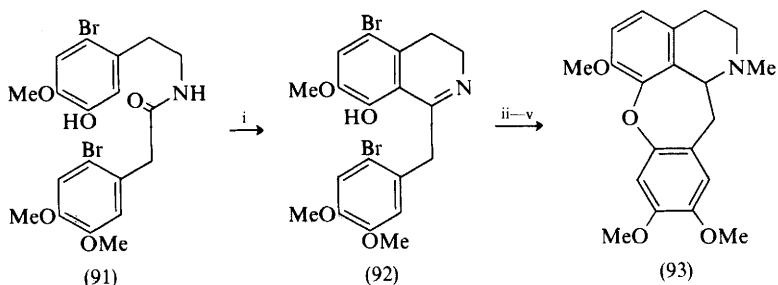
²²⁸ D. R. Stormbeck, *Life Sci.*, 1973, 12, 211.

²²⁹ R. J. Owellen, A. H. Owens, jun., and D. W. Donigian, *Biochem. Biophys. Res. Comm.*, 1972, 47, 685.

10 Cularine

Cularine (93) is mentioned briefly in a review of alkaloids embodying seven-membered oxygen rings.²³⁰

The (*S*) absolute configuration has been assigned to cularine on the basis of an *X*-ray crystallographic analysis of its methiodide.²³¹



Reagents: i, POCl_3 ; ii, NaBH_4 ; iii, methylation; iv, Ullmann reaction; v, LiAlH_4 .

Scheme 11

Three reports of alkaloid synthesis using similar logistics and involving an intramolecular Ullmann reaction as the key step have appeared.^{232–234} For example (Scheme 11),²³³ the presence of the bromo-substituent in ring A of compound (91) forced the Bischler–Napieralski reaction unidirectionally, to provide the isoquinoline (92). Two unexceptional steps followed by Ullmann reaction and removal of the bromo blocking function gave (\pm)-cularine (93). In similar fashion, (\pm)-cularimine,²³³ (\pm)-cularicine,²³² and (\pm)-isocularine²³⁴ were synthesized.

11 Protoberberine Alkaloids

Table 5^{235–247} summarizes alkaloid isolation work over the past year. The isolation of dehydrocheilanthifoline (94; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) from *Bocconia cordata* represents the third source of this alkaloid. It has been previously

²³⁰ P. J. Scheuer, *Chem. Heterocyclic Compounds*, 1972, **26**, 560.

²³¹ T. Kametani, T. Honda, H. Shimanouchi, and Y. Sasada, *J.C.S. Chem. Comm.*, 1972, 1072.

²³² H. Iida, H.-C. Hsu, T. Kikuchi, and K. Kawano, *Yakugaku Zasshi*, 1972, **92**, 1242 (*Chem. Abs.*, 1973, **78**, 16 343k).

²³³ H.-C. Hsu, T. Kikuchi, S. Aoyagi, and H. Iida, *Yakugaku Zasshi*, 1972, **92**, 1030 (*Chem. Abs.*, 1972, **77**, 140 365n).

²³⁴ T. Kametani, K. Fukumoto, and M. Fujihara, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1800.

²³⁵ F. R. Stermitz, R. J. Ito, S. M. Workman, and W. M. Klein, *Phytochemistry*, 1973, **12**, 381.

²³⁶ A. L. Bandoni, R. V. D. Rondina, and J. D. Coussio, *Phytochemistry*, 1972, **11**, 3547.

²³⁷ M. Haroon-ur-Rashid and M. N. Malik, *Pakistan J. Forest.*, 1972, **22**, 43 (*Chem. Abs.*, 1972, **77**, 149 688c).

Table 5 Isolation of protoberberine alkaloids

Source	Alkaloid (Structure) ^a	Ref.
<i>Argemone echinata</i>	Berberine	235
<i>A. subfusiformis</i> subvar. <i>subfusiformis</i>	Berberine	236
<i>Berberis jaeschkeana</i> ,	Palmatine	237
<i>B. lycium</i> ,	Unknown alkaloid ^b	237
<i>B. vulgaris</i>		
<i>Bocconia cordata</i>	Dehydrocheilanthifoline (94; R ¹ = Me, R ² = H)	238
<i>Cocculus carolinus</i>	Palmatine	114
<i>Corydalis incisa</i>	(-)-Tetrahydrocorysamine ^b	239
<i>C. pallida</i> ^c	Corydaline	240
	Unknown alkaloid ^b , m.p. 239–250 °C	240
<i>C. tashiroi</i>	(±)-Tetrahydropalmatine	241
	(-)-Tetrahydropalmatine	241
	Palmatine	241
<i>Fumaria rostellata</i> ,	Sinactine (95; R ¹ = R ² = Me, R ³ + R ⁴ = CH ₂)	242, 243
<i>Fumaria</i> sp.	Stylophine	242, 243
<i>Glaucium</i>	(-)- β -Canadine methohydroxide	244
<i>corniculatum</i>	(-)-Stylophine methohydroxide	244
<i>G. flavum</i>	Aurotensine [(–)- and (±)-scoulerine]	116
<i>Hydrastis canadensis</i>	Canadine	245
<i>Leontice</i>	Tetrahydropalmatine	246
<i>leontopetalum</i>	Palmatine	246
<i>Mitrella kentii</i>	Aequaline	121
<i>Schefferomitra</i>	Aequaline ^b (95; R ¹ = R ³ = H, R ² = R ⁴ = Me)	126
<i>subaequalis</i>	Alkaloid Y ^b , C ₁₇ H ₁₃ NO ₃ , m.p. 257–258 °C	126
	Schefferine ^b (95; R ¹ = R ² = R ⁴ = Me, R ³ = H)	126
<i>Thalictrum minus</i> ,	Berberine	129
race B	Oxyberberine (Berlambine)	129
	Palmatine	129
<i>T. rugosum</i>	Berberine	247
	Thalidasine	247

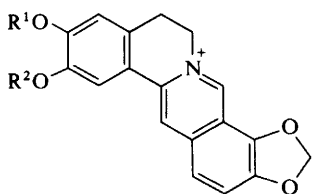
^a See footnote (a), Table 3; ^b New alkaloid; ^c A number of unknown alkaloids, TN-4, -5, -12, -21, and -23, were also isolated.

²³⁸ N. Takao, Y. Yasumoto, and K. Iwasa, *Yakugaku Zasshi*, 1973, **93**, 242 (*Chem. Abs.*, 1973, **78**, 136 485e).

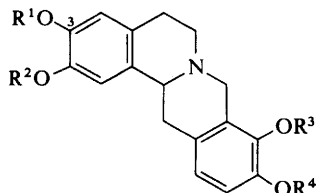
²³⁹ G. Nonaka, H. Okabe, I. Nishioka, and N. Takao, *Yakugaku Zasshi*, 1973, **93**, 87 (*Chem. Abs.*, 1973, **78**, 108 189t).

²⁴⁰ A. F. Polyakova, B. K. Rostotskii, and N. S. Dubinin, *Tr. Alma-At. Med. Inst.*, 1970, 456 (*Chem. Abs.*, 1972, **77**, 85 631u).

obtained from *Menispermum canadense* L. (cf. Vol. 3 of these Reports) and, as indicated in a recent structural revision,²⁴⁸ from *Coptis groenlandica*. Another alkaloid obtained from the latter species and originally formulated as isocoptisine has now been shown to be coptisine (95; $R^1 + R^2 = R^3 + R^4 = CH_2$).²⁴⁸ (For earlier structures, cf. Vol. 2 of these Reports). N.m.r. evidence for the structure of alkaloid B, also isolated from *C. groenlandica* and formulated as a methoxy-hydroxy-coptisine (cf. Vol. 2 of these Reports) is available.²⁴⁹ Alkaloid B was examined as part of a systematic correlation of chemical shifts of aromatic and alkoxy protons of 18 protoberberinium compounds; the structure (94; $R^1 = H$, $R^2 = Me$) and new trivial name groenlandicine have been suggested for alkaloid B.²⁴⁹



(94)



(95)

The amounts of berberine and stylopine in relation to benzophenanthridine alkaloids in *Chelidonium majus* have been determined.²⁵⁰ The optimum harvest time for isolation of berberine alkaloids from the rhizomes of *Coptis japonica* has been studied.²⁵¹

An important review on the application of N.O.E. studies to structural elucidation problems of protoberberine and other benzyloquinoline alkaloids has appeared.²⁵²

²⁴¹ S. -T. Lu, C. -N. Lun, and T. -S. Wu, *J. Chinese Chem. Soc. (Taipei)*, 1972, **19**, 41 (*Chem. Abs.*, 1972, **77**, 123 829z).

²⁴² Kh. G. Kiryakov and P. P. Panov, *Doklady Bolg. Akad. Nauk*, 1972, **25**, 345 (*Chem. Abs.*, 1972, **77**, 58 795u).

²⁴³ N. M. Mollov and G. I. Yakimov, *Doklady Bolg. Akad. Nauk*, 1972, **25**, 59 (*Chem. Abs.*, 1972, **77**, 85 674k).

²⁴⁴ V. Novak, L. Dolejs, and J. Slavik, *Coll. Czech. Chem. Comm.*, 1972, **37**, 3346.

²⁴⁵ J. Gleye and E. Stanislas, *Plant Med. Phytother.*, 1972, **6**, 306 (*Chem. Abs.*, 1973, **78**, 94 857v).

²⁴⁶ P. P. Panov, L. N. Panova, and N. M. Mollov, *Doklady Bolg. Akad. Nauk*, 1972, **25**, 55 (*Chem. Abs.*, 1972, **77**, 72 554w).

²⁴⁷ L. A. Mitscher, W. -N. Wu, R. W. Doskotch, and J. L. Beal, *Lloydia*, 1972, **35**, 167.

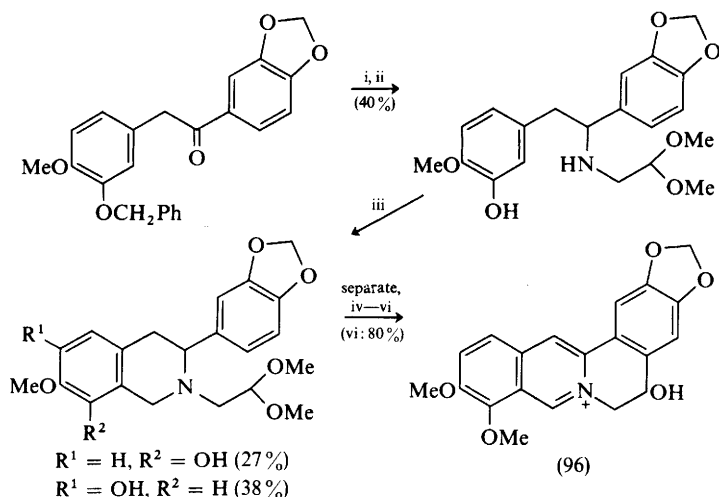
²⁴⁸ S. F. Cooper, J. A. Mockle, and F. Santavy, *Planta Med.*, 1972, **21**, 313 (*Chem. Abs.*, 1972, **77**, 62 193p).

²⁴⁹ K. Jewers, A. H. Manchanda, and P. N. Jenkins, *J.C.S. Perkin II*, 1972, 1393.

²⁵⁰ A. Gheorghiu, E. Ionescu-Matiu, and V. Lupulescu, *Studii Cercetari Biochim.*, 1972, **15**, 161 (*Chem. Abs.*, 1972, **77**, 111 571w).

²⁵¹ T. Sawada, J. Yamahara, N. Ohashi, and H. Tutihasi, *Shoyakugaku Zasshi*, 1972, **26**, 12 (*Chem. Abs.*, 1973, **78**, 33 844s).

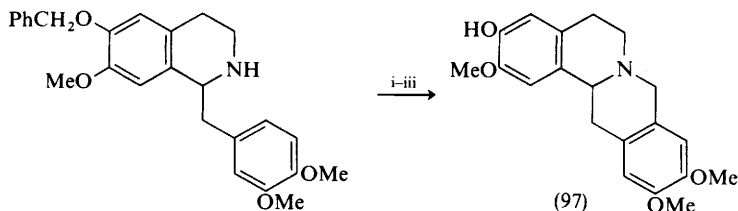
²⁵² R. A. Bell and J. K. Saunders, *Topics Stereochem.*, 1973, **7**, 1.



Reagents: i, $\text{H}_2\text{NCH}_2\text{CH}(\text{OMe})_2$; ii, H_2 , Pd; iii, CH_2O , MeOH , H_2O ; iv, CH_2N_2 ; v, 6N-HCl; vi, dehydrogenation.

Scheme 12

The utility of lactone synthons for berberine alkaloid elaboration has been noted.²⁵³ Details concerning the interesting synthesis of (\pm)-xylopinine by thermolysis of a 1-benzocyclobutenylisoquinoline, which has been previously described (*cf.* Vol. 3 of these Reports), are now available.²⁵⁴ The first synthesis of berberastine (96) has been accomplished (Scheme 12).²⁵⁵ (–)-Discretine (97) has been synthesized by use of an intramolecular Mannich condensation as the key step (Scheme 13).²⁵⁶ The desired cyclization result is accompanied by some reductive *N*-methylation. (\pm)-Xylopine (98) has also been neatly obtained by devising an appropriate enamide photocyclization reaction (Scheme 14).²⁵⁷ A protoberberine to spirobenzylisoquinoline alkaloid rearrangement is described in Section 16.



Reagents: i, 37% formalin, HOAc; ii, resolution with (–)-di-*p*-toluoyltartaric acid; iii, HCl, EtOH.

Scheme 13

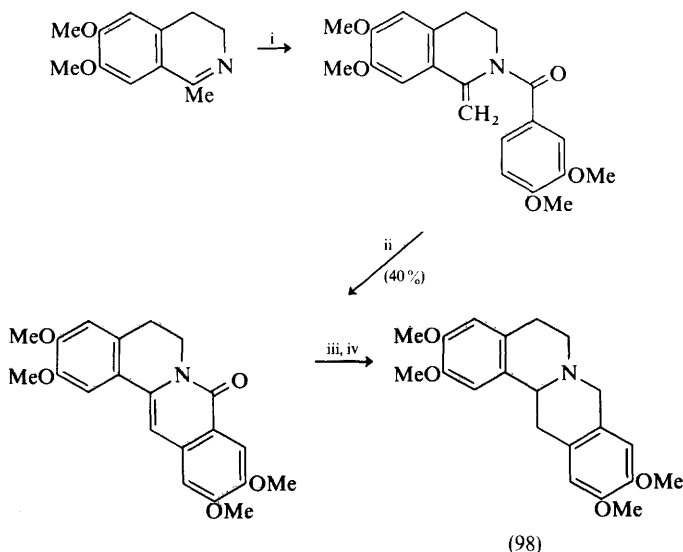
²⁵³ F. Zymalkowski, *Deut. Apoth. -Ztg.*, 1972, **112**, 1614 (*Chem. Abs.*, 1973, **78**, 43 807w).

²⁵⁴ T. Kametani, K. Ogasawara, and T. Takahashi, *Tetrahedron*, 1973, **29**, 73.

²⁵⁵ S. F. Dyke and E. P. Tiley, *Tetrahedron Letters*, 1972, 5175.

²⁵⁶ T. Kametani, M. Takeshita, and S. Takano, *J.C.S. Perkin I*, 1972, 2834.

²⁵⁷ I. Ninomiya and T. Naito, *J.C.S. Chem. Comm.*, 1973, 137.



Reagents: i, 3,4-(OMe)₂C₆H₃COCl, Et₃N, PhH; ii, *hν*, low press. Hg; iii, LiAlH₄; iv, NaBH₄.

Scheme 14

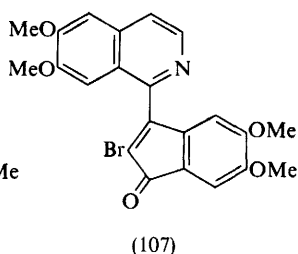
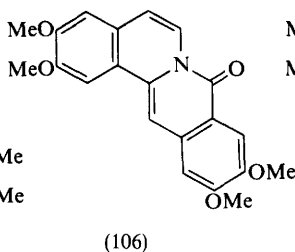
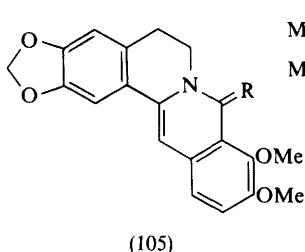
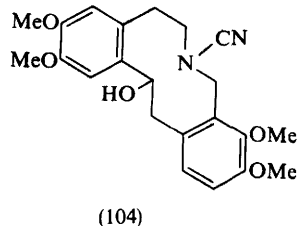
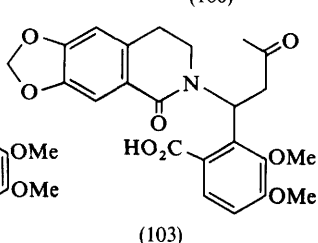
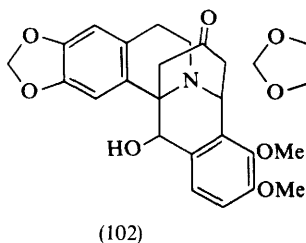
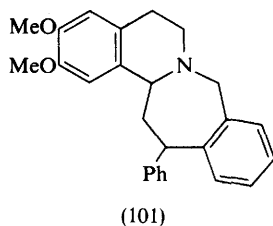
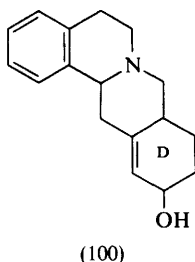
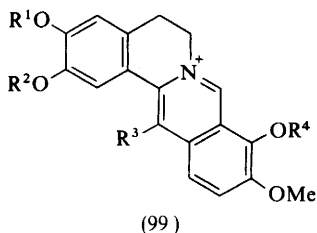
A number of dehydrocorydalines, 13-substituted berberines, and *O*-demethylated dehydrocorydalines (99; R¹ + R² = CH₂, R³ = Me, Et, CH₂CH=CH₂, Pr, CO₂Et, CH₂C≡CH, and CH₂CO₂Et, R⁴ = Me), (99; R¹ = R³ = R⁴ = Me, R² = H), (99; R¹ = R² = R³ = Me, R⁴ = H), and (99; R¹ = R³ = Me, R² = R⁴ = H) have been prepared for evaluation as antigastric ulcer agents.²⁵⁸ The tetracyclic alcohol (100) was obtained by elaboration of ring D *via* an intramolecular aldol reaction.^{259a} Dehydration (TsOH, xylene) followed by dehydrogenation (Pd–SrCO₃, cyclohexane) gave tetrahydropprotoberberine. A number of compounds related to (100) and its tricyclic precursor have been prepared,^{259b,259c} involving, in one case,^{259c} a new synthetic strategy. The homoprotoberberine (101)²⁶⁰ and a variety of C(3)-esters of the protoberberine type²⁶¹ have been synthesized for pharmacological evaluation.

²⁵⁸ S. Naruto and H. Kaneko, *Yakugaku Zasshi*, 1972, **92**, 1017 (*Chem. Abs.*, 1972, **77**, 114 605w).

²⁵⁹ (a) A. A. Akhrem, A. M. Moiseenkov, and V. S. Malishevskii, *Doklady Akad. Nauk S.S.S.R.*, 1973, **208**, 1089 (*Chem. Abs.*, 1973, **78**, 136 486f); (b) L. Szabo, K. Honty, L. Toke, I. Toth, and C. Szantay, *Chem. Ber.*, 1972, **105**, 3215; L. Szabo, K. Honty, L. Toke, and C. Szantay, *ibid.*, p. 3231; (c) A. A. Akhrem, A. M. Moiseenkov, V. A. Krivoruchko, Yu. G. Chernov, and V. S. Malishevskii, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 2376 (*Chem. Abs.*, 1973, **78**, 30 044v).

²⁶⁰ A. L. Mndzhoyan, E. A. Markaryan, T. M. Martirosyan, L. P. Solomina, and E. S. Marashyan, *Khim. geterotsikl. Soedinenii*, 1971, 1683 (*Chem. Abs.*, 1972, **77**, 34 280w).

²⁶¹ T. Kametani, K. Nyu, I. Noguchi, and M. Ihara, *Yakugaku Zasshi*, 1972, **92**, 238 (*Chem. Abs.*, 1972, **77**, 19 855u).



Some interesting transformations of protoberberines have been studied. Products (102) and (103) obtained²⁶² from the permanganate oxidation of acetoneberberine are analogous to those isolated from the reaction of 13-methylacetoneberberine with this reagent (*cf.* Vol. 3 of these Reports). An improvement on the von Braun reaction of protoberberines, yielding protopine derivatives, has been devised.²⁶³ For example, treatment of tetrahydropalmatine with cyanogen bromide and magnesium oxide in aqueous solution gave the cyano-amine (104) in 94% yield. The reaction of berberine with ethyl diazoacetate affords compounds (105; R = H, CN₂CO₂Et), (105; R = CHCO₂Et), and oxyberberine (105; R = O).²⁶⁴ The dehydrogenated oxyberberine (106) together with the purple indanyl isoquinoline derivative (107) were obtained from the hypobromite reaction of 6'-acetylpapaverine.²⁶⁵ An attempt to convert protoberberine-type compounds into useful intermediates for the synthesis of spirobenzylisoquinoline and rheadine alkaloids led instead to the discovery of an unusual

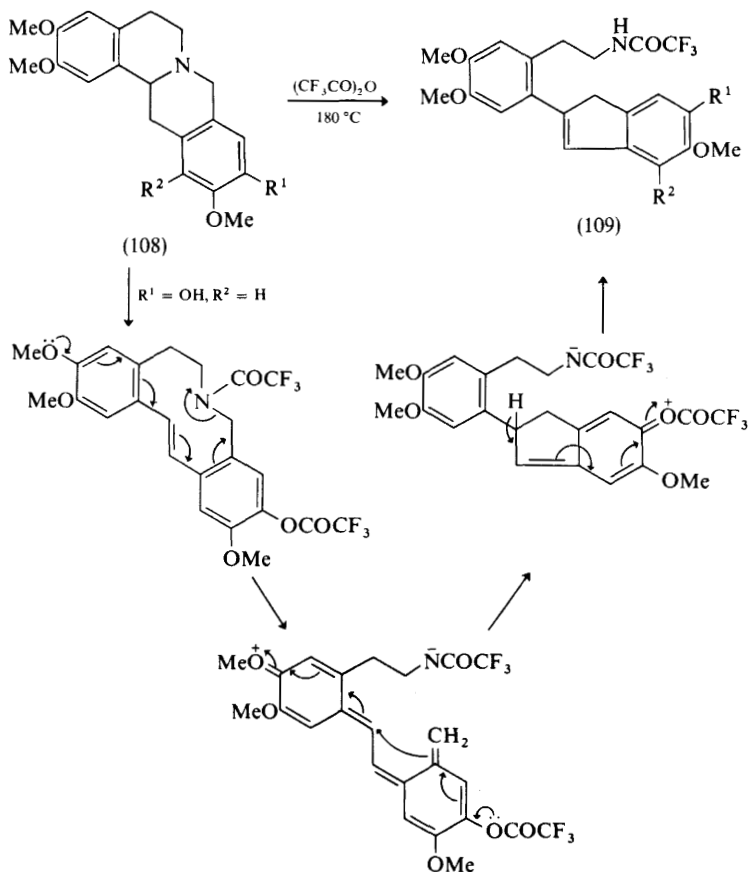
²⁶² Y. Kondo and T. Takemoto, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2134.

²⁶³ H. Roensch, *J. prakt. Chem.*, 1972, **314**, 382.

²⁶⁴ B. Goeber, *Pharmazie*, 1972, **27**, 472.

²⁶⁵ W. Wiegreb, H. Reinhart, H. Budzikiewicz, and U. Krueger, *Biochem. Physiol. Alkaloids, Int. Symp.*, 4th 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 305.

rearrangement (Scheme 15).²⁶⁶ Compounds (108; $R^1 = \text{OH}$, $R^2 = \text{H}$) and (108; $R^1 = \text{H}$, $R^2 = \text{OH}$), when treated with trifluoroacetic anhydride at elevated temperatures, gave the indene derivatives (109; $R^1 = \text{OH}$, $R^2 = \text{H}$) and (109; $R^1 = \text{H}$, $R^2 = \text{OH}$), respectively, in fair yield. A possible mechanism for this transformation is shown for one of the isomers (Scheme 15). It has been reported that thermolysis of the methiodides of tetrahydrocoptisine and tetrahydroprotoberberine derivatives gives, in some cases, 13-methyltetrahydroberberine-type products.²⁶⁷ Redox processes would appear to be involved in these transformations.

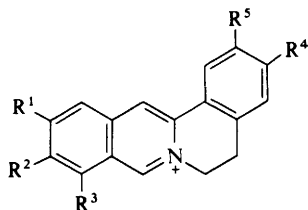


Scheme 15

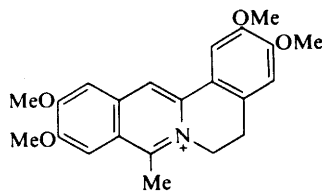
²⁶⁶ T. Kametani, S. Shibuya, S. Hirata, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2570.

²⁶⁷ C. Tani, S. Takao, and K. Tagahara, *Yakugaku Zasshi*, 1973, **93**, 197 (*Chem. Abs.*, 1973, **78**, 124 776n).

Extensive application of i.r., u.v., and n.m.r. spectroscopic and polarographic methods has yielded information concerning positions of equilibria among quaternary salt, carbinolamine, and open-chain aldehyde in protoberberinium and other benzyloisoquinoline alkaloids.²⁶⁸ For compounds (110; $R^1 = R^2 = R^3 = R^4 = R^5 = H$), (110; $R^1 = H, R^2 = R^3 = R^4 = R^5 = OMe$), (110; $R^1 = H, R^2 = R^3 = OMe, R^4 + R^5 = OCH_2O$), and (110; $R^1 = H, R^2 + R^3 = R^4 + R^5 = OCH_2O$), the formation of the carbinolamine in basic medium was established. On the other hand, for compounds (110; $R^1 = R^4 = R^5 = OMe, R^2 = R^3 = H$), (110; $R^1 = R^2 = R^4 = R^5 = OMe, R^3 = H$), (110; $R^1 + R^2 = OCH_2O, R^3 = H, R^4 = R^5 = OMe$), and (110; $R^1 + R^2 = R^4 + R^5 = OCH_2O, R^3 = H$) the carbinolamine form could not be detected, thus showing that there is an effect of the positions of oxygen substituents on the position of the equilibrium. Only in the case of coralynium chloride (111) was the open-chain (ketonic) tautomer observed. The effect of solvent on the equilibrium positions was also studied.



(110)



(111)

Elution properties on CM-Sephadex columns²⁶⁹ and fluorescence characteristics²⁷⁰ of berberine have been reported.

A number of pharmacological effects of berberine sulphate have been described.²⁷¹ The antibacterial activities of berberine^{272,273} and coptisine, jatrorrhizine, and palmatine²⁷³ have been studied. Tetrahydroberberine has been shown to exhibit weak ataractic effects.²⁷⁴ Other pharmacological properties of a number of protoberberine alkaloids have been studied.^{156a}

²⁶⁸ V. Simanek, V. Preininger, S. Hegerova, and F. Santavy, *Coll. Czech. Chem. Comm.*, 1972, **37**, 2746.

²⁶⁹ T. Sawada, J. Yamahara, and C. Iwao, *Shoyakugaku Zasshi*, 1972, **26**, 15 (*Chem. Abs.*, 1973, **78**, 33 962d).

²⁷⁰ A. C. Metha and R. A. Chalmers, *Chem. analit.*, 1972, **17**, 565 (*Chem. Abs.*, 1973, **78**, 33 952a).

²⁷¹ S. K. Kulkarni, P. C. Dandiya, and N. L. Varandani, *Jap. J. Pharmacol.*, 1972, **22**, 11.

²⁷² Z. Kowalewski, W. Kedzia, and I. Mirska, *Arch. Immunol. Ther. Exp.*, 1972, **20**, 353.

²⁷³ T. Sawada, J. Yamahara, K. Goto, and M. Yamamura, *Shoyakugaku Zasshi*, 1971, **25**, 74 (*Chem. Abs.*, 1972, **77**, 122 005r).

²⁷⁴ B. L. Danilevskii, N. T. Tulyaganov, and F. S. Sadritdinov, *Doklady Akad. Nauk Uzbek. S.S.R.*, 1972, **29**, 37 (*Chem. Abs.*, 1973, **78**, 38 001z).

12 Protopine Alkaloids

In a review concerning alkaloid occurrence in more than 50 *Corydalis* species found in Russia, it is noted that only protopines should be considered to be specific for the *Corydalis* genus.²⁷⁵ Alkaloid sources investigated in the past year are shown in Table 6.²⁷⁶⁻²⁷⁸

Table 6 Isolation of protopine alkaloids

Source	Alkaloid (Structure) ^a	Ref.
<i>Argemone echinata</i>	Cryptopine	235
<i>A. fruticosa</i>	Alloccryptopine	235
	Cryptopine	235
	Hunnemannine (112; $R^1 + R^2 = CH_2$, $R^3 = O$, $R^4 = H_2$, $R^5 = H$, $R^6 = R^7 =$ Me)	235
<i>A. subfusiformis</i> subvar. <i>subfusiformis</i>	Alloccryptopine	236
	Protopine	236
<i>Corydalis incisa</i> ^b	Corycavine (112a)	239
	Protopine	239
<i>C. persica</i>	Protopine	276
<i>C. tashiroi</i>	Protopine	241
<i>Fagara viitensis</i>	2,3,10,11-bis(methylenedioxy)protopine	277
<i>Fumaria rostellata</i> ,	Cryptopine	242, 243
<i>Fumaria</i> sp.	Protopine	242, 243
<i>Glaucium flavum</i>	Protopine	116
<i>Macleaya microcarpa</i> (cultivated)	Alloccryptopine	278
	Cryptopine	278
	Protopine	278
<i>Papaver somniferum</i>	β -Alloccryptopine	77
	Cryptopine	125
	Protopine	125

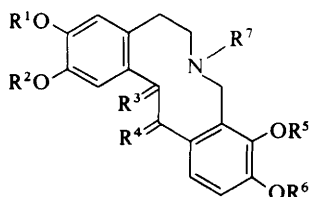
^a See footnote (a), Table 3; ^b Five other alkaloids have been isolated whose structures have not been elucidated.

²⁷⁵ B. K. Rostotskii and I. A. Gubanov, *Herba Polon.*, 1971, **17**, 396 (*Chem. Abs.*, 1972, **77** 52 257y).

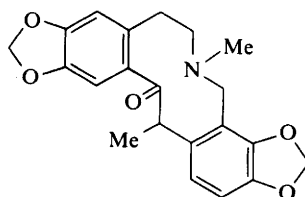
²⁷⁶ N. N. Margvelashvili and D. A. Pakaln, *Khim. prirod. Soedinenii*, 1973, 133 (*Chem. Abs.*, 1973, **78**, 156 640e).

²⁷⁷ F. Fish and P. G. Waterman, *Phytochemistry*, 1972, **11**, 1528.

²⁷⁸ V. A. Chelombit'ko, *Herba Polon.*, 1971, **17**, 388 (*Chem. Abs.*, 1972, **77**, 58 870q).



(112)

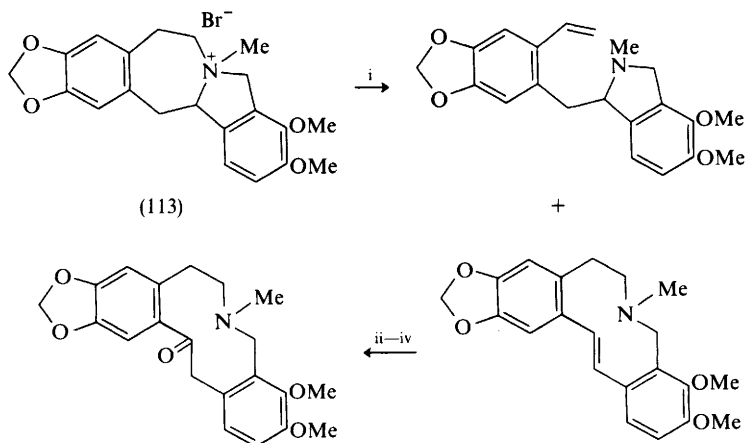


(112a)

A detailed description of the procedure for extraction of protopine from *Corydalis pallida* nodules is available.¹³³

An analysis of protopine content in *Fumaria officinalis* during its growth and development has been published.²⁷⁹ Uptake and distribution of protopine in *Chelidonium majus* leaf tissue has been studied with the aid of radioactive alkaloid.²⁸⁰

The ¹³C n.m.r. spectra of allocryptopine, cryptopine, hunnemannine (112; R¹ + R² = CH₂, R³ = O, R⁴ = H₂, R⁵ = H, R⁶ = R⁷ = Me), muramine (112; R¹ = R² = R⁵ = R⁶ = Me, R³ = O, R⁴ = H₂, R⁷ = Me), and protopine have been analysed with the aid of the pulse FT technique.²⁸¹ It was possible to make self-consistent assignments for all resonances and to obtain evidence for the transannular amino-carbonyl interaction in these alkaloids.



(112; R¹ + R² = CH₂, R³ = O, R⁴ = H₂, R⁵ = R⁶ = R⁷ = Me)

Reagents: i, IRA-400, OH⁻, red. press.; ii, H₂, PtO₂, 3N-HCl; iii, *m*-ClC₆H₄CO₃H, 5 °C; iv, HOAc, conc. HCl, 100 °C.

Scheme 16

²⁷⁹ D. A. Murav'eva and B. A. Figurkin, *Biol. Nauki*, 1972, **15**, 87 (*Chem. Abs.*, 1973, **78**, 13 760h).

²⁸⁰ D. Neumann and E. Mueller, *Biochem. Physiol. Pflanz.*, 1972, **163**, 375.

²⁸¹ T. T. Nakashima and G. E. Maciel, *Org. Magn. Resonance*, 1973, **5**, 9.

Schoepf-Schweickert amine VI methobromide (113), available from an appropriate phthalideisoquinoline alkaloid, has been converted into α -allocryptopine (Scheme 16).²⁸² The preparation of protopine-type compounds by von Braun reaction on protoberberines is discussed in Section 11.

α -Allocryptopine has been found to show antiarrhythmic activity.²⁸³

13 Benzophenanthridine Alkaloids

Recent sources of benzophenanthridine alkaloids are listed in Table 7.^{284,285} The X-ray crystallographic analysis of corynoline *p*-bromobenzoate has recently established structure (114; R = H) for this alkaloid;²⁸⁶ this information may aid in conformational analysis of the related bases isolated from *Corydalis incisa*. Bocconine, previously isolated from *Bocconia cordata* and assigned an unusually substituted ring A benzophenanthridine structure (*cf.* Vol. 2 of these Reports), has been shown to be identical with chelirubine (116) (from *Chelidonium majus*)

Table 7 Isolation of benzophenanthridine alkaloids

Source	Alkaloid (Structure) ^a	Ref.
<i>Argemone subfusiformis</i> subvar. <i>subfusiformis</i>	Chelerythrine	236
	Sanguinarine	236
<i>Corydalis incisa</i> ^b	Acetylcorynoline ^c (114; R = Ac)	239
	Acetyliscorynoline ^c	239
	Corynoline (114; R = H)	239
	Isocorynoline	239
<i>C. persica</i>	Chelerythrine	276
	Sanguinarine	276
<i>Fagara vitiensis</i>	Chelerythrine	277
	Nitidine	277
<i>F. zanthoxyloides</i>	Fagaronine ^c (115)	284
<i>Glaucium flavum</i>	Chelerythrine	116
	Sanguinarine	116
<i>Macleaya microcarpa</i>	Chelerythrine	278
	Sanguinarine	278
<i>Romneya coulteri</i>	Dihydrosanguinarine	285
	Sanguinarine	285

^a See footnote (a), Table 3; ^b Contains five other alkaloids which were isolated but not structurally elucidated; ^c New alkaloid.

²⁸² S. Teitel, J. Borgese, and A. Brossi, *Helv. Chim. Acta*, 1973, **56**, 553.

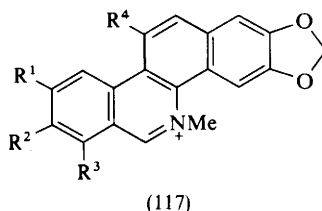
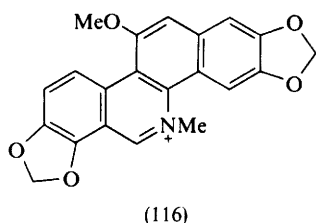
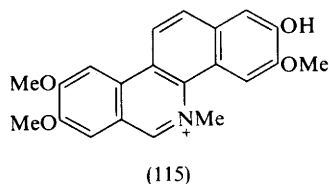
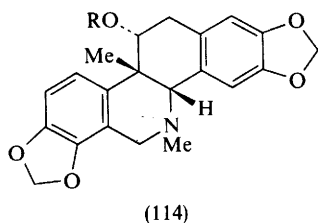
²⁸³ Z. S. Akbarov, Kh. U. Aliev, and M. B. Sultanov, *Doklady Akad. Nauk Uzbek. S.S.R.*, 1972, **29**, 38 (*Chem. Abs.*, 1973, **78**, 38 003b).

²⁸⁴ W. M. Messmer, M. Tin-Wa, H. H. S. Fong, C. Bevelle, N. R. Farnsworth, D. J. Abraham, and J. Trojanek, *J. Pharm. Sci.*, 1972, **61**, 1858.

²⁸⁵ F. R. Stermitz, D. K. Kim, and L. Teng, *Phytochemistry*, 1972, **11**, 2644.

²⁸⁶ T. Kametani, T. Honda, M. Ihara, H. Shimanouchi, and Y. Sasada, *Tetrahedron Letters*, 1972, 3729.

by direct comparison of samples.²⁸⁷ Analysis of n.m.r. and u.v. spectral data together with biogenetic considerations support structure (116) for chelirubine.



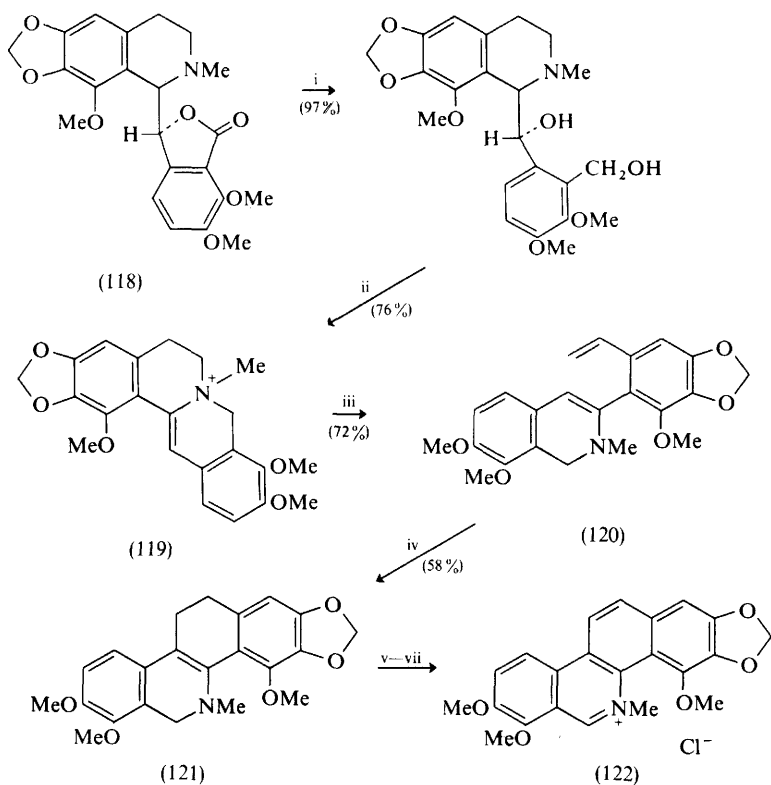
An improved method for the purification of sanguinarine has been reported.²⁸⁸ Crude sanguinarine sulphate was reduced with sodium borohydride to dihydro-sanguinarine, which was purified and then oxidized to sanguinarine using photochemical and chemical procedures. The best conditions for the oxidation reaction employ silver nitrate and palladium on carbon in refluxing ethanol. Commercial samples of sanguinarine sulphate are normally obtained from *Corydalis* species. It has now been found that at least an equally good source (up to 0.96% of alkaloid) is *Chelidonium majus*.²⁸⁹ A more detailed analysis of chelerythrine, chelidonine, and sanguinarine content in *C. majus* has been described.²⁵⁰

Structural elucidation studies of alkaloids by application of N.O.E. experiments have been reviewed.²⁵² The quaternary amine-carbinolamine equilibria of alkaline solutions of a number of benzophenanthridine alkaloids (117; $R^1 = R^2 = \text{OMe}$, $R^3 = R^4 = \text{H}$), (117; $R^1 = R^4 = \text{H}$, $R^2 = R^3 = \text{OMe}$), (117; $R^1 = R^4 = \text{H}$, $R^2 + R^3 = \text{OCH}_2\text{O}$), (117; $R^1 = \text{H}$, $R^2 = R^3 = R^4 = \text{OMe}$), and (117; $R^1 = \text{H}$, $R^2 + R^3 = \text{OCH}_2\text{O}$, $R^4 = \text{OMe}$) have been studied.²⁶⁸ In all cases, evidence for carbinolamine formation but not for the further open-chain aldehyde tautomerism has been obtained from a combination of i.r., u.v., and n.m.r. spectroscopic and polarographic investigations.

²⁸⁷ J. Slavik and F. Santavy, *Coll. Czech. Chem. Comm.*, 1972, **37**, 2804.

²⁸⁸ R. D. Stipanovic, C. R. Howell, and A. A. Bell, *J. Heterocyclic Chem.*, 1972, **9**, 1453.

²⁸⁹ L. D. Yakhontova, O. N. Tolkachev, and P. N. Kubal'chich, *Farmatsiya (Moscow)*, 1973, **22**, 31 (*Chem. Abs.*, 1973, **78**, 133 418z).



Reagents: i, LiAlH_4 , THF; ii, SOCl_2 , K_2CO_3 , CHCl_3 ; iii, KOH , MeOH ; iv, $h\nu$, high press. Hg, PhH, N_2 ; v, Pd-C, cymene; vi, DDQ, PhH; vii, HCl.

Scheme 17

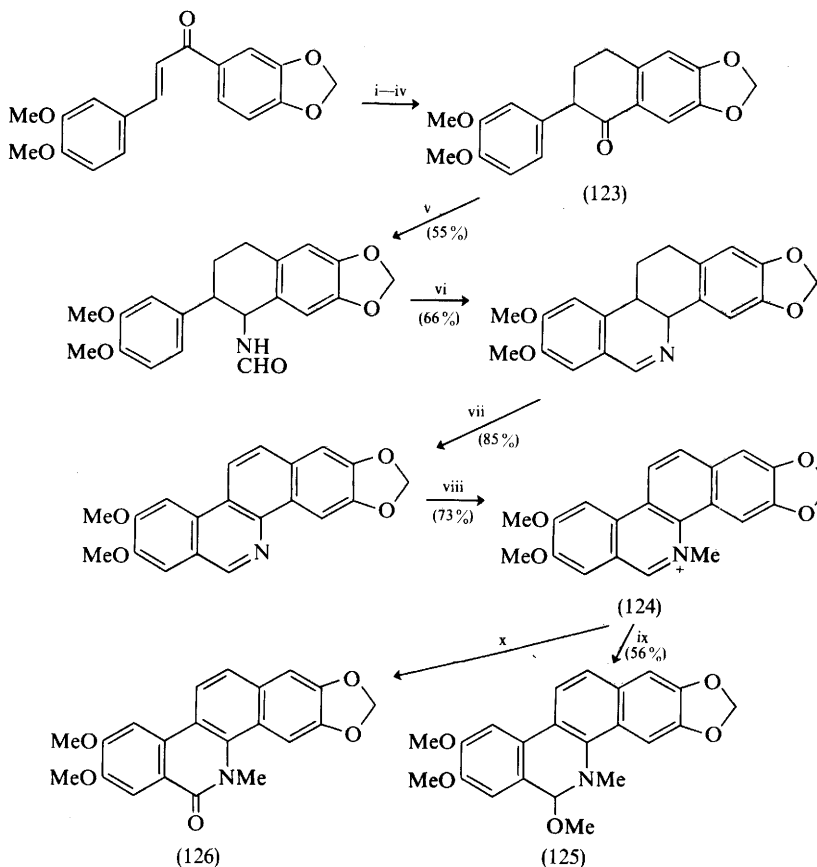
By analogy with previous work (*cf.* Vol. 2 of these Reports), a transformation of *l*-α-narcotine (118) into a benzophenanthridine derivative (122) has been achieved (Scheme 17).²⁹⁰ The route proceeds *via* a dihydroprotoberberine intermediate (119) and involves a key photochemical step (120) \rightarrow (121). This sequence shows promise as a general method for the phthalideisoquinoline to benzophenanthridine interconversion.

The discovery of antileukaemic activity of nitidine (124) and 5,6-dihydro-6-methoxynitidine (125) prompted the development of a practical synthesis of these two compounds (Scheme 18).²⁹¹ The procedure is based on an early synthesis except that in most steps improvements in yield were achieved to give an

²⁹⁰ M. Onda and K. Kawakami, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1484.

²⁹¹ K. -Y. Zee-Cheng and C. C. Cheng, *J. Heterocyclic Chem.*, 1973, **10**, 85.

overall 15% yield of (123). A similar synthetic attack using the tetralone (123) but involving additional steps has also yielded nitidine (125).²⁹² In addition, this paper describes the production of oxonitidine (126) from nitidine (Scheme 18).



Reagents: i, KCN; ii, NaOH, H₂O-EtOH, iii, H₂, Pd-C, HOAc, HClO₄, 60 °C, press.; iv, PCl₅, CHCl₃; v, (NH₄)₂SO₄, HCONH₂, HCO₂H; vi, POCl₃, PhMe, 115 °C; vii, Pd-C, Dow Corning 550 fluid, 225 °C; viii, Me₂SO₄, PhNO₂, 190 °C; ix, aq. NH₃, MeOH; x, K₃Fe(CN)₆, H₂O, 80 °C.

Scheme 18

Details of a photochemical synthesis of benzophenanthridines from acyl enamines which had been previously described (*cf.* Vol. 2 of these Reports) are now available.²⁹³

²⁹² T. Kametani, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Heterocyclic Chem.*, 1973, **10**, 31.

²⁹³ I. Ninomiya, T. Naito, and T. Mori, *J.C.S. Perkin I*, 1973, 505.

Chelerythrine, nitidine, and sanguinarine have been shown to inhibit oxygen uptake by *Saccharomyces cerevisiae*.¹⁰⁴ Inhibition of photosynthetic phosphorylation in spinach chloroplasts *in vitro* by chelerythrine, chelidonine, and sanguinarine has been reported.²⁹⁴ The toxicity of sanguinarine to *Verticillium dahliae* has been studied.²⁹⁵

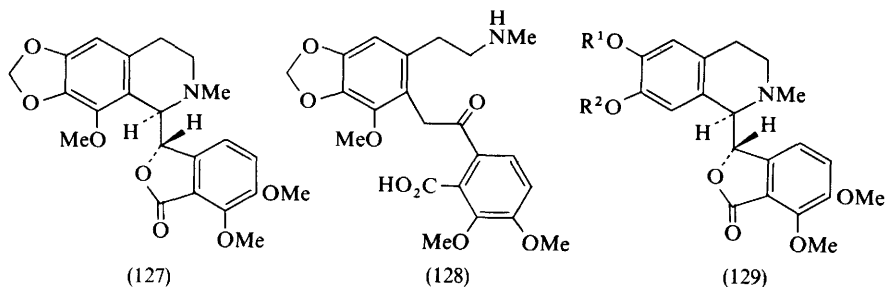
14 Phthalideisoquinoline Alkaloids

Recent sources of known alkaloids are listed in Table 8.²⁹⁶

Table 8 Isolation of phthalideisoquinoline alkaloids

Source	Alkaloid (Structure)	Ref.
<i>Corydalis rosea</i>	<i>l</i> -Adlumidine	296
	<i>l</i> -Adlumine	296
<i>Fumaria rostellata</i>	<i>d</i> -Adlumine	242
<i>Hydrastis canadensis</i>	<i>l</i> - α -Hydrastine	245
	<i>l</i> - β -Hydrastine	245
<i>Papaver somniferum</i>	Gnoscopine	77
	Narcotine	77
	Narcotoline	196

A classical synthesis of (\pm)-narcotine (127) has been outlined in the proceedings of a recent symposium.²⁹⁷ The conversion of the *N*-benzyl salt of narcotine in two steps (Hofmann degradation and catalytic debenzylation) into nornarceine (128) in good yield has now been fully described.²⁹⁸ The latter is a useful intermediate for rheoadine alkaloid synthesis (*cf.* Vol. 3 of these Reports). The transformation of a phthalideisoquinoline alkaloid into a benzophenanthridine derivative is discussed in Section 13.



²⁹⁴ R. H. Vallejos, *Biochim. Biophys. Acta*, 1973, **292**, 193.

²⁹⁵ C. R. Howell, R. D. Stipanovic, and A. A. Bell, *Pesticide Biochem. Physiol.*, 1972, **2**, 364.

²⁹⁶ N. N. Margvelashvili, A. T. Kir'yanova, and O. N. Tolkachev, *Khim. prirod. Soedinenii*, 1972, 127 (*Chem. Abs.*, 1972, **77**, 58 825d).

²⁹⁷ R. Bogner and P. Kerekes, *Biochem. Physiol. Alkaloide, Int. Symp.*, 4th 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 307.

²⁹⁸ W. Kloetzer, S. Teitel, and A. Brossi, *Monatsh.*, 1972, **103**, 1210.

Treatment of (–)- β -hydrastine (129; $R^1 + R^2 = CH_2$) with boron trichloride gives the diphenol (129; $R^1 = R^2 = H$) in 81% yield which, in the presence of diazomethane, provides (–)-cordrastine II (129; $R^1 = R^2 = Me$).²⁹⁹ This represents another example of phthalideisoquinoline alkaloid interrelationship based on preferential dealkylation reactions of certain methoxy or methylene-dioxy functions (*cf.* Vol. 3 of these Reports).

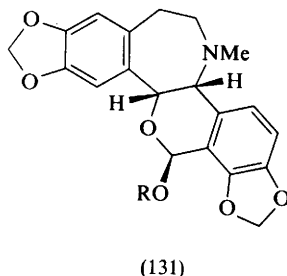
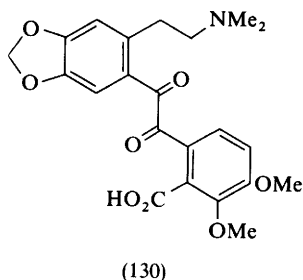
Hydrastinine has been quantitatively analysed by a spectrophotometric method with reduced phosphomolybdic acid.³⁰⁰ Quantitative gas-chromatographic analysis⁹⁸ and polarographic behaviour³⁰¹ of narcotine have been reported. The separation of narcotine from cotarnine on Sephadex columns has been achieved.⁶⁸ A more accurate determination of narcotine content in *Papaver somniferum* by combination chromatography–spectrophotometry has been claimed.⁹⁵

Noscapine has been shown to possess antitussive action.³⁰² Bicuculline has been found both to potentiate and antagonize γ -aminobutyric acid.³⁰³

15 Rhoeadine and Papaverrubine Alkaloids

Oxo-*N*-methylhydrasteine has been isolated from a *Fumaria* species and shown to possess structure (130) by the application of spectroscopic methods and by synthesis from *N*-methylhydrasteine.³⁰⁴

The X-ray crystallographic analysis³⁰⁵ of the methiodide of rhoeagenine has confirmed the (5*R*, 6*R*, 9*S*) absolute configuration (131; $R = H$) for this alkaloid, which was earlier established by application of the aromatic chirality rule (see Vol. 3 of these Reports).



²⁹⁹ S. Teitel, J. O'Brien, and A. Brossi, *J. Org. Chem.*, 1972, **37**, 3368.

³⁰⁰ D. De Carvalho, A. B. Prado, H. C. Silva, and L. Larini, *Arq. Inst. Biol., Sao Paulo*, 1972, **39**, 159 (*Chem. Abs.*, 1972, **77**, 151 651z).

³⁰¹ R. Kalvoda and R. G. Clem, *MPI Appl. Notes*, 1972, **7**, 25 (*Chem. Abs.*, 1973, **78**, 91 763a).

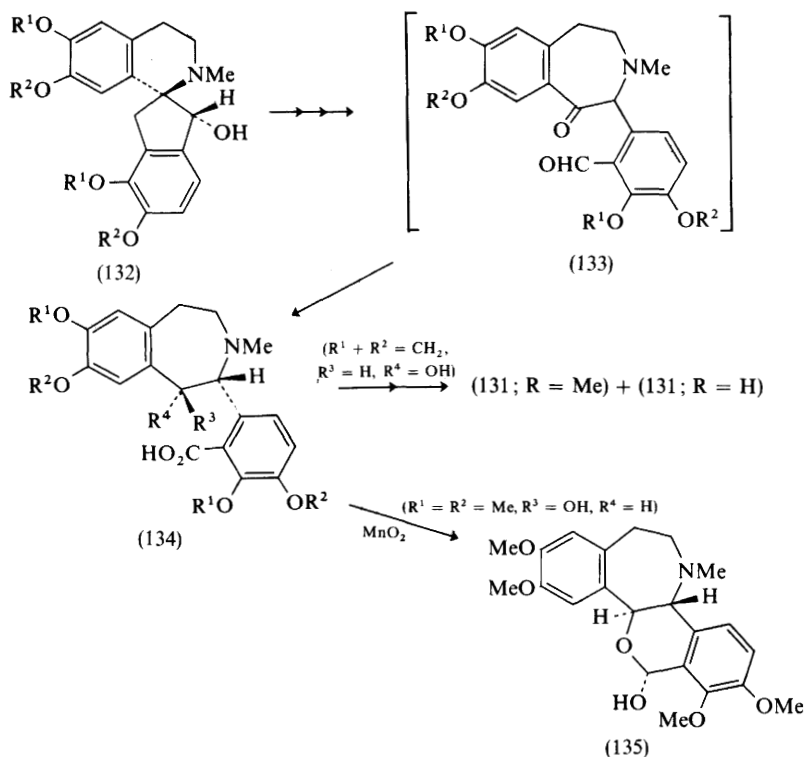
³⁰² A. Bertoni, *Studi Urbinati, Fac. Farm.*, 1971, **44**, 71 (*Chem. Abs.*, 1973, **78**, 132 029m).

³⁰³ R. G. Hill, M. A. Simmonds, and D. W. Straughan, *Brit. J. Pharmacol.*, 1971, **42**, 639p.

³⁰⁴ P. Forgacs, J. Provost, R. Tiberghien, J. F. Desconclois, G. Buffard, and M. Pesson, *Compt. rend.*, 1973, **276**, D, 105.

³⁰⁵ C. S. Huber, *Acta Cryst.*, 1972, **B28**, 982.

Experimental details of a short synthesis of (+)-rheadine (131; R = Me) and its unnatural (–)-isomer from the phthalideisoquinoline alkaloid (–)-bicuculline, which had been previously outlined (Vol. 3 of these Reports), have appeared.³⁰⁶ Details are also available concerning the conversion of a spirobenzylisoquinoline derivative (132; R¹ + R² = CH₂) into (±)-rheagenine diol (134; R¹ + R² = CH₂, R³ = H, R⁴ = OH) (Scheme 19).³⁰⁷ Since naturally occurring (+)-rheagenine (131; R = H) and (+)-rheadine (131; R = Me) have been reconstituted from chiral rheagenine diol, this work is formally a total synthesis of these alkaloids. (±)-Alpinigenine (135) was also synthesized by an analogous route starting with compound (132; R¹ = R² = Me). It may be worthwhile to note that the intermediate keto-aldehyde (133; R¹ = R₂ = Me) was reduced with lithium perhydro-9b-boraphenalenylhydride to provide a 40% yield of the required (*trans*-) (±)-alpinigenine diol (134; R¹ = R² = Me, R³ = OH, R⁴ = H), which was converted by manganese dioxide oxidation into (±)-alpinigenine (135) in low yield.

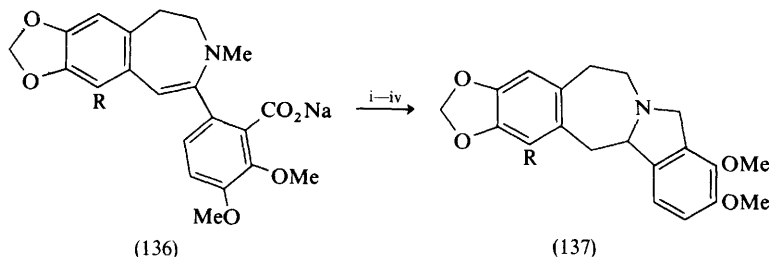


Scheme 19

³⁰⁶ W. Kloetzer, S. Teitel, and A. Brossi, *Helv. Chim. Acta*, 1972, **55**, 2228.

³⁰⁷ H. Irie, S. Tani, and H. Yamane, *J.C.S. Perkin I*, 1972, 2986.

An alternative synthesis of Schoepf-Schweickert amine VI (137; R = H) (*cf.* also Vol. 3 of these Reports) and the analogous benzazepine (137; R = OMe) has been devised starting with the enamines (136; R = H) and (136; R = OMe), respectively (Scheme 20).³⁰⁸ Compounds (136; R = H) and (136; R = OMe) were obtained from the phthalideisoquinoline alkaloids (–)-hydrastine and (–)-narcotine, respectively, and used previously for rheadine alkaloid synthesis.



Reagents: i, HOAc, H₂O, ii, LiBH₄, THF; iii, Ac₂O, reflux; iv, B₂H₆, THF.

Scheme 20

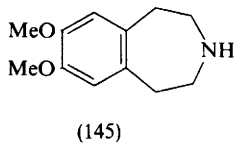
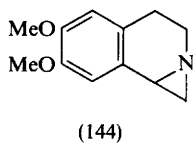
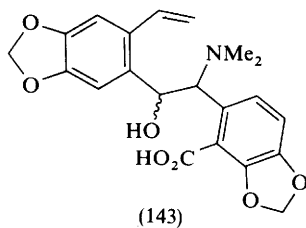
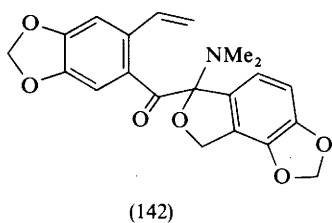
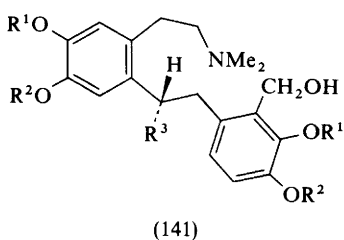
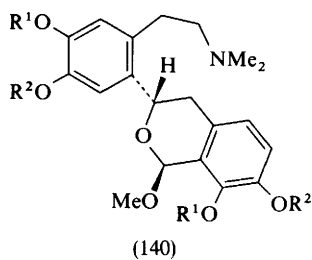
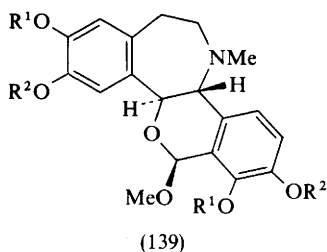
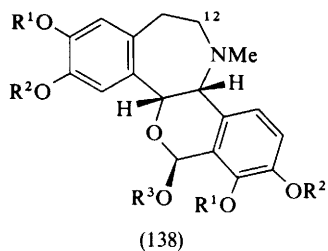
It has been reported that the main products of the Emde degradation of the methiodides of 1-epi-alpinine (138; R¹ = R² = R³ = Me) and *O*-methylalpinigenine (139; R¹ = R² = Me) are the isocoumaran derivative (–)-(140; R¹ = R² = Me) and its enantiomer, respectively.³⁰⁹ However, an inconsistency has arisen in that the Emde degradation product (+)-(140; R¹ + R² = CH₂) of the methiodide of rheadine (138; R¹ + R² = CH₂, R³ = Me) shows c.d. bands of opposite sign to those for compound (–)-(140; R¹ = R² = Me).³¹⁰ C.d. spectra of the same sign are expected since these compounds are derived from rheadine and 1-epi-alpinine, which possess the same absolute configuration at all centres of chirality. Reinvestigation of the Emde degradation of rheadine (138; R¹ + R² = CH₂, R³ = Me) methiodide has yielded, besides the previously isolated (+)-(140; R¹ + R² = CH₂) (major product), the optically inactive base (141; R¹ + R² = CH₂, R³ = H).³¹⁰ On the basis of n.m.r. data for the latter compound, the minor product obtained³⁰⁹ from 1-epi-alpinine (138; R¹ = R² = R³ = Me) may be reassigned structure (141; R¹ = R² = Me, R³ = H). Emde reaction of rheoagenine (138; R¹ + R² = CH₂, R³ = H) methiodide gave a small amount of (+)-(141; R¹ + R² = CH₂, R³ = H), the major product being compound (+)-(141; R¹ + R² = CH₂, R³ = OH). The lack of consistency between the results in the two reports^{309,310} is to be noted and invites further investigation. The Hofmann degradation of rheoagenine (138; R¹ + R² = CH₂, R³ = H) methiodide has been shown to yield, besides the expected products of N–C(12)

³⁰⁸ S. Teitel, W. Kloetzer, J. Borgese, and A. Brossi, *Canad. J. Chem.*, 1972, **50**, 2022.

³⁰⁹ H. Roensch, *Tetrahedron Letters*, 1972, 4431.

³¹⁰ V. Simanek, A. Klasek, and F. Santavy, *Tetrahedron Letters*, 1973, 1779.

cleavage, the amino-lactone (142) and the amino-acid (143) resulting from further rearrangement and oxidation.³¹¹

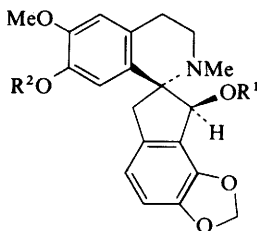


³¹¹ M. D. Rozwadowska and J. W. ApSimon, *Tetrahedron*, 1972, **28**, 4125.

The transformation of Schoepf-Schweickert amine VI (137; R = H) into the protopine alkaloid α -allocryptopine has been described (*cf.* Section 12). An 'aqueous' von Braun reaction of alpinine has been reported.²⁶³ The reductive ring cleavage (H_2 , Raney Ni) of the aziridine (144) into the benzazepine (145) in 87% yield may be of synthetic interest.³¹²

16 Spirobenzylisoquinoline Alkaloids

Known alkaloids are fumariline from *Fumaria rostellata*²⁴² and 'Herba Fumaria',²⁴³ fumaritridine and parfumine from *F. rostellata*,²⁴² and fumarophycine from 'Herba Fumaria'.²⁴³ Fumarostelline from *F. rostellata*²⁴² and *O*-methylfumarophycine (146; R¹ = Ac, R² = Me), *O*-methylfumarophyciniol (146; R¹ = H, R² = Me), and parfumidine (?) from 'Herba Fumaria'²⁴³ are new isolated bases.



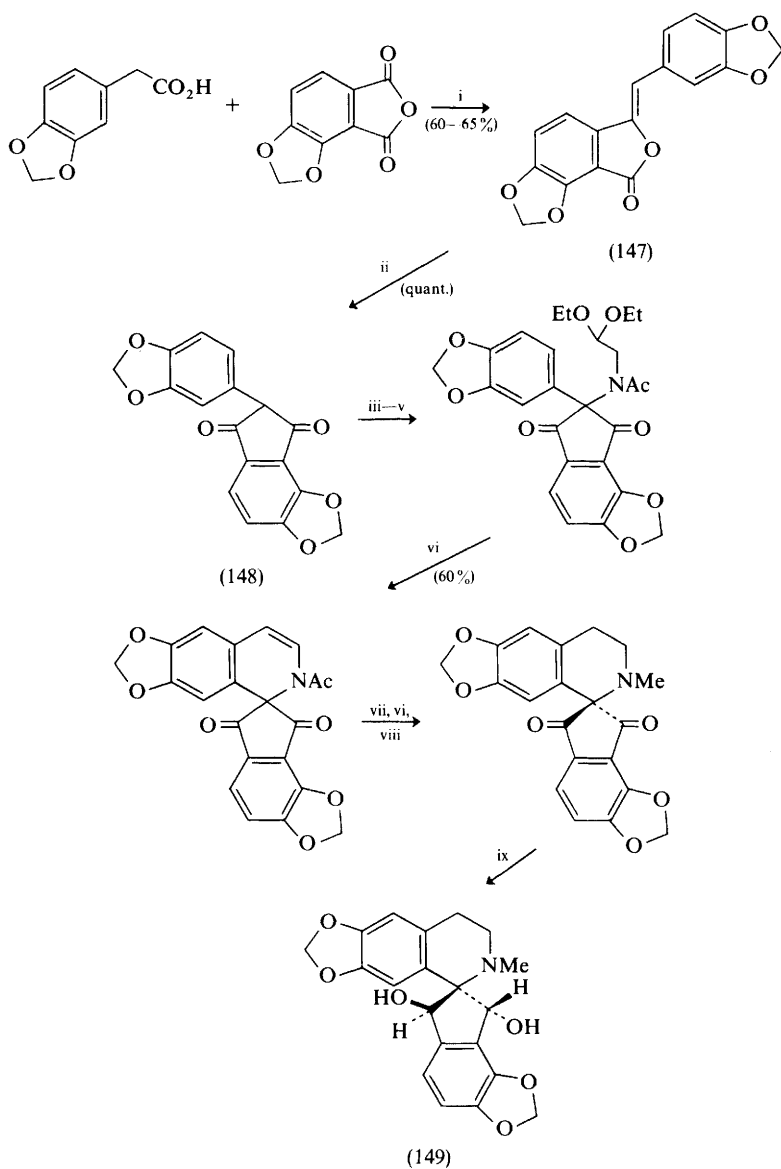
(146)

Examples of the application of N.O.E. experiments to the structural elucidation of spirobenzylisoquinoline alkaloids form part of a general review on the subject.²⁵²

Several syntheses of spirobenzylisoquinoline alkaloids based on an 'indanone' approach have been developed (see Vol. 3 of these Reports). This year marks the introduction of two new approaches to these interesting molecules. In one of these (Scheme 21),³¹³ a synthesis of (\pm)-ochroberine (149) has been achieved. A Perkin condensation is used to derive the phthalide (147), which upon base-catalysed rearrangement gives the indane-1,3-dione (148). In the remaining steps leading to (\pm)-ochroberine (149), the slight modification of the Bobbitt isoquinoline synthesis and the high degree of stereospecificity in the ultimate step are to be noted.

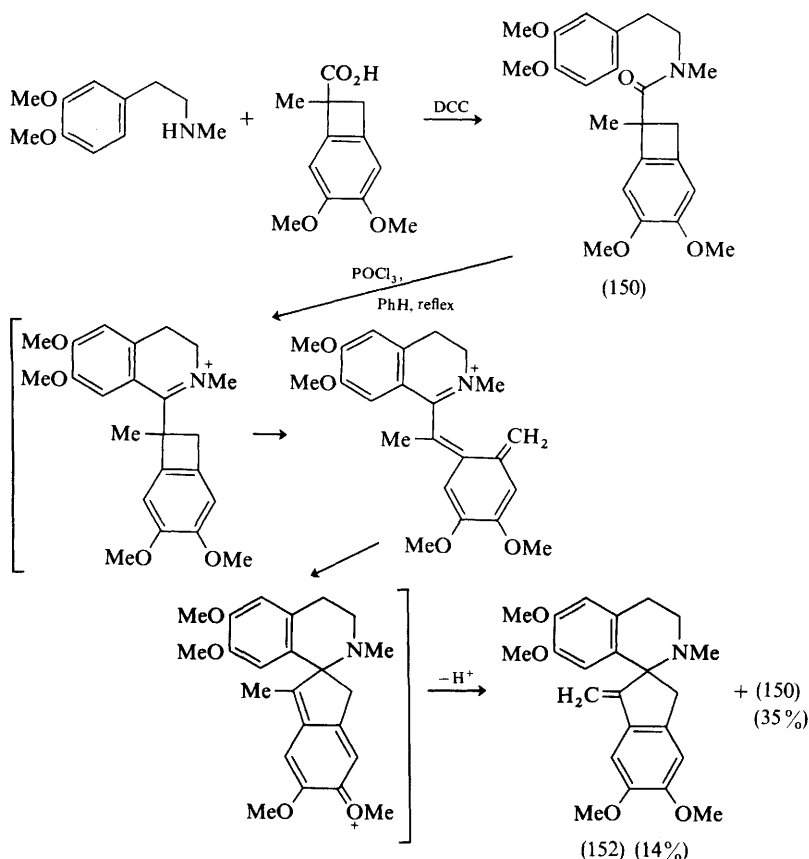
³¹² J. Kobor and K. Koczka, *Szegedi Tanárképző Főiskola Tud. Közlem.*, 1969, 185 (*Chem. Abs.*, 1972, 77, 151 861x).

³¹³ N. E. Cundasawmy and D. B. MacLean, *Canad. J. Chem.*, 1972, 50, 3028.



Reagents: i, NaOAc, 240–250 °C; ii, NaOMe, MeOH; iii, Br₂, HOAc; iv, H₂NCH₂-CH(OEt)₂, Et₂O; v, Ac₂O, pyridine; vi, 6N-HCl, EtOH, H₂O; vii, H₂, Pt, HOAc; viii, HCHO, HCO₂H; ix, NaBH₄, EtOH.

Scheme 21



Scheme 22

The other approach involves, as the key step, the thermal rearrangement of a benzocyclobutenyl derivative (150) to the spirobenzylisoquinoline (152), a compound not yet isolated from natural sources (Scheme 22).³¹⁴ It is interesting to note that the mechanistic postulate involves an intermediate (151) which corresponds closely to one which has been proposed as a biogenetic model for the spirobenzylisoquinolines (see Vols. 2 and 3 of these Reports).

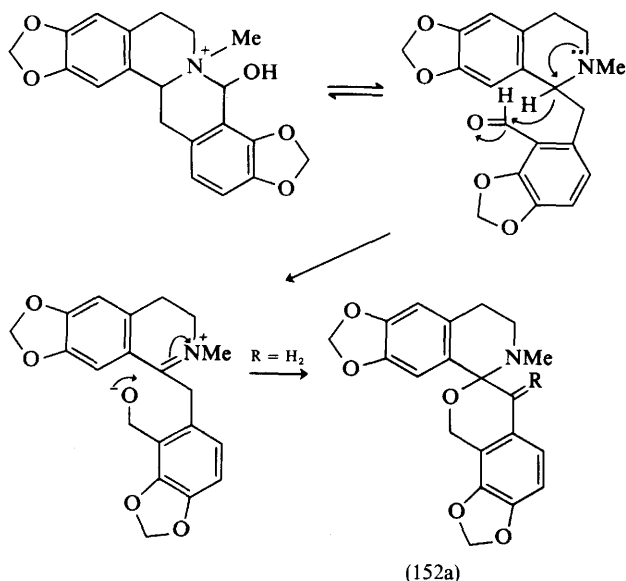
17 Alkaloids from *Hypocoum erectum*

Structures (152a; R = H₂) and (152a; R = O) have been proposed for hypecorine and hypecorinine, respectively, isolated from *Hypocoum erectum*.³¹⁵ Assuming

³¹⁴ T. Kametani, T. Takahashi, and K. Ogasawara, *Tetrahedron Letters*, 1972, 4847.

³¹⁵ L. D. Yakhontova, M. N. Komarova, M. E. Perel'son, K. F. Blinova, and O. N. Tolkachev, *Khim. prirod. Soedinenii*, 1972, 624 (*Chem. Abs.*, 1973, **78**, 108 177n).

that these structures are correctly assigned and that the alkaloids are not artifacts, it is intriguing to speculate upon their biogenetic relationship with protoberberine and/or spirobenzylisoquinoline bases. For example, the sequence outlined in Scheme 23 involving an intramolecular Cannizzaro-type reaction may be envisaged.



Scheme 23

18 Ipecacuanha Alkaloids

A personal account of significant synthetic work on emetine (153; $R = Me$) is not readily accessible.³¹⁶

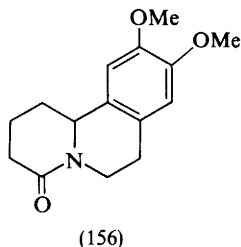
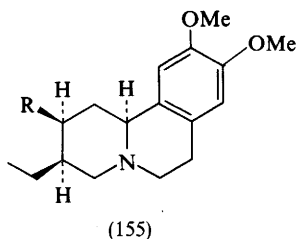
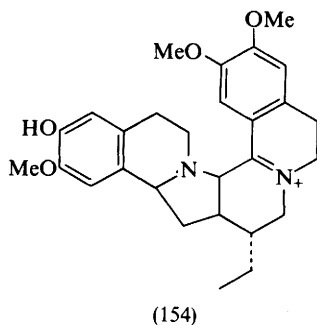
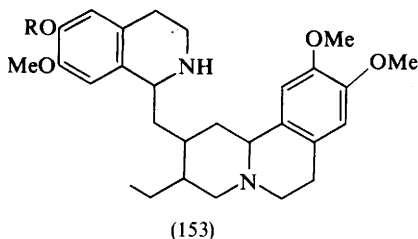
Emetine and cephaeline have been obtained from *Cephaelis ipecacuanha*, a species indigenous to Brazil but cultivated in Burma for the isolation work.³¹⁷ A method for emetine extraction from buffered aqueous solutions using fatty acid-organic solvent mixtures has been developed.¹⁹⁹

Treatment of cephaeline (153; $R = H$) with a large excess of mercuric acetate gave the cyclized product (154); with two equivalents of $Hg(OAc)_2$, only the quinolizidinium salt of (153; $R = H$) was obtained.³¹⁸

³¹⁶ C. Szantay, *Kem. Kozlem.*, 1971, **36**, 37 (*Chem. Abs.*, 1971, **75**, 110 470j).

³¹⁷ T. T. Ohn, Y. Y. Khaing, M. M. Gale, and M. Thein, *Union Burma J. Sci. Technol.*, 1970, **3**, 251 (*Chem. Abs.*, 1973, **78**, 108 223z).

³¹⁸ K. A. Kovar, P. Andreas, and H. Auterhoff, *Arch. Pharm. (Weinheim)*, 1972, **305**, 940.



A number of benzoquinolizidine-type compounds (155) which are potential intermediates for emetine have been prepared.³¹⁹ A standard synthesis of the lactam (156) has been described.³²⁰

The recommendations for official methods of analysis of ipecac alkaloids are available.¹⁶ Chromatographic,⁴⁶ u.v. spectrophotometric,^{321,322} and photodensitometric³²³ methods for determination of ipecac preparations have been reported.

Confirmation of the irreversibly inhibiting effects of emetine on RNA synthesis has been received.^{324,325} However, certain structural analogues of emetine have been found to show minimal effects on protein synthesis.³²⁶ The cardiotoxicity of emetine has also been studied.³²⁷

³¹⁹ M. Barczai-Beke, G. Dornyei, J. Tamas, and C. Szantay, *Chem. Ber.*, 1972, **105**, 3244; M. Barczai-Beke, G. Dornyei, J. Tamas, and C. Szantay, *Magyar Kém. Folyóirat*, 1973, **79**, 154 (*Chem. Abs.*, 1973, **78**, 159 940p).

³²⁰ B. Pecherer, F. Humiec, and A. Brossi, *Synthetic Comm.*, 1972, **2**, 315.

³²¹ E. Smith, M. F. Sharkey, and J. Levine, *J. Assoc. Offic. Analyt. Chemists*, 1971, **54**, 609.

³²² M. F. Sharkey, E. Smith, and J. Levine, *J. Assoc. Offic. Analyt. Chemists*, 1971, **54**, 614.

³²³ V. Massa, F. Gal, P. Susplugas, and G. Maestre, *Trav. Soc. Pharm. Montpellier*, 1970, **30**, 301 (*Chem. Abs.*, 1971, **75**, 25 448p).

³²⁴ Z. Gilead and Y. Becker, *European J. Biochem.*, 1971, **23**, 143.

³²⁵ N. Entner and A. P. Grollman, *J. Protozool.*, 1973, **20**, 160 (*Chem. Abs.*, 1973, **78**, 80 561g).

³²⁶ G. Hite, A. P. Grollman, and S. Rosen, *J. Medicin. Chem.*, 1971, **14**, 885.

³²⁷ R. K. Morrison, D. E. Brown, E. K. Timmens, M. A. Nieglos, and C. D. Molins, U.S. Clearinghouse Fed. Sci. Tech. Inform., PB Rep. 1970, No. 195705, 226 pp. (*Chem. Abs.*, 1971, **75**, 47 357k).

19 Dimeric Benzylisoquinoline Alkaloids

A review on alkaloids which possess seven-membered oxygen rings briefly discusses insularine (157; R = Me) and insularioline (157; R = H).²³⁰

Table 9 Isolation of dimeric benzylisoquinoline alkaloids

Source	Alkaloid (Structure) ^a	Ref.
<i>Anisocyclea gradidieri</i>	12'-O-Demethyltrilobine ^b (158; R ¹ = R ² = H, R ³ = Me)	328
	Epistephanine ^b (159)	328
	Stebisimine (160)	328
	Trilobine (158; R ¹ = H, R ² = R ³ = Me)	328
<i>Berberis jaeschkeana</i> , <i>B. lycium</i> , <i>B. vulgaris</i>	Berberamine	237
<i>Cyclea</i> sp.	Tetrandrine	328a
<i>Daphnandra</i> sp.	NO-Dimethylmicranthine ^b [158; R ¹ = R ² = R ³ = Me, A and B are (R)]	329
	Fangchinoline ^b (161; R ¹ = R ³ = R ⁴ = Me, R ² = H)	329
	O-Methylmicranthine ^b [158; R ¹ = R ² = Me, R ³ = H, A and B are (R)]	329
	Nortenuipine	329
	Telobine [158; R ¹ = R ² = Me, R ³ = H, A is (S), B is (R)]	329
<i>Nemuaron vieillardii</i>	Nemuarine ^b (162)	122a, 330
<i>Pachygone pubescens</i>	Isotrilobine (163)	157
<i>Pycnarrhena australiana</i>	Berberamine	331
	Isotetrandrine (161; R ¹ = R ² = R ³ = R ⁴ = Me)	331
	2-N-Norberbamine ^b (161; R ¹ = R ³ = H, R ² = R ⁴ = Me)	331
	2-N-Borobamegine ^b (161; R ¹ = R ² = R ³ = H, R ⁴ = Me)	331
<i>P. ozantha</i>	NN-Bisnoraromoline (164; R ¹ = R ² = R ³ = R ⁴ = H)	332
	2-N-Norobamegine	332
<i>Sanguinaria canadensis</i>	Sanguidimerine ^b (165)	333

³²⁸ E. Schlittler and N. Weber, *Helv. Chim. Acta*, 1972, **55**, 2061.

^{328a} C. Goepel, S. Von Kuerten, T. Yupraphat, P. Pachaly, and F. Zymalkowski, *Planta Med.*, 1972, **22**, 402.

³²⁹ I. R. C. Bick, J. B. Bremner, H. M. Leow, and P. Wiriyachitra, *J. C. S. Perkin I*, 1972, 2884.

³³⁰ I. R. C. Bick, H. M. Leow, and N. W. Preston, *J. C. S. Chem. Comm.*, 1972, 980.

³³¹ A. A. Sioumis and V. N. Vashist, *Austral. J. Chem.*, 1972, **25**, 2251.

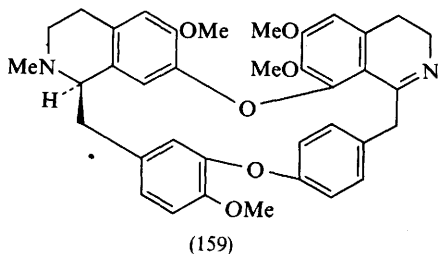
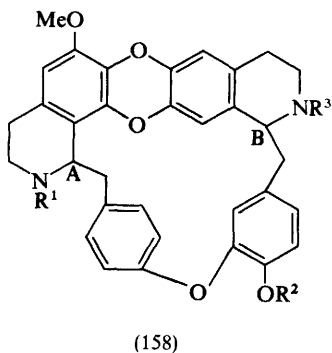
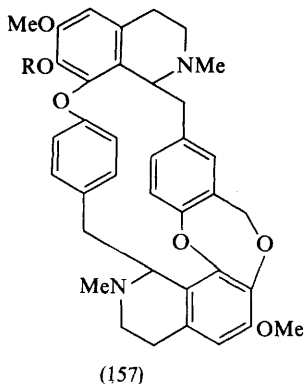
³³² J. W. Loder and R. H. Nearn, *Austral. J. Chem.*, 1972, **25**, 2193.

³³³ M. Tin-Wa, H. H. S. Fong, D. J. Abraham, J. Trojanek, and N. R. Farnsworth, *J. Pharm. Sci.*, 1972, **61**, 1846.

Table 9—continued

Source	Alkaloid (Structure) ^a	Ref.
<i>Stephania japonica</i>	Stepinonine ^b (166)	334
<i>Thalictrum minus</i> , race B	Adiantifoline	129
	Thalicarpine	129
<i>T. polygamum</i>	Thalictrogamine ^b (167; R = H)	335
	Thalictropine ^b (167; R = Me)	335
<i>T. rugosum</i>	Alkaloid D ^c	247
	Obamegine (161; R ¹ = R ⁴ = Me, R ² = R ³ = H)	247
	Thalidasine	247
	Thalrugosidine ^b (168)	247
	Thalrugosine ^b (161; R ¹ = R ³ = R ⁴ = Me, R ² = H)	247
<i>Tiliacora funifera</i>	Nortiliacorine A (Isotiliarine) (169; R ¹ , R ² = Me, H or vice versa; R ³ , R ⁴ = Me, H or vice versa)	336
	Nortiliacorinine A (\equiv Pseudotiliarine) (169; R ¹ , R ² = Me, H or vice versa; R ³ , R ⁴ = Me, H or vice versa)	336

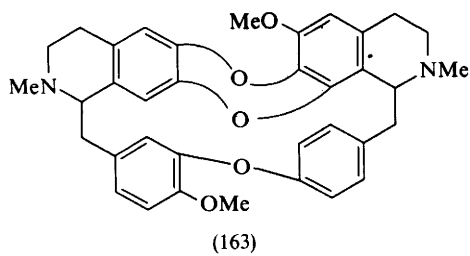
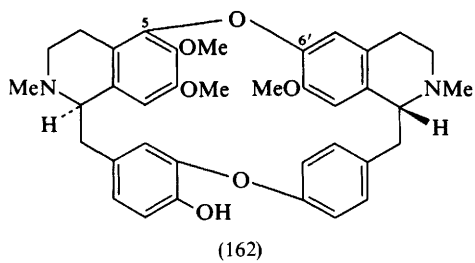
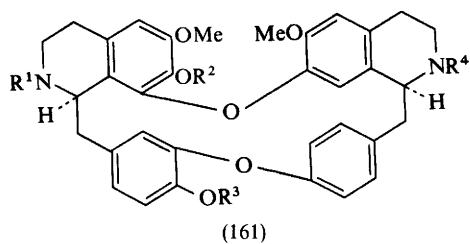
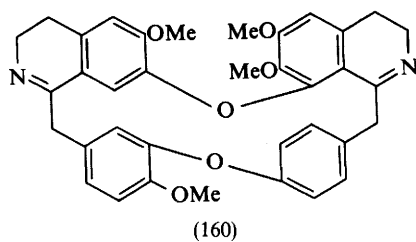
^a See footnote (a), Table 3; ^b New alkaloid; ^c m.p. 197 °C, identical to alkaloid previously isolated from *T. rochebrunianum*.

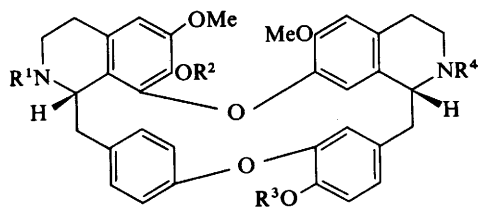


³³⁴ T. Ibuka, T. Konoshima, and Y. Inubushi, *Tetrahedron Letters*, 1972, 4001.

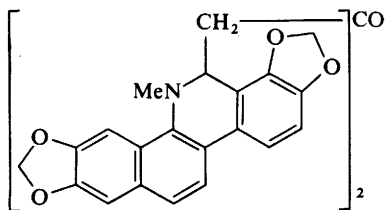
³³⁵ M. Shamma and J. L. Moniot, *Tetrahedron Letters* 1973, 775.

³³⁶ A. N. Tackie, D. Dwuma-Badu, J. E. Knapp, and P. L. Schiff, jun., *Phytochemistry*, 1973, 12, 203.

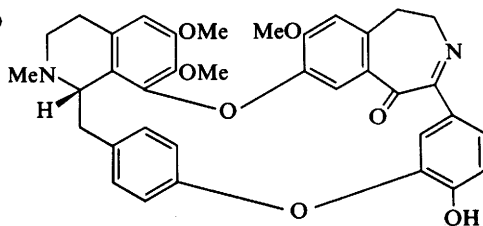




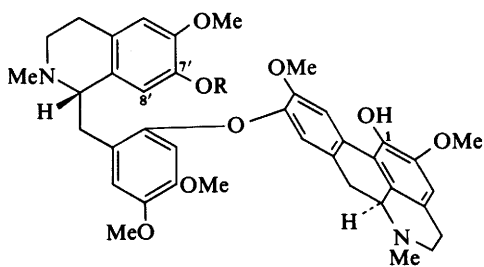
(164)



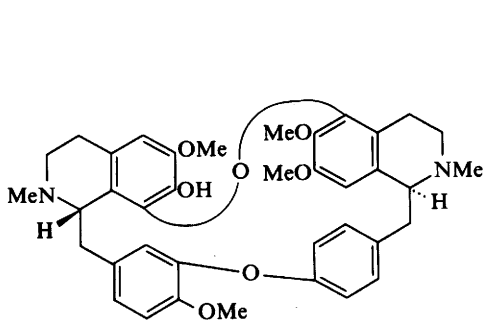
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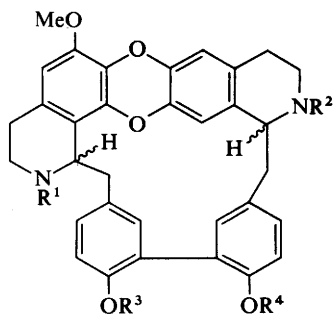
(166)



(167)



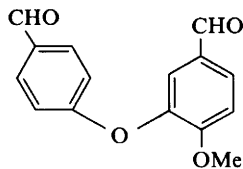
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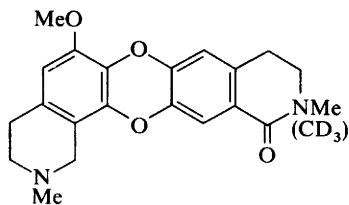
(169)

Sources of alkaloids are listed in Table 9.³²⁸⁻³³⁶ (-)-Epistephanine (159) from *Anisocyclea gradidieri* was identified by comparison of its spectral properties and its specific rotation with the known (+)-epistephanine.³²⁸ 12'-*O*-Demethyl-trilobine (158; $R^1 = R^2 = H$, $R^3 = Me$), the other alkaloid isolated from *A. gradidieri*, was converted by treatment with diazomethane into trilobine (158; $R^1 = H$, $R^2 = R^3 = Me$), which upon reductive methylation with formic acid-formaldehyde reagent gave isotrilobine (158; $R^1 = R^2 = R^3 = Me$).

The structure of *O*-methylmicranthine (158; $R^1 = R^2 = Me$, $R^3 = H$), isolated from an as yet unnamed *Daphnandra* species, was methylated to give *NO*-dimethylmicranthine (158; $R^1 = R^2 = R^3 = Me$), which also turned out to be a minor component of the alkaloidal extract.³²⁹ The latter had mass and n.m.r. spectra identical with those of isotrilobine [158; $R^1 = R^2 = R^3 = Me$, A and B are (S)] but it showed a specific rotation of opposite sign. *NO*-Dimethylmicranthine is thus the enantiomer in which A and B are (R) of (158; $R^1 = R^2 = R^3 = Me$), and since this isomer had been previously synthesized, a direct comparison was carried out for confirmation purposes. Comparison of *N*-methyl chemical shifts in the n.m.r. spectra of trilobine [158; $R^1 = H$, $R^2 = R^3 = Me$, A and B are (S)] and *O*-methylmicranthine [158; $R^1 = R^2 = Me$, $R^3 = H$, A and B are (R)] clarified the different location of the *N*-methyl functions in these two alkaloids. Similar spectral, specific rotation, and chemical relationships were used to assign the structure of telobine [158; $R^1 = R^2 = Me$, $R^3 = H$, A is (S), B is (R)], a diastereoisomer of *O*-methylmicranthine, except that, in addition, a photo-oxidative degradation was used in order to locate the secondary amine function of telobine. Application of this reaction, now a well-established method for dimeric benzylisoquinoline degradation (*cf.* Vol. 3 of these Reports for another example), on partially deuteriated *N*-methyltelobine (158; $R^1 = R^2 = Me$, $R^3 = \text{partial } CD_3$) gave the dialdehyde (170) and a product which was reduced by sodium borohydride to the lactam (171). The same two products were obtained by a parallel degradation sequence on partially deuteriated *NO*-dimethylmicranthine (158; $R^1 = R^2 = Me$, $R^3 = \text{partial } CD_3$). Thus the structural identity of *O*-methylmicranthine and telobine was established. An additional important facet of this report³²⁹ is the description of details regarding the reassignment of structure to micranthine, one of the earliest alkaloids isolated from the *Daphnandra* genus. On the basis of spectroscopic and chemical evidence, micranthine is represented by [158; $R^1 = Me$, $R^2 = R^3 = H$, A and B are (R)].



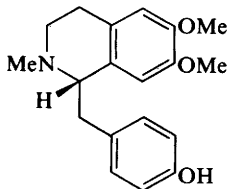
(170)



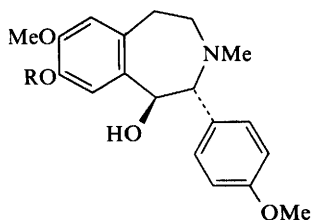
(171)

Nemuarine (162) from *Nemuaron vieillardii* is a 5-6'-linked dimeric alkaloid, a structural type not previously encountered in Nature.^{122a} The structures of 2-*N*-norberbamine (161; $R^1 = R^3 = H, R^2 = R^4 = Me$) and 2-*N*-norobamegine (161; $R^1 = R^2 = R^3 = H, R^4 = Me$), isolated from *Pycnarrhena australiana*, are based on extensive spectroscopic data and their methylation to berbamine (161; $R^1 = R^2 = R^4 = Me, R^3 = H$) and obamegine (161; $R^1 = R^4 = Me, R^2 = R^3 = H$), respectively.³³¹ Similarly, *NN*-bisnoraromoline (164; $R^1 = R^2 = R^3 = R^4 = H$) from *P. ozantha* was chemically correlated with obamegine.³³²

The dimeric benzophenanthridine alkaloid sanguidimerine (165) isolated from *Sanguinaria canadensis* is the fourth representative of this structural type; speculation has been advanced that some of the monomeric alkaloids may be artifacts resulting from degradation of the dimers under the previously used harsh isolation conditions.³³³ Sanguidimerine (165) was synthesized by base-catalysed condensation of the monomeric alkaloid with acetonedicarboxylic acid. Stepinonine (166), isolated from *Stephania japonica*, is an interesting first example of a benzyloisoquinoline-benzazepine dimer.³³⁴ Reduction of stepinonine with sodium borohydride gave a tetrahydro-derivative which was methylated (formalin- $NaBH_4$, followed by CH_2N_2) and subjected to sodium in liquid ammonia degradation to give (*S*)-armepavine (172) and the benzazepinol (173; $R = H$). The latter was ethylated with diazoethane to give (173; $R = Et$), which was synthesized by an unequivocal route. The position of the hydroxy-group and the location of the diphenyl ether linkage were established by classical degradation experiments. An interesting general observation was made regarding conformational properties of benzyloisoquinoline-aporphine dimers in connection with the structural elucidation of thalictrogamine (167; $R = H$) and thalictropine (167; $R = Me$) isolated from *Thalictrum polygamum*.³³⁵ Apparently as a result of hydrogen-bonding of the C(7')-hydroxy-group with either the C(1)-oxygen or the aporphine nitrogen functions, in (167; $R = H$) the C(8')-aromatic proton resonance is shifted downfield by about 0.2 p.p.m., thus serving as a diagnostic tool for the presence of the C(7')-hydroxy-group. Nortiliacorine A from *Tiliacora funifera*, upon treatment with formaldehyde-sodium borohydride, gave tiliacorine, as shown by direct comparison.³³⁶ Nortiliacorine A is thus an *N*-demethyltiliacorine but the exact structure must await the definite formulation of tiliacorine as (169; $R^1 = R^2 = R^3 = Me, R^4 = H$) or (169; $R^1 = R^2 = R^4 = Me, R^3 = H$).

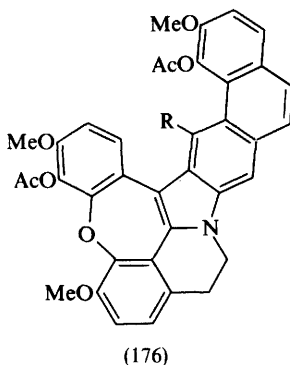
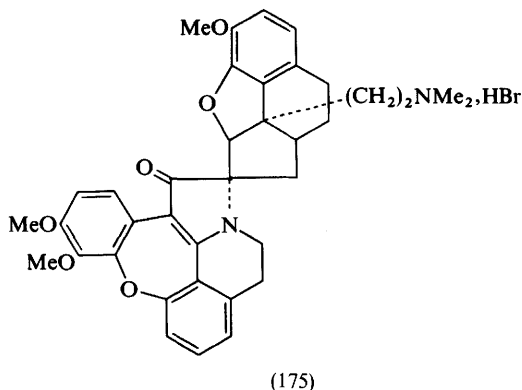
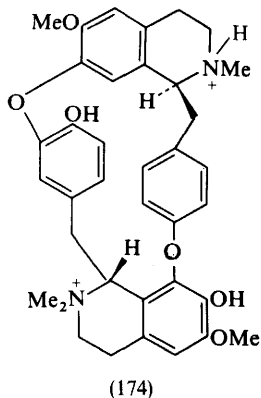


(172)



(173)

As a result of the neuromuscular blocking action of tubocurarine chloride (174) and related derivatives, recent work has been aimed at the determination of conformational properties of these alkaloids. The comparison of the *X*-ray crystal structures of (+)-tubocurarine chloride^{337,338} (174) and its *OO'**N*-trimethyl derivative³³⁹ indicates a great deal more conformational flexibility in the latter compound. The preliminary *X*-ray-crystallographic analysis of the related alkaloids warifteine and dimethylwarifteine has also been reported.³³⁸ Information regarding the conformation of (+)-tubocurarine (174) in solution has been obtained from variable-temperature n.m.r. studies.³⁴⁰



Details of the studies on the structure and absolute configuration of compound (175), the key degradation product which led to the structural elucidation of the unusual morphine-curarine dimer cancentrine (*cf.* Vols. 2 and 3 of these Reports),

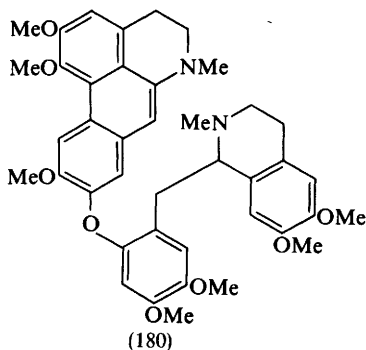
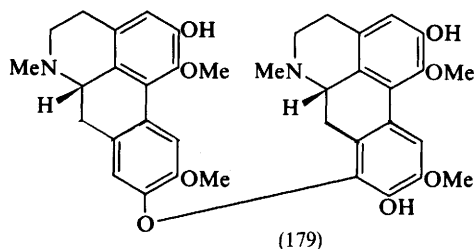
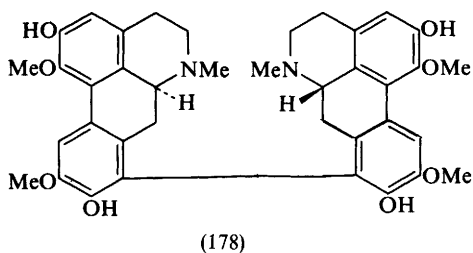
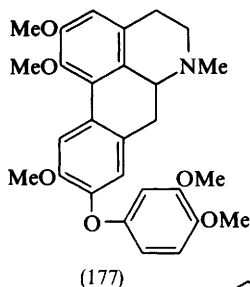
³³⁷ P. W. Coddington and M. N. G. James, *J. C. S. Chem. Comm.*, 1972, 1174.

³³⁸ C. Gorinsky, R. A. Palmer, C. D. Reynolds, and R. P. Bywater, *J. Cryst. Mol. Struct.*, 1971, 1, 307.

³³⁹ H. M. Sobell, T. D. Sakore, S. S. Tavale, F. G. Canepa, P. Pauling, and T. J. Petcher, *Proc. Nat. Acad. Sci. U.S.A.*, 1972, 69, 2212.

³⁴⁰ R. S. Egan, R. S. Stanaszek, and D. E. Williamson, *J. C. S. Perkin II*, 1973, 716.

are now available.³⁴¹ It is interesting to note that the absolute stereochemistry of the morphine fragment of (175) is opposite to that found in morphine. The reaction of canconrine methiodide with acetic anhydride-sodium acetate gave two products whose complicated structures remained unknown until the structure of the alkaloid was deduced from the degradation product (175). U.v. and n.m.r. spectral analysis of the two acetolysis products and synthetic model compounds together with reasonable mechanistic rationale has resulted in the formulations (176; R = H) and [176; R = CH₂CH₂N(Me)Ac] for these compounds.³⁴² Some of the information obtained from N.O.E. experiments which aided in the structural elucidation of canconrine has been summarized in a review.²⁵²



³⁴¹ G. R. Clark and G. J. Palenik, *J. C. S. Perkin II*, 1972, 1219.

³⁴² R. Rodrigo, R. H. F. Manske, V. Smula, D. B. MacLean, and L. Baczynskyj, *Canad. J. Chem.*, 1972, **50**, 3900.

A potential precursor (177) for the synthesis of thalicarpine has been prepared by a new general route which has been outlined in Section 7 (Scheme 4).^{140,141} Treatment of (*S*)-boldine with horseradish peroxidase and hydrogen peroxide gives the dimeric aporphine bases bisboldine (178) and bisboldine ether (179) in 12% and 8% yields, respectively.³⁴³ Oxidation of the benzyloquinoline-aporphine dimer thalicarpine with iodine and sodium acetate in refluxing dioxan produces dehydrothalicarpine (180) in 45% yield.¹⁴⁸

The anti-inflammatory activity of a number of alkaloids has been studied: cycleanine,^{156a} dauricine,^{156a} hernandesine (thalicsimine),³⁴⁴⁻³⁴⁶ dihydrothal-simine,^{345,346} thalsimine,^{345,346} thalmine,^{346,347} *O*-methylthalicberine,³⁴⁷ thalic-trinine,³⁴⁶ fetidine,^{346,348} thalfetidine,³⁴⁸ *O*-methylthalfetidine,³⁴⁸ and thaliso-pine.³⁴⁸ In addition, the tuberculostatic activity of tetrandrine³⁴⁹ and the curare-like effects of *d*-tubocurarine³⁵⁰ and cycleanine dimethiodide^{156a} have been studied.

³⁴³ K. L. Stuart and A. Callender, *Rev. Latinoamer. Quim.*, 1972, 3, 19 (*Chem. Abs.*, 1972, 77, 126 904f).

³⁴⁴ F. Sadritdinov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 117 (*Chem. Abs.*, 1973, 78, 79 629d).

³⁴⁵ N. Tulyaganov and F. Sadritdinov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 132 (*Chem. Abs.*, 1973, 78, 79 631y).

³⁴⁶ F. Sadritdinov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 122 (*Chem. Abs.*, 1973, 78, 79 555b).

³⁴⁷ F. Sadritdinov and M. B. Sultanov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 120 (*Chem. Abs.*, 1973, 78, 66 916v).

³⁴⁸ I. Khamdamov, F. Sadritdinov, and M. B. Sultanov, *Farmakol. Alkaloidov Serdechnykh Glikozidov*, 1971, 135 (*Chem. Abs.*, 1972, 77, 122 095v).

³⁴⁹ S. A. Vichkanova, L. V. Makarova, and L. F. Solov'eva, *Farmakol. Toksikol. (Moscow)*, 1973, 36, 74 (*Chem. Abs.*, 1973, 78, 106 079h).

³⁵⁰ J. I. Hubbard and D. F. Wilson, *J. Physiol. (London)*, 1973, 228, 307.

1 Introduction

Three extensive reviews on the aporphine alkaloids have appeared in the past.¹⁻³ Recently, three shorter chapters on this subject have also been published.⁴⁻⁶ This chapter deals mostly with developments since 1967, that is since the last comprehensive review of the field.³

More than forty new aporphines have been characterized during the past seven years. Noteworthy among these are variabiline, which possesses a dibenzyl-amino-group as an aromatic substituent,⁷ thalphenine, which incorporates the rare methylenoxy bridge,⁸ and steporphine⁹ and cataline,¹⁰ which have a hydroxyl substituent at C-4. Several aporphines are now known in their $\Delta^{6(7)}$ -dehydro form including dehydroglaucine,¹¹ dehydrodicentrine,¹² dehydro-ocopodine,¹³ and dehydro-ocoteine.¹⁴ There is also a possibility that didehydro-ocoteine may accompany dehydro-ocoteine in nature.¹⁴

Efficient methods for the oxidation of aporphines to dehydroaporphines or oxoaporphines are now available.¹⁵ Oxidation of magnoflorine methine has

¹ R. H. F. Manske, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1954, Vol. 4, p. 119.

² M. Shamma and W. A. Slusarchyk, *Chem. Rev.*, 1964, **64**, 59.

³ M. Shamma, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1967, Vol. 9, p. 1.

⁴ M. P. Cava and A. Venkateswarlu, 'Annual Reports of Medicinal Chemistry, 1968', ed. C. K. Cain, Academic Press, New York, 1969, p. 331.

⁵ R. Charubala and B. R. Pai, in 'Some Recent Developments in the Chemistry of Natural Products', ed. S. Rangaswami and N. V. Subba Rao, Prentice-Hall of India, New Delhi, 1972, p. 214.

⁶ M. Shamma, 'The Isoquinoline Alkaloids', Academic Press, New York, and Verlag Chemie, Weinheim, 1972, p. 194.

⁷ M. P. Cava, M. Behforouz, and M. J. Mitchell, *Tetrahedron Letters*, 1972, 4647.

⁸ M. Shamma, J. L. Moniot, S. Y. Yao, and J. A. Stanko, *J.C.S. Chem. Comm.*, 1972, 408.

⁹ J. Kunitomo, Y. Okamoto, E. Yuge, and Y. Nagai, *Tetrahedron Letters*, 1969, 3287.

¹⁰ I. Ribas, J. Sueiras, and L. Castedo, *Tetrahedron Letters*, 1972, 2033.

¹¹ H. G. Kiryakov, *Chem. and Ind.*, 1968, 1807; H. G. Kiryakov and P. Panov, *Doklady Bolg. Akad. Nauk*, 1969, **22**, 1019 (*Chem. Abs.*, 1970, **72**, 51 776b).

¹² M. P. Cava, Y. Watanabe, K. Bessho, M. J. Mitchell, A. I. daRocha, B. Hwang, B. Douglas, and J. A. Weisbach, *Tetrahedron Letters*, 1968, 2437.

¹³ M. P. Cava and A. Venkateswarlu, *Tetrahedron*, 1971, **27**, 2639.

¹⁴ F. Baralle, N. Schvarzberg, M. Vernengo, and J. Comin, *Experientia*, 1972, **28**, 875.

¹⁵ M. P. Cava, A. Venkateswarlu, M. Srinivasan, and D. L. Edie, *Tetrahedron*, 1972, **28**, 4299.

allowed the chemical conversion of magnoflorine into the dilactonic alkaloid taspine.¹⁶

Some of the photochemical routes to the aporphines have been improved to the point where they have become superior to the classical routes involving Pschorr cyclization.¹⁷⁻¹⁹ Other very promising approaches to the aporphines include the oxidative cyclization of monophenolic benzyloisoquinolines using vanadium oxyfluoride²⁰ or lead tetra-acetate.²¹

Impressive progress has been made towards an understanding of aporphine biosynthesis in plants, and three such routes have now been detected. These proceed from tetrahydrobenzyloisoquinolines and involve either direct phenolic oxidative coupling,²²⁻²⁶ or the intermediacy of proaporphines^{27,28} or neo-proaporphines.²⁹

An exciting development has been the discovery that (-)-apomorphine can be used in the treatment of Parkinsonism.^{30,31} This finding has triggered increasing interest in the chemistry and pharmacology of aporphines in general.

All of the above topics are covered below. In particular, Section 7 contains a complete listing of all naturally occurring aporphines arranged in order of increasing complexity of the substituents. Counting enantiomers as different compounds, one can count 107 aporphines, not including the racemates of isoboldine and

¹⁶ M. Shamma and J. L. Moniot, *Chem. Comm.*, 1971, 1065.

¹⁷ M. P. Cava, P. Stern, and K. Wakisaka, *Tetrahedron*, 1973, **29**, 2249.

¹⁸ S. M. Kupchan, J. L. Moniot, R. M. Kanojia, and J. B. O'Brien, *J. Org. Chem.*, 1971, **36**, 2413.

¹⁹ R. J. Spangler and D. C. Boop, *Tetrahedron Letters*, 1971, 4851.

²⁰ S. M. Kupchan and A. J. Liepa, *J. Amer. Chem. Soc.*, 1973, **95**, 4062. For a somewhat related transformation see M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Amer. Chem. Soc.*, 1973, **95**, 612.

²¹ O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Comm.*, 1971, 1533. For another route to C-4 oxygenated aporphines see M. P. Cava and I. Noguchi, *J. Org. Chem.*, 1973, **38**, 60.

²² G. Blaschke, *Arch. Pharm.*, 1968, **301**, 432.

²³ G. Blaschke, *Arch. Pharm.*, 1970, **303**, 358.

²⁴ E. Brochmann-Hanssen, C.-C. Fu, and L. Y. Misconi, *J. Pharm. Sci.*, 1971, **60**, 1880.

²⁵ E. Brochmann-Hanssen, C.-H. Chen, H.-C. Chiang, and K. McMurtrey, *J.C.S. Chem. Comm.*, 1972, 1269.

²⁶ E. Brochmann-Hanssen, C.-H. Chen, H.-C. Chiang, C.-C. Fu, and H. Nemoto, *J. Pharm. Sci.*, 1973, **62**, 1291.

²⁷ A. R. Battersby, R. T. Brown, J. H. Clements, and G. G. Iverach, *Chem. Comm.*, 1965, 230; A. R. Battersby, T. J. Brocksom, and R. Ramage, *ibid.*, 1969, 464; see also R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1, p. 19.

²⁸ D. H. R. Barton, D. S. Bhakuni, G. M. Chapman, and G. W. Kirby, *Chem. Comm.*, 1966, 259; *J. Chem. Soc. (C)*, 1967, 2134.

²⁹ A. R. Battersby, J. L. McHugh, J. Staunton, and M. Todd, *Chem. Comm.*, 1971, 985; see also J. Staunton, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1972, Vol. 2, p. 12.

³⁰ R. S. Schwab, L. V. Amador, and J. Y. Lettvin, *Trans. Amer. Neurol. Assoc.*, 1951, **76**, 251.

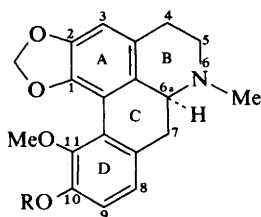
³¹ G. C. Cotzias, P. S. Papavasiliou, C. Fehling, B. Kaufman, and E. Mena, *New England J. Medicine*, 1970, **282**, 31; S. Duby, G. C. Cotzias, A. Steck, and P. S. Papavasiliou, *Fed. Proc.*, 1971, **30**, 216; S. Duby, G. C. Cotzias, A. Steck, and P. S. Papavasiliou, as quoted in *Chem. Eng. News*, April 19, 1971, p. 49.

wilsonirine. This places the aporphines together with the bisbenzylisoquinolines as the most numerous subgroup among the isoquinoline alkaloids.

In the discussions which follow, n.m.r. spectra were obtained in CDCl_3 unless indicated otherwise. Oxoaporphines are not covered since they have been previously reviewed.^{31a}

2 New Alkaloids

***O*-Methylbulbocapnine.**—*O*-Methylbulbocapnine (1), $\text{C}_{20}\text{H}_{21}\text{O}_4\text{N}$, m.p. 129–130 °C, $[\alpha]_D^{26} + 248^\circ$ ($c = 0.67$, CHCl_3), was obtained in small yield from the trunk and leaves of *Lindera oldhamii* Hemsl. (Lauraceae).³² The methiodide melts 244–245 °C (decomp.), $[\alpha]_D^{29} + 143^\circ$ ($c = 0.70$, MeOH). The u.v. spectrum of the free base, $\lambda_{\text{max}}^{\text{EtOH}}$ 236, 269, and 309 nm, is characteristic of that for a 1,2,10,11-tetrasubstituted aporphine. The methylenedioxy hydrogens appeared in the n.m.r. spectrum as a doublet of doublets, centred at δ 5.87 and 6.05 ($J_{\text{gem}} = 1$ Hz). The two methoxy-groups showed up as singlets at δ 3.77 and 3.87. Diazo-methane *O*-methylation of the known (+)-*N*-methylnandigerine (2) gave material identical with the new natural product in all respects.



(1) R = Me

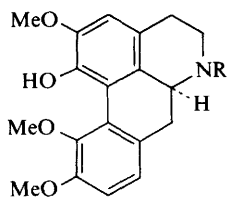
(2) R = H

Norcorydine.—A *Popowia* species, *Popowia* cf. *cyanocarpa* Laut. and K. Schum. (Annonaceae), native to New Guinea, has supplied a variety of aporphines, among which was found norcorydine (3), which could not be obtained in crystalline form, $\text{C}_{19}\text{H}_{21}\text{O}_4\text{N}$, methiodide m.p. 210–212 °C (acetone) and $[\alpha]_D + 135^\circ$ ($c = 0.04$, MeOH).³³ The 100 MHz n.m.r. spectrum of the alkaloid showed no *N*-methyl signal, but there were signals for three methoxy-groups, two of which were coincident in chemical shift at δ 3.90, while one gave a signal at δ 3.72 and could be assigned to the C-11 position. The signals for the three aromatic protons, a singlet at δ 6.68 (C-3 H) and a pair of AB doublets ($J = 8.0$ Hz) at δ 6.84 and 7.04, assigned to the C-9 H and C-8 H, respectively, indicated that the substituents were placed at C-1, 2, 10, and 11. *N*-Methylation by the formaldehyde-sodium

^{31a} M. Shamma and R. L. Castenson, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1973, Vol. 14, p. 225.

³² S.-T. Lu, S.-J. Wang, P.-H. Lai, C.-M. Lin, and L.-C. Lin, *J. Pharm. Soc. Japan*, 1972, **92**, 910.

³³ S. R. Johns, J. A. Lamberton, C. S. Li, and A. A. Sioumis, *Austral. J. Chem.*, 1970, **23**, 363.

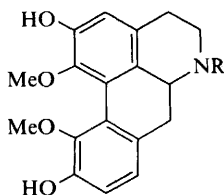


(3) R = H

(4) R = Me

borohydride method gave corydine (4), and further *N*-methylation with methyl iodide gave corydine methiodide.

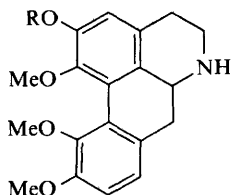
***N*-Methylhernovine.**—*N*-Methylhernovine (5) was obtained from *Croton wilsonii* Griseb. (Euphorbiaceae) and was characterized as the hydrochloride, $C_{19}H_{21}O_4N \cdot HCl$, m.p. 244—245 °C (decomp.), $[\alpha]_D^{23} + 209^\circ$ ($c = 0.55$, MeOH), λ_{max}^{EtOH} 218, 273, and 305 nm ($\log \epsilon$ 4.41, 4.02, and 3.63).³⁴ The alkaloid was found to be identical with the product obtained from the *N*-methylation of (+)-hernovine (6).



(5) R = Me

(6) R = H

10-*O*-Methylhernovine.—Another base found in *Croton wilsonii* Griseb. (Euphorbiaceae) is 10-*O*-methylhernovine (7), $C_{19}H_{21}O_4N$, m.p. 157—158 °C (decomp.), $[\alpha]_D^{17} + 188^\circ$ ($c = 1.0$, EtOH), λ_{max}^{EtOH} 220, 273, and 305 nm ($\log \epsilon$ 4.56, 4.11, and 3.70).³⁴ The n.m.r. spectrum showed three methoxyl singlets at δ 3.50, 3.60, and 3.82. The C-8 and C-9 protons appeared as a singlet at δ 6.91, and the C-3 proton singlet was relatively upfield at δ 6.63. The 1,2,10,11-tetrasubstituted



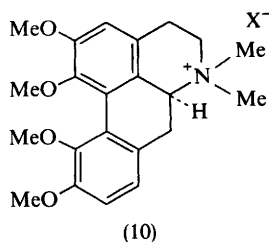
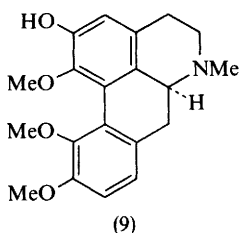
(7) R = H

(8) R = Me

³⁴ K. L. Stuart and C. Chambers, *Tetrahedron Letters*, 1967, 4135.

pattern was confirmed by *O*-methylation with diazomethane to give the known catalpifoline (8). The position of the phenolic group was established when it was found that the n.m.r. spectrum of the *ON*-diacetyl derivative shows a downfield shift (δ 6.63 \rightarrow 7.01) for the C-3 proton, consonant with the presence of an acetoxyl function at C-2.

***N*-Methyl-10-*O*-methylhernovine.**—*N*-Methyl-10-*O*-methylhernovine (9) is one of five phenolic aporphines found in *Croton wilsonii* Griseb. (Euphorbiaceae).³⁴ It was obtained as the hydrochloride salt, $C_{20}H_{23}O_4N \cdot HCl$, m.p. 218–219 °C (decomp.), $[\alpha]_D^{23} + 139^\circ$ ($c = 0.51$, MeOH). The u.v. spectrum of the base λ_{max}^{EtOH} 220, 273, and 304 nm ($\log \epsilon$ 4.55, 4.11, and 3.69) suggested a 1,2,10,11-substitution pattern, and indeed diazomethane *O*-methylation followed by treatment with methyl iodide gave *OO*-dimethylmagnoflorine iodide (10). *N*-Methyl-10-*O*-methylhernovine (9) could also be obtained by *N*-methylation of 10-*O*-methylhernovine (7), thus establishing the site of the phenolic function.

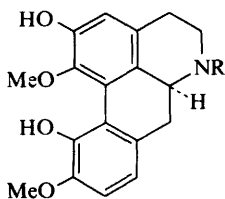


Lindcarpine.—Lindcarpine (11), isolated from the roots of *Lindera pipericarpa* Boerl (Lauraceae), analyses for $C_{18}H_{19}O_4N$, m.p. 195 °C (decomp.) (ethyl acetate), $[\alpha]_D^{22} + 166^\circ$ (EtOH), hydrochloride dihydrate salt m.p. 200 °C (dil. HCl).³⁵ The u.v. spectrum of the free base showed λ_{max}^{EtOH} 218, 267, and 303 nm ($\log \epsilon$ 4.57, 4.14, and 3.82). Although phenolic, it gave, like isocorydine, a negative ferric chloride test in ethanol. Additionally, the Gibb's test was positive whereas the Gaebel and Quastel tests were negative.

The n.m.r. spectrum in $[^2H_6]DMSO$ confirmed the presence of two methoxy-groups (δ 3.58 and 3.78) and three aromatic protons and the absence of an *N*-methyl function.

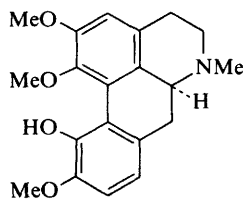
N-Methylation of lindcarpine with formaldehyde and sodium borohydride gave *N*-methyl-lindcarpine, m.p. 196 °C (decomp) (acetone-methanol), $[\alpha]_D^{22} + 222^\circ$ (MeOH), methiodide m.p. 187 °C (decomp) (aq. methanol). Both *N*-methyl-lindcarpine (12) and lindcarpine hydrochloride reacted with diazomethane to give (+)-isocorydine (13). This reaction together with the positive Gibb's test given by lindcarpine established the presence of a hydroxy-group at C-11, and consequently of a methoxy-group at C-1. Since lindcarpine gave a negative Quastel test for a catechol system, it was assigned structure (11).

³⁵ A. K. Kiang and K. Y. Sim, *J. Chem. Soc. (C)*, 1967, 282.



(11) R = H

(12) R = Me

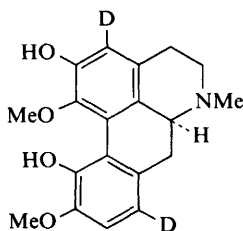


(13)

***N*-Methyl-lindcarpine.**—The title alkaloid was obtained from *Phoebe clemensii* Allen (Lauraceae), a rain-forest tree occurring in New Guinea, and was characterized independently from the previously mentioned lindcarpine (11).³⁶ *N*-Methyl-lindcarpine (12), $C_{19}H_{21}O_4N$, m.p. 198–200 °C (decomp) (benzene-chloroform), $[\alpha]_D + 160^\circ$ ($c = 0.21$, $CHCl_3$), λ_{max} 270 and 303 nm ($\log \epsilon$ 4.2 and 3.8), exhibited an n.m.r. spectrum with signals for an *N*-methyl group (δ 2.51) and two methoxy-groups (δ 3.63 for the C-1 methoxyl and 3.88 for the C-10 methoxyl). A one-proton singlet at δ 6.63 was assigned to the C-3 proton, and a sharp two-proton signal at δ 6.82 to the C-8 and C-9 protons, which coincide in chemical shift.

O-Methylation of *N*-methyl-lindcarpine (12) gave isocorydine (13). A catechol structure for *N*-methyl-lindcarpine could be discarded since the alkaloid with ferric chloride in ethanol gave a purple coloration which was completely discharged upon addition of a little water.

Reaction of the alkaloid with deuterium oxide at 135 °C afforded the dideuterio-derivative (14), which showed only one aromatic proton signal, as a singlet at δ 6.82, so that this proton must be located at C-9.



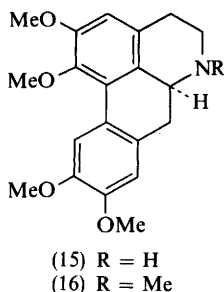
(14)

Norglaucine.—(+)-Norglaucine (15) accompanies (–)-dicentrine and (+)-duguetine in an incompletely characterized Brazilian *Duguetia* species (Annonaceae).³⁷ Norglaucine was obtained as the hydrobromide salt, $C_{20}H_{23}O_4N \cdot HBr$, m.p. 247–249 °C, $[\alpha]_D + 99^\circ$ ($c = 1$, EtOH), λ_{max}^{EtOH} 282 and 302 nm ($\log \epsilon$ 4.08 and 4.17). The n.m.r. spectrum of the salt in $[^2H_5]$ pyridine– D_2O revealed two

³⁶ S. R. Johns and J. A. Lamberton, *Austral. J. Chem.*, 1967, **20**, 1277.

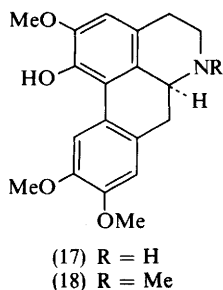
³⁷ C. Casagrande and G. Ferrari, *Farmaco, Ed. Sci.*, 1970, **25**, 442.

methoxy-groups at δ 3.86, one at δ 3.81, and one at δ 3.94. The three uncoupled protons were at δ 6.87 (C-3 H), δ 6.95 (C-8 H), and δ 8.47 (C-11 H). Treatment of norglaucine free base with formaldehyde and sodium borohydride yielded (+)-glaucine (16).



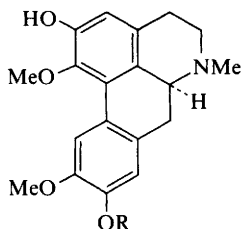
Wilsonirine (17).—Another alkaloid found in *Popowia cf cyanocarpa*, $C_{19}H_{21}NO_4$, was obtained as colourless needles, m.p. 108—110 °C, $[\alpha]_D + 47^\circ$ ($c = 0.13$, MeOH).³³ The 100 MHz n.m.r. spectrum showed three one-proton singlets at δ 8.09, 6.71, and 6.52, assignable to the C-11, C-8, and C-3 protons, respectively. Three methoxyl absorptions were nearly superimposed at δ 3.88, so that the alkaloid appeared to be (+)-1-hydroxy-2,9,10-trimethoxynor-aporphine. Indeed, *N*-methylation (formaldehyde–sodium borohydride) gave rise to (+)-thaliporphine (18), m.p. 191—192 °C, $[\alpha]_D + 46^\circ$ ($c = 0.08$, $CHCl_3$).

In point of fact, the structure determined for the *Popowia* alkaloid had already been assigned to an alkaloid from *Croton wilsonii* Griseb. (Euphorbiaceae), λ_{max}^{EtOH} 221, 271 sh, 281, and 306 nm ($\log \epsilon$ 4.45, 3.92, 4.02, and 4.02), but with m.p. 211—213 °C.³⁴ Both alkaloids showed identical solution i.r. spectra. On acetylation, they were converted into the *NO*-diacetyl derivatives, of which that from the *Popowia* alkaloid melted 243—246 °C and that from the *Croton* base melted 229—231 °C. It was then determined that wilsonirine from *Croton* is nearly racemic, with $[\alpha]_D + 5^\circ$ (MeOH). The occurrence of racemates is not a very common phenomenon among the aporphine alkaloids.



Predicentrine.—A number of 1,2,9,10- and 1,2,10,11-tetrasubstituted aporphines have been obtained from *Beilschmiedia podagrica* Kostermans (Lauraceae), among which was found the phenolic 2-hydroxy-1,9,10-trimethoxyaporphine, also called predicentrine (19), $C_{20}H_{23}O_4N$, HBr salt m.p. 200—205 °C (decomp) (MeOH) with $[\alpha]_D + 97^\circ$ ($c = 0.2$, EtOH) and λ_{max}^{EtOH} 283 and 302 nm ($\log \epsilon$ 4.17 and 4.18),^{4,38} The 100 MHz n.m.r. spectrum of the free base regenerated from the hydrobromide showed three-proton singlets at δ 3.52 (C-1 OMe) and at δ 3.83 and 3.87 (C-9 and C-10 OMe), as well as at δ 2.49 (NMe). One-proton singlets were present at δ 6.53 (C-3 H), 6.76 (C-8 H), and 7.96 (C-11 H). A slight broadening of the C-3 and C-8 proton signals by comparison with the signal from the C-11 proton arose from coupling to the *ortho*-situated benzylic methylene groups.

Proof that the hydroxy-group is at C-2 was obtained by heating a solution of the alkaloid in D_2O containing sodium hydroxide at 140 °C, which resulted in exchange of the C-3 hydrogen for deuterium since the n.m.r. spectrum now lacked the signal at δ 6.53 attributed to the C-3 proton. (+)-2-Hydroxy-1,9,10-trimethoxyaporphine had previously been obtained in the laboratory by the partial methylation of (+)-boldine (20) with diazomethane.³⁹



(19) R = Me

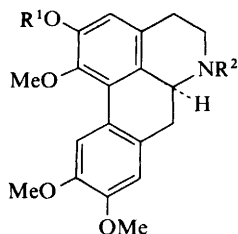
(20) R = H

Norpredicentrine (21).—This alkaloid, $C_{19}H_{21}O_4N$, accompanies predicentrine (19) in *B. podagrica*, and was actually isolated as its crystalline *N*-acetyl amide (22) containing one mole of methanol, m.p. 133—135 °C, $[\alpha]_D + 406^\circ$ ($c = 0.10$, $CHCl_3$), λ_{max}^{EtOH} 282 and 302 nm ($\log \epsilon$ 4.12 and 4.12).³⁸ The n.m.r. spectrum of the phenolic amide showed a three-proton singlet at δ 3.59 (C-1 OMe), two coincident three-proton singlets at δ 3.92 (C-9 and C-10 OMe), a three-proton singlet at δ 2.20 (NCOMe), and three one-proton signals at δ 6.71 (C-3 H), 6.81 (C-8 H), and 8.02 (C-11 H). Further acetylation of the phenolic amide with acetic anhydride in pyridine furnished the amorphous *ON*-diacetyl derivative.

Evidence in favour of structure (21) for the alkaloid was obtained by studying the n.m.r. spectra of (19) and its *O*-acetyl, *N*-acetyl, and *ON*-diacetyl derivatives. It was observed that *O*-acetylation in each case caused a significant downfield

³⁸ S. R. Johns, J. A. Lamberton, A. A. Sioumis, and H. J. Tweeddale, *Austral. J. Chem.*, 1969, 22, 1277.

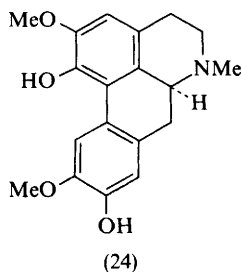
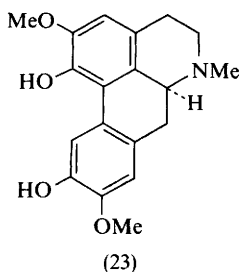
³⁹ R. Tschesche, P. Welzel, and G. Legler, *Tetrahedron Letters*, 1965, 445.

(21) $R^1 = R^2 = H$ (22) $R^1 = H, R^2 = Ac$

shift of the signal assigned to the C-3 proton, a fact readily explained by the introduction of an *O*-acetyl group at C-2.

Bracteoline.—The phenolic basic extracts of *Papaver bracteatum* Lindl. (Papaveraceae) have yielded bracteoline (23), $C_{19}H_{21}O_4N$, m.p. 218–221 °C (ether), $[\alpha]_D^{20} + 35^\circ \pm 8^\circ$ ($c = 0.16$, $CHCl_3$), λ_{max}^{MeOH} 218, 268 sh, 278, and 304 nm ($\log \epsilon$ 4.56, 4.02, 4.12, and 4.15), λ_{min}^{MeOH} 254 and 286 nm ($\log \epsilon$ 3.74 and 3.96).⁴⁰

O-Methylation (CH_2N_2) gave glaucine (16) as well as thaliporphine (18). Since the alkaloid is not an *ortho*-diphenol, and since it does not correspond to isoboldine (24), it was assigned structure (23).

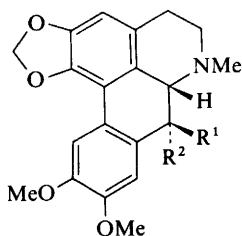


(–)-**Dicentrine.**—Three aporphines have been isolated from a Brazilian *Duguetia* species, the classification of which is still incomplete. Two of these proved to be new, namely (–)-dicentrine (25), and its corresponding C-7 hydroxy-analogue (–)-duguetine (26). The known alkaloid was (+)-norglaucine (15).³⁷

(–)-Dicentrine, $C_{20}H_{21}O_4N$, m.p. 162–163 °C (ethanol), $[\alpha_D] - 53^\circ$ ($c = 1$, $CHCl_3$), HCl salt m.p. 233–235 °C, showed a t.l.c. behaviour and a KBr i.r. spectrum identical with that of the known (+)-dicentrine. The n.m.r. spectrum in $[^2H_5]$ pyridine showed an *N*-methyl singlet at δ 2.51, two *O*-methyl singlets at δ 3.90 and 3.96, and a methylenedioxy-group represented by a doublet (in reality a doublet of doublets) at δ 6.09 and δ 6.21. The aromatic proton peaks were as singlets at δ 6.69 (C-3 H), 7.09 (C-8 H), and 8.08 (C-11 H).^{*} This is a rare instance of the occurrence of a laevorotatory 1,2,9,10-tetrasubstituted aporphine in

⁴⁰ K. Heydenreich and S. Pfeifer, *Pharmazie*, 1967, 22, 124.

^{*} The chemical shift of the C-11 proton, δ 8.08, is further downfield than would be expected.



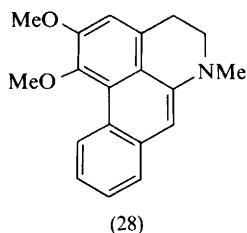
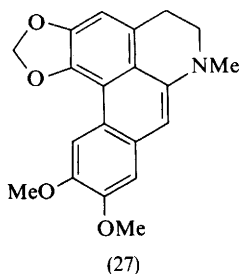
(25) $R^1 = R^2 = H$

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

Nature. It would have been more satisfying if the *Duguetia* species had been securely classified.

Dehydrodicentrine.—Dehydrodicentrine (27), $C_{20}H_{19}O_4N$, originating from *Ocotea macropoda* (Lauraceae), crystallized from chloroform in golden yellow needles, m.p. 218 °C. The u.v. spectrum, λ_{max}^{EtOH} 263, 302, and 340 nm ($\log \epsilon$ 4.74, 3.85, and 4.10), indicated a highly conjugated system similar to that of dehydronuciferine (28).¹² The n.m.r. spectrum revealed an *N*-methyl group (δ 3.04), two methoxy-groups (δ 4.00), a methylenedioxy-group (δ 6.18 s), and four unsplit aromatic protons (δ 6.51, 6.87, 7.02, and 8.41). The aromatic proton at low field (δ 8.41) and the unusually deshielded *N*-methyl (δ 3.04) are typical of a C-11 hydrogen and an *N*-methyl of a dehydroaporphine.

Identification of the new base as dehydrodicentrine (27) was obtained by mild permanganate oxidation of dicentrine. Dehydrodicentrine represents the first example of a monomeric dehydroaporphine from natural sources.



(±)-Isoboldine.—A sample of *Glaucium flavum* (Papaveraceae) has yielded almost equal amounts of (+)-isoboldine and (±)-isoboldine [racemic (24)]. The racemate melted 130—131 °C (methanol), and was identical with (+)-isoboldine in terms of u.v. and mass spectra and t.l.c. R_f values.⁴¹

Duguetine.—Duguetine (26), $C_{20}H_{21}O_5N$, m.p. 149—150 °C (methanol), $[\alpha]_D - 41.3^\circ$ ($c = 1$, EtOH), λ_{max}^{EtOH} 284 and 305 nm ($\log \epsilon$ 4.14 and 4.21), was found

⁴¹ J. Slavík, *Coll. Czech. Chem. Comm.*, 1968, 33, 323.

together with (-)-dicentrine (25) and (+)-norglaucine (15) in an unidentified *Duguetia* species.³⁷

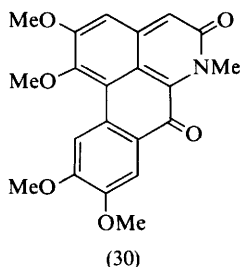
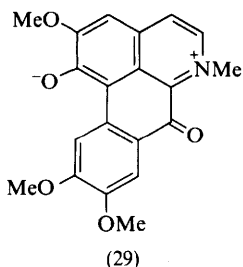
Under mild acetylating conditions, duguetine (26) gave the *O*-acetyl derivative, m.p. 168–169 °C (DMF–water and acetone–water), $[\alpha]_D + 2.8^\circ$ ($c = 1$, EtOH), indicating the presence of an alcoholic function. Boiling duguetine in 6*N*-HCl produced the known natural product dehydrodicentrine (27), whose hydrogenation with Adams' catalyst in acetic acid furnishes (\pm)-dicentrine.

The n.m.r. spectrum of duguetine (26) in [²H₅]pyridine revealed an *N*-methyl group (δ 2.66), two methoxy-groups (δ 3.90 and 3.96), a methylenedioxy-group (presumably as a doublet of doublets at δ 6.10 and 6.21), and three uncoupled aromatic protons [δ 6.70 for C-3 H, δ 7.96 (?) for C-8 H, and δ 8.08 for C-11 H].* The alcoholic function had to be situated at C-7, and the C-6a and C-7 hydrogens had to be *trans* to each other since there was also present in the n.m.r. spectrum a doublet centred near δ 5.04, $J_{6a,7} = 12$ Hz (C-7 H), and another doublet near δ 3.76, $J_{6a,7} = 12$ Hz (C-6a H).*

The absolute configuration of duguetine was established by means of o.r.d. measurements, the curve obtained being closely related, but opposite in sign, to that reported for (+)-dicentrine (+)-(25).

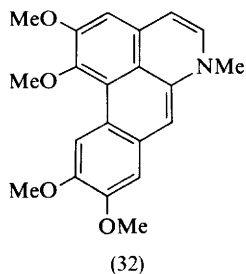
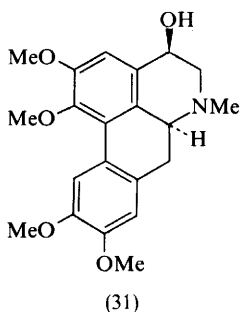
Cataline.—Besides the oxoaporphines corunnine (29) and pontevedrine (30), the Papaveraceae plant *Glaucium flavum* Cr. var. *vestitum* has yielded the new non-phenolic aporphine cataline (31).¹⁰ Cataline, C₂₁H₂₅O₅N, was obtained as colourless crystals, m.p. 183 °C, $[\alpha]_D + 166^\circ$ (CHCl₃), $\lambda_{\text{max}}^{\text{EtOH}}$ 282 and 303 nm ($\log \epsilon$ 4.14 and 4.14). The chloroform i.r. spectrum showed absorption due to an intramolecularly hydrogen-bonded hydroxy-group at 3520 cm⁻¹, and the n.m.r. spectrum revealed an *N*-methyl group at δ 2.78, four aromatic methoxy-groups at δ 3.88 (3H), 4.20 (3H), and 4.27 (6H), three aromatic one-proton singlets at δ 7.10, 7.23, and 8.40,† and very importantly a one-proton absorption at δ 4.83 which appeared as a poorly resolved triplet.

O-Acetylation of cataline yielded a monoacetate, m.p. 91–92 °C, whose most salient feature in the n.m.r. spectrum was a poorly resolved C-4 one-proton triplet at δ 6.03, thus requiring the existence of a secondary hydroxy-group at



* The n.m.r. data given in the original literature are unclear.

† The C-11 proton peak at δ 8.40 is further downfield than with most other aporphines possessing such a hydrogen.

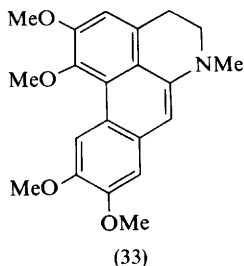


C-4 in the alkaloid. Catalytic hydrogenolysis of cataline using a palladium on carbon catalyst in acetic acid containing a few drops of perchloric acid yielded (+)-glaucine (16). The stereochemistry of the C-4 alcohol function as β was adumbrated from the fact that the C-4 proton of cataline had appeared as a poorly resolved triplet in the n.m.r. spectrum.

Treatment of cataline (31) with aqueous sulphuric acid (1:1) resulted in both dehydration and oxidation and afforded a mixture of didehydroglaucine (32), corunnine (29), and traces of pontevodrine (30).

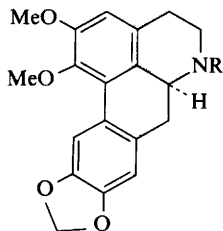
Dehydroglaucine.—Chromatography of the basic extracts from *Glaucium flavum* Crantz and/or *G. flavum* var. *leocarpum* (Papaveraceae) afforded pale yellow prisms of optically inactive dehydroglaucine (33), $C_{21}H_{23}O_4N$, m.p. 133—134°C (ethanol). Hydrogenation using Adams' catalyst in acetic acid gave glaucine (\pm)-(16), which could be reoxidized with potassium permanganate in acetone to regenerate (33).¹¹

Low-field C-11 aromatic proton and N-methyl proton absorptions are typical of dehydroaporphines, and in the case of dehydroglaucine (33) these signals appeared at δ 9.06 and 2.98, respectively. The four methoxy-group absorptions were found at δ 3.85, 3.95, 3.96, and 3.98, and the remaining three aromatic and vinylic protons were at δ 6.51, 6.88, and 7.00. The alkaloid showed a u.v. spectrum with maxima at 260.5 and 334 nm.



Normantenine.—*Cassytha racemosa* Nees (Lauraceae), a trailing parasitic vine of Western Australia, has yielded a variety of aporphines, among which is normantenine (34), $C_{19}H_{19}O_4N$, m.p. 163—164°C (acetone-petroleum ether), $[\alpha]_D + 85^\circ$

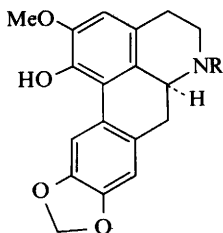
($c = 0.75$, CHCl_3), λ_{max} 218, 272 sh, 282, 308, and 318 sh nm ($\log \epsilon$ 4.61, 3.98, 4.06, 4.15, and 4.11).⁴² The n.m.r. spectrum showed two methoxy-group singlets at δ 3.67 (C-1 OMe) and 3.86 (C-2 OMe), a two-proton singlet at δ 5.92 (C-9,10 O—CH₂—O), and one-proton singlets at δ 6.57 (C-3 H), 6.69 (C-8 H), and 7.92 (C-11 H). Like other noraporphines, nornantenine rapidly darkens on exposure to air and light, and is difficult to purify on a large scale. The *N*-acetyl derivative was recrystallized from ethanol and melted at 294 °C. *N*-Methylation of nornantenine by the Eschweiler–Clarke procedure yielded (+)-nantenine (35).



(34) R = H

(35) R = Me

Nordomesticine.—The Australian trailing parasitic vine *Cassytha pubescens* R. Br. (Lauraceae) is the source of nordomesticine (36), an amorphous base, $\text{C}_{18}\text{H}_{17}\text{O}_4\text{N}$.⁴³ Acetylation gave *ON*-diacetylnordomesticine, $\text{C}_{22}\text{H}_{21}\text{O}_6\text{N}$, m.p. 252—254 °C (ethanol). Eschweiler–Clarke *N*-methylation of nordomesticine furnished (+)-domesticine (37), which is also present in the same plant. The n.m.r. spectrum of nordomesticine is quite simple and shows a singlet at δ 3.83 (C-2 OMe), a singlet at δ 5.88 (C-9,10 O—CH₂—O), and singlets at δ 6.50, 6.67 and 7.93 (C-3, C-8, and C-11 protons, respectively). The n.m.r. spectrum of nordomesticine was also compared with those of isoboldine, glaucine, domesticine, and nantenine.



(36) R = H

(37) R = Me

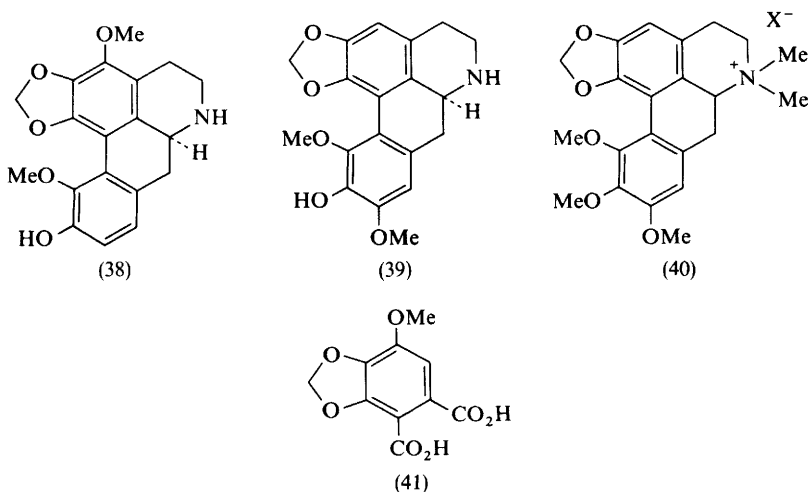
⁴² S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1967, **20**, 1457.

⁴³ S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1966, **19**, 2331.

Hernandine.—Two alkaloids named hernandine are known,^{44,45} one of which is an aporphine.⁴⁵ The phenolic aporphine hernandine (38), $C_{19}H_{19}O_5N$, m.p. 240—241 °C, $[\alpha]_D^{27} + 347^\circ$; HCl salt m.p. 260—261 °C (decomp.), was isolated from *Hernandia bivalvis* Benth. (Hernandiaceae), and was found to possess two methoxy- and one methylenedioxy-groups, but no *N*-methyl group; structure (39) was originally assigned to it.⁴⁵ At a later date 1,2-methylenedioxy-9,10,11-trimethoxyaporphine methiodide (40) was synthesized and was found to be different from *ON*-dimethylhernandine methiodide. The new structure (38) was then advanced for hernandine mainly on the strength of n.m.r. data.⁴⁶ A doublet of doublets at δ 5.94 and 6.15 ($J_{gem} = 1.5$ Hz) was assigned to the methylenedioxy protons, at C-1,2. A high-field aromatic proton absorption near δ 6.69 was missing, indicating that a methoxy-group was present at C-3. The only aromatic proton signal present in the spectrum was a singlet (2H) at δ 6.97 assigned to the C-8 and C-9 protons. Two methoxyl singlets (absorption at δ 3.65 and 4.10) were assigned to the C-11 and C-3 positions, respectively.

It is known that when ring D contains methoxy-groups at C-10 and C-11 a normal AB type quartet is found for the protons at C-8 and C-9;⁴⁷ and indeed *ON*-dimethylhernandine methiodide exhibited in its n.m.r. spectrum (solvent unspecified) a doublet of doublets centred at δ 7.12 ($\Delta\nu$ 19.6 Hz, $J = 8.3$ Hz), corresponding to the C-8 and C-9 protons.

Finally, alkaline potassium permanganate oxidation of hernandine yielded isocotarnic acid (41).



⁴⁴ T. N. Il'inskaya, D. A. Fesenko, L. L. Fadeeva, M. E. Perel'son, and O. N. Tolkachev, *Khim. prirod Soedinenii*, 1971, 7, 180 (*Chem. Abs.*, 1971, 75, 36 408b).

⁴⁵ R. Greenhalgh and F. N. Lahey, 'Heterocyclic Chemistry', Butterworths, London, 1958, pp. 100–102.

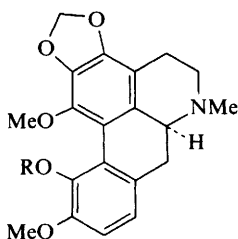
⁴⁶ K. S. Soh, F. N. Lahey, and R. Greenhalgh, *Tetrahedron Letters*, 1966, 5279.

⁴⁷ W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach, and B. Douglas, *J. Chem. Soc.*, 1964, 4778.

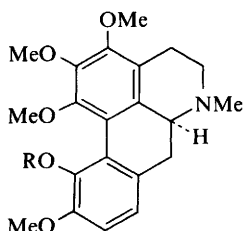
Ocokryptine.—An incompletely identified *Ocotea* species (Lauraceae) collected in the vicinity of Manaus, Brazil, yielded the phenolic alkaloids ocokryptine (42) and oconovine (43).¹² Ocokryptine, $C_{20}H_{21}O_5N$, m.p. 160–161 °C (ether), $[\alpha]_D^{27} + 164^\circ$ ($c = 0.4$, $CHCl_3$), λ_{max}^{EtOH} 222, 284, and 299 sh nm ($\log \epsilon$ 4.53, 4.08, and 3.42) with a bathochromic shift in base, showed in its n.m.r. spectrum the presence of two aromatic protons (both at δ 6.77), one methylenedioxy-group (close doublets at δ 5.92 and 5.98), two methoxy-groups (both at δ 3.91), and an *N*-methyl group (δ 2.50).

A positive Gibb's test was indicative of a free position *para* to the phenol, and this finding, together with the absence of a low-field C-11 proton signal in the n.m.r. spectrum, led to placement of the phenolic function at C-11.

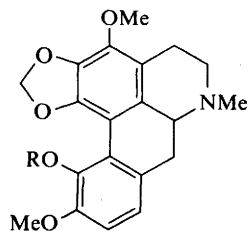
Ocokryptine reacted very slowly with diazomethane to give *O*-methyl-ocokryptine (44), m.p. 170–171 °C, whose n.m.r. spectrum showed, in addition to the *N*-methyl group (δ 2.49), a methylenedioxy-group (close doublets at δ 5.88 and 5.91), three methoxy-groups (δ 3.63, 3.84, and 3.97), and two *ortho* aromatic protons as an AB quartet centred at δ 6.82. A study of the n.m.r. spectra of other aporphines had shown that the *ortho*-protons at C-8 and C-9 appear as an AB quartet when methoxy-groups are present at both C-10 and C-11; but the same protons appear as a singlet when either the C-10 or C-11 oxygen is part of a phenol. At this stage ocokryptine could be represented by either structure (42) or (45). Structure (45) was eliminated by i.r. and n.m.r. spectral comparison of *O*-methyl-ocokryptine (44) with *ON*-dimethylhernandine (46), which proved to be spectrally different. Ocokryptine was, therefore, assigned structure (42). The alkaloid is the first known aporphine bearing a methylenedioxy-group between C-2 and C-3.



(42) R = H
(44) R = Me



(43) R = H
(47) R = Me



(45) R = H
(46) R = Me

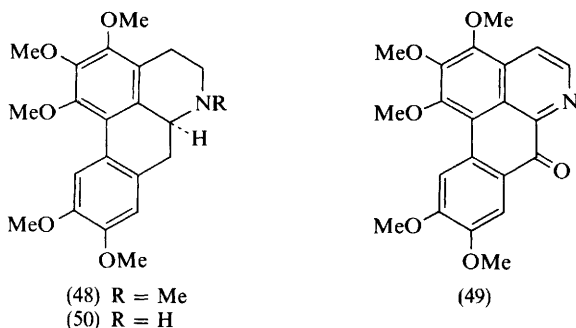
Oconovine.—The amorphous base oconovine (43), $C_{21}H_{25}O_5N$, $[\alpha]_D^{27} + 156^\circ$ ($c = 0.2$, $CHCl_3$), methiodide salt m.p. 204–205 °C, was obtained together with ocokryptine (42) from an incompletely characterized *Ocotea* species (Lauraceae).¹² The u.v. spectrum λ_{max}^{EtOH} 222, 276, and 310 sh nm ($\log \epsilon$ 4.54, 4.15, and 3.70) was similar to that of ocokryptine (42). Like ocokryptine, oconovine is cryptophenolic and gave a positive Gibb's test, suggesting the same substitution pattern in ring D. The n.m.r. spectrum of oconovine showed an *N*-methyl singlet at δ 2.50 and two aromatic protons as a singlet at δ 6.84, assigned to the C-8 and C-9 hydrogens.

The C-1, C-2, C-3, and C-10 methoxy-groups showed signals at δ 3.76, 3.92, 3.98, and 3.92, respectively. No downfield aromatic proton absorption near δ 7.9 was present, so that the phenolic group was placed at C-11.¹²

Diazomethane reacted slowly with the alkaloid to furnish the amorphous *O*-methyloconovine (47), whose n.m.r. spectrum showed the C-8 and C-9 *ortho* protons as an AB quartet characteristic of a 10,11-dimethoxyaporphine.^{12,47}

Thalicsimidine (purpureine).—Thalicsimidine (48), $C_{22}H_{27}O_5N$, has been found in *Thalictrum simplex* (Ranunculaceae)⁴⁸ and *Annona purpurea* L. (Annonaceae),⁴⁹ m.p. 131—132 °C (acetone), $[\alpha]_D + 66.9^\circ$ ($c = 1.42$, EtOH), methiodide salt m.p. 227—229 °C. The u.v. spectrum exhibited λ_{\max}^{EtOH} 273 sh, 282, 303, and 312 sh nm ($\log \epsilon$ 4.26, 4.36, 4.33, and 4.29). The n.m.r. spectrum showed an *N*-methyl singlet at δ 2.54 and five methoxyl singlets at δ 3.71, 3.88, 3.91(2), and 3.94. Two aromatic proton singlets were at δ 6.77 and 7.95, and the latter was assigned to the C-11 hydrogen. A C-3 proton usually absorbs upfield near δ 6.6, so that the δ 6.77 peak could presumably be assigned instead to the C-8 hydrogen.⁴⁹

Oxidation of the alkaloid with chromium trioxide in pyridine provided a small yield of the corresponding oxoaporphine, oxopurpureine (49), also present in *A. purpurea*.⁴⁹



Norpurpureine.—Norpurpureine (50), $C_{21}H_{25}O_5N$, m.p. 115—117 °C, accompanies thalicsimidine (48) (\equiv purpureine) in *Annona purpurea* L. (Annonaceae), and gives an *N*-methyl methiodide salt, m.p. 227—229 °C, identical with the methiodide of thalicsimidine.⁴⁹ The n.m.r. spectrum of the noraporphine showed five methoxyl singlets at δ 3.72, 3.90(3), and 3.94, and two aromatic proton singlets at δ 6.75 (C-8 H) and δ 7.98 (C-11 H). The u.v. spectrum of the alkaloid closely resembles that of thalicsimidine and shows λ_{\max}^{EtOH} 272 sh, 280, 300, and 311 sh nm ($\log \epsilon$ 4.13, 4.20, 4.13, and 4.07).

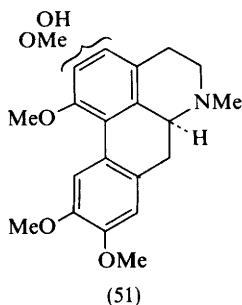
***O*-Demethylpurpureine.**—Yet another aporphine found in *Annona purpurea* L. (Annonaceae) is *O*-demethylpurpureine (51), ($C_{21}H_{25}O_5N$), which was only partially characterized and for which no melting point was recorded.⁴⁹

⁴⁸ Z. F. Ismailov, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1968, 4, 136 (*Chem. Abs.*, 1968, 69, 67 581h).

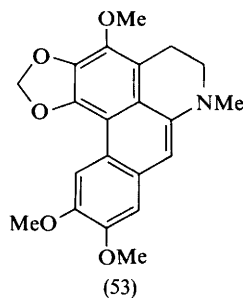
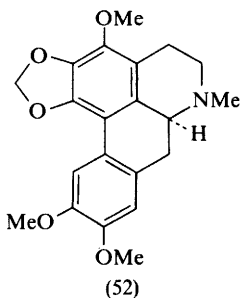
⁴⁹ P. E. Sonnet and M. Jacobson, *J. Pharm. Sci.*, 1971, 60, 1254.

O-Methylation of the alkaloid gave thalicsimidine [\equiv purpureine (48)]. The n.m.r. spectrum showed an *N*-methyl singlet at δ 2.54, and four methoxyl singlets at δ 3.70, 3.90(2), and 3.96. Two aromatic proton singlets were present, one at δ 6.76 assignable to the C-8 hydrogen, and the other downfield at δ 7.89 and due to the C-11 hydrogen.

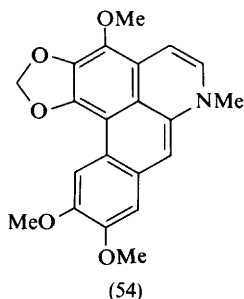
No downfield or upfield shift of the two aromatic protons could be observed when the spectrum was run in $[^2\text{H}_6]\text{DMSO}$ and base, so that the phenolic function in *O*-demethylpurpureine (51) may be either at C-2 or C-3. Additionally, the alkaloid did not incorporate deuterium when treated under conditions that normally cause protons *ortho* or *para* to phenolic hydroxy-groups to be exchanged.



Dehydro-ocoteine.—*Ocotea puberula* (Nees et Mart.) Nees (Lauraceae) had been known as a source of ocoteine (52). A re-investigation of this plant yielded the new aporphine dehydro-ocoteine, $\text{C}_{21}\text{H}_{21}\text{O}_5\text{N}$, m.p. 203—204 °C (ethyl acetate), which was unstable to light.¹⁴ The presence of a u.v. absorption maximum or shoulder between 252 and 265 nm is diagnostic of a C-6a to C-7 double bond, and dehydro-ocoteine showed $\lambda_{\text{max}}^{\text{EtOH}}$ 220, 263, and 335 nm ($\log \epsilon$ 4.56, 4.80, and 4.06). The n.m.r. spectrum exhibited low-field C-11 aromatic proton and *N*-methyl proton signals typical of dehydroaporphines, namely at δ 8.45 (1H) and 3.10 (3H), respectively. The spectrum also showed methoxyl peaks at δ 4.08 (6H) and 4.12 (3H), a methylenedioxy singlet (rather than doublet as in the aporphines) at δ 6.12 (2H), and aromatic proton singlets at δ 6.60 and 7.10 for the C-8 and C-7 protons. Permanganate in acetone oxidation of ocoteine (52) yielded some dehydro-ocoteine (53).



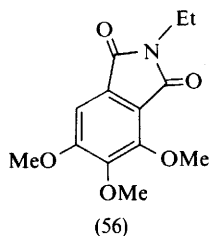
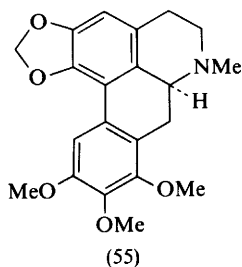
Didehydro-ocoteine.—Didehydro-ocoteine (54), $C_{21}H_{19}O_5N$, has not been isolated in pure form, and may accompany ocoteine (52) and dehydro-ocoteine (53) in *O. puberula*. Its structure was inferred from mass spectral data, where a molecular ion m/e 365 is present.¹⁴



Ocopodine.—*Ocotea macropoda* (Lauraceae) of Brazilian origin has yielded two new alkaloids, dehydroidicentrine (27), discussed above, and ocopodine (55), $C_{21}H_{23}O_5N$, m.p. 116 °C (ethanol), $[\alpha]_D^{25} + 87^\circ$ ($c = 0.82$, EtOH), λ_{\max}^{EtOH} 223, 281, and 305 nm ($\log \epsilon$ 4.57, 4.30, and 4.08).¹² The n.m.r. spectrum of ocopodine showed a methylenedioxy-group (close doublet at δ 5.86 and 6.03), an *N*-methyl group (δ 2.52), three methoxy-groups (δ 3.82, 3.85, and 3.87), and two aromatic protons (δ 6.48 and 7.47). The more deshielded aromatic proton was assigned to the C-11 position, the high-field proton being typical of a C-3 hydrogen.

The positions of the three methoxy-groups were determined as follows. Strong acid hydrolysis of ocopodine, followed by permanganate oxidation of the resulting catechol derivative, produced an acid fraction. Conversion of this acid fraction into its *N*-ethylimide furnished *N*-ethyl-3,4,5-trimethoxyphthalimide (56).

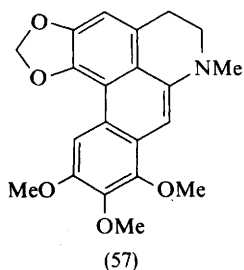
Ocopodine is the first natural aporphine characterized to have three substituents attached to ring D. The racemic form of ocopodine had been synthesized several years previously,⁵⁰ and a direct solution i.r. comparison proved the two compounds to be identical.¹²



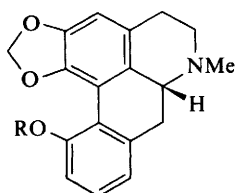
⁵⁰ M. Tomita and K. Hirai, *J. Pharm. Soc. Japan*, 1960, **80**, 608.

Dehydro-ocopodine.—Dehydro-ocopodine (57), $C_{21}H_{21}NO_5$, golden yellow plates (ethanol), m.p. 113°C , is one of the bases obtained from *Ocotea macropoda* (Lauraceae).¹³ The u.v. spectrum, $\lambda_{\text{max}}^{\text{EtOH}}$ 220, 262 sh, 267, and 340 nm ($\log \epsilon$ 4.37, 4.65, 4.66, and 4.50), was indicative of a dehydroaporphine because of the shoulder at 262 nm.

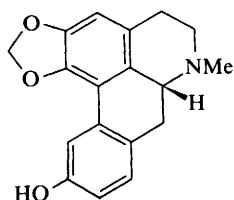
The n.m.r. spectrum revealed an *N*-methyl group (δ 3.07), three methoxy-groups (δ 4.02, 4.00, and 3.97), a methylenedioxy-group (singlet δ 6.15), and three unsplit aromatic protons (δ 6.83, 6.98, and 8.26); the aromatic proton at low field and the deshielded *N*-methyl group are typical of a C-11 proton and the *N*-methyl group of a dehydroaporphine. Confirmation of the new base as dehydro-ocopodine (57) was obtained by preparing it in 27% yield from ocopodine (55) by mild permanganate oxidation in acetone at room temperature.



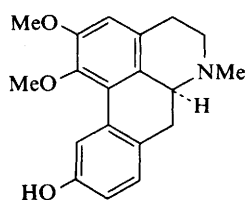
O-Methylpukateine.—A re-investigation of the alkaloids of *Laurelia novae-zelandiae* A. Cunn. (Monimiaceae) yielded two new aporphines, namely O-methylpukateine (58) and (–)-mecambroline (59).⁵¹ O-Methylpukateine (58), $C_{19}H_{19}O_3N$, crystallized from ether, m.p. $136\text{--}138^\circ\text{C}$, and diazomethane methylation of the accompanying and known (–)-pukateine (60) gave material identical with (58). The new alkaloid showed $[\alpha]_D^{25} -293.4^\circ \pm 3^\circ$ ($c = 0.199$, CHCl_3) or $-271.0^\circ \pm 3^\circ$ ($c = 0.105$, EtOH); its o.r.d. curve has been recorded. The u.v. spectrum exhibited $\lambda_{\text{max}}^{\text{EtOH}}$ 213, 272, and 300 nm ($\log \epsilon$ 4.52, 4.15, and 3.95).



(58) R = Me
(60) R = H



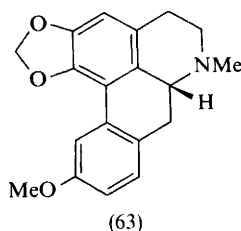
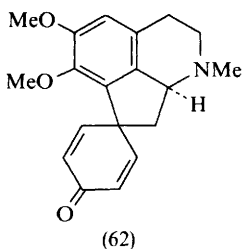
(59)



(61)

⁵¹ K. Bernauer, *Helv. Chim. Acta*, 1967, **50**, 1583.

Nuciferoline.—One of the several alkaloids present in *Papaver caucasicum* Marsch.-Bieb. (Papaveraceae) is the phenolic nuciferoline, $C_{19}H_{21}O_3N$, m.p. 219—221 °C (ether) or 225—227 °C (ethanol), $[\alpha]_D^{21} + 160^\circ \pm 3^\circ$ ($c = 0.31$, EtOH).⁵² The u.v. spectrum with λ_{max}^{EtOH} 215, 265, 273, and 302 nm ($\log \epsilon$ 4.57, 4.15, 4.15, and 3.89) was characteristic of a 1,2,10-trisubstituted aporphine. The methiodide salt had a melting point of 220—222 °C (methanol-ether), very close to that of the known *N*-methyltuduranine methiodide (224 °C) which corresponds to its enantiomer. Additionally, nuciferoline (61) was found to be identical with the dienone-phenol rearrangement product from (–)-pronuciferine (62).



(–)-Mecamproline.—Two independent isolations of (–)-mecamproline (59) appeared in 1967.^{36,51} In the first report, the plant source was the New Guinean tree *Phoebe clemensii* Allen (Lauraceae).³⁶ The alkaloid, $C_{18}H_{17}O_3N$, exhibited m.p. 220—222 °C with darkening at 210 °C ($CHCl_3$), hydrochloride salt darkening at 250 °C but still unmelted at 330 °C, $[\alpha]_D - 76.5^\circ$ ($c = 0.366$, $CHCl_3$). The n.m.r. spectrum showed a singlet at δ 2.55 (*N*-methyl), a pair of one-proton AB doublets at δ 5.65 and 5.72 ($J = 1.5$ Hz) ($O-CH_2-O$), a high-field aromatic proton singlet at δ 6.41 (C-3 H), and a three-aromatic-proton ABX system for the C-8, -9, and -11 hydrogens (C-11 H at δ 7.47, $J_{9,11}$ 2.5 Hz; C-9 H at δ 6.61, $J_{9,11}$ 2.5 Hz, and $J_{8,9}$ 7.5 Hz; and C-8 H at δ 7.00, $J_{8,9}$ 7.5 Hz). Diazomethane *O*-methylation of this alkaloid gave a base of m.p. 97—99 °C taken to be (–)-laureline (63). The laevorotatory alkaloid methiodide melted 237—239 °C ($CHCl_3$).

In the second report, the natural source was a member of the Monimiaceae family, *Laurelia novae-zelandiae* A. Cunn.⁵¹ The free base melted 230—234 °C (ethanol), $[\alpha]_D^{25} - 77.0^\circ \pm 1^\circ$ ($c = 0.110$, $CHCl_3$), λ_{max}^{EtOH} 232, 263, 273, and 308 nm ($\log \epsilon$ 4.42, 4.09, 4.12, and 3.90). The hydrochloride salt had not melted at 330 °C. The i.r. spectrum of the base was found to be identical with that of its known enantiomer (+)-mecamproline which had been isolated from *Meconopsis cambrica* Vig. (Papaveraceae).⁵³

A year later, in 1968, the presence of (–)-mecamproline (59) was also confirmed in *Roemeria refracta* (Stev.) DC. (Papaveraceae).⁵⁴ The racemate, formed by mixing equal quantities of the enantiomers, melted 251—252 °C (methanol).

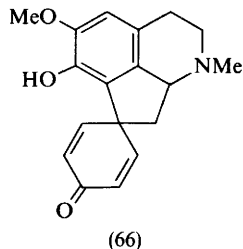
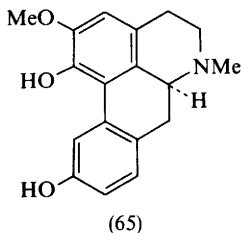
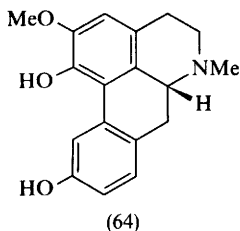
⁵² S. Pfeifer and L. Kühn, *Pharmazie*, 1968, **23**, 267 (*Chem. Abs.*, 1969, **70**, 4319d).

⁵³ J. Slavík and L. Slavíková, *Coll. Czech. Chem. Comm.*, 1963, **28**, 1720 (*Chem. Abs.*, 1963, **59**, 11 886).

⁵⁴ J. Slavík, L. Slavíková, and L. Dolejš, *Coll. Czech. Chem. Comm.*, 1968, **33**, 4066.

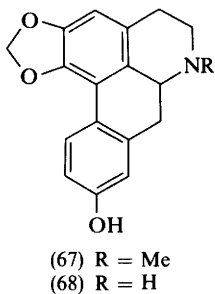
(-)-**Apoglaziovine**.—(-)-Apoglaziovine (64) originates in *Ocotea glaziovii* Mez. (Lauraceae), and its chemistry has already been summarized.³

(+)-Apoglaziovine (65) has recently been isolated from a different source, and comparison of melting points and optical rotations indicated that (-)-apoglaziovine is probably a mixture of laevo and racemic materials.⁷



(+)-**Apoglaziovine**.—(+)-Apoglaziovine (65), $C_{18}H_{19}O_3N$, m.p. 249—252 °C (decomp.), $[\alpha]_D^{25} = +165^\circ$ ($CHCl_3$), was isolated from *Ocotea variabilis* (Lauraceae).⁷ The solution i.r. and n.m.r. spectra were identical with those of the racemic base prepared by acid rearrangement of racemic glaziovine (66).

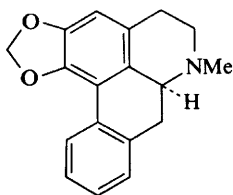
Roemeroline.—Roemeroline (67), $C_{18}H_{17}O_3N$, m.p. 228—231 °C (methanol), turning brown when exposed to air, hydrochloride salt m.p. 220—225 °C (dil. HCl), was isolated together with several other alkaloids from *Roemeria refracta* (Stev.) DC. (Papaveraceae).⁵⁴ At the concentration used, the rotation was too small to be measured accurately. Roemeroline (67) was found to be identical in terms of t.l.c. R_f values with a sample of *N*-methylanolobine obtained by *N*-methylation of anolobine (68).



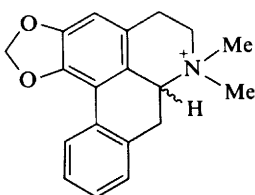
(+)-**Roemerine** (\equiv **Aporheine**).—The alkaloid (-)-roemerine has been known for several years. More recently an investigation of the alkaloidal constituents of *Papaver dubium* L. (Papaveraceae) provided (+)-roemerine (69), $C_{18}H_{17}O_2N$, m.p. 102—103 °C (ether-petroleum ether), $[\alpha]_D^{22} + 80^\circ \pm 3^\circ$ ($c = 0.50$, EtOH); hydrochloride salt m.p. 266—267 °C (ethanol or water); methiodide salt m.p. 232—233 °C (methanol).⁵⁵ Hofmann β -elimination of the methiodide salt

⁵⁵ J. Slavík, *Coll. Czech. Chem. Comm.*, 1963, **28**, 1738.

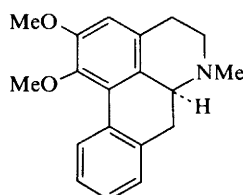
supplied a methine base identical with that obtained by similar treatment of (–)-roemerine. (+)-Roemerine has also been identified in a variety of other *Papaver* species.⁵⁶ The u.v. spectrum of the alkaloid showed $\lambda_{\text{max}}^{\text{EtOH}}$ 233, 270, and 316 nm (log ϵ 4.21, 4.29, and 3.63).



(69)



(70)

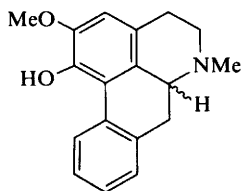


(71)

Remrefidine.—The water soluble alkaloid remrefidine (70), $\text{C}_{19}\text{H}_{20}\text{O}_2\text{N}^+\text{OH}^-$, m.p. 223–224 °C, has been obtained from *Roemeria refracta* DC. (Papaveraceae).⁵⁷ The structure was established by comparison with other 1,2-disubstituted aporphines, particularly roemerine, which is the corresponding tertiary base.

(+)-Nuciferine.—(+)-Nuciferine (71), like (+)-roemerine, has been isolated from *Papaver* species.⁵⁶ (+)-Nuciferine, m.p. 164–166 °C (methanol), $[\alpha]_{\text{D}}^{20} + 165^\circ$ ($c = 0.26$, EtOH), $\lambda_{\text{max}}^{\text{MeOH}}$ 226, 269, and 310 sh nm (log ϵ 4.38, 4.30, and 3.42), was found to be identical with material obtained by dienone–benzene rearrangement of the alcohol derived from the proaporphine (–)-pronuciferine (62).

O-Demethylnuciferine.—In the course of a continuing study of Papaveraceae alkaloids, the simple aporphine *O*-demethylnuciferine (72), $\text{C}_{18}\text{H}_{19}\text{O}_2\text{N}$, was isolated from *Papaver persicum* Lindl.⁵⁸ The free base melted 214–215 °C; hydrochloride salt m.p. 256–257 °C (water). The u.v. spectrum of *O*-demethylnuciferine showed $\lambda_{\text{max}}^{\text{EtOH}}$ 228 sh, 273, and 305 sh nm (log ϵ 4.1, 3.97, and 3.07). The i.r. spectrum indicated the presence of a phenolic hydroxy-group, and *O*-methylation with diazomethane gave material identical (i.r., u.v., t.l.c.) with nuciferine (71). The position of the phenolic hydroxy-group in (72) was settled



(72)

⁵⁶ S. Pfeifer and L. Kühn, *Pharmazie*, 1968, 23, 199.

⁵⁷ S. T. Akramov and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1968, 4, 199 (*Chem. Abs.*, 1968, 69, 87 254g).

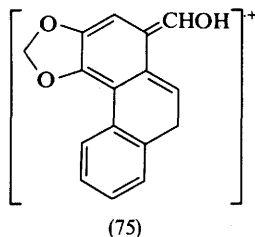
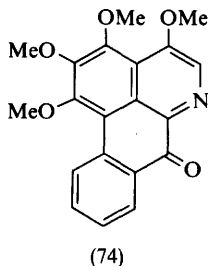
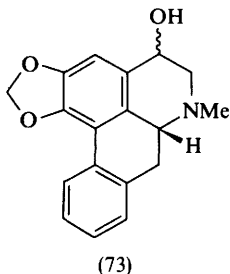
⁵⁸ V. Preininger, J. Appelt, L. Slavíková, and J. Slavík, *Coll. Czech. Chem. Comm.*, 1967, 32, 2682.

by comparison with a synthetic sample. No specific rotation measurements have been recorded for (72).

Steporphine.—Genera belonging to the family Menispermaceae have been a rich source of isoquinoline alkaloids over the years, and an unusual base isolated from a member of the Menispermaceae, *Stephania sasakii* Hayata, is steporphine (73), which is the first aporphine found to be hydroxylated at C-4.⁹ The other aporphine also bearing a hydroxy-group at C-4 is cataline (31); and the oxo-aporphine imenine (74) possesses a methoxy-group at that site.⁵⁹

Steporphine (73), m.p. 177–179 °C (acetone–ether), $[\alpha]_D - 90.6^\circ$ (MeOH), shows a molecular ion peak m/e 295 corresponding to $C_{18}H_{17}O_3N$. The u.v. spectrum, λ_{\max}^{EtOH} 238, 273, 293, and 312 nm ($\log \epsilon$ 4.25, 4.25, 3.07, and 3.55) is characteristic of a 1,2-disubstituted aporphine. The n.m.r. spectrum revealed an *N*-methyl group at δ 2.58, a methylenedioxy-group as a doublet of doublets at δ 5.95 and 6.12 ($J_{\text{gem}} = 2$ Hz), and five aromatic protons with one upfield as a singlet at δ 6.84 (C-3 H), the remaining four appearing between δ 7.20 and 8.22. There was also present a one-proton triplet at δ 4.47 ($J_{4,5} = 2.5$ Hz) which could be ascribed to a C-4 hydrogen geminal to a hydroxy-group.

O-Acetylation of the alkaloid gave a monoacetate whose most salient n.m.r. spectrum feature was a one-proton triplet at δ 5.86 ($J_{4,5} = 2.5$ Hz) corresponding to the C-4 hydrogen geminal to the acetate. The mass spectrum of the alkaloid showed a base peak (75) m/e 252 which can best be explained if the alcoholic hydroxy-group in steporphine is placed at C-4.⁹



(±)-**Variabiline.**—Careful separation of the alkaloids of *Ocotea variabilis* (Lauraceae) yielded white crystals of optically inactive variabiline (76), $C_{32}H_{32}O_2N_2$, m.p. 116–117 °C; dihydrochloride salt m.p. 185–187 °C (decomp.), and monohydrochloride m.p. 230–232 °C (decomp.).⁷

The following spectral data for variabiline suggested a 1,2,10-trisubstituted aporphine structure, λ_{\max}^{EtOH} 213, 233, 265, 280 sh, and 318 nm ($\log \epsilon$ 4.55, 4.45, 4.44, 4.26, 3.74), with a bathochromic shift in base; n.m.r. δ 5.90 (1H, s, OH), δ 2.50 (3H, s, N-CH₃), δ 3.82 (3H, s, OCH₃), δ 4.68 (4H, s, 2 × benzylic CH₂), δ 7.24 (10H, s, 2 × C₆H₅), δ 6.50 (1H, s, C-3H), δ 6.57 (1H, doublet of doublets, $J_{9,10} =$

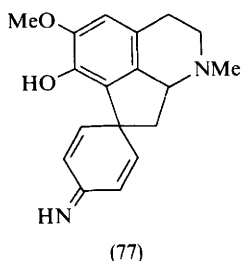
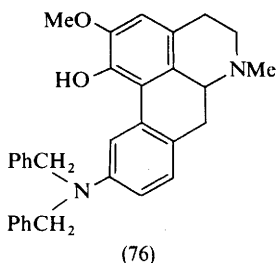
⁵⁹ M. D. Glick, R. E. Cook, M. P. Cava, M. Srinivasan, J. Kunitomo, and A. I. daRocha, *Chem. Comm.*, 1969, 1217.

2.5 Hz and $J_{8,9} = 8$ Hz, C-9 H), δ 7.02 (1H, d, $J_{8,9} = 8$ Hz, C-8 H), and finally δ 7.95 (1H, d, $J_{9,11} = 2.5$ Hz, C-11 H).

In addition to the molecular ion m/e 476, the most revealing peaks in the mass spectrum corresponded to $M - 91$ and $M - 182$, consistent with the loss of one and two benzyl groups, respectively.

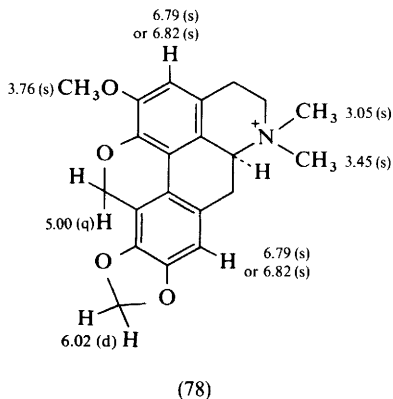
In view of the presence of (\pm)-glaziovine (66) and (+)-apoglaziovine (65) in *O. variabilis*, structure (76) appeared likely for variabiline. Indeed, when (\pm)-glaziovine (66) was heated to 200–210 °C for two hours with a mixture of dibenzylamine and dibenzylamine hydrochloride, a 40% yield of variabiline was obtained.

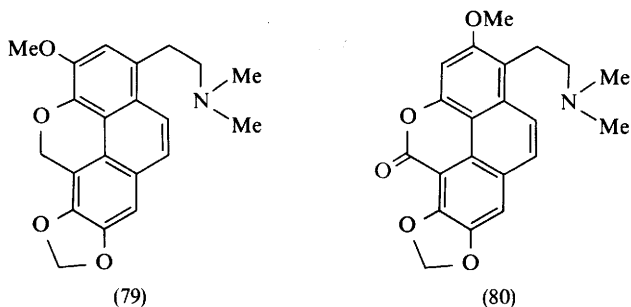
Variabiline may arise in the plant by rearrangement of the N-unsubstituted imine (77) of glaziovine, followed by reductive benzylation, with benzaldehyde serving as the source of the benzyl groups.



Thalphenine.—Thalphenine (78) is the first isolated aporphine with a methylenoxy bridge. It was obtained as the chloride, $C_{21}H_{22}O_4NCl$, m.p. 185–186 °C (MeOH–acetone), $[\alpha]_D + 69^\circ$ ($c = 1.3$, EtOH), from the quaternary alkaloid fraction of the giant meadow rue, *Thalictrum polygamum* Muhl. (Ranunculaceae).⁸

The u.v. spectrum of thalphenine chloride resembled somewhat that of aporphines, λ_{max}^{EtOH} 221, 230 sh, 280 sh, 288, 317, and 328 sh nm ($\log \epsilon$ 4.32, 4.21, 3.69, 3.83, 3.97, and 3.87). The main features of the n.m.r. spectrum of this salt in





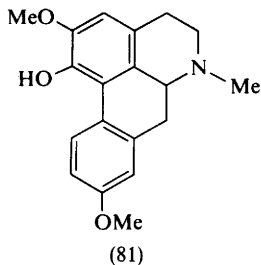
[$^2\text{H}_6$]DMSO are summarized in (78). Noteworthy is the absence of a peak between δ 7.5 and 8.00, denoting substitution at C-11.

The alkaloid readily undergoes Hofmann β -elimination to yield thalphenine methine (79), also found as a natural product in the same plant.

A single-crystal *X*-ray analysis of the pale yellow plates of thalphenine iodide, m.p. 198—199 °C (water–acetone), completed the structural determination. The doubly bridged biphenyl system has a skew angle of 18.1°, significantly less than singly bridged biphenyl systems. The absolute configuration of thalphenine was derived from its positive rotation as well as by the *X*-ray anomalous dispersion method.⁸ The synthesis of (\pm)-thalphenine is described in a later section.

It should be mentioned in passing that phenanthrene-type alkaloids such as thalphenine methine clearly originate biogenetically from quaternary aporphines, and that all natural aporphines, quaternary, tertiary, or secondary, are substituted at C-1 and C-2. The structure (80) assigned to thalicsine,⁶⁰ a new phenanthrene alkaloid found in *Thalictrum longipedunculatum* (Ranunculaceae) must, therefore, be in error since it would require as precursor an aporphine unsubstituted at C-2.

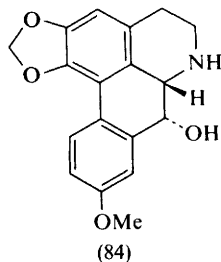
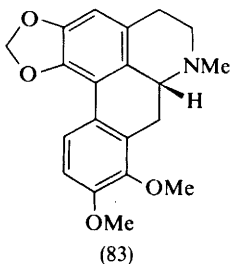
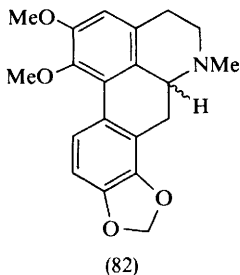
Lirinine.—Lirinine (81) has very recently been found in the leaves of the tulip tree, *Liriodendron tulipifera* L. (Magnoliaceae). The structure was assigned on the basis of spectral evidence, the details of which were not available to the Reporters at the time of writing.^{60a}



⁶⁰ V. G. Khodzhaev, S. K. Maekh, and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1973, 441 (*Chem. Abs.*, 1973, 79, 92 445f).

^{60a} R. Ziyaev, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 9, 67 (*Chem. Abs.*, 1973, 78, 159 939v).

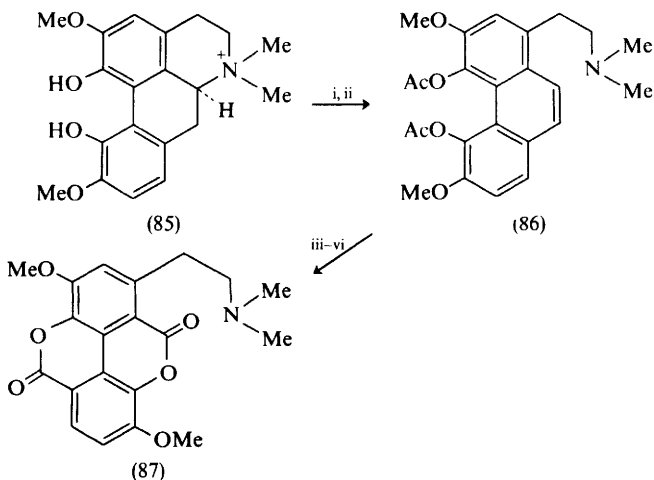
1,2-Dimethoxy-8,9-methylenedioxyaporphine (82).—There is an unsubstantiated claim of the isolation of this base, $C_{20}H_{21}O_4N$, from *Stephania venosa* (Bl.) Spreng. (Menispermaceae), native to South Eastern Asia. No physical constants were quoted.⁶¹ If true, this alkaloid would be structurally related to (–)-crebanine (83).



Michelanugine (84).—The structure of this new alcoholic aporphine from *Michelia lanuginosa* Wall. (Magnoliaceae) has been given, but the structural elucidation work has not yet been described in print.^{61a}

3 Reactions of Aporphines

Conversion of Magnoflorine into Taspine.—The optically inactive alkaloid taspine (87) is probably derived biogenetically from the widely occurring quater-



Reagents: i, Hofmann; ii, Ac_2O ; iii, O_3 ; iv, Ag_2O ; v, HCl , Δ ; vi, base.

Scheme 1

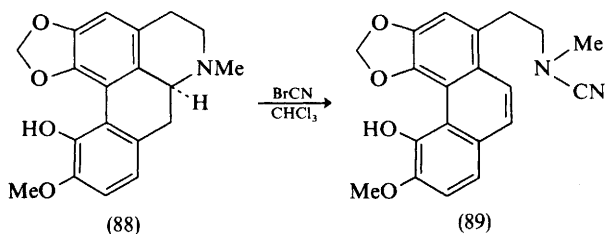
⁶¹ R. Delavigne and J.-P. Fourneau, F.P. 112 587, No. 1 535 720, Laboratoires Houdé (Seine), June 30, 1967 (*Chem. Abs.*, 1969, **71**, 109 924w).

^{61a} S. K. Talapatra, A. Patra, D. S. Bhar, and B. Talapatra, *Phytochemistry*, 1973, **12**, 2305.

nary aporphine magnoflorine (85), and this same transformation has now been carried out *in vitro*. Diacetylmagnoflorine methine (86) was ozonized to give a dialdehyde diacetate. Silver oxide oxidation followed by treatment with acid furnished taspine hydrochloride from which taspine could be liberated (Scheme 1).¹⁶

N-Demethylation, and Hofmann and Emde Degradations.—It is difficult to achieve the *N*-demethylation of a tertiary aporphine because of β -elimination, *i.e.* competitive cleavage of the N-6 to C-6a bond with formation of a substituted phenanthrene. In one method, the aporphine was converted into its *N*-oxide using hydrogen peroxide, and reductive demethylation with liquid sulphur dioxide followed by acid hydrolysis gave a yield of around 25% of the noraporphine.⁶²

Small changes in reaction conditions can affect the course of the Hofmann degradation of quaternary aporphines; and the distribution of substituents within the ring system is also a significant factor.⁶³ Two products are possible, one resulting from cleavage of the C-5 to N-6 bond, to give an isomethine, and the other from the formation of an aromatic phenanthrene derivative, also called a methine base. Treatment of several tertiary aporphines with cyanogen bromide resulted in cleavage of the C-6a to C-7 bond with aromatization to phenanthrenes (methines) rather than causing *N*-demethylation to noraporphines, *e.g.* bulbo-carpine (88) to (89).⁶⁴



The use of a bulky base such as the potassium salt of triethylmethanol in triethylmethanol on the *NOO*-trimethylapomorphine salt (90) gave a 74% yield of the isomethine base (91) and only a small amount of the methine (92), so that some control in the direction of the β -elimination is possible. On the other hand, when the dimethyl ether of apomorphine was treated with acetic anhydride, an excellent yield of the acetylaminoethylphenanthrene (93) was obtained.⁶⁵ An attempt to use azodicarboxylic acid esters as dealkylating agents also led to methines rather than to noraporphines.⁶⁶

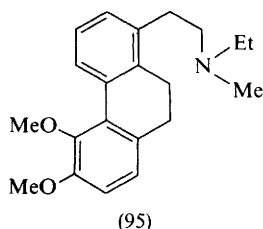
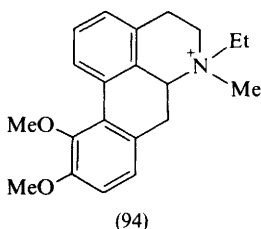
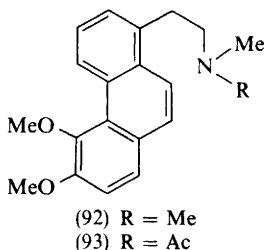
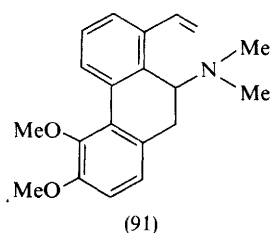
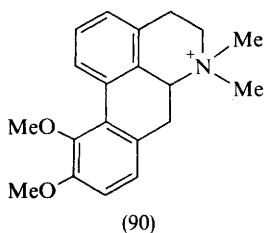
⁶² M. P. Cava and M. Srinivasan, *J. Org. Chem.*, 1972, **37**, 330.

⁶³ R. G. Cooke and H. F. Haynes, *Austral. J. Chem.*, 1954, **7**, 99.

⁶⁴ E. E. Smissman, A. C. Makriyannis, and E. J. Walaszek, *J. Medicin. Chem.*, 1970, **13**, 640.

⁶⁵ J. G. Cannon, R. J. Bergman, M. A. Allen, and J. P. Long, *J. Medicin. Chem.*, 1973, **16**, 219.

⁶⁶ E. E. Smissman and A. C. Makriyannis, *J. Org. Chem.*, 1973, **38**, 1652.



When a salt such as (94) is subjected to reduction with sodium amalgam (Emde degradation) the amine (95) is generated in 80% yield.⁶⁵

The *N*-demethylation of a quaternary aporphine salt can be readily carried out using the nucleophile thiophenolate anion.⁶⁷ In this fashion *OON*-trimethyl-apomorphine methosulphate was demethylated to the corresponding tertiary base.⁶⁸

***O*-Demethylation.**—A superior reagent for *O*-demethylation is boron tribromide in methylene chloride; no heating is required and diaryl ether bonds are unaffected.⁶⁹ Diborane with iodine at room temperature or below can also effect *O*-demethylation.⁷⁰

⁶⁵ M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Letters*, 1966, 1375.

⁶⁸ J. G. Cannon, R. V. Smith, A. Modiri, S. P. Sood, R. J. Bergman, and M. A. Aleem, *J. Medicin. Chem.*, 1972, **15**, 273.

⁶⁹ J. F. W. McOmie and D. E. West, *Org. Synthesis*, 1969, **49**, 50.

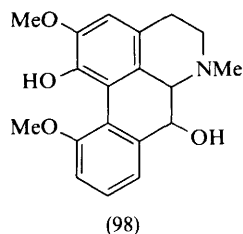
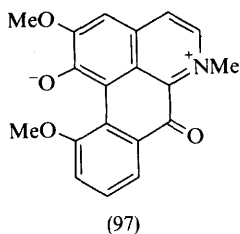
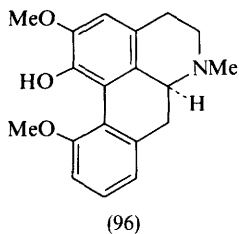
⁷⁰ L. H. Long and G. F. Freeguard, *Nature*, 1965, **207**, 403.

O-Demethylation of the hindered C-1 methoxy-group can be achieved more readily than a C-2 methoxy-group. Thus (+)-nantenine (35) with 36% hydrobromic acid gave a 38% yield of (\pm)-domesticine, whereas with the thioethoxide anion in DMF a 71% yield of (+)-domesticine (37) was achieved.⁷¹

Oxidation.—Mild permanganate oxidation of an aporphine yields the corresponding dehydroaporphine.⁷² Stronger oxidation, using chromium trioxide in pyridine, leads to the corresponding oxoaporphine, but in low yield.^{73,74}

In a recent systematic study of the oxidation of aporphines and related compounds, it was established that an efficient method of oxidizing non-phenolic aporphines to dehydroaporphines was through the use of iodine in dioxan. Iodine in ethanol oxidation of non-phenolic noraporphines proceeded all the way to the oxoaporphine stage. With dehydroaporphines, high-yield oxidation to the corresponding oxoaporphines could be brought about with oxygen at pH 6 McIlvain buffer. Dehydronuciferine (28) has also been oxidized in good yield to its analogous oxoaporphine, lysicamine, using peracetic acid or benzoyl peroxide.¹⁵

Aporphines carrying a phenolic group at C-1 or C-11, or two phenolic groups at C-10 and C-11, are oxidized to green oxidation products by air, iodine, or mercuric acetate. In the case of (+)-isothebaine (96) the green oxidation product was assigned the phenolic structure (97) corresponding to that of the oxoaporphine alkaloid PO-3. Reduction of PO-3 with Adams' catalyst furnished (\pm)-7-hydroxyisothebaine (98).⁷⁵



The oxidation of (–)-apomorphine (99) has been investigated in some detail. Using potassium dichromate between pH 2 and 7, the unstable *ortho*-quinone (100) is formed. But in an alkaline medium with oxygen as the oxidizing agent, the two products formed are (101) and (102).⁷⁶

⁷¹ K. Kunitomo, K. Morimoto, S. Tanaka, and S. Hayata, *J. Pharm. Soc. Japan*, 1972, **92**, 207.

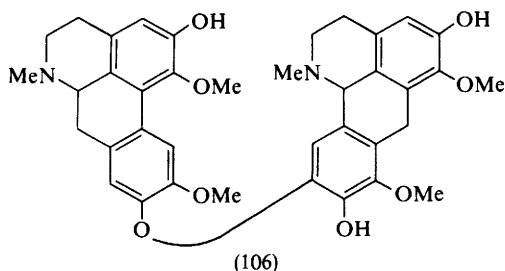
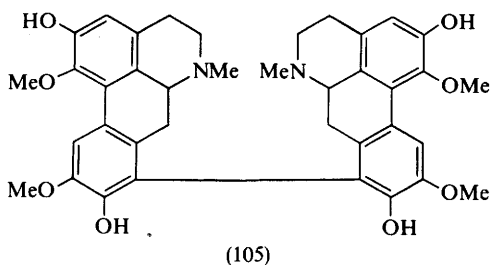
⁷² N. M. Mollov and H. B. Dutschewski, *Tetrahedron Letters*, 1966, 853.

⁷³ T.-H. Yang, *J. Pharm. Soc. Japan*, 1962, **82**, 794.

⁷⁴ M. Tomita, T.-H. Yang, H. Furukawa, and H.-M. Yang, *J. Pharm. Soc. Japan*, 1962, **82**, 1574.

⁷⁵ V. Preininger, J. Hrbek, jun., Z. Samek, and F. Šantavý, *Arch. Pharm.*, 1969, **302**, 808.

⁷⁶ K. Rehse, *Arch. Pharm.*, 1969, **302**, 487.



Ether Formation.—Reaction of apomorphine with the Musliner–Gates reagent, 1-phenyl-5-chlorotetrazole, yielded the corresponding 10,11-bisether together with some of the 10-monoether.^{79a}

4 Synthesis

Bischler–Napieralski Cyclization and Pschorr Ring Closure.—Aporphines recently prepared by the Bischler–Napieralski cyclization of an amide, a transformation eventually followed by a Pschorr ring closure, include bracteoline (23),⁸⁰ domesticine (37),⁸¹ isodomesticine (2-hydroxy-1-methoxy-9,10-methylenedioxy-aporphine),⁸² predi-centrine (19),^{83–85} mecambroline (59),⁸⁶ michepressine iodide

^{79a} R. Bognár, Gy. Gaal, P. Kerekes, and E. Debreczeni, *Acta Phys. Chim. Debrecina*, 1971, 17, 234 (*Chem. Abs.*, 1973, 78, 43 797t).

⁸⁰ P. Kerekes, *Tetrahedron Letters*, 1970, 2483; P. Kerekes, K. Délenk-Heydenreich, and S. Pfeifer, *Chem. Ber.*, 1972, 105, 609.

⁸¹ T. R. Govindachari, N. Viswanathan, R. Charubala, and B. R. Pai, *Indian J. Chem.*, 1969, 7, 841.

⁸² T. R. Govindachari, N. Viswanathan, R. Charubala, and B. R. Pai, *Indian J. Chem.*, 1970, 8, 16.

⁸³ R. Charubala, B. R. Pai, T. R. Govindachari, and N. Viswanathan, *Chem. Ber.*, 1968, 101, 2665.

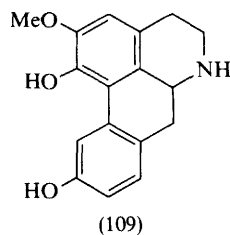
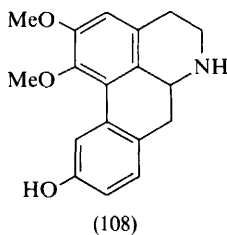
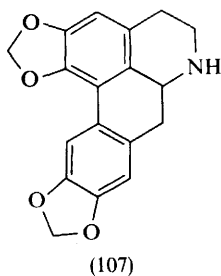
⁸⁴ T. Kametani, T. Sugahara, H. Yagi, K. Fukumoto, B. R. Pai, and R. Charubala, *J. Chem. Soc. (C)*, 1970, 624.

⁸⁵ T. Kametani, K. Takahashi, T. Sugahara, M. Koizumi, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 1032.

⁸⁶ S. Narayanaswami, S. Prabhakar, B. R. Pai, and G. Shanmugasundaram, *Indian J. Chem.*, 1969, 7, 755.

(59, MeI), laureline (63),⁸⁶ norneolitsine (107),¹⁷ *N*-acetylnornantenine (34-Ac),⁸⁷ pukateine (60),⁸⁸ thalicsimidine (48),^{85,89} 1,2,3,10-tetramethoxy-9-hydroxyaporphine,⁸⁹ nantenine (35),⁹⁰ and 1-ethoxy-2-methoxyaporphine.⁹¹

The required intermediate for the Pschorr ring closure may also be obtained by nitration of a tetrahydrobenzylisoquinoline. Thalicsimidine (48) and precicentrine (19) were obtained by such a route.⁸⁵



***o*-Nitrotoluene Approach and Pschorr Ring Closure.**—Involved in this sequence is the base-catalysed condensation of an *o*-nitrotoluene with an isoquinolinium or dihydroisoquinolinium salt, to be followed at a later stage by a Pschorr cyclization. Aporphines so synthesized are thaliporphine (18),⁹² nuciferine (71),⁹² glaucine (16),⁹² tuduranine (108),⁹³ 9,10-dimethoxyaporphine,⁹⁴ 9,10-dihydroxyaporphine,⁹⁴ laureline (63),⁹⁵ 1,2-methylenedioxy-9-methoxyaporphine (norxylopine),⁹⁵ sparsiflorine (109),⁹⁶ apoglaziovine (65),⁹⁶ 1-hydroxy-2,10-dimethoxyaporphine,⁹⁷ and 2-hydroxy-1,10-dimethoxyaporphine.⁹⁷

Some remarks concerning this Pschorr cyclization to aporphines and noraporphines are in order at this point. The yield of the Pschorr reaction decreases as the oxygenation level of the precursor increases.^{98,99} The presence of a

⁸⁷ C. R. Ghosal and S. K. Shah, *Chem. and Ind.*, 1972, 889.

⁸⁸ F. Zymalkowski and K. H. Happel, *Tetrahedron Letters*, 1969, 219; *Chem. Ber.*, 1969, **102**, 2959.

⁸⁹ R. W. Doskotch, J. D. Phillipson, A. B. Ray, and J. L. Beal, *J. Org. Chem.*, 1971, **36**, 2409.

⁹⁰ J. R. Merchant and H. K. Desai, *Indian J. Chem.*, 1973, **11**, 342.

⁹¹ H. A. Priestap, E. A. Ruveda, S. M. Albonico, and V. Deulofeu, *Anales Asoc. quim. argentina*, 1972, **60**, 309.

⁹² S. M. Kupchan, V. Kameswaran, and J. W. A. Findlay, *J. Org. Chem.*, 1972, **37**, 405; 1973, **38**, 405.

⁹³ S. Narayanaswami, S. Prabhakar, and B. R. Pai, *Indian J. Chem.*, 1969, **7**, 945.

⁹⁴ J. G. Cannon and M. A. Aleem, *J. Heterocyclic Chem.*, 1971, **8**, 305.

⁹⁵ T. Govindachari, N. Viswanathan, S. Narayanaswami, and B. R. Pai, *Indian J. Chem.*, 1970, **8**, 475.

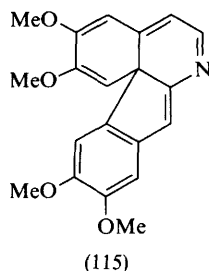
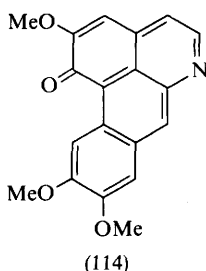
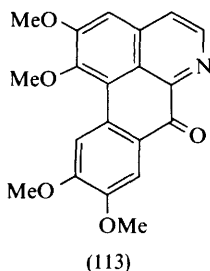
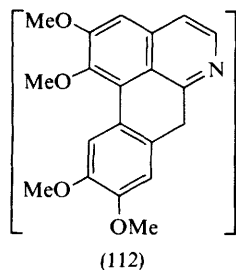
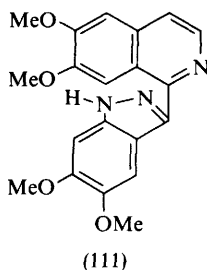
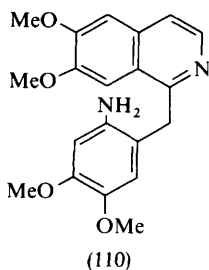
⁹⁶ S. Narayanaswami, B. R. Pai, and C. S. Swaminathan, *Indian J. Chem.*, 1971, **9**, 509.

⁹⁷ S. Narayanaswami, C. S. Swaminathan, and B. R. Pai, unpublished results.

⁹⁸ D. F. DeTar, *Org. Reactions*, 1957, **9**, 490.

⁹⁹ J. A. Weisbach, C. Burns, E. Macko, and B. Douglas, *J. Medicin. Chem.*, 1963, **6**, 91.

C-7 hydroxy-group in the tetrahydrobenzylisoquinoline precursor is of substantial assistance in the Pschorr closure.¹⁰⁰ The yield of the Pschorr product can also be increased by increasing the bulk of the substituent on the nitrogen in the tetrahydrobenzylisoquinoline precursor.¹⁰¹ Diazotization of 6'-aminopapaverine (110) in dilute sulphuric acid, followed by treatment with copper, gave the imidazole (111) as the major product.¹⁰² The oxoaporphine (113), derived from the normal Pschorr product (112), was the minor component formed. In contrast, diazotization of (110) in 46% sulphuric acid, followed by Pschorr cyclization, gave papaverine (4.3%), the oxoaporphine (114) (2.4%), and the indenoisoquinoline (115) (30%). Glaucine (16) and thaliporphine (18) could be derived chemically from (115) and (114), respectively.¹⁰³



As an extension of the formation of imidazoles from the Pschorr procedure, it is also possible to effect cleavage of the tetrahydrobenzylisoquinoline. Thus diazotization and attempted Pschorr ring closure of the amine (116) gave not only the required 1,2,9-trimethoxyaporphine, but also the tetrahydroisoquinoline (118) and 5-methoxyindazole (119), with the last two products probably formed through reductive cleavage of the imidazole (117).¹⁰⁴

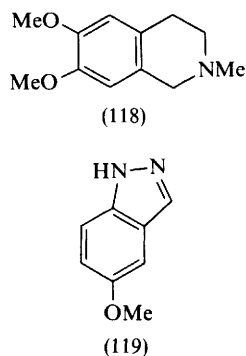
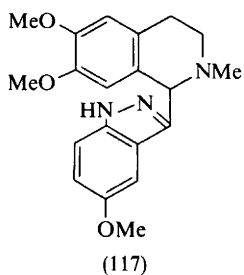
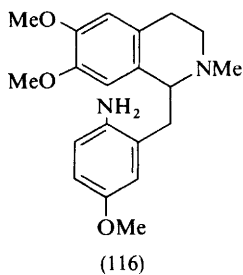
¹⁰⁰ S. M. Kupchan, V. Kameswaran, and J. W. A. Findlay, *J. Org. Chem.*, 1973, **38**, 406.

¹⁰¹ D. R. Dalton and A. A. Abraham, *Synth. Comm.*, 1972, **2**, 303.

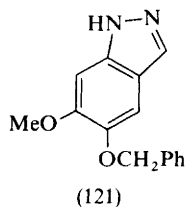
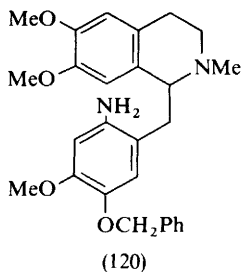
¹⁰² R. Pschorr, *Ber.*, 1904, **37**, 1926.

¹⁰³ M. P. Cava, I. Noguchi, and K. T. Buck, *J. Org. Chem.*, 1973, **38**, 2394.

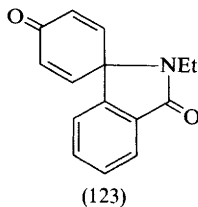
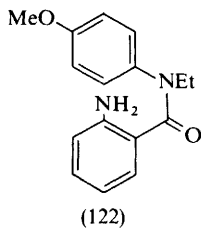
¹⁰⁴ M. Tomita and T. Kitamura, *J. Pharm. Soc. Japan*, 1959, **79**, 997.



In like fashion, Pschorr treatment of the amine (120) provided the corresponding aporphine, the deaminated tetrahydrobenzylisoquinoline, as well as species (118) and (121).¹⁰⁵



The formation of a dienone as a side-product is another common result of the Pschorr procedure. Diazotization of the substituted benzanilide (122) led, among other products, to the dienone (123).^{106,107}

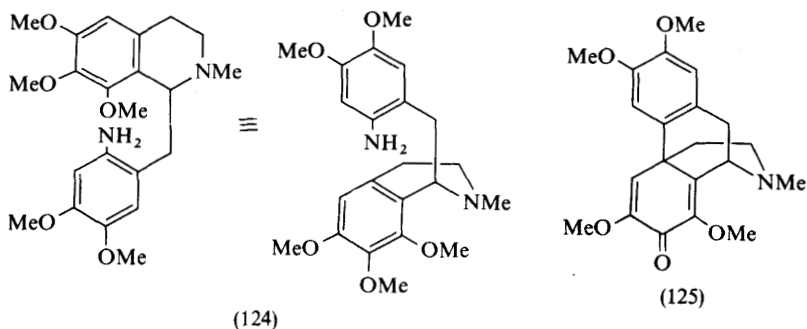


¹⁰⁵ I. Kikkawa, *J. Pharm. Soc. Japan*, 1961, **81**, 1210. See also T. Kametani, Y. Aizawa, T. Sugahara, S. Shibuya, M. S. Premila, and B. R. Pai, *Indian J. Chem.*, 1972, **10**, 987.

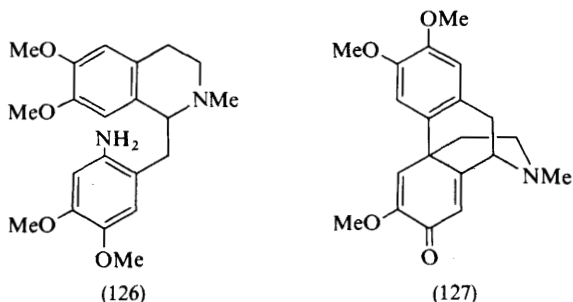
¹⁰⁶ T. R. Govindachari and N. Amurugam, *J. Sci. Ind. Res. (India)*, 1954, **13B**, 694; 1955, **14B**, 250.

¹⁰⁷ D. H. Hey, J. A. Leonard, T. M. Moynihan, and C. W. Rees, *J. Chem. Soc.*, 1961, 232.

Diazotization of the amine (124) supplied the dienone (125), protostephanone, in 25% yield.¹⁰⁸



Similarly, diazotization and ring closure of the amine (126) provided three products, glaucine (16), the deaminated tetrahydrobenzylisoquinoline, and *O*-methylflavinantine (127).¹⁰⁹

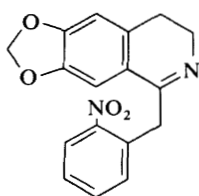


Problems can also arise in the synthesis of noraporphines. Repeated attempts at quaternization of the imine (128) with benzyl bromide were to no avail, the starting material being recovered unchanged. Since the aim was to achieve a synthesis of anonaine, the imine (128) was instead reduced with sodium borohydride to the secondary amine, which was benzoylated to the amine (129). Diborane reduction then afforded the required tertiary amine (130). Reduction with hydrazine and palladium provided the diamine, which underwent smooth Pschorr ring closure. Catalytic debenzoylation then furnished (\pm)-anonaine (131).¹¹⁰

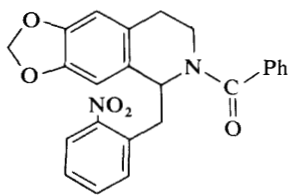
¹⁰⁸ A. R. Battersby, A. K. Bhatnagar, P. Hackett, C. W. Thornber, and J. Staunton, *Chem. Comm.*, 1968, 1214.

¹⁰⁹ T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Comm.*, 1968, 1398; *J. Chem. Soc. (C)*, 1969, 520.

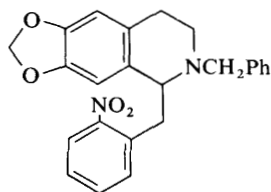
¹¹⁰ M. P. Cava and D. R. Dalton, *J. Org. Chem.*, 1966, **31**, 1281.



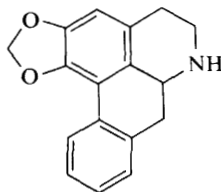
(128)



(129)



(130)



(131)

Syntheses of 7-Hydroxyaporphines through Pschorr Ring Closure.—A sequence has been worked out by which the benzylisoquinoline (132) may be converted cleanly into *cis*-7-hydroxyaporphine (133) or the corresponding noraporphine (134) (Scheme 2).¹¹¹

A somewhat simpler approach to the *cis*-7-hydroxyaporphine series involves the highly stereoselective two-step reduction of the ketonic dihydroisoquinoline (135) to the alcoholic tetrahydroisoquinoline (136). Pschorr reaction then provided (\pm)-norushinsunine (michelalbine) (137) (Scheme 3). The absolute configuration of ushinsunine itself was established through its chemical interrelationship with (–)-roemerine (138) of known chirality.¹¹²

Syntheses via Modified Pschorr Ring Closure.—The amino-group required for Pschorr closure may be located in ring A of the tetrahydrobenzylisoquinoline precursor. Diazotization followed by work-up yields a mixture of products including an aporphine, a deaminated tetrahydrobenzylisoquinoline, and sometimes a proaporphine. Thus, the precursor (139) led to (\pm)-nuciferine (71) and the deaminated tetrahydrobenzylisoquinoline.¹¹³ By contrast, (140) gave rise to 1,2,10-trimethoxyaporphine, (\pm)-pronuciferine (62), and the deaminated tetrahydrobenzylisoquinoline.¹¹³

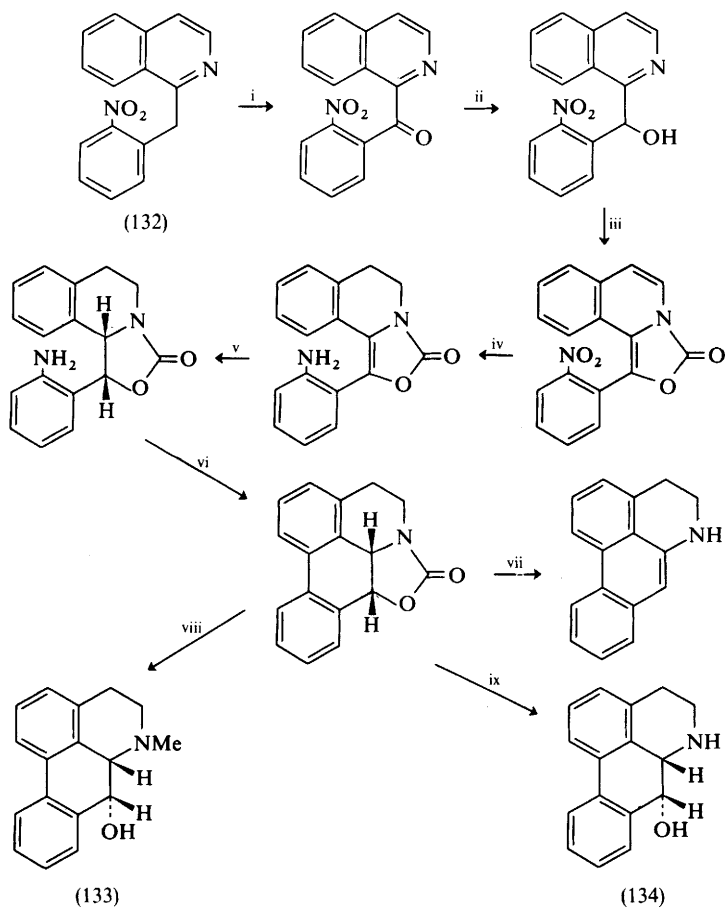
Pschorr treatment of the more highly substituted aminated tetrahydrobenzylisoquinoline (141) furnished three products, namely glaucine (16) and the two separable dienones corresponding to structure (142).¹¹⁴

¹¹¹ J. L. Neumeyer and F. E. Granchelli, *Tetrahedron Letters*, 1970, 5261.

¹¹² J. Kunitomo, M. Miyoshi, E. Yuge, T.-S. Yang, and C.-M. Chen, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1502.

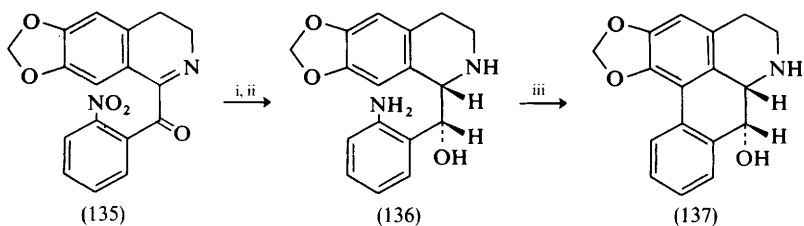
¹¹³ S. Ishiwata and K. Itakura, *Chem. and Pharm. Bull. (Japan)*, 1969, **17**, 1298, 2261.

¹¹⁴ S. Ishiwata and K. Itakura, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1224.



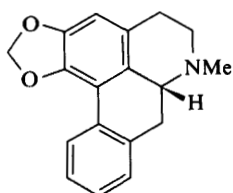
Reagents: i, $\text{Na}_2\text{Cr}_2\text{O}_7$, HOAc ; ii, NaBH_4 ; iii, COCl_2 ; iv, H_2 -Pd, HOAc ; v, H_2 -Pt, HOAc ; vi, Pschorr; vii, TFA; viii, LiAlH_4 ; ix, MeLi.

Scheme 2

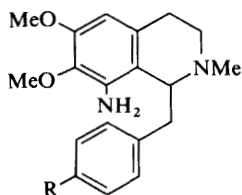


Reagents: i, H_2 -Raney nickel; ii, NaBH_4 ; iii, Pschorr

Scheme 3

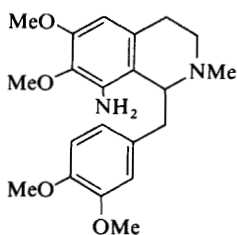


(138)

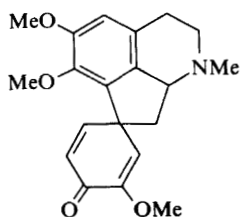


(139) R = H

(140) R = OMe

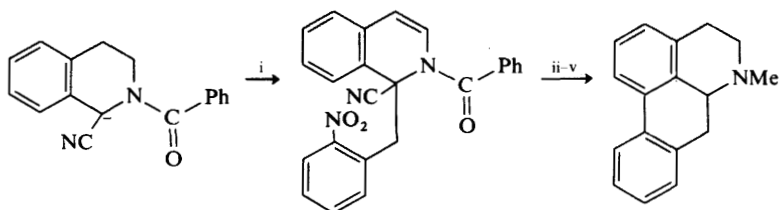


(141)



(142)

Reissert Alkylation and Pschorr Ring Closure.—The first aporphine prepared *via* Reissert intermediates is aporphine itself (Scheme 4). The Reissert anion is best formed using sodium hydride in DMF. An alternative approach to aporphine involving photolysis of 1-(*o*-iodobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline gave a poorer yield.^{115,116}



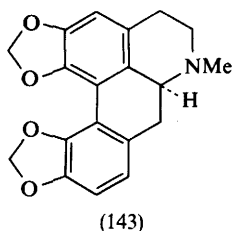
Reagents: i, *o*-nitrobenzyl chloride; ii, KOH, MeOH; iii, MeI; iv, H₂-Pt; v, Pschorr

Scheme 4

Other aporphines prepared by the Reissert–Pschorr route are apomorphine and 10,11-dimethoxyaporphine, in which phenyl-lithium was used to generate

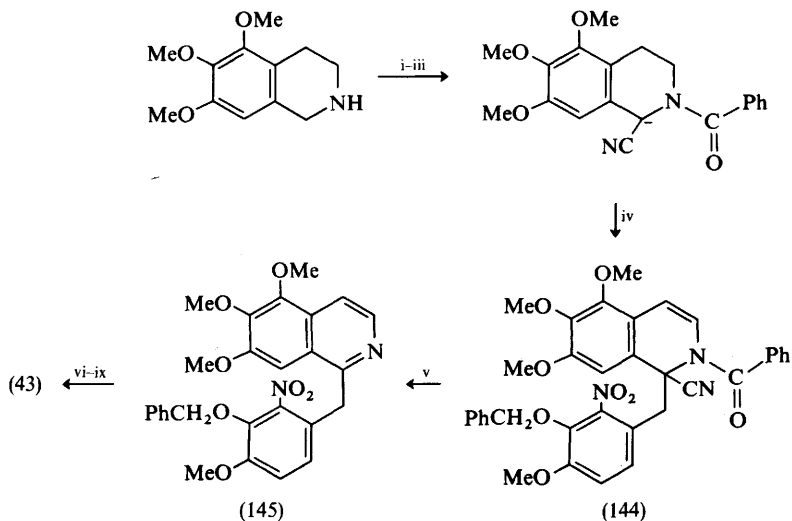
¹¹⁵ J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, *Tetrahedron Letters*, 1967, 3107.

¹¹⁶ J. L. Neumeyer, K. H. Oh, K. K. Weinhardt, and B. R. Neustadt, *J. Org. Chem.*, 1969, **34**, 3786.



the Reissert anion,¹¹⁷ and oconovine (43),¹¹⁸ *N*-methyllovigerine (143),¹¹⁹ 9,10-dimethoxyaporphine, and 9,10-dihydroxyaporphine.¹²⁰

The synthesis of oconovine, which was more complex than the others, is outlined in Scheme 5. Attempted hydrolysis of the alkylated Reissert compound (144) by alcoholic alkali gave an undesired anthranil, but hydrolysis using Triton B produced the benzyloquinoline (145) which was *N*-methylated under forcing



Reagents: i, Pd; ii, KCN, benzoyl chloride; iii, NaH, DMF; iv, 3-benzyloxy-4-methoxy-2-nitrobenzyl chloride; v, Triton B, DMF, r.t.; vi, MeI, DMF, Δ ; vii, NaBH₄; viii, Zn, HOAc; ix, Pschorr

Scheme 5

¹¹⁷ J. L. Neumeyer, B. R. Neustadt, and K. K. Weinhardt, *J. Pharm. Sci.*, 1970, **59**, 1850.

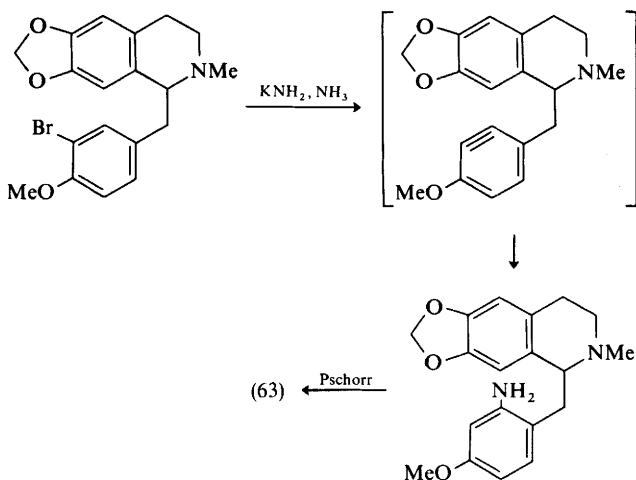
¹¹⁸ M. P. Cava and M. V. Lakshmikantham, *J. Org. Chem.*, 1970, **35**, 1867.

¹¹⁹ M. P. Cava and M. Srinivasan, *Tetrahedron*, 1970, **26**, 4649.

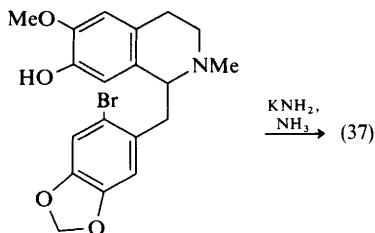
¹²⁰ J. L. Neumeyer, C. B. Boyce, B. R. Neustadt, M. McCarthy, K. H. Oh, and K. K. Weinhardt, 106th National Meeting of the Amer. Chem. Soc., Chicago, Sept. 1970, No. MED137.

conditions before it could be sequentially converted into oconovine (43). Interestingly enough, *O*-debenzylation occurred in the course of the Pschorr reaction.¹¹⁸

Benzyne Generation with or without Pschorr Ring Closure.—Since an aromatic primary amine is required for the Pschorr reaction, generation of a benzyne intermediate in the presence of the amide anion can also lead to aporphine synthesis as exemplified in the case of laureline (63).¹²¹



In a variation on this theme, domesticine (37), which possesses a phenolic function at C-1, was obtained without the necessity of a formal Pschorr ring closure.^{122,123}

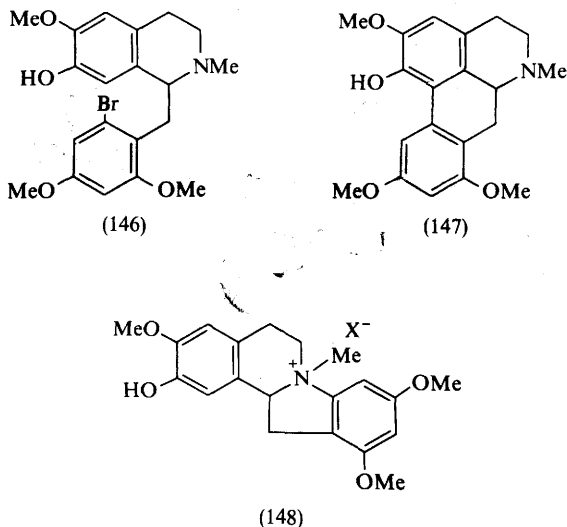


¹²¹ M. S. Gibson and J. M. Walthew, *Chem. and Ind.*, 1965, 185; M. S. Gibson, G. W. Prenton, and J. W. Walthew, *J. Chem. Soc. (C)*, 1970, 2234.

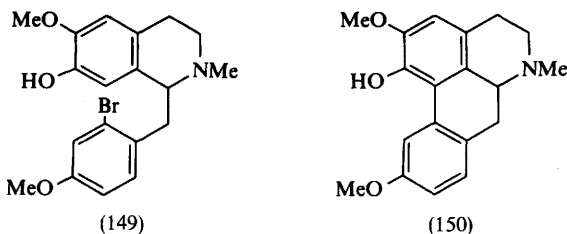
¹²² S. V. Kessar, S. Batra, and S. S. Gandhi, *Indian J. Chem.*, 1970, 8, 468.

¹²³ T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Chem. Soc. (C)*, 1971, 2712.

Dibenzopyrrocoline salts are also produced from benzyne intermediates, since treatment of (146) with sodium amide in liquid ammonia provided the aporphine (147) and the salt (148).¹²⁴



Treatment of (149) with potassium amide in liquid ammonia led to the aporphine (150) (20%). Side-products corresponded to the dibenzopyrrocoline salt and a dienone base of the amurine type.¹²⁵

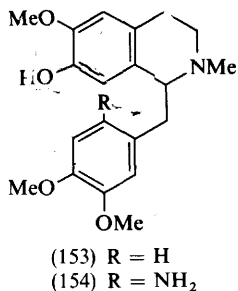
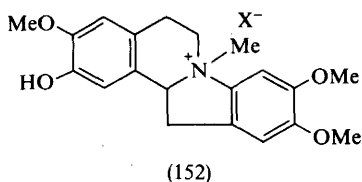
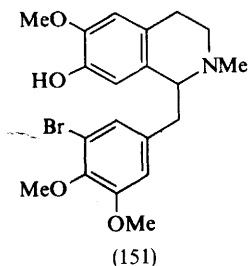


Cryptaustoline iodide (152), thaliporphine (18), and the tetrahydrobenzylisoquinolines (153) and (154) were obtained from the sodium amide in liquid ammonia treatment of (151).¹²⁶

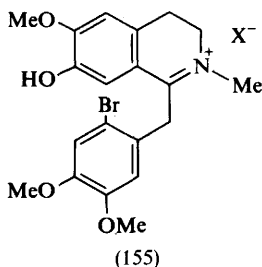
¹²⁴ T. Kametani, K. Fukumoto, and T. Nakano, *Tetrahedron*, 1972, **28**, 4667.

¹²⁵ S. V. Kessar, K. Randhawa, and S. S. Gandhi, *Tetrahedron Letters*, 1973, 2923.

¹²⁶ T. Kametani, K. Fukumoto, and T. Nakano, *J. Heterocyclic Chem.*, 1972, **9**, 1363. For more recent developments see T. Kametani, A. Ujue, T. Takahashi, T. Nakano, T. Suzuki, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 766.



It is also possible to generate dehydroaporphines by the benzyne route, e.g. treatment of the methiodide (155) with the strong base sodium methylsulphinyldimethanide in DMSO afforded dehydrothaliporphine, which upon reduction gave thaliporphine (18).¹²⁷

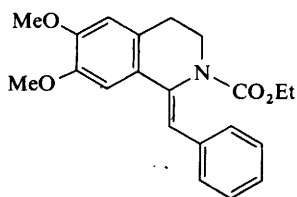


Photochemical Routes.—A variety of photochemical routes to the aporphines is available, some of them high-yield.

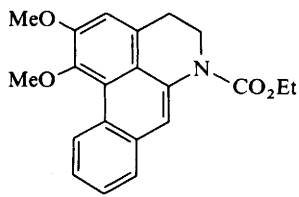
Irradiation of the urethane (156) in the presence of iodine and cupric acetate produced the dehydroaporphine urethane (157) in 35% yield which could be reduced to dehydronuciferine and then to nuciferine (71).¹²⁸

¹²⁷ T. Kametani, S. Shibuya, and S. Kano, *J.C.S. Perkin I*, 1973, 1212.

¹²⁸ M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Letters*, 1966, 2937; M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, 1970, 35, 175.



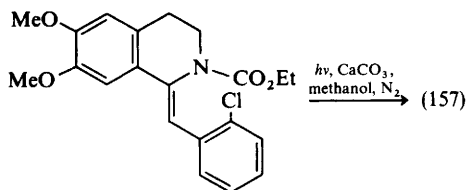
(156)



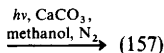
(157)

Neolitsine, which is 1,2;9,10-bismethylenedioxyaporphine, was prepared by a similar route.¹²⁹

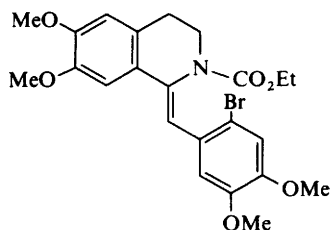
A cleaner variation of the above stilbene-phenanthrene photocyclization consists of the non-oxidative formation of the urethanes (157) and (160) by the irradiation of the 2'-halogeno-derivatives (158) and (159) in yields of 32 and 24%, respectively. The two urethanes were then reduced to the corresponding aporphines, nuciferine and glaucine.¹²⁸



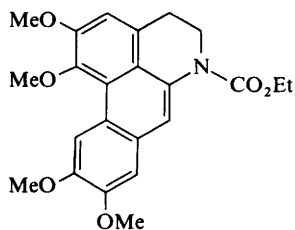
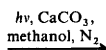
(158)



(157)



(159)

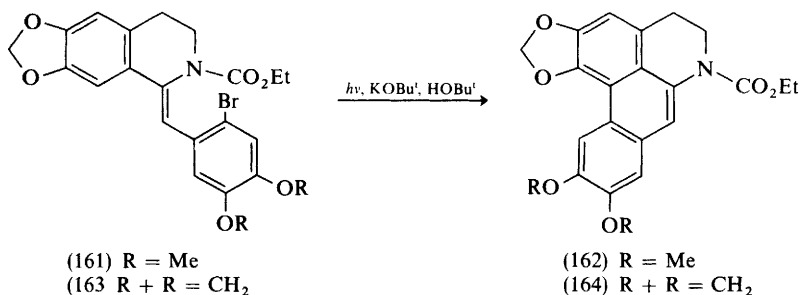


(160)

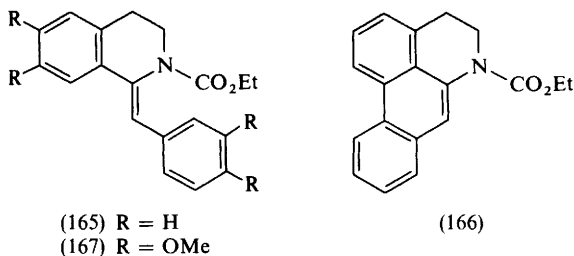
Another improvement is the irradiation of a halogenostilbene such as (161) in the presence of potassium *t*-butoxide. The cyclization product, *N*-ethoxycarbonyldehydronordicentrine (162), was isolated in 56% yield, and was then reduced stepwise to dehydrodicentrine and dicentrine.¹⁷ Comparable irradiation of the bromostilbene (163) gave *N*-ethoxycarbonyldehydronorneolitsine (164) in 72% yield, which could be converted into dehydronelitsine.¹⁷

A transformation similar to, but independent from, those discussed above involves irradiation of the benzylidene (165) in the presence of iodine, a procedure

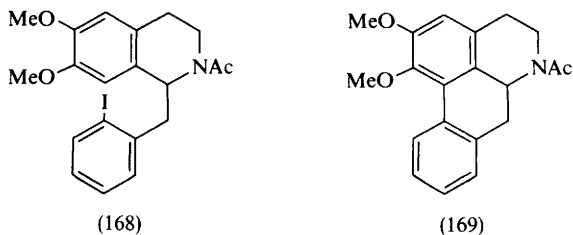
¹²⁹ G. Y. Moltrasio, R. M. Sotelo, and D. Giacomello, *J.C.S. Perkin I*, 1973, 349.



which yielded the dehydronoraporphine urethane (166) in 65% yield. The reaction did not proceed satisfactorily if the pair of electrons was available on the nitrogen. Likewise, irradiation of (167) produced (160).¹³⁰

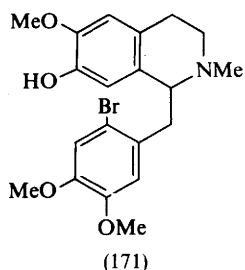
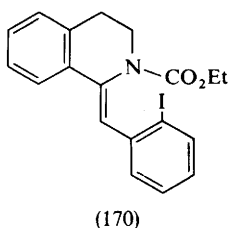


The direct photocyclization of a 1-(*o*-iodobenzyl)tetrahydroisoquinoline protected on the nitrogen, in the presence of benzene and sodium thiosulphate, can also lead to aporphines in good yields. Irradiation of (168) gave *N*-acetylnornuciferine (169) in 45% yield, which could be converted efficiently into nornuciferine by the triethyloxonium fluoroborate method.¹⁸



Similarly, irradiation of the benzylidene (170) furnished *N*-ethoxycarbonyl-dehydronoraporphine (166) in 67% yield. It has also been possible to obtain *N*-ethoxycarbonyldehydronornuciferine by this route.¹⁸

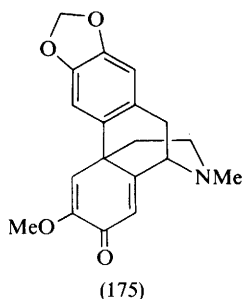
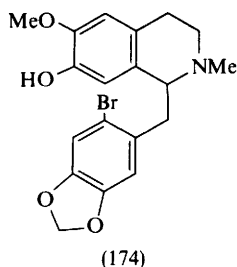
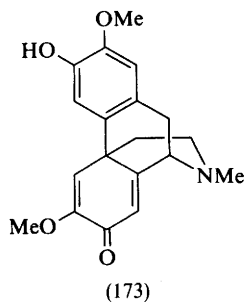
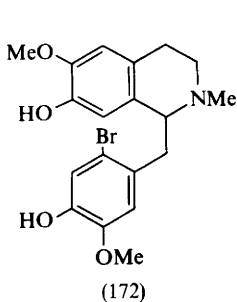
¹³⁰ N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Letters*, 1966, 2941.



Irradiation of halogenated tetrahydrobenzylisoquinolines possessing a basic nitrogen, even in acidic solution, leads to poorer yields. Aporphine¹¹⁶ and 1,9,10-trimethoxyaporphine¹³¹ were prepared by such means.

A useful variation is the photolysis of an appropriate bromophenoxide. Irradiation of the bromophenol (171) in basic solution supplied a 92% yield of crude thaliporphine (18). This method does not require a nitrogen-protective group, and proceeds directly to the aporphine.¹⁹

Independently of the above, it was determined that photolysis of (172) generated bracteoline (23) and flavinantine (173); domesticine (37) and amurine (175) were obtained from (174).¹³²

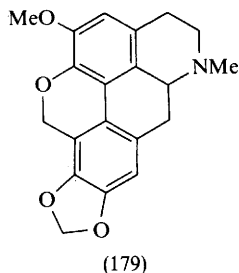
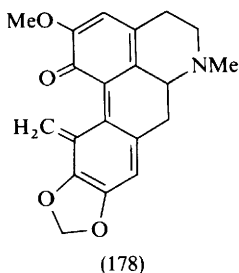
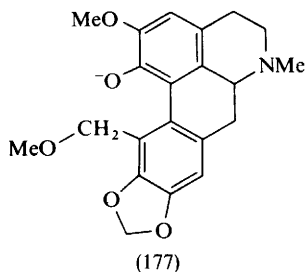
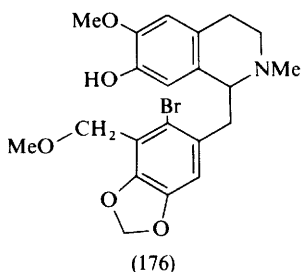


¹³¹ T. Kametani, K. Fukumoto, and M. Fujihara, *J.C.S. Perkin I*, 1972, 394.

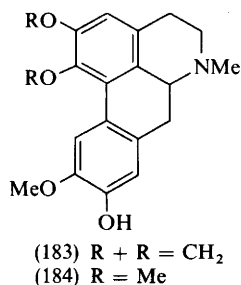
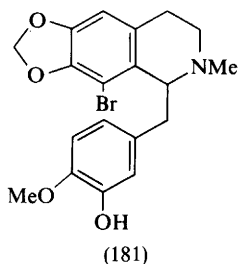
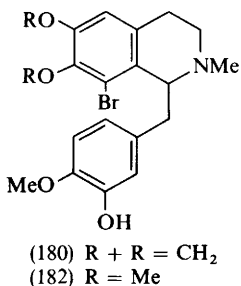
¹³² T. Kametani, S. Shibuya, H. Sugi, O. Kusama, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 2446.

Isoboldine (24) has been obtained from 6'-bromoreticuline.¹³³

As a recent extension of the above sequences, a synthesis of thalphenine has been carried out. Photolysis of the phenolic tetrahydrobenzylisoquinoline (176) in basic solution generated in one step de-*N*-methylthalphenine (179), through the intermediacy of (177) and the quinone methide (178). *N*-Methylation of (179) then furnished thalphenine (78).¹³⁴



Another modification consists of placing the halogen in ring A of the tetrahydrobenzylisoquinoline precursor. It was thus possible to convert by photochemical means the precursors (180)–(182) into cassythicine (183), pukateine (60), and *N*-methyl-laurotetanine (184).¹³⁵

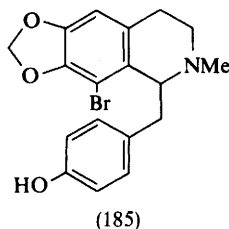


¹³³ T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Tetrahedron*, 1971, 27, 5375.

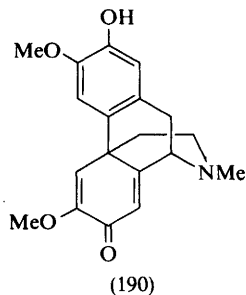
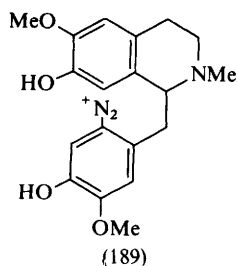
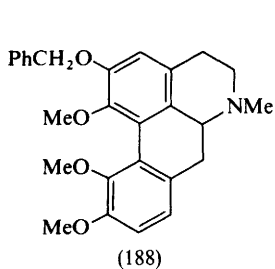
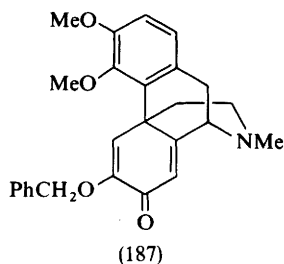
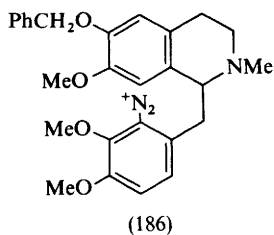
¹³⁴ M. Shamma and D.-Y. Hwang, *Heterocycles*, 1973, 1, 31.

¹³⁵ T. Kametani, K. Fukumoto, S. Shibuya, H. Nemoto, T. Nakano, T. Sugahara, T. Takahashi, Y. Aizawa, and M. Toriyama, *J.C.S. Perkin I*, 1972, 1435.

A small yield of mecambroline (59) was obtained from the photolysis of (185) where the phenolic group is not properly situated for activation at the reaction site.¹³³



The photo-Pschorr cyclization has also been investigated as an avenue to the aporphines. Photolysis of the diazonium salt (186) gave low yields of the morphinandienone (187), and the aporphine (188) which on debenzylolation afforded *N*-methyl-10-*O*-methylhernovine (9).¹³⁶ Photolysis of (189) led to small amounts of flavinantine (173) and bracteoline (23).¹³³



Phenolic Oxidative Coupling.—Most aspects of the phenolic oxidative route to aporphines have already been reviewed.^{3,6,137}

¹³⁶ T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 1923. See also Ref. 84.

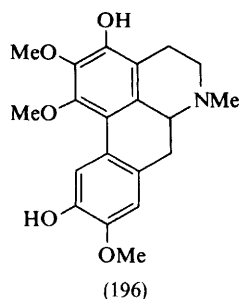
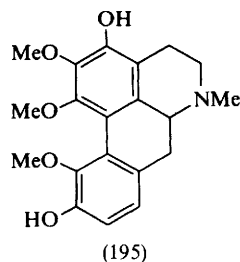
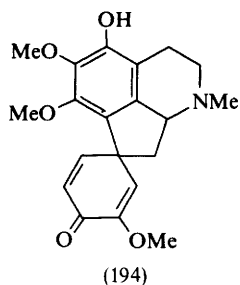
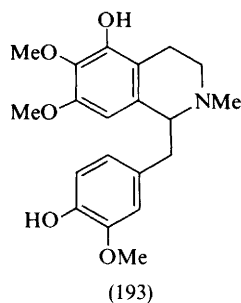
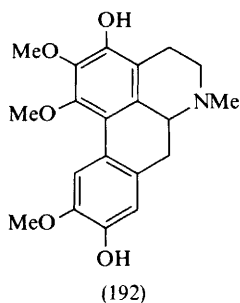
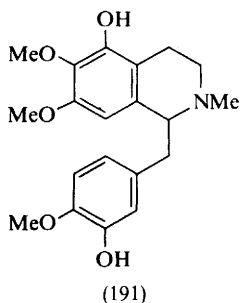
¹³⁷ T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657.

Several studies of the oxidation of reticuline using ferricyanide or ferric ions have appeared, and the two free bases formed are isoboldine (24) and isosalutaridine (190).¹³⁸⁻¹⁴²

Oxidation of laudanosoline at relatively high (0.2 mol l^{-1}) ferric chloride concentration gives 1,2,9,10-tetrahydroxyaporphine, but at lower concentration of the oxidizing agent (0.015 mol l^{-1}) it is the dibenzopyrrocoline salt that is formed.^{138,143}

Details of the interesting and significant biogenetic-type synthesis of isothebaine from oriental line have been discussed.²⁷

Ferricyanide oxidation of (191) afforded (192), whereas oxidation of (193) led to the two diastereoisomeric proaporphines represented by (194). Dienone—phenol rearrangement of (194) produced the aporphines (195) and (196). Aporphines (192) and (196) give thalicsimidine (48) upon *O*-methylation with diazomethane.¹⁴⁴



¹³⁸ B. Franck, G. Dunkelmann, and H. J. Lubs, *Angew. Chem. Internat. Edn.*, 1967, **6**, 1075.

¹³⁹ A. H. Jackson and J. A. Martin, *Chem. Comm.*, 1965, 420; *J. Chem. Soc. (C)*, 1966, 2061, 2222.

¹⁴⁰ W. W.-C. Chan and P. Maitland, *J. Chem. Soc. (C)*, 1966, 753.

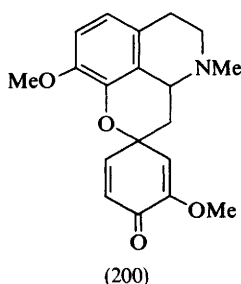
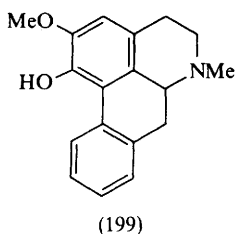
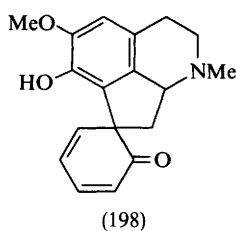
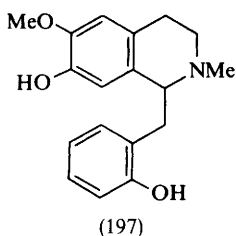
¹⁴¹ T. Kametani, K. Fukumoto, A. Kozuka, H. Yagi, and M. Koizumi, *J. Chem. Soc. (C)*, 1969, 2034.

¹⁴² T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *Tetrahedron*, 1969, **28**, 3667.

¹⁴³ B. Franck and L.-F. Tietze, *Angew. Chem. Internat. Edn.*, 1967, **6**, 799.

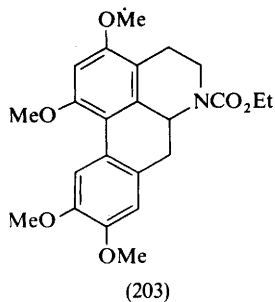
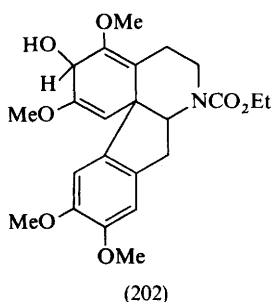
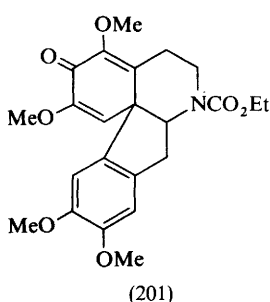
¹⁴⁴ T. Kametani, K. Takahashi, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 3617.

Ferric chloride oxidation of the tetrahydrobenzylisoquinoline (197) led to limited yields of the dienone (198) which upon borohydride reduction and dienol-benzene rearrangement afforded *N*-methylcaaverine (199).¹⁴⁵



Acid-catalysed rearrangement of either of the two diastereoisomeric dienones (200), obtained through phenolic oxidative coupling, produced after *O*-methylation 1,9,10-trimethoxyaporphine instead of the expected cularine derivative.¹³¹

In a separate study, it was stated that the dienone (201) did not rearrange in acid to an aporphine; and that the corresponding dienol (202) led to the aporphine (203) in less than 1% yield using methyl fluorosulphonate.^{146,147}

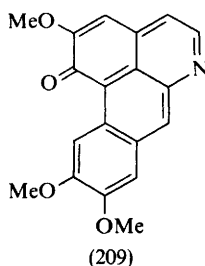
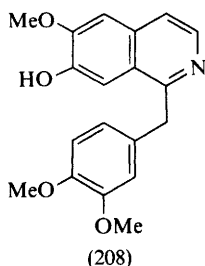


¹⁴⁵ T. Kametani and I. Noguchi, *J. Chem. Soc. (C)*, 1969, 502

¹⁴⁶ T. Kametani, K. Takahashi, T. Honda, M. Ihara, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1973.

¹⁴⁷ T. Kametani, K. Takahashi, K. Ogasawara, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 662.

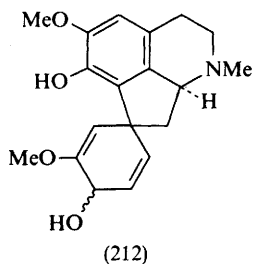
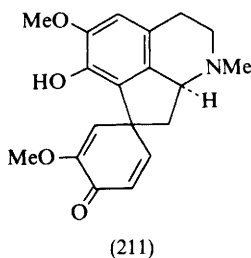
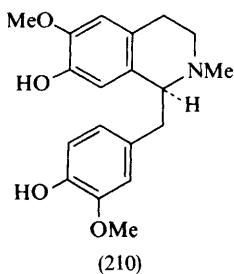
in trifluoroacetic acid more than doubled this yield. Catalytic reduction of (209) gave wilsonirine (17). Nordomesticine (36) was similarly prepared from the appropriate precursors.²⁰



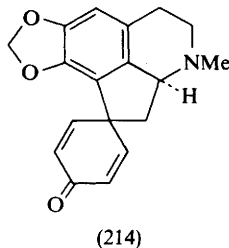
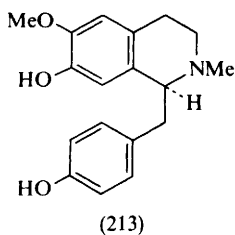
5 Biosynthesis

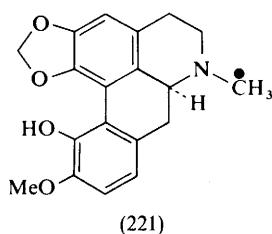
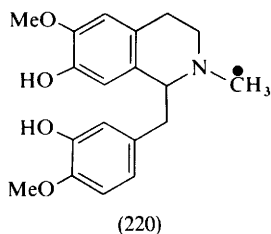
As a result of careful *in vivo* experiments with labelled precursors, three biogenetic routes to the aporphines are now recognized, and these are summarized below.

Coupling to Proaporphines.—The benzyloquinoline (+)-orientaline (210) is the precursor for (+)-isothebaine (96) in *Papaver orientale* L. The intermediates are the proaporphines orientalinone (211) and orientalinol (212).²⁷

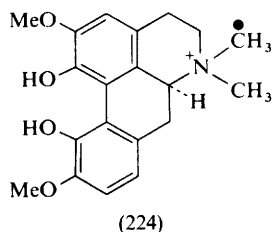
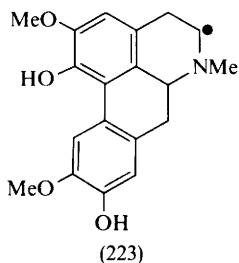
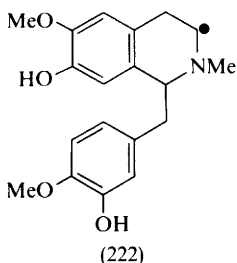


Working with *Papaver dubium* L., it has been shown that (+)-*N*-methylcoclaurine (213) is incorporated into (+)-roemerine (69) through the intermediacy of the proaporphine (214).²⁸

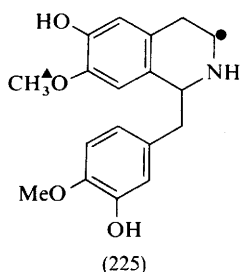




group in an *Aquilegia* hybrid showed an impressive 12.1% incorporation into labelled magnoflorine (224), whereas labelled norprotosinomenine was not incorporated.²⁵



Administration of either (\pm)-orientaline (\pm)-(210) labelled on the *N*-methyl group or 7-*O*-[^3H]methyl[3- ^{14}C](\pm)-norprotosinomenine (225) to the opium poppy did not lead to labelled isoboldine. This amounts to strong evidence that isoboldine in opium is not formed through a proaporphine of a neoproaporphine mechanism, but is generated by direct oxidation of reticuline.²⁶



Looking in retrospect at each of the above three mechanisms for the natural production of aporphines, it can be stated first that they are all rational and supported by very strong experimental evidence. Yet the pathway through neoproaporphines raises some challenging questions which are difficult to answer at present. Why is it that no neoproaporphines have been isolated from natural sources to date? Assuming that neoproaporphines do exist, it would be likely that they could be reduced in plants to neoproaporphinols which could undergo a dienol-benzene rearrangement to furnish aporphines unsubstituted at C-2, yet all known aporphines are substituted at that site. Thirdly, synthetic

neoproaporphines incorporating a dienone system apparently fail to rearrange in acid to the aporphine skeleton,¹⁴⁶ so that this may not be a facile transformation *in vitro*.

6 Pharmacology

The paramount aporphine in the realm of pharmacology is (–)-apomorphine (99), which interestingly enough is not a natural base but the acid-catalysed rearrangement product of morphine. In years past, apomorphine hydrochloride has been used, and is still used, as a prompt and efficient centrally acting emetic, producing results in a matter of minutes. It is best used hypodermically, but in larger doses it can have a hypnotic effect.¹⁵³ It exerts a direct stimulating action on the vomiting centre in the brain, and thus initiates emesis. The biochemical mechanism of this action is still obscure. The diacetate ester has emetic activity nearly identical with that of apomorphine.¹⁵⁴

An exciting development in the pharmacological use of apomorphine came only recently when it was observed that (–)-apomorphine stimulates the dopaminergic system in the corpus striatum of rats,^{155–157} and produces a dopamine-like renal vasodilation in dogs.¹⁵⁸ Because of its dopamine receptor stimulating properties, apomorphine was investigated for the treatment of Parkinsonism^{30,31,159} and chronic manganese.³¹

It was found that subcutaneous injections of apomorphine temporarily controlled involuntary movement (the major side-effect induced by L-dopa in Parkinsonism patients) for about one hour.³¹ Tremor in Parkinsonism patients not receiving L-dopa was eliminated by apomorphine for a maximum of three hours. Research into the synthesis and pharmacology of aporphines was greatly stimulated by these findings, and a brief history of apomorphine follows.

The first preparation of (–)-apomorphine from morphine dates back to more than a hundred years ago.¹⁶⁰ Systematic degradative work on apomorphine was conducted between 1900 and 1907 and led to the correct structural assignment, which incidentally was also the first assignment of an aporphine structure to an organic compound.^{161,162} The earliest authenticated report of a synthesis of (–)-apomorphine dimethyl ether dates from 1929.¹⁶³ Improved syntheses appeared in 1956¹⁶⁴ and 1958,¹⁶⁵ and the preparation of apomorphine itself was recently carried out.¹¹⁷

¹⁵³ The Dispensary of the U.S.A., 25th Edn., Lippincott, Philadelphia, 1955, p. 102.

¹⁵⁴ J. G. Cannon, J. F. Hensiak, and A. M. Burkman, *J. Pharm. Sci.*, 1963, **52**, 1112.

¹⁵⁵ A. M. Ernst and P. G. Smelik, *Experientia*, 1966, **22**, 837.

¹⁵⁶ A. M. Ernst, *Psychopharmacologia*, 1967, **10**, 316.

¹⁵⁷ N. E. Andén, A. Rubenson, K. Fuxe, and T. Hökfelt, *J. Pharm. Pharmacol.*, 1967, **19**, 627.

¹⁵⁸ L. I. Goldberg, P. F. Sonnevile, J. L. McNay, and L. W. King, *J. Pharmacol.*, 1968, **163**, 188.

¹⁵⁹ P. Castaigne, D. Laplane, and G. Dordain, *Res. Comm. Chem. Pathol. Pharmacol.*, 1971, **2**, 154.

¹⁶⁰ A. Matthiessen and C. R. A. Wright, *Proc. Roy. Soc.*, 1869, **17**, 455; *Ann. Suppl.*, 1870, **7**, 170.

¹⁶¹ R. Pschorr, B. Jaekel, and H. Fecht, *Ber.*, 1902, **35**, 4377.

¹⁶² R. Pschorr, *Ber.*, 1906, **39**, 3124.

¹⁶³ E. Späth and O. Hromatka, *Ber.*, 1929, **62**, 325.

¹⁶⁴ D. H. Hey and A. L. Palluel, *J. Chem. Soc.*, 1956, 4123; 1957, 2926.

¹⁶⁵ S. Sugawara and R. Tachikawa, *Tetrahedron*, 1958, **4**, 205.

Apomorphine can be used as an experimental probe of the central nervous system.¹⁶⁶ While the level of homovanillic acid in the neostriatum of rats decreased after treatment with apomorphine, the level of dopamine remained unchanged.¹⁶⁷ Apomorphine elicits a gnawing, sniffing, licking, agitation and aggressive compulsion in mice or rats, a consequence of the stimulation of the dopaminergic neurons in the corpus striatum.¹⁶⁸⁻¹⁷⁰ An intact tuberculum olfactorium is essential for the induction of the gnawing and related responses in rats after administration of apomorphine.¹⁶⁹

Apomorphine given to mice reduced the brain levels of noradrenaline, and retarded the rate of disappearance of dopamine.^{171,172} In a separate but related study with mice, apomorphine administration decreased brain noradrenaline, and also decreased the levels of adrenaline and dopa in the adrenal glands.¹⁷³ These results may be related to the finding that apomorphine inhibits tyrosine hydroxylase activity both *in vivo* and *in vitro*.¹⁷⁴

Apomorphine exerts an antagonistic effect on the sedative action of reserpine, a direct result of its interaction with the dopaminergic system of the corpus striatum.¹⁷⁵

Simple monoamines are probably critically involved in the control of sexual behaviour in the male rat, and sexual behaviour could be abolished after an injection of the tetrahydroisoquinoline tranquillizer tetrabenazine. But in line with the aforementioned findings, a subsequent injection of apomorphine antagonized this suppression.¹⁷⁶

A method for protecting patients from taking an overdose of a physiologically active ingredient depends upon the preferential absorption into the gastric mucosa of apomorphine as compared with the therapeutic substance. The dosage form is such that up to a predetermined level of the therapeutic agent only a sub-emetic dose of apomorphine is ingested. At toxic levels of the therapeutic drug, sufficient apomorphine (5—10 mg) is ingested to cause emesis.¹⁷⁷

A variety of analogues of apomorphine has lately been synthesized and tested. 10-Hydroxy-11-methoxyaporphine (isoapocodeine) is inert as an emetic in

¹⁶⁶ J. Scheel-Kruger, *Acta Pharmacol. Toxicol.*, 1970, **28**, 1.

¹⁶⁷ B. E. Roos, *J. Pharm. Pharmacol.*, 1969, **21**, 263.

¹⁶⁸ M. Fekete, A. M. Kurti, and I. Pribusz, *J. Pharm. Pharmacol.*, 1970, **22**, 377 (*Chem. Abs.*, 1970, **73**, 2446f).

¹⁶⁹ G. M. McKenzi, *Brain Res.*, 1971, **34**, 323. Also *Psychopharmacologia*, 1972, **23**, 212 (*Chem. Abs.*, 1972, **76**, 149 148f).

¹⁷⁰ J. R. Boissier, P. Etevenou, M. C. Piarroux, and P. Simon, *Res. Comm. Chem. Pathol. Pharmacol.*, 1971, **2**, 829 (*Chem. Abs.*, 1972, **76**, 121 625k).

¹⁷¹ H. Nyback, J. Schubert, and G. C. F. Sedvall, *J. Pharm. Pharmacol.*, 1970, **22**, 622 (*Chem. Abs.*, 1970, **73**, 75 413c).

¹⁷² T. Persson, *Acta Pharmacol. Toxicol.*, 1970, **28**, 378 (*Chem. Abs.*, 1970, **73**, 129 257a).

¹⁷³ E. L. Shchelkunov and E. M. Stabrovskii, *Farmakol. Toksikol. (Moscow)*, 1971, **34**, 653 (*Chem. Abs.*, 1972, **76**, 94 789h).

¹⁷⁴ M. Goldstein, L. S. Freedman, and T. Backstrom, *J. Pharm. Pharmacol.*, 1970, **22**, 715.

¹⁷⁵ M. Vitolina, R. Vitolins, and V. Freide, *Latv. P.S.R. Zinat. Akad. Vestis*, 1969, 105 (*Chem. Abs.*, 1970, **73**, 129 374m).

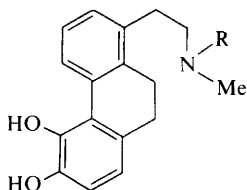
¹⁷⁶ L. L. Butcher, S. G. Butcher, and K. Larsson, *European J. Pharmacol.*, 1969, **7**, 283 (*Chem. Abs.*, 1970, **72**, 30 114u).

¹⁷⁷ W. C. Gibson, B.P. 1 138 154 (*Chem. Abs.*, 1970, **73**, 112 990m).

pigeons and dogs, and as an inducer of the gnawing response in mice and of the 'pecking syndrome' in pigeons. Both phenolic groups of apomorphine must be free for the compound to exert significant vomiting effects.⁶⁸ *N*-Ethylnor-apomorphine shows emetic stimulant activity in dogs superior to that of apomorphine.¹⁷⁸

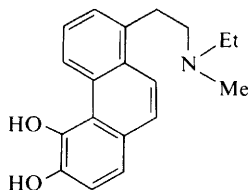
(+)-Apomorphine, its dimethyl ether, and the dimethyl ether of (–)-apomorphine do not possess significant apomorphine-like activity as a stimulator of dopamine receptor properties.¹⁷⁹

The compulsive, dopamine-like, gnawing syndrome elicited by low doses of apomorphine in rodents¹⁸⁰ was also observed for the tricyclic analogues (226)–(228).⁶⁵



(226) R = Me

(227) R = Et



(228)

Some studies on the metabolism of apomorphine have been conducted.^{181,182}

Isoboldine inhibits the insect feeding on the leaves of *Cocculus trilobus* DC.¹⁸³ Glaucine, bulbocapnine, corydine, and isocorydine exhibited adrenolytic action in anaesthetized cats and rabbits, with glaucine showing the highest activity. Glaucine also possessed strong antitussive properties in tolerable doses, and did not cause catalepsy.¹⁸⁴

The pharmacology of quaternary derivatives of corydine, glaucine, and *O*-methylcorydine, and of corytuberine methiodide, has been investigated using mice and rabbits. These salts are toxic, causing a decrease in mobility, difficult breathing, and then death; some decrease of blood pressure was noticed in dogs.¹⁸⁵ The muscular relaxant roemorine ethochloride (remaxane) has been

¹⁷⁸ M. V. Koch and J. G. Cannon, *J. Medicin. Chem.*, 1968, **11**, 977. See also S. Archer, U.S.P. 3 717 643 (*Chem. Abs.*, 1973, **78**, 111 578z).

¹⁷⁹ W. S. Saari, S. W. King, and V. J. Lotti, *J. Medicin. Chem.*, 1973, **16**, 171.

¹⁸⁰ R. M. Pinder, D. A. Buxton, and D. M. Green, *J. Pharm. Pharmacol.*, 1971, **23**, 995 (*Chem. Abs.*, 1972, **76**, 94 678w).

¹⁸¹ P. N. Paul, E. Brochmann-Hanssen, and E. Leong Way, *J. Pharm. Sci.*, 1961, **50**, 840.

¹⁸² P. N. Kaul and M. W. Conway, *J. Pharm. Sci.*, 1971, **60**, 93.

¹⁸³ K. Wada and K. Munakata, *J. Agric. Food Chem.*, 1968, **16**, 471.

¹⁸⁴ V. V. Berezhinskaya, E. E. Aleshinskaya, and Y. A. Aleshkina, *Farmakol. Toksikol.*, 1968, **31**, 44 (*Chem. Abs.*, 1968, **68**, 94 521z).

¹⁸⁵ Kh. S. Shakhabutdinova, I. K. Kamilov, and S. F. Fakhrutdinov, *Farmakol. Alkaloidov Glikozidov*, 1967, 142 (*Chem. Abs.*, 1969, **70**, 2219x). See also *Chem. Abs.*, 1969, **70**, 2220r and 2221s.

used in experimental narcosis using dogs.¹⁸⁶ (+)-Roemerine free base has also shown some activity as an antibacterial agent.¹⁸⁷

The aporphines actinodaphnine, launobine, ocoteine, dicentrine, *N*-methyl-laurotetanine, and especially xylopine are growth inhibitors of the micro-organism *Scenedesmus obliquus*.¹⁸⁸

The well-known catatonic effect of bulbocapnine has been studied in cats; the cataleptic condition lasting for over two hours.¹⁸⁹ Morphine sulphate as well as bulbocapnine hydrochloride when injected into rats induced a state of catatonia.¹⁹⁰ Bulbocapnine has also been shown to be an α -adrenergic blocking agent, which explains its catatonic action.¹⁹¹

The *in vitro* metabolism of nornuciferine and several of its derivatives by rat, rabbit, and guinea-pig liver microsomes was studied. Nornuciferine was found as a metabolite of the *N*-alkylated analogue. The conversion of nornuciferine into the corresponding oxoaporphine lysicamine was observed metabolically with rat and rabbit microsomes.¹⁹²

N-Propyl-laurotetanine possesses antifibrillatory activity.^{192a}

7 Specific Rotations, Absolute Configurations, and Structural Relationships among Aporphines

Definite trends can be distinguished among naturally occurring aporphines relating to specific rotations, absolute configurations, and structures.¹⁹³ Specific rotation is a good indicator of absolute configuration for an aporphine. If the alkaloid is strongly positive in rotation, then its absolute configuration is such as to possess an *alpha* C-6a hydrogen, and *vice versa*.¹⁹³

For the purposes of this discussion, all the known aporphines have been listed below in terms of their substitution patterns. Dehydroaporphines do not possess asymmetry, and are optically inactive. In a few instances the absolute configuration has been deduced by the Reporters from structural relationships with other aporphines of known stereochemistry.

In the case of 1,2-substitution, where ring D is unsubstituted, the trend is towards laevorotation. (+)-Nuciferine and (+)-roemerine are exceptions, and it is interesting to note that they both originate in the family Papaveraceae. There is only one 1,2,3-substituted aporphine known, namely guatterine, and it

¹⁸⁶ S. F. Fakhrutdinov, I. K. Kamilov, and I. N. Zimon, *Farmakol. Alkaloidov Glikozidov*, 1967, 151 (*Chem. Abs.*, 1969, **70**, 2222t).

¹⁸⁷ N. A. Akhmedov and S. F. Fakhrutdinov, *Farmakol. Alkaloidov Glikozidov*, 1967, 245.

¹⁸⁸ J. R. Jatimliansky and E. M. Sivori, *Anales Soc. Cient. Argentina*, 1969, **187**, 49 (*Chem. Abs.*, 1970, **72**, 974g; 1971, **74**, 95 958h).

¹⁸⁹ P. Borenstein, F. Gekiere, P. Alaonard, J. Gruet-Masson, and G. Allegre, *Semaine Hop. Paris*, 1969, **45**, 1247 (*Chem. Abs.*, 1969, **71**, 89 898k).

¹⁹⁰ R. E. Nichols, C. S. Patterson, and E. J. Walaszek, *Arch. Internat. Pharmacodyn. Therap.*, 1970, **184**, 19 (*Chem. Abs.*, 1970, **73**, 12 861b).

¹⁹¹ E. E. Smissman, S. El-Antably, L. W. Hedrich, E. J. Walaszek, and L.-F. Tseng, *J. Medicin. Chem.*, 1973, **16**, 109. See also L. F. Tseng, E. Wei, and H. H. Loh, *European J. Pharmacol.*, 1973, **22**, 363 (*Chem. Abs.*, 1973, **79**, 100 657u).

¹⁹² R. V. Smith and S. Sood, *J. Pharm. Sci.*, 1971, **60**, 1654.

^{192a} Laboratoire R. Bellou, F.P. 2 130 107 (*Chem. Abs.*, 1973, **78**, 136 492e).

¹⁹³ M. Shamma and M. J. Hillman, *Experientia*, 1969, **25**, 544.

too is laevorotatory. In the case of C-1,2- or C-1,2,3-substituted aporphines, it has also been noted that when the C-1 substituent is a methoxy-group the magnitude of the specific rotation is larger than 145° ; but if a hydroxy- or a methylenedioxy-group is present at C-1, then the magnitude is less than 120° .¹⁹³

Stephanine is the only known 1,2,8-substituted aporphine, and it exhibits a negative rotation. The trend in 1,2,9-substitution also appears to be negative, although the values for the rotations of michelanugine, roemeroline, and lirinine were not available to the Reporters. Aporphines substituted in a 1,2,10-pattern exhibit small specific rotations which makes the absolute configuration difficult to determine and somewhat uncertain. In this group no trend can be discerned, and both dextro- and laevo-enantiomers have been isolated; in addition the interesting aporphine variabiline is a racemate.

In 1,2,11-substitution, isothebaine found in Papaveraceae species is dextro-rotatory, but the remaining three bases are laevorotatory. There is only one fully authenticated case of a 1,2,8,9-substituted aporphine, crebanine, and it is laevorotatory.

Of the 31 aporphines with 1,2,9,10-substitution, all but a few exhibit dextro-rotation. Exceptions are the rare (–)-phanostenine, and the recently isolated (–)-dicentrine and (–)-duguetine. Additionally, (±)-isoboldine has been reported, again from a Papaveraceae source.

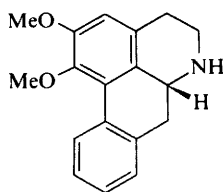
With no exception, the 22 1,2,10,11-substituted aporphines show dextro-rotation. The one notorious exception, (–)-laurepukine, has now been shown to be the *N*-oxide of pukateine, a 1,2,11-trisubstituted aporphine.¹⁹⁴

Aporphines of the 1,2,3,9,10-substitution pattern are all dextrorotatory, and the same can be stated for aporphines with 1,2,3,10,11-, 1,2,8,9,10-, and 1,2,9,10,11-substitution patterns.¹⁹³

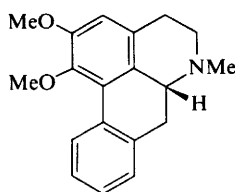
It should be noted that positions 1 and 2 are always substituted in aporphines, and that whenever C-11 is also substituted the specific rotation will be quite large, in the order of $\pm 200^\circ$.¹⁹³

In the listing that follows, the ‡ symbol denotes that the alkaloid is described in the present review.

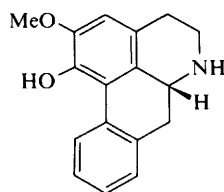
1,2-Substitution



(–)-Nornuciferine²

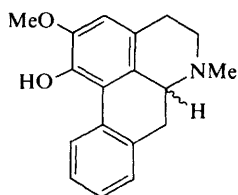


(–)-Nuciferine²
[(+)-Nuciferine]‡

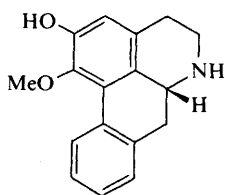


(–)-Caaverine³

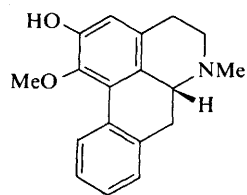
¹⁹⁴ Ek. Weiss, K. Bernauer, and A. Girardet, *Helv. Chim. Acta*, 1971, **54**, 1342.



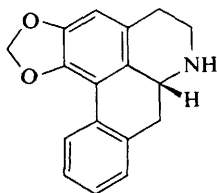
O-Demethylnuciferine[†]



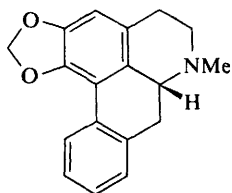
(-)-Asimilobine³



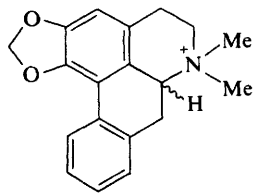
(-)-1-Methoxy-2-hydroxy-aporphine²



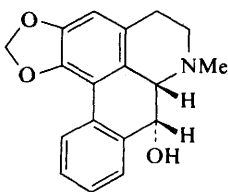
(-)-Anonaine^{1,2}



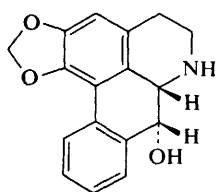
(-)-Roemerine^{1,2}
[(+)-Roemerine][†]



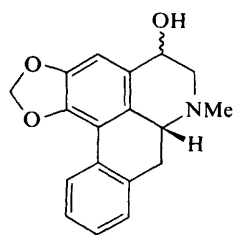
Remrefidine[†]



(-)-Ushinsunine²

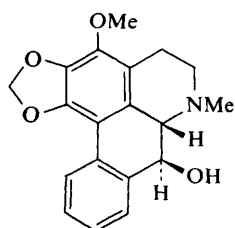


(-)-Norushinsunine

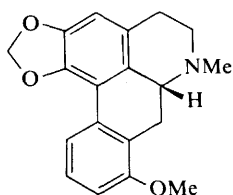
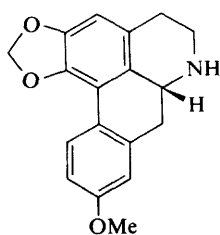
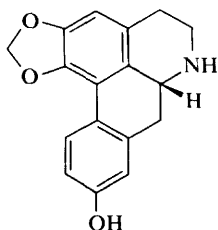
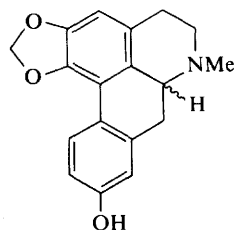
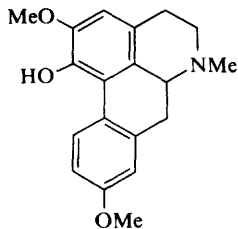
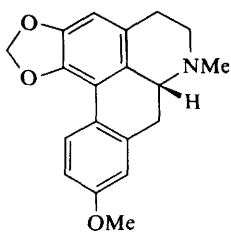
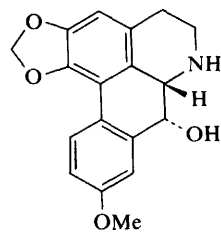
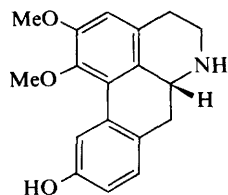
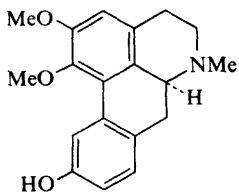
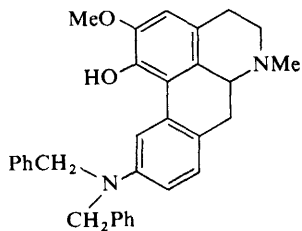


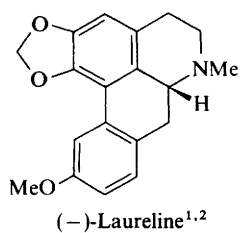
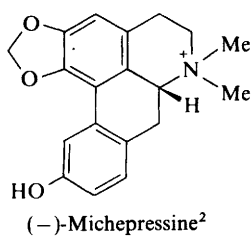
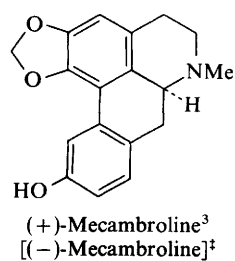
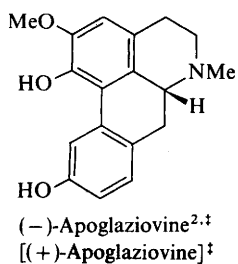
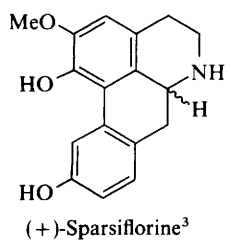
(-)-Steporphine[†]

1,2,3-Substitution

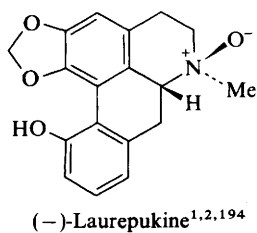
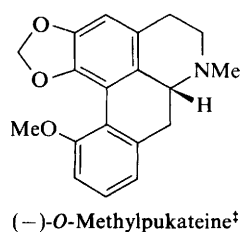
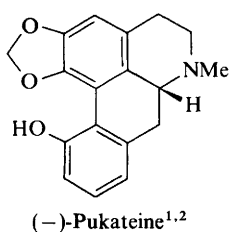
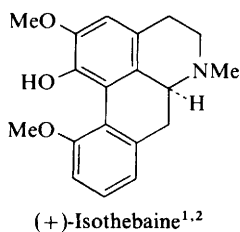


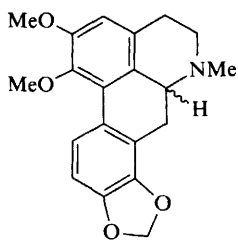
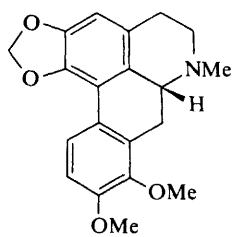
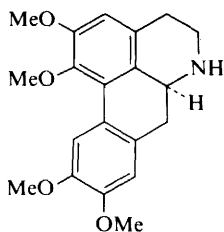
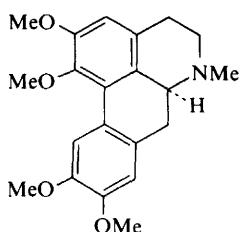
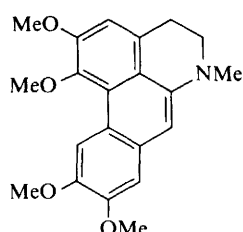
(-)-Guatterine³

1,2,8-Substitution**(-)-Stephanine^{1,2}****1,2,9-Substitution****(-)-Xylopinine²****(-)-Anolobine^{1,2}****Roemeroline[†]****Lirinine[‡]****(-)-Isolaureline^{194a}****Michelanugine^{61a‡}****1,2,10-Substitution****(-)-Tuduranine^{1,2}****(+)-Nuciferoline[‡]****(±)-Variabiline[‡]**^{194a}J. Schmutz, *Helv. Chim. Acta*, 1959, **42**, 335.

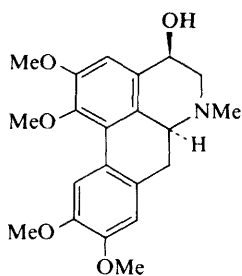
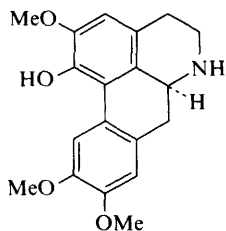
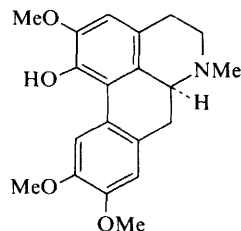
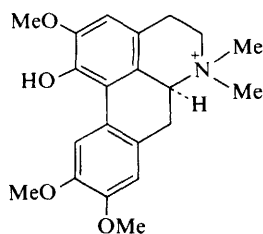
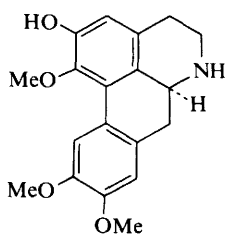
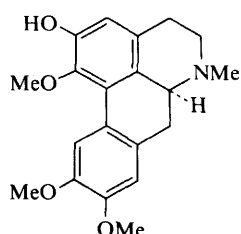


1,2,11-Substitution



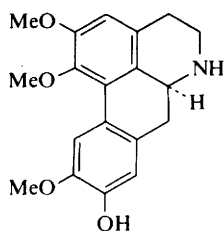
1,2,8,9-SubstitutionUnnamed base[†](-)-Crebanine^{1,2}**1,2,9,10-Substitution**(+) -Norglaucine[†](+) -Glaucine^{1,2}

Dehydroglaucine

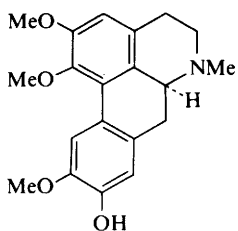
(+) -Cataline[†](+) -Wilsonirine[†](+) -Thaliporphine^{2,3,195}(+) -Fagara alkaloid^{2,3}(+) -Norpredicentrine[†](+) -Predicentrine[†]

* The stereochemistry of (+)-cataline at C-4 is not certain.

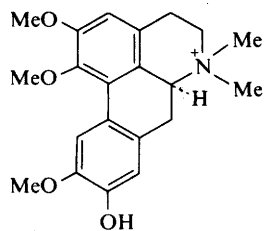
¹⁹⁵ M. Shamma, M. J. Hillman, R. Charubala, and B. R. Pai, *Indian J. Chem.*, 1969, 7, 1056.



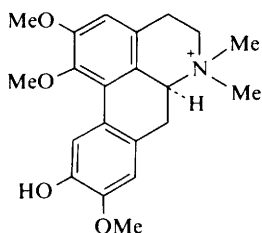
(+)-Laurotetanine^{1,2}



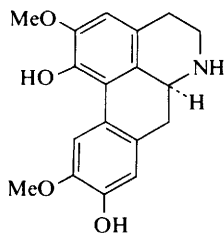
(+)-N-Methyl-laurotetanine^{1,2}



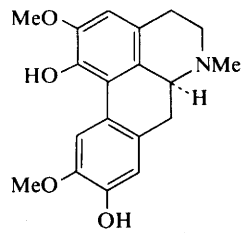
(+)-Xanthoplanine²



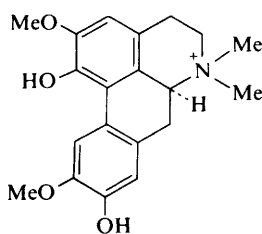
(+)-Cocsarmine²



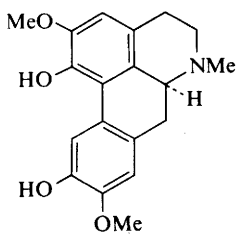
(+)-Laurelliptine^{3,196}
(≡ Norisoboldine)



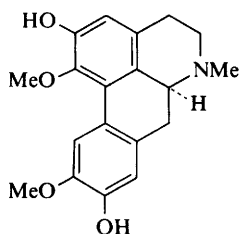
(+)-Isoboldine²
[[±]-Isoboldine][‡]



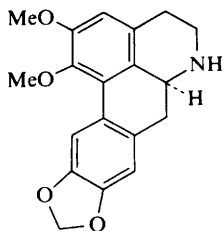
(+)-Laurifoline²



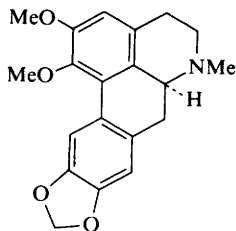
(+)-Bracteoline[‡]



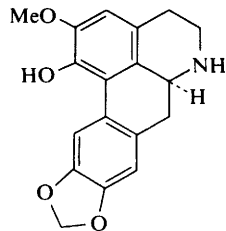
(+)-Boldine^{1,2}



(+)-Nornantenine[‡]

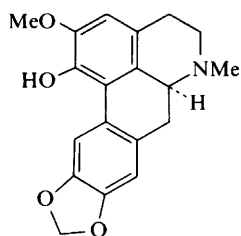
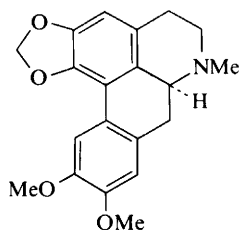
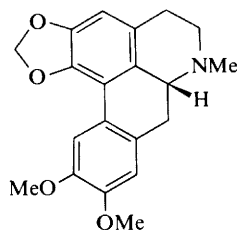
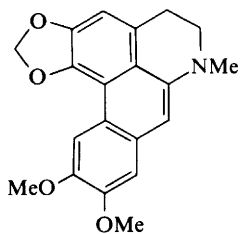
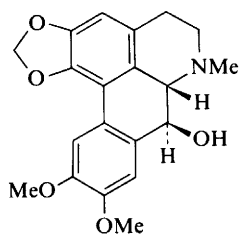
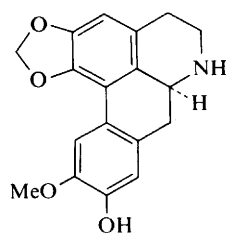
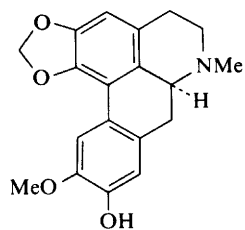
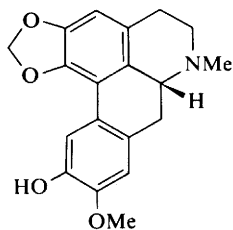
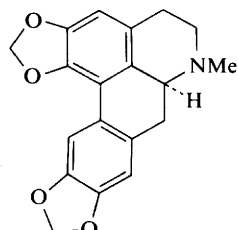
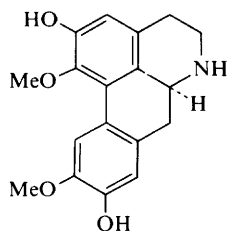


(+)-Nantenine^{1,2}

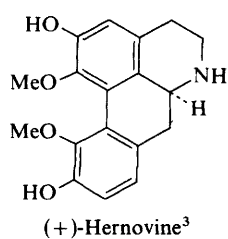
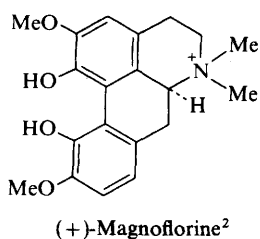
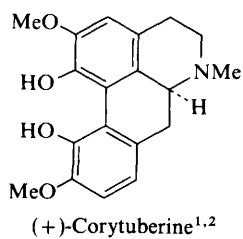
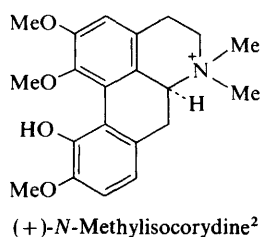
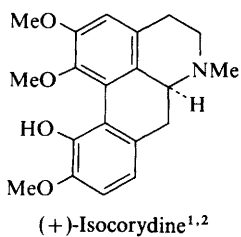
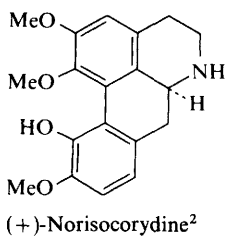
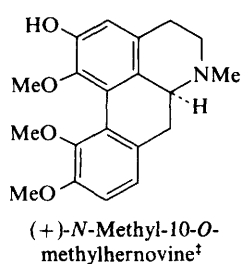
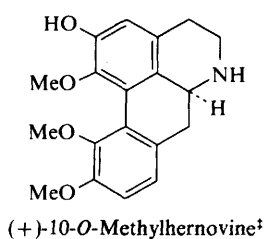
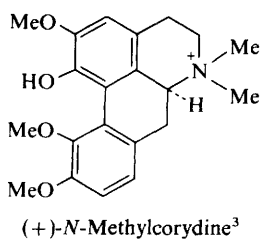
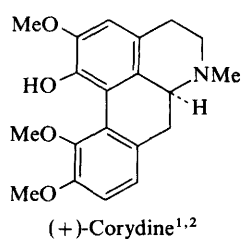
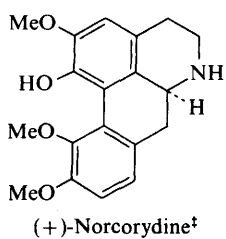
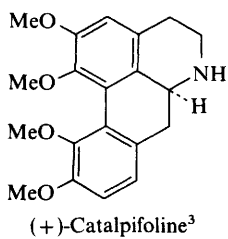


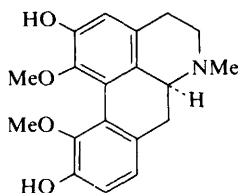
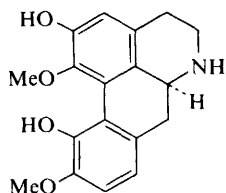
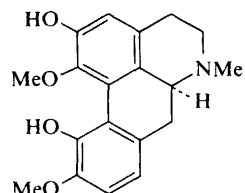
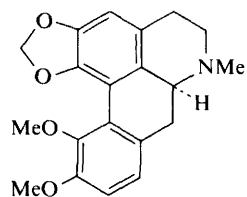
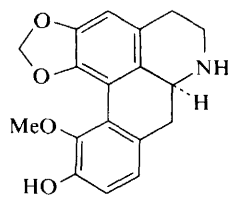
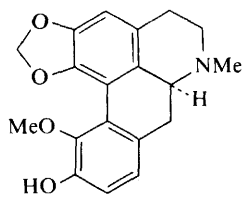
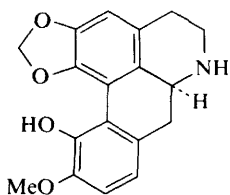
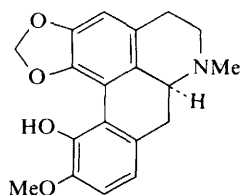
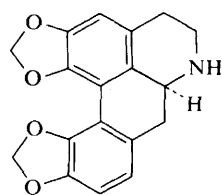
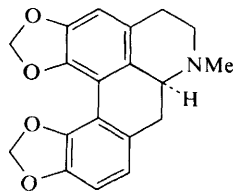
(+)-Nordomesticine[‡]

¹⁹⁶ T. Kametani, Y. Satoh, K. Fukumoto, and B. R. Pai, *Indian J. Chem.*, 1971, **9**, 770.

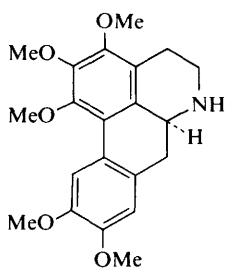
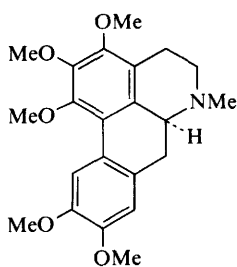
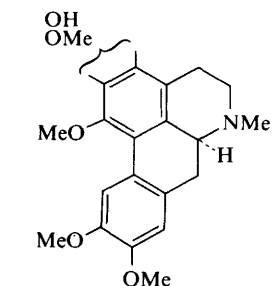
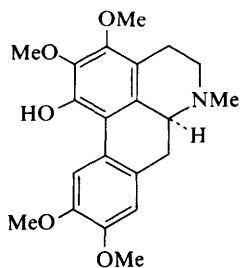
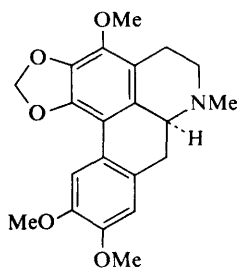
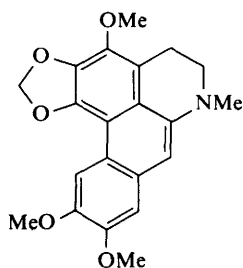
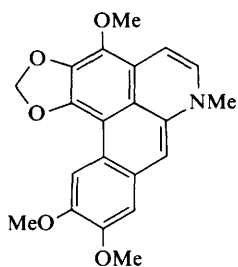
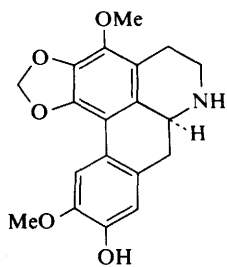
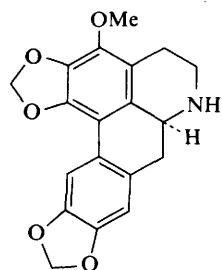
(+) -Domesticine^{1,2}(+) -Dicentrine^{1,2}(-) -Dicentrine[‡]Dehydrodicentrine[‡](-) -Duguetine[‡](+) -Actinodaphnine^{1,2}(+) -N-Methylactinodaphnine³(-) -Phanostenine^{1,2}(+) -Neolitsine³(+) -Lauiolitsine²

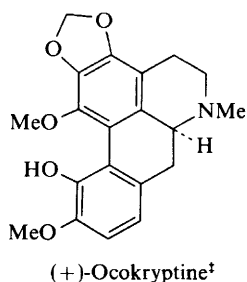
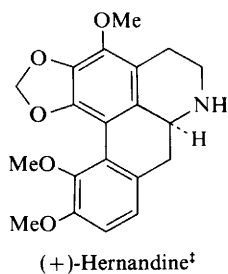
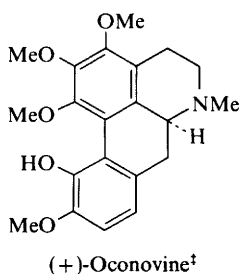
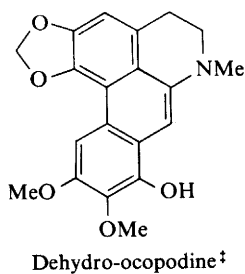
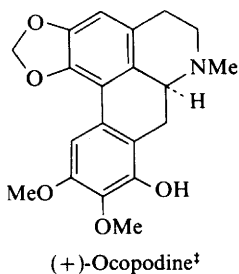
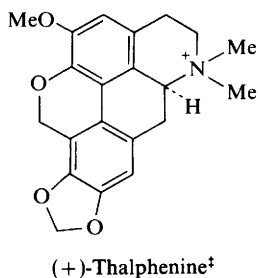
1,2,10,11-Substitution



**(+)-N-Methylhernovine[†]****(+)-Lindcarpine[†]****(+)-N-Methyl-lindcarpine[†]****(+)-O-Methylbulbocarpine[†]****(+)-Nandigerine³****(+)-N-Methylnandigerine³****(+)-Launobine³****(+)-Bulbocarpine^{1,2}****(+)-Ovigerine³****(+)-N-Methylovigerine³**

1,2,3,9,10-Substitution

**(+)-Norpurpureine[†]****(+)-Thalicsimidine[†]
[≡(+)-Purpureine]****(+)-O-Demethylpurpureine[†]****(+)-Preocoteine³****(+)-Ocoteine^{2,196a}****Dehydro-ocoteine[†]****Didehydro-ocoteine[†]****(+)-Cassyfiline³****(+)-Cassythidine³**^{196a} G. Y. Moltrasio, D. Giacomello, and M. J. Vernengo, *Austral. J. Chem.*, 1973, **26**, 2035.

1,2,3,10,11-Substitution**1,2,8,9,10-Substitution****1,2,9,10,11-Substitution****8 N.M.R. Spectroscopy and Labelled Aporphines**

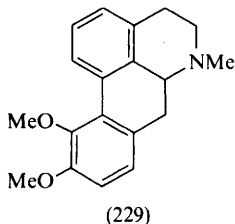
Much of the n.m.r. spectral data on the aporphines has already been summarized.^{2,3,6,47,139,197-199}

¹⁹⁷ I. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Vernengo, *J. Chem. Soc.*, 1961, 1896.

¹⁹⁸ T.-H. Yang, *J. Pharm. Soc. Japan*, 1962, **82**, 804.

¹⁹⁹ D. S. Bhakuni, S. Tewari, and M. M. Dhar, *Phytochemistry*, 1972, **11**, 1819.

10,11-Dimethoxy[8-²H]aporphine has recently been synthesized through bromination of 10,11-dimethoxyaporphine (229) in acetic acid, followed by catalytic deuteration. When the n.m.r. spectrum of (229) was measured in the presence of increasing quantities of $\text{Eu}(\text{fod})_3$, a large downfield shift of the C-10 methoxyl protons was observed. Since the substituents at C-9 and C-10 were methoxyls, the C-8 and C-9 protons were split as a quartet, and it was possible to conclude that in the absence of $\text{Eu}(\text{fod})_3$, the C-9 H appears upfield from the C-8 H. The use of $\text{Eu}(\text{fod})_3$ enabled the resolution of all the aromatic protons.²⁰⁰



Tritiated apomorphine has been prepared from morphine and tritiated phosphoric acid. An analysis of the ABX spectrum of apomorphine due to H-1, H-2, and H-3 yielded the following chemical shifts: δ 8.20, 7.17, and 7.00, respectively, with coupling constants $J_{1,2} = 7.40$ Hz, $J_{1,3} = 0.93$ Hz, and $J_{2,3} = 7.77$ Hz. Study of the AB pattern due to the two aromatic protons of ring c gave δ 6.73 and 6.60 as the chemical shifts for H-9 and H-8, respectively.²⁰¹ This assignment of chemical shifts is apparently at variance with the assignment in the case of 10,11-dimethoxyaporphine discussed above.

Within 15 minutes after apomorphine was treated at 95 °C with D_3PO_4 , H-8 and H-9 had been exchanged. Two hours later, 40% of H-1 had also been exchanged for ²H. Finally, after raising the temperature to 140 °C, up to four aromatic deuterium atoms had been introduced in the molecule. The hydrogen at C-2, δ 7.33, was the least reactive towards such electrophilic substitution.²⁰¹

9 U.V. Spectroscopy

Tables describing the u.v. curves of aporphines have already appeared.^{2,3,6} The u.v. spectra of monophenolic aporphines in basic solution can yield useful information. The presence of a phenolic function at C-9 results in strong absorption between 315 and 330 nm upon the addition of base.²⁰²

An absorption maximum or shoulder between 252 and 265 nm is diagnostic of a dehydroaporphine.⁶

Note added in proof: For an addendum to this chapter, see p. 428.

²⁰⁰ R. V. Smith and A. W. Stocklinski, *Tetrahedron Letters*, 1973, 1819.

²⁰¹ J. Z. Ginos, A. LoMonte, G. C. Cotzias, A. K. Bose, and R. J. Brambilla, *J. Amer. Chem. Soc.*, 1973, **95**, 2991.

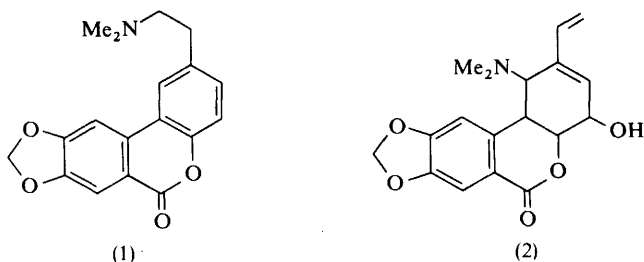
²⁰² M. Shamma, S. Y. Yao, B. R. Pai, and R. Charubala, *J. Org. Chem.*, 1971, **36**, 3253.

BY V. A. SNIECKUS

Syntheses of Amaryllidaceae alkaloids which have been achieved by phenol oxidative coupling¹ and photocyclodehydrohalogenation² reactions have been reviewed.

Four new bases from *Crinum glaucum*, criglaucine ($C_{17}H_{21}NO_5$), criglaucidine ($C_{17}H_{19}NO_5$), alkaloid-CG2 ($C_{17}H_{19}NO_4$), and alkaloid-CG6 ($C_{18}H_{21}NO_5$), have been identified by g.c.-m.s. analysis of their trimethylsilyl ether derivatives.³ Details concerning the structural elucidation of galanthusine isolated from *Galanthus caucasicus* (see Vol. 2 of this Report) are now available.⁴ Galanthamine is found in *Leucojum vernum* (see Vol. 2) but not in *L. vernum* var. *carpathicum*.⁵ Homolycorine was also found in the latter species. A detailed description of the procedure for the isolation of lycorine from *Ungernia sewerzowi* has appeared.⁶

1-De-*N*-methylungerine and 1-de-*N*-methylhippeastrine, the presumed Hofmann degradation products of the corresponding alkaloids, have been assigned structures (1) and (2) respectively on the basis of spectroscopic data.⁷ Compound (2) would appear to be highly unstable on the basis of certain contained structural features.



¹ T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657.

² T. Kametani and K. Fukumoto, *Accounts Chem. Res.*, 1972, 5, 212.

³ D. S. Millington, D. E. Games, and A. H. Jackson, Proceedings of the International Symposium on Gas Chromatography and Mass Spectrometry, ed. A. Frigerio, Tamburini, Milan, 1972, p. 275.

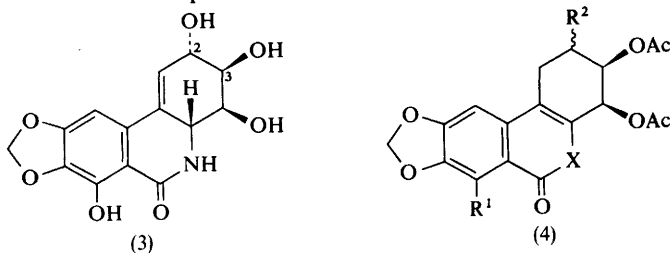
⁴ S. Yu. Yunusov, T. N. Kiparenko, R. Razakov, A. Abdusamatov, and D. M. Tsakadze, *Soobshch. Akad. Nauk Gruz. S.S.R.*, 1972, 65, 333 (*Chem. Abs.*, 1972, 77, 45 496x).

⁵ S. Kohlmuenzer and E. Cyunel, *Postep Dziedzinnie Leku Rosl., Pr. Ref. Dosw. Wygloszone Symp.*, 1970, 109 (*Chem. Abs.* 1973, 78, 55 297t).

⁶ T. Sadikov and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1972, 8, 134 (*Chem. Abs.*, 1972, 77, 58 762f).

⁷ M. R. Yagudaev and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, 8, 505 (*Chem. Abs.*, 1972, 77, 164 897p).

The structure and stereochemistry of narciclasine (3) have been determined by *X*-ray analysis of its tetra-*O*-acetate.⁸ In the crystal state, the heterocyclic ring of narciclasine adopts an approximate boat conformation and the cyclohexane ring approaches a distorted half-chair conformational form.⁸ The relative stereochemistry of narciclasine obtained by *X*-ray analysis is in agreement with that deduced from chemical and spectroscopic data⁹ although this view represents a revision of the original formulation (3; 2 β -OH) (see Vol. 2). Comparison of the n.m.r. spectra of isonarciclasine tetra-*O*-acetate (4; R¹ = OAc, R² = α -OAc, X = NH) and the synthetic compounds (4; R¹ = H, R² = α -OAc, X = O) and (4; R¹ = H, R² = β -OAc, X = O) of known stereochemistry led to the unequivocal relative stereochemical assignment for narciclasine (3). The splitting pattern and chemical shift of the methylene protons in isonarciclasine tetra-*O*-acetate (4; R¹ = OAc, R² = α -OAc, X = NH) were very similar to those of compound (4; R¹ = H, R² = α -OAc, X = O) but quite different from those observed in compound (4; R¹ = H, R² = β -OAc, X = O). The structure (3) as written also represents the absolute configuration of narciclasine as deduced from biosynthetic experiments.⁸ The *X*-ray crystallographic analysis of mesembranol (5)¹⁰ and the interesting pyrido-mesembranol relative Alkaloid A₄ (6)¹¹ have also been completed.



Important papers have appeared dealing with the high-resolution mass spectroscopic analysis of crinine (7; R = H₂) and *C*-11-oxygenated crinine (7; R = H, OH or R = O) alkaloids.^{12,13} The results lead to a better general understanding of *Amaryllis* alkaloid fragmentation patterns and correct several previous misinterpretations. Notable features in the mass spectra of the crinine (7; R = H₂) derivatives are the stability of the molecular ions, the importance of the aromatic ring in ion stabilization, and the facility with which the nitrogen atom is lost as a neutral or radical species.¹² In the *C*-11-OH series (7; R = H, OH), the fragmentation pattern is strongly governed by the ability of the hydroxylic hydrogen to undergo rearrangement and by certain stereochemical features.¹³

⁸ A. Immirzi and C. Fuganti, *J. C. S. Chem. Comm.*, 1972, 240; C. Fuganti and M. Mazza, *ibid.*, p. 239.

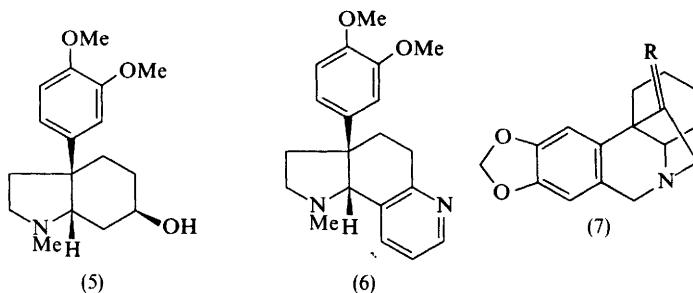
⁹ A. Mondon and K. Krohn, *Tetrahedron Letters*, 1972, 2085.

¹⁰ P. A. Luhan and A. T. McPhail, *J. C. S. Perkin II*, 1973, 51.

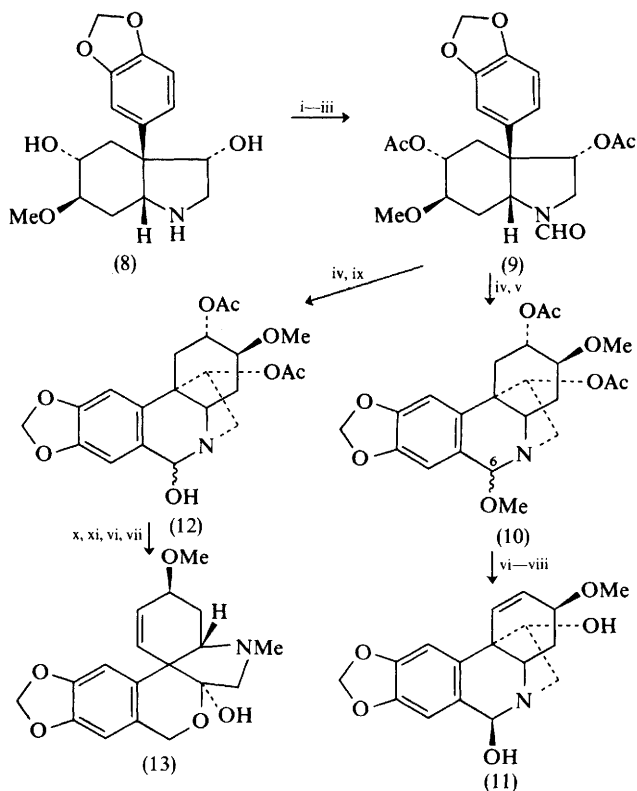
¹¹ P. A. Luhan and A. T. McPhail, *J. C. S. Perkin II*, 1972, 2006.

¹² P. Longevialle, D. H. Smith, A. L. Burlingame, H. M. Fales, and R. J. Highet, *Org. Mass Spectrometry*, 1973, 7, 401.

¹³ P. Longevialle, H. M. Fales, R. J. Highet, and A. L. Burlingame, *Org. Mass Spectrometry*, 1973, 7, 417.



A number of interesting synthetic contributions have appeared in the past year. (\pm)-Haemanthidine (11) and (\pm)-tazettine (13) have been synthesized¹⁴ (Scheme 1) starting with the perhydroindole (8), a key intermediate used previously



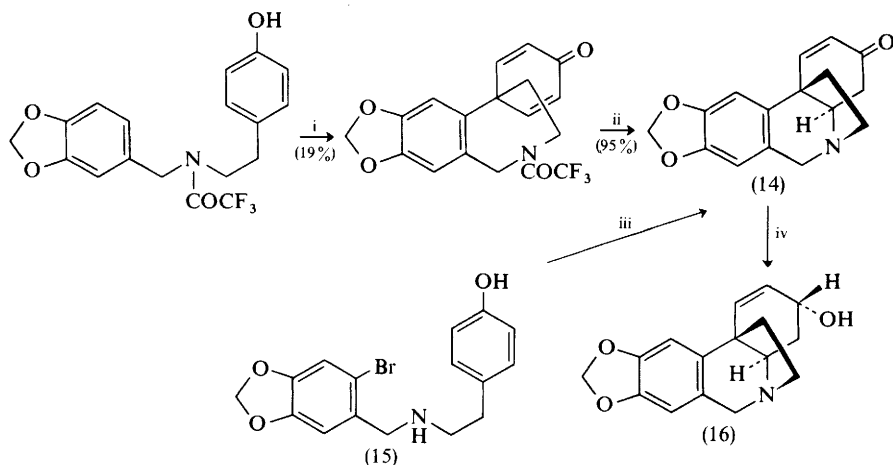
Reagents: i, HCO_2Ac ; ii, $\text{NaHCO}_3\text{-MeOH}$; iii, $\text{Ac}_2\text{O-C}_5\text{H}_5\text{N}$; iv, $\text{POCl}_3\text{-xylene}$; v, MeOH ; vi, $\text{TsCl-C}_5\text{H}_5\text{N}$; vii, DBU-DMSO ; viii, 50% HOAc ; ix, $\text{Na}_2\text{CO}_3\text{-H}_2\text{O}$; x, MeI-MeOH ; xi, 20% aq. NaOH .

Scheme 1

¹⁴ Y. Tsuda, A. Ukai, and K. Isobe, *Tetrahedron Letters*, 1972, 3153.

in the preparation of another Amaryllidaceae alkaloid (see Vol. 3). An interesting step in this sequence is the Bischler–Napieralski reaction of (9), which presumably yields the C-6-chloro-derivative corresponding to structure (10). Solvolysis of this compound then gives compound (10) in which the C-6-methoxy-group serves as a protective group to prevent a hemanthidine (11) \rightarrow tazettine (13) skeletal rearrangement. On the other hand, this rearrangement was induced on the C-6-OH derivative (12) and thus (\pm)-tazettine (13) was also synthesized from the intermediate (9) by an appropriate change of conditions.

A simple synthesis of (\pm)-oxocrinine (14) has been effected using a two-electron phenol oxidative coupling reaction with thallium(III) trifluoroacetate (Scheme 2).¹⁵ Another synthesis of (\pm)-oxocrinine (14) and its conversion into (\pm)-epicrinine (16) using a photochemical reaction [(15) \rightarrow (14)] as a key step have been reported (Scheme 2).¹⁶ This type of reaction, which must involve a photocyclodehydrohalogenation followed by an internal Michael reaction, was also used in the low-yield synthesis of the narwedine-like enones (17; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$) and (17; $R^1 = \text{Me}$, $R^2 = \text{H}$).¹⁷ The enone (17; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$) was also prepared in low yield by a phenol oxidative coupling reaction using potassium ferricyanide in chloroform solution.¹⁷ Syntheses of similar origin for (\pm)-*N*-norgаланthamine (18; $R = \text{H}$) and (\pm)-*N*-norlycoramine (18; $R = \text{H}$, x,y saturated) have been devised.¹⁸



Reagents: i, $\text{Ti}(\text{OAc})_3\text{-CH}_2\text{Cl}_2$; ii, $\text{Na}_2\text{CO}_3\text{-MeOH-H}_2\text{O}$; iii, $h\nu$; iv, Meerwein–Ponndorf reduction.

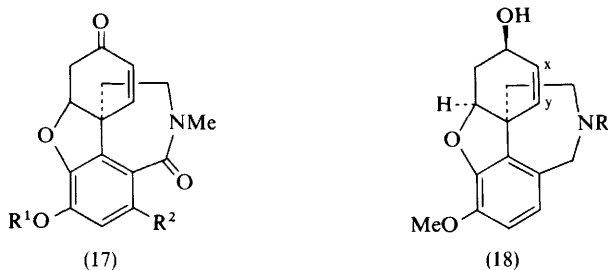
Scheme 2

¹⁵ M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Amer. Chem. Soc.*, 1973, **95**, 612.

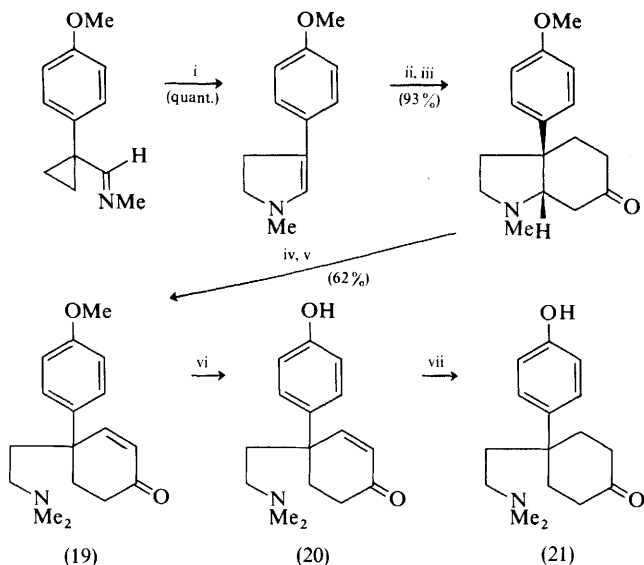
¹⁶ T. Kametani, T. Kohno, R. Charubala, S. Shibuya, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1488.

¹⁷ T. Kametani, K. Yamaki, T. Terui, S. Shibuya, and K. Fukumoto, *J. C. S. Perkin I*, 1972, 1513.

¹⁸ T. Kametani, K. Yamaki, and T. Terui, *J. Heterocyclic Chem.*, 1973, **10**, 35.



The *Sceletium* alkaloids (\pm)-joubertiamine (19), (\pm)-*O*-methyljoubertiamine (20), and (\pm)-dihydrojoubertiamine (21) have been synthesized by the application of certain general methods used previously (*cf.* Vol. 2) for the preparation of Amaryllidaceae and other alkaloids (Scheme 3).¹⁹



Reagents: i, NH_4Cl , 140°C , N_2 ; ii, $\text{HCl-Et}_2\text{O}$; iii, $\text{CH}_2=\text{CHCOMe-MeCN}$, reflux; iv, MeI , reflux; v, 0.5N-KOH ; vi, $48\% \text{HBr}$; vii, $\text{H}_2\text{-Pd/C-MeOH}$.

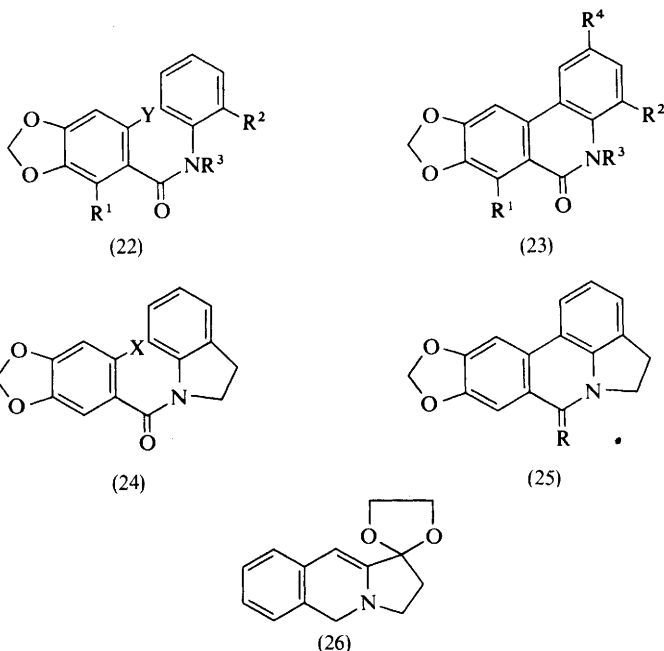
Scheme 3

A number of model photochemical syntheses of narciprimine analogues (23) from the corresponding benzanilides (22) were undertaken in order to define the effect of substituents in the mode of the photocyclization reaction.²⁰ The synthesis of narciprimine was achieved as follows: irradiation of (22; $\text{R}^1 = \text{R}^2 = \text{OCH}_2\text{Ph}$, $\text{R}^3 = \text{H}$, $\text{Y} = \text{Br}$) gave the phenanthridone (23; $\text{R}^1 = \text{R}^2 = \text{OCH}_2\text{Ph}$,

¹⁹ R. V. Stevens and J. T. Lai, *J. Org. Chem.*, 1972, **37**, 2138.

²⁰ A. Mondon and K. Krohn, *Chem. Ber.*, 1972, **105**, 3726.

$R^3 = R^4 = H$) which upon complete debenzoylation gave narciprimine (23; $R^1 = R^2 = OH$, $R^3 = R^4 = H$). The bromine substituent in (22) was found to be crucial for the success of the photocyclization reaction. An alternative approach to narciprimine-type compounds *via* a Pschorr reaction has also been reported.²¹ Thus the diazonium salt of (22; $R^1 = R^2 = OMe$, $R^3 = Me$, $Y = NH_2$) gives a moderate yield of permethylnarciprimine (23; $R^1 = R^2 = OMe$, $R^3 = Me$, $R^4 = H$). Permethylnarciprimine (23; $R^1 = R^4 = OMe$, $R^2 = H$, $R^3 = Me$) was similarly synthesized.



A photochemical route to anhydrolycorine (25; $R = H_2$) has been announced.²² Irradiation of the indoline (24; $X = Br$) gave a 67% yield of the lactam (25; $R = O$), which was reduced with lithium aluminium hydride to anhydrolycorine (25; $R = H_2$). Interestingly, photolysis of (24; $X = H$) resulted only in the photo-Fries rearrangement. An interesting but unsuccessful approach to the lycorine skeleton *via* an annelation reaction on the 1,2-dihydroisoquinoline intermediate (26) has been described.²³

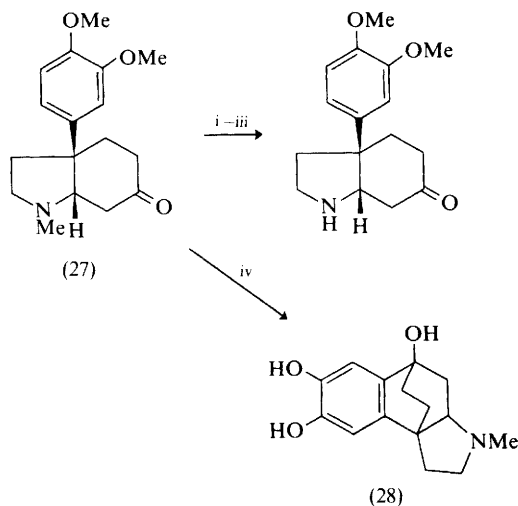
Of more than passing interest is the report describing demethylation reactions of mesembrine (27) (Scheme 4).²⁴ Although *N*-demethylation is straightforward, *O*-demethylation proceeds with rearrangement to (28).

²¹ G. Savona and F. Piozzi, *J. Heterocyclic Chem.*, 1971, **8**, 681.

²² H. Hara, O. Hoshino, and B. Umezawa, *Tetrahedron Letters*, 1972, 5031.

²³ S. F. Dyke, M. Sainsbury, and J. R. Evans, *Tetrahedron*, 1973, **29**, 213.

²⁴ P. Pfaeffli and H. Hauth, *Helv. Chim. Acta*, 1973, **56**, 347.



Reagents: i, $\text{HOCH}_2\text{CH}_2\text{OH} \cdot \text{H}^+$; ii, $p\text{-O}_2\text{NC}_6\text{H}_4\text{OCOC}_6\text{H}_5$, reflux; iii, KOH , 90°C ; iv, BBr_3 .

Scheme 4

The comparative pharmacological activities of galanthamine (18; $\text{R} = \text{Me}$) and epigalanthamine have been studied.²⁵ The structural relative narwedine, extracted from *Narcissus cyclamineus*, has been shown to enhance the pharmacological effects of caffeine in mice.²⁶ Pseudolycorine appears to show some promise as an anticarcinogenic agent.²⁷ The hypotensive activities of dihydrodiacetyl-lycorine²⁸ and apogalanthamine and its derivatives²⁹ have been investigated.

²⁵ U. B. Zakirov and Sh. S. Umarova, *Farmakol. Alkaloidov Serdech. Glikozidov*, 1971, 96 (*Chem. Abs.*, 1972, 77, 109 461s).

²⁶ E. D. Bazhenova, Kh. U. Aliev, and U. B. Zakirov, *Farmakol. Alkaloidov Serdech. Glikozidov*, 1971, 100 (*Chem. Abs.*, 1972, 77, 109 460r).

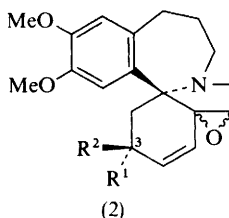
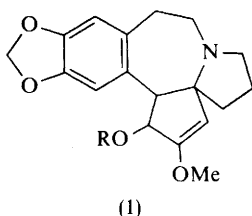
²⁷ E. Furusawa, N. Suzuki, S. Ramanathan, S. Furusawa, and W. Cutting, *Proc. Soc. Exp. Biol. Med.*, 1972, **140**, 1034.

²⁸ U. B. Zakirov and Kh. U. Aliev, *Farmakol. Alkaloidov Serdech. Glikozidov*, 1971, 111 (*Chem. Abs.* 1972, 77, 122 093t).

²⁹ Kh. U. Aliev, U. B. Zakirov, and K. V. Nadzhimutdinov, *Farmakol. Alkaloidov Serdech. Glikozidov*, 1971, 107 (*Chem. Abs.*, 1972, 77, 109 455t).

An extensive review concerning the synthesis of *Erythrina* and other alkaloids by the phenol oxidation coupling reaction has appeared.¹

In contrast to other *Cephalotaxus* species, *C. wilsoniana* yields only a minor amount of cephalotaxine (1; R = H), the major alkaloid being the homoerythrina-type compound wilsonine (2; R¹ = H, R² = OMe).² The C-3 epimer (2; R¹ = OMe, R² = H) of wilsonine and acetylcephalotaxine (1; R = Ac) were also isolated from *C. wilsoniana*. The structures of (2; R¹ = H, R² = OMe) and (2; R¹ = OMe, R² = H) were deduced from spectral data; furthermore, (2; R¹ = OMe, R² = H) was found to be identical with alkaloid 7 previously isolated from *Phelline comosa*. The absolute stereochemistry of all known homoerythrina alkaloids is assumed for wilsonine and its C-3 epimer but the epoxide stereochemistry remains to be determined.



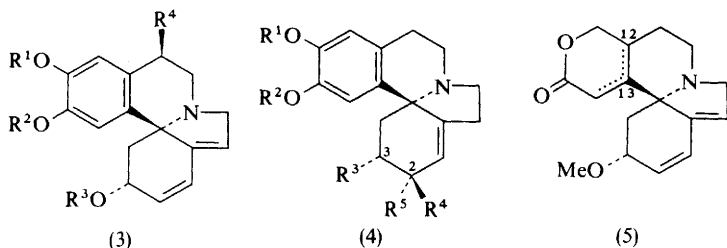
Examination and re-examination of a number of *Erythrina* species has yielded several new alkaloids.³ *E. lysistemon* (see also Vol. 2 of this Report) gave the known erysodine (3; R¹ = R⁴ = H, R² = R³ = Me) and a new base, erythristemine (3; R¹ = R² = R³ = Me, R⁴ = OMe), whose structure and stereochemistry were elucidated by spectral (in particular, n.m.r. with INDOR experiments) and X-ray crystallographic analysis. *E. abyssinica* yielded erythristemine, erythraline (3; R¹ + R² = CH₂, R³ = Me, R⁴ = H), and erythratine (4; R¹ + R² = CH₂, R³ = OMe, R⁴ = OH, R⁵ = H). From *E. poeppigiana* there were obtained the known α - and β -erythroidines (5; Δ^{12} -double bond) and (5; Δ^{13} -double bond),

¹ T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657.

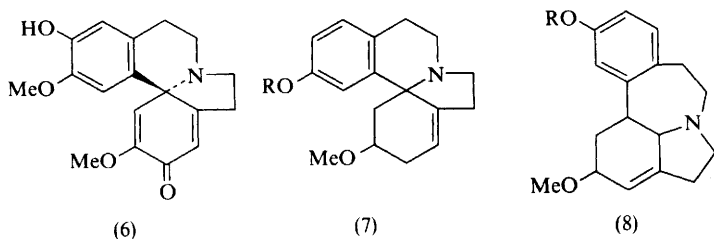
² R. G. Powell, K. L. Mikolajczak, D. Weisleder, and C. R. Smith, jun., *Phytochemistry*, 1972, 11, 3317.

³ D. H. R. Barton, A. A. L. Gunatilaka, R. M. Letcher, A. M. F. T. Lobo, and D. A. Widdowson, *J. C. S. Perkin I*, 1973, 874.

respectively. Only one alkaloid, erysotrine (3; $R^1 = R^2 = R^3 = \text{Me}$, $R^4 = \text{H}$), was obtained from *E. fusca* although a number of *Erythrina* bases have been isolated from this species by other workers. Finally, *E. lithosperma* proved to be most interesting in that it yielded, besides erythraline and erysotrine (3; $R^1 = R^2 = R^3 = \text{Me}$, $R^4 = \text{H}$), the new compounds erythratidinone (4; $R^1 = R^2 = \text{Me}$, $R^3 = \text{OMe}$, $R^4 + R^5 = \text{O}$) and 3-demethoxyerythratidinone (4; $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 + R^5 = \text{O}$), whose structures rest on extensive



spectral analysis and chemical correlation. In this connection, the structure and stereochemistry of erythratidine, isolated previously from *E. falcata*, was fully defined. Sodium borohydride reduction of erythratidinone (4; $R^1 = R^2 = \text{Me}$, $R^3 = \text{OMe}$, $R^4 + R^5 = \text{O}$) gave a mixture of epimers, one of which was identical with erythratidine. Application of Mills' rule to specific rotation data for the two epimers indicated that erythratidine possesses the (2*S*) absolute configuration. Other spectral and chemical information allowed the assignment of structure and absolute stereochemistry (4; $R^1 = R^2 = \text{Me}$, $R^3 = \text{OMe}$, $R^4 = \text{H}$, $R^5 = \text{OH}$) for erythratidine. The biogenesis of some of these alkaloids, in particular the unique 3-demethoxyerythratidinone, was also discussed in this paper.³ In connection with this work, it should be noted that another group has reported on the isolation of erysotrine and erythraline, as well as the other known alkaloids erythramine, erysodine, erythratine, erysopine, and erysonine, from *E. lithosperma*.⁴

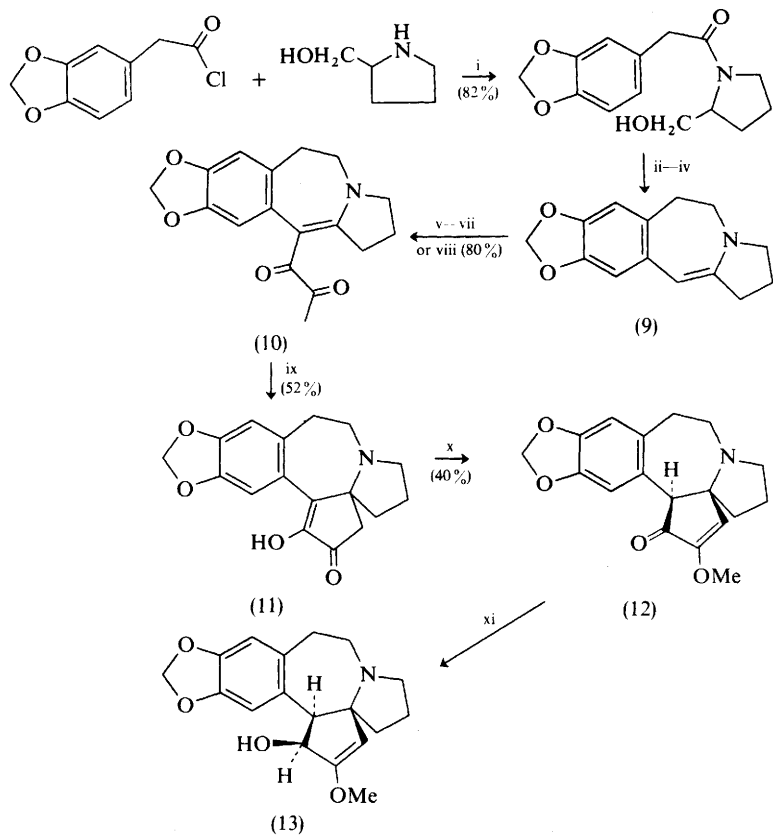


Besides ten known *Erythrina* bases, the new alkaloid erythrasine (3; $R^1 = R^2 = R^3 = \text{Me}$, $R^4 = \text{OAc}$) has been isolated from the seeds of *E. arborescens*.⁵ The possibility that erythrasine may be an artifact was not considered. Details

⁴ D. K. Ghosh and D. N. Majumdar, *Current Sci.*, 1972, **41**, 578 (*Chem. Abs.*, 1972, **77**, 111 475t).

⁵ S. Ghosal, A. Chakraborti, and R. S. Srivastava, *Phytochemistry*, 1972, **11**, 2101.

of the isolation and structural elucidation of erysotrine (3; $R^1 = R^2 = R^3 = \text{Me}$, $R^4 = \text{H}$), erysodine, erysovine, erythraline, erysopine, erysopitine (4; $R^1 = R^2 = \text{H}$, $R^3 = \text{OMe}$, stereochemistry unspecified, R^4 , $R^5 = \text{H, OH}$ or *vice versa*), erysonine (3; $R^1 = R^3 = R^4 = \text{H}$, $R^2 = \text{Me}$), and erysodienone (6), isolated from *E. variegata* var. *orientalis*, are now available.⁶ Erysopitine appears to be a new alkaloid; erysodienone has been previously obtained from *E. lithosperma* (cf. ref. 3), and erysotrine, which until recently was known only as a synthetic material, has now been isolated from *E. fusca*,³ *E. suberosa*⁷ (see also Vol. 1), and *E. variegata*.⁸



Reagents: i, $\text{K}_2\text{CO}_3\text{--MeCN}$; ii, $\text{DCC--Cl}_2\text{CHCO}_2\text{H--DMSO}$; iii, $\text{BF}_3\text{--Et}_2\text{O--CHCl}_3$; iv, $\text{LiAlH}_4\text{--THF}$; v, $\text{MeCH(OAc)COCl--NaHCO}_3\text{--MeCN}$; vi, $\text{K}_2\text{CO}_3\text{--MeOH}$; vii, $\text{PbO}_2\text{--PhMe}$; viii, $\text{MeCOCO}_2\text{CO}_2\text{Et}$; ix, $\text{Mg(OMe)}_2\text{--MeOH}$; x, $\text{Me}_2\text{C(OMe)}_2\text{--TsOH--MeOH--dioxan}$; xi, $\text{NaBH}_4\text{--MeOH}$.

Scheme 1

⁶ S. Ghosal, S. K. Dutta, and S. K. Bhattacharya, *J. Pharm. Sci.*, 1972, **61**, 1274.

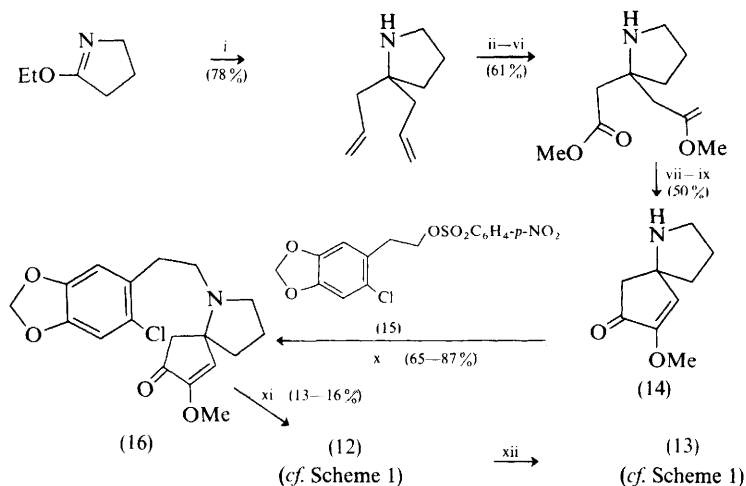
⁷ G. A. Miana, M. Ikram, F. Sultana, and M. I. Khan, *Lloydia*, 1972, **35**, 92.

⁸ S. Ghosal, D. K. Ghosh, and S. K. Dutta, *Phytochemistry*, 1970, **9**, 2397.

Cocculine and cocculidine had been previously assigned the *Erythrina*-type structures (7; R = H) and (7; R = Me) respectively on the basis of n.m.r. and mass spectral studies of the alkaloids and their Hofmann degradation products (see Vol. 2). A different group of workers has now proposed structures (8; R = H) and (8; R = Me) for cocculine and cocculidine, respectively, on the basis of the same kinds of information.⁹ Further investigation is necessary to establish conclusively these structures which, if correct, represent a new alkaloid class.

Cephalotaxine (13), the major alkaloid isolated from several *Cephalotaxus* species,² has been synthesized by two refreshing and different routes.^{10,11} In one of these (Scheme 1),¹⁰ the key enamine intermediate (9) was converted into the α -diketone (10) by two different routes. The spiro carbocyclic ring annelation was completed by treatment of (10) with magnesium methoxide to give demethylcephalotaxine (11) which upon *trans*-acetalization provided cephalotaxinone (12). Reduction of the latter occurred stereospecifically to give cephalotaxine (13). The advantage of this route is that it also provides compounds (11) and (12), both of which have been recently isolated from *Cephalotaxus* species.

The other reported approach to cephalotaxine (13) and cephalotaxinone (12) involves a convergent synthesis based on the two fragments (14) and (15) (Scheme 2).¹¹ Although standard procedures were used for the preparation of the phenethyl alcohol (15), the heterospirocycle (14) was synthesized by a challenging



Reagents: i, 3 equiv. $\text{CH}_2=\text{CHCH}_2\text{MgBr-Et}_2\text{O}$, 25 °C; ii, $\text{N}_3\text{COBu}^t\text{-H}_2\text{O-THF}$; iii, $\text{O}_3\text{-MeOH}$, -78 °C; iv, $\text{H}_2\text{O-dioxan}$, 80 °C; v, $\text{Ag}_2\text{O-KOH}$; vi, $\text{MeOH-HC(OMe)}_3\text{-HCl}$; vii, $\text{K-Na-Me}_3\text{SiCl-PhH}$; viii, $\text{Br}_2\text{-CH}_2\text{Cl}_2$, -78 °C; ix, $\text{CH}_3\text{N}_2\text{-EtOH-CH}_2\text{Cl}_2$, 0 °C; x, $\text{EtNPr}_2\text{-MeCN}$, 55 °C; xi, two-fold excess $\text{Ph}_3\text{CK-DME}$, 50 °C; xii, $\text{Bu}_2\text{AlH-PhH}$, 25 °C.

Scheme 2

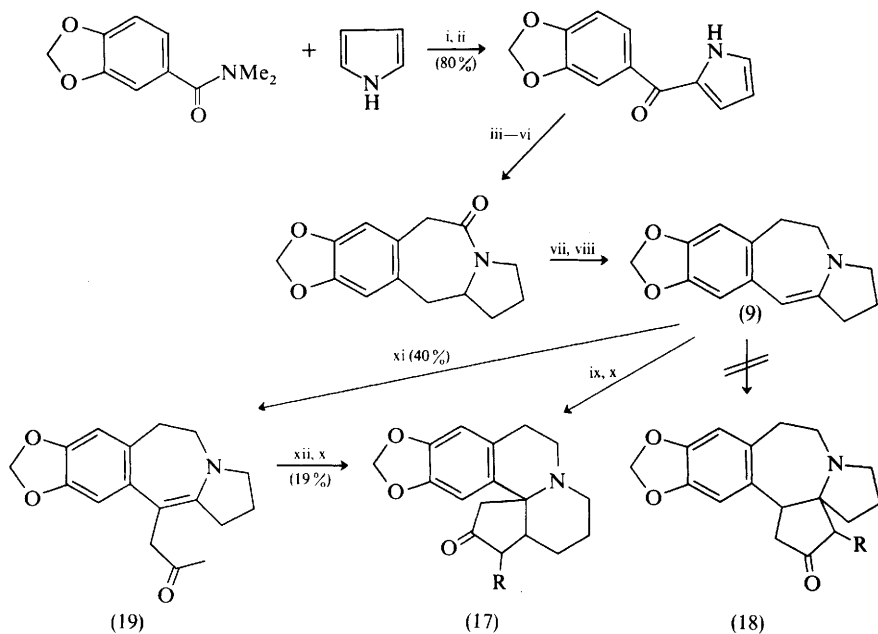
⁹ N. S. Vul'fson and V. N. Bochkarev, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 500 (*Chem. Abs.*, 1972, 77, 62 194q).

¹⁰ J. Auerbach and S. M. Weinreb, *J. Amer. Chem. Soc.*, 1972, **94**, 7172.

¹¹ M. F. Semmelhack, B. P. Chong, and L. D. Jones, *J. Amer. Chem. Soc.*, 1972, **94**, 8629.

route. These two fragments were then combined to give (16), which was subjected to conditions favourable for the formation of a benzyne intermediate and gave cephalotaxinone (12). Reduction of the latter provided cephalotaxine (13). Although several modifications are planned in order to achieve a more efficient synthesis, it may be noted that the present approach provides 8–9 g of cephalotaxinone (12) from 100 g of 2-pyrrolidone and 75 g of piperonal.

A third approach to cephalotaxine unfortunately failed as a result of an intriguing rearrangement in the final stages of the synthesis (Scheme 3).¹² A different approach to the previously described enamine (9) (Scheme 1) was developed which was then treated with ethyl γ -bromoacetoacetate to produce the β -keto-ester (17; R = CO₂Me) rather than the desired cephalotaxine precursor (18; R = CO₂Me). The structure of (17; R = CO₂Me) was indicated from its spectra and those of the corresponding de-ethoxycarbonylated material (17; R = H). The structure was finally confirmed by direct comparison of the



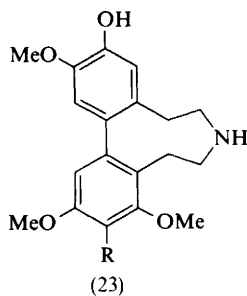
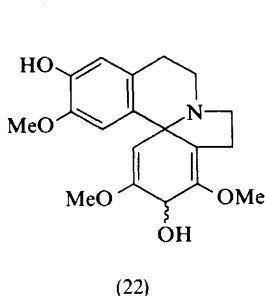
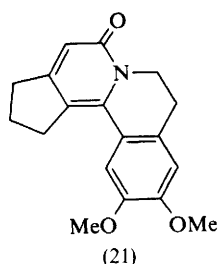
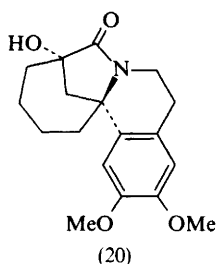
Reagents: i, POCl₃-Cl₂C=CCl₂; ii, NaOAc-H₂O; iii, NaBH₄-dioxan, reflux; iv, H₂-Rh/Al₂O₃-HOAc; v, ClCOCH₂Cl-K₂CO₃-CH₂Cl₂-H₂O; vi, hv, EtOH-N₂; vii, LiAlH₄-THF, reflux; viii, Hg(OAc)₂-HOAc; ix, BrCH₂COCH₂CO₂Et-MeCN, reflux; x, 5% H₂SO₄-H₂O; xi, BrCH₂COMe-MeCN, reflux; xii, pyrrolidine-TsOH, molecular sieves.

Scheme 3

¹² L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, 1972, 37, 3691.

de-keto parent tetracyclic base of (17; R = H) with an authentic sample. Reasonable mechanistic speculation led to the conclusion that the deep-seated rearrangement may be prevented by using α -bromoacetone rather than γ -bromoacetate as an alkylating agent for (9). In the event, the ketone (19) was obtained which resisted any reaction under a variety of conditions. When (19) finally did undergo reaction, it gave the same type of rearrangement product (17; R = H), thus thwarting any related modifications to achieve the synthesis of the cephalotaxine skeleton (18).

On the basis of spectral and mechanistic data the structures (20) and (21) were assigned to the Wolff-Kishner reduction products of 6 α -bromo-15,16-dimethoxy-*trans*-erythrinane-7,8-dione (see Vol. 2). Independent syntheses of (20)¹³ and (21)¹⁴ have fully confirmed the original structural assignments.



Acid-catalysed rearrangement of the dienol (22) gave the dibenzazonine (23; R = OH) in 50% yield rather than the desired protostephanine precursor (23; R = H).¹⁵ In another attempt to obtain a protostephanine precursor, the proerythrinadienol (24) was treated with methyl fluorosulphonate.¹⁶ However, only the aporphine (25) and a low yield of the dienone (26) were obtained. A

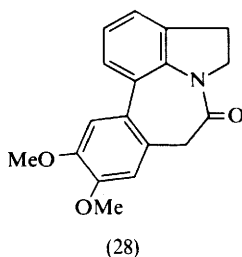
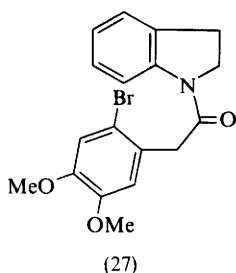
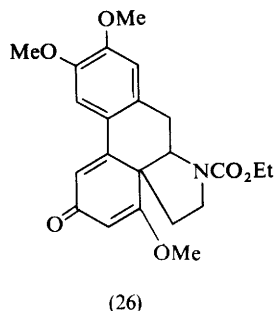
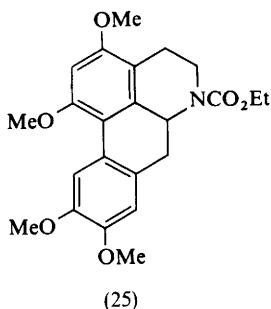
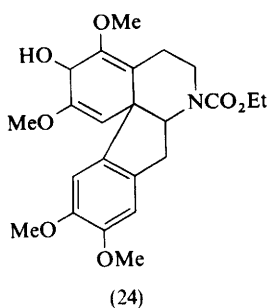
¹³ A. Mondon, G. Aumann, and E. Oelrich, *Chem. Ber.*, 1972, **105**, 2025.

¹⁴ A. Mondon, E. Oelrich, and R. Schickfluss, *Chem. Ber.*, 1972, **105**, 2036.

¹⁵ T. Kametani, T. Kohno, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1678.

¹⁶ T. Kametani, K. Takahashi, K. Ogasawara, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 662.

photochemical synthesis of dimethylapoerysopin-7-one (28) from the acylindoline (27) has been achieved, albeit only in 4.4% yield.¹⁷



Cocculine (8; R = H) and cocculidine (8; R = Me) (see p. 276) have been shown to possess hypotensive but not central nervous system activity.¹⁸ A number of pharmacological effects of selected alkaloids of *Erythrina variegata* have been studied.^{6,19} Erysotrine (3; R¹ = R² = R³ = Me, R⁴ = H) appears to be a competitive neuromuscular blocking agent.²⁰

¹⁷ H. Hara, O. Hoshino, and B. Umezawa, *Tetrahedron Letters*, 1972, 5031.

¹⁸ U. B. Zakirov, Kh. U. Aliev, and N. V. Abdumalikova, *Farmakol. Alkaloidov Serdech. Glikozidov*, 1971, 197 (*Chem. Abs.*, 1972, 77, 135 092s).

¹⁹ S. K. Bhattacharya, P. K. Debnath, A. K. Sanyal, and S. Ghosal, *J. Res. Indian Med.*, 1971, 6, 235 (*Chem. Abs.*, 1973, 78, 52 895a).

²⁰ A. Qayum, K. Khanum, and G. A. Miana, *Pakistan Med. Forum*, 1971, 6, 35 (*Chem. Abs.*, 1972, 77, 148 526m).

A list of indole alkaloids whose structures have been settled in the period 1968—mid-1972 has been compiled¹ and will serve as a most useful supplement to the two volumes² of Hesse's 'Indole Alkaloids in Tables', the second of which was published in 1968. Though not as fully documented as the Hesse Tables, this new compilation gives name, structure, botanical origin, molecular formula and weight, and literature reference for the 191 alkaloids listed in alphabetical order; also appended are separate molecular weight and plant indices for the group.

In a pioneering study³ Djerassi and Bunnenberg have applied the magnetic circular dichroism (m.c.d.) technique to a selection of nine indole and dihydro-indole (indoline) alkaloids and to oxindole and indoline. The indole chromophore gives rise to two bands, with some fine structure, of more or less equal intensities and following a + - sign sequence in going from high to low wavelength. Figure 1 shows a typical spectrum, of akuammidine acetate in this case, and gives the c.d. and u.v. spectra of the same alkaloid for comparison. An examination of this spectrum by those familiar with the use of u.v. spectroscopy in indole chemistry will immediately reveal that the first and sharper of these bands corresponds very closely in wavelength to the ubiquitous small maximum (ca. 288—293 nm) which appears on the side of the main 280 nm u.v. absorption band of indole and C-alkyl-substituted indoles. Indeed this characteristic sharp positive band in the m.c.d. spectrum, at a position corresponding to the highest u.v. absorption maximum of the alkaloid in question, is shown in all of the indole curves recorded in this study. Importantly, it is still present even in more complex indoles—having homoaromatic oxy- (though with broadening) or N_a -alkyl- or N_a -acyl-substituents or even, as in uleine, further conjugation—the u.v. absorption curves of which are often not so easily positively identified as indolic.

Although it is possible in most instances to distinguish by u.v. spectroscopy between an indole and an indoline chromophore, in some more highly substituted cases this is not so. The clear-cut difference in m.c.d. between indole and indoline systems, however, can achieve this distinction without any ambiguity. The indoline

¹ B. Gabetta, *Fitoterapia*, 1973, **44**, 3.

² M. Hesse, 'Indolalkaloide in Tabellen', Springer Verlag, Berlin-Göttingen-Heidelberg, 1964; Ergänzungswerk, Springer Verlag, Berlin-Heidelberg-New York, 1968.

³ G. Barth, R. E. Linder, E. Bunnenberg, and C. Djerassi, *Helv. Chim. Acta*, 1972, **55**, 2168.

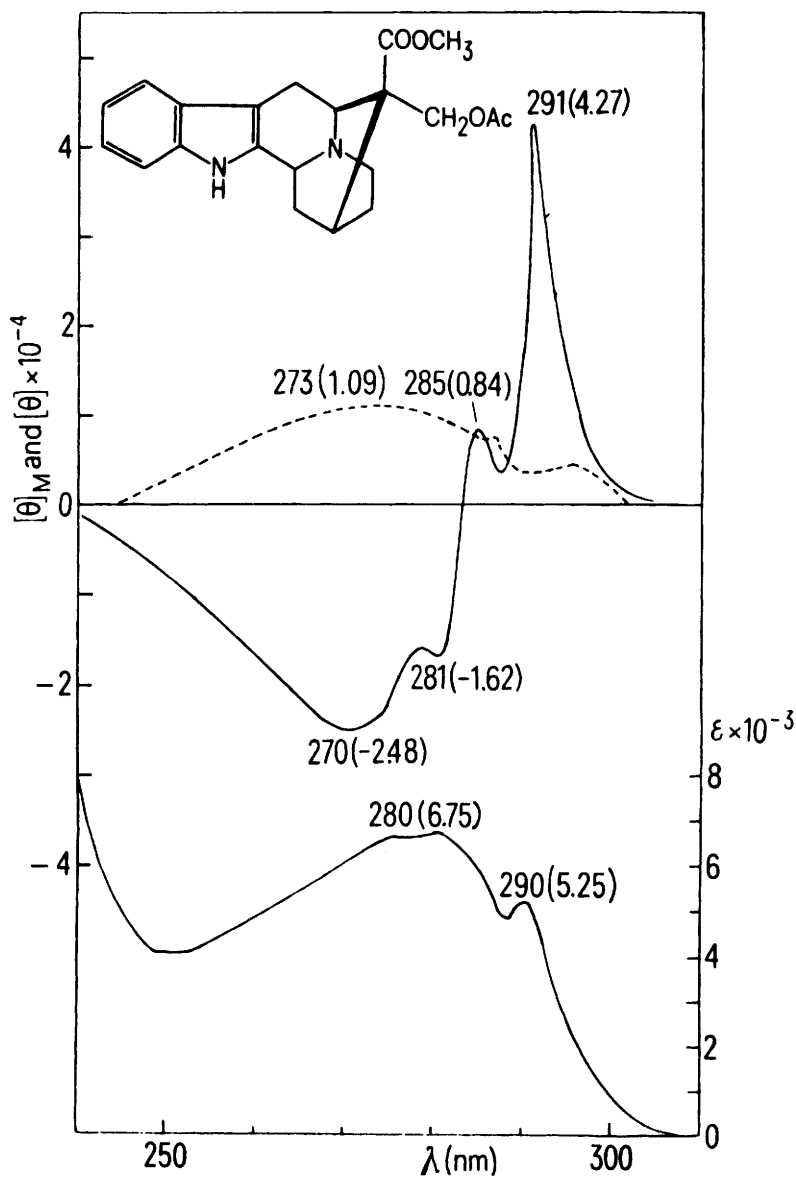


Figure 1 M.c.d. (—), c.d. (---), and absorption (lower curve) spectra of acetylkauamidine in methanol

(Reproduced by permission from *Helv. Chim. Acta*, 1972, **55**, 2168)

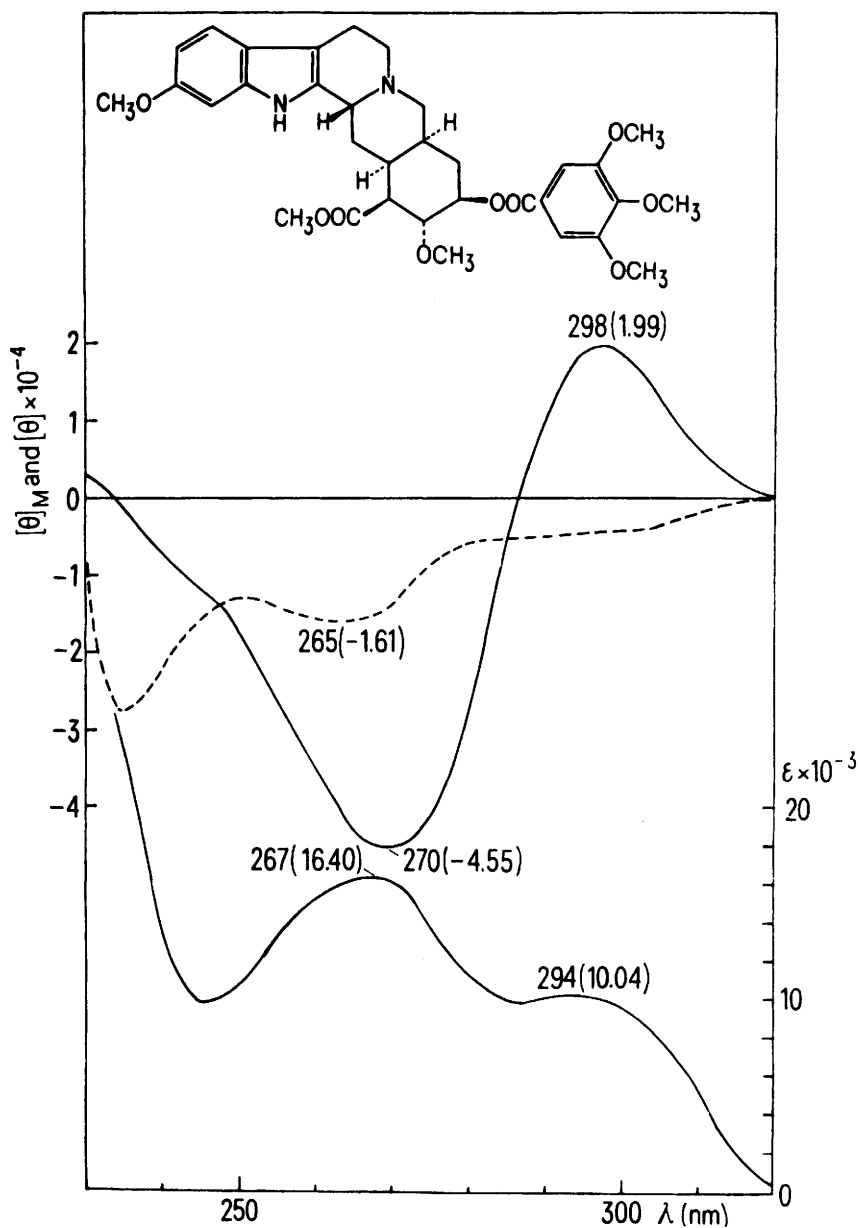


Figure 2 M.c.d. (—), c.d. (---), and absorption (lower curve) spectra of reserpine in methanol

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and N_a -acylindoline chromophores, and indeed the oxindole chromophore, give two-banded m.c.d. spectra like those of indoles *but* with a sign sequence of $- +$. The difference is illustrated by the spectra of reserpine and brucine given in Figures 2 and 3. For this pair, chosen to illustrate the occasional fortuitous similarity of substituted-indole and substituted-indoline u.v. absorption, the m.c.d. curves distinguish the indole from the indoline in striking fashion.

Within the limited scope of this initial study, it was concluded that variations in stereochemistry and strain in the aliphatic portions of indole alkaloids are reflected to such a slight extent in their m.c.d. spectra that no useful information can be gained from this technique on the stereochemical features of the molecule.

The chemical sequences currently available for transforming one indole alkaloidal structural type into another have received the attention of another

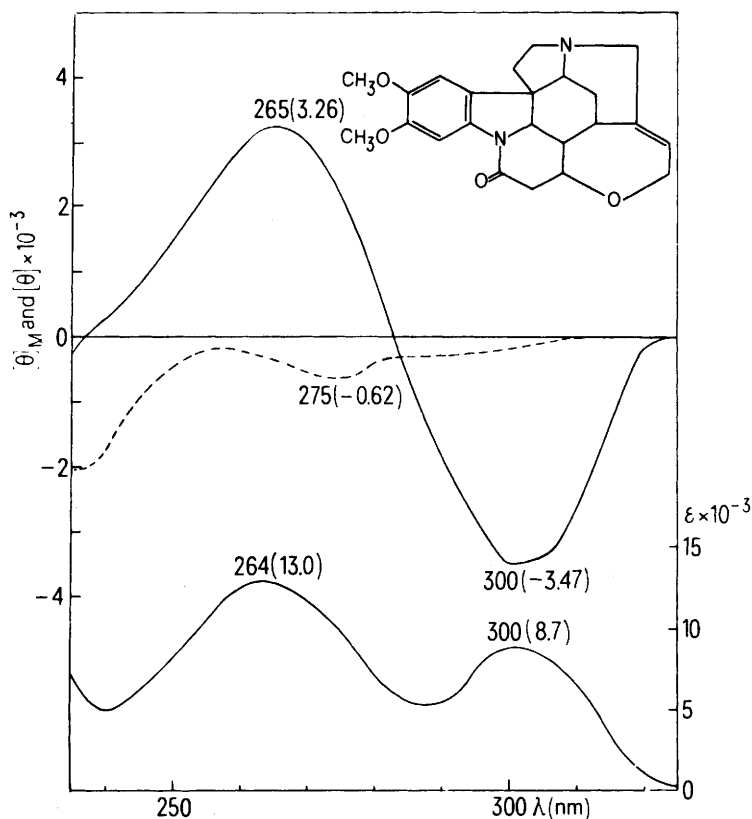


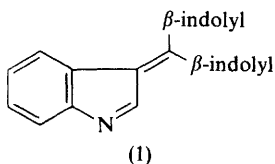
Figure 3 *M.c.d.* (—), *c.d.* (---), and absorption (lower curve) spectra of brucine sulphate in methanol

(Reproduced by permission from *Helv. Chim. Acta*, 1972, **55**, 2168)

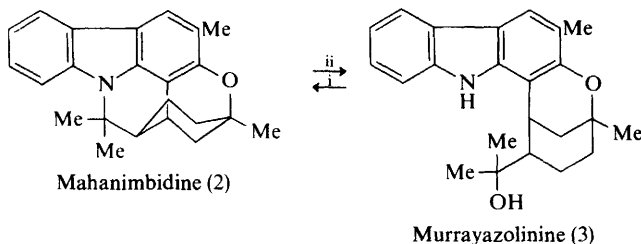
review⁴ (see also ref. 5a); thus formation of quinine and oxindole alkaloids from indoles and the reverse and the transformations of indole alkaloids into 2-acylindole, camptothecin, and secamine types are covered.

1 Simple Alkaloids

Non-tryptamines.—The orange-yellow di- β -indolylmethyleneindolenine (1) was isolated⁶ from a strain of *Saccharomyces cerevisiae*.



Further comparisons⁷ have re-affirmed that glycozolidine^{5b} is 2,6-dimethoxy-3-methylcarbazole. An X-ray crystallographic analysis^{8a} has confirmed the structure (2) postulated^{9a} for mahanimbidine (= murrayazoline^{8b} = currayangine^{8c, 8d, 10a}). Murrayazoline (3), isolated from the stem bark of *Murraya*



Reagents: i, POCl₃; ii, aq. AcOH or aq. H₂SO₄

Scheme 1

⁴ S. Sakai, *Yuki Gosei Kagaku Kyokai Shi (J. Soc. Org. Synthetic Chem., Japan)* 1972, **30**, 434 (*Chem. Abs.*, 1972, **77**, 164 894); see also ref. 3 in ref. 5a.

⁵ (a) J. A. Joule, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1973, vol. 3, p. 187; (b) *ibid.*, p. 188; (c) *ibid.*, p. 190; (d) *ibid.*, p. 221; (e) *ibid.*, p. 192; (f) *ibid.*, p. 202; (g) *ibid.*, p. 199; (h) *ibid.*, p. 204; (i) *ibid.*, p. 211; (j) *ibid.*, pp. 214, 225; (k) *ibid.*, p. 216; (l) *ibid.*, pp. 217–221; (m) *ibid.*, pp. 223, 224.

⁶ H. Budzikiewicz, H. Eckau, and M. Ehrenberg, *Tetrahedron Letters*, 1972, 3807.

⁷ F. Anwer, R. S. Kapil, and S. P. Popli, *Indian J. Chem.*, 1972, **10**, 959.

⁸ (a) J. Bordner, D. P. Chakraborty, B. K. Chowdhury, S. N. Ganguly, K. C. Das, and B. Weinstein, *Experientia*, 1972, **28**, 1406; (b) D. P. Chakraborty, J. Dutta, and A. Ghosh, *Science and Culture*, 1965, **31**, 529; (c) N. L. Dutta, C. Quasim, and M. S. Wadia, *Indian J. Chem.*, 1969, **7**, 1061; (d) see footnote in ref. 10a.

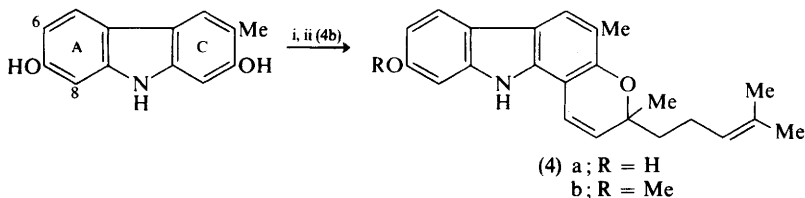
⁹ (a) J. A. Joule, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, vol. 1, p. 152; (b) *ibid.*, p. 155; (c) *ibid.*, p. 160; (d) *ibid.*, p. 173; (e) *ibid.*, p. 185; (f) *ibid.*, p. 190; (g) *ibid.*, p. 194; (h) *ibid.*, p. 198; (i) *ibid.*, p. 171.

¹⁰ (a) J. A. Joule, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London 1972, vol. 2, p. 209; (b) *ibid.*, p. 231; (c) *ibid.*, p. 239; (d) *ibid.*, p. 223; (e) *ibid.*, p. 219.

koenigii, could be converted¹¹ into mahanimbidine by treatment with phosphorus oxychloride and the reverse process effected with a variety of aqueous acids (Scheme 1).

In an attempted synthesis of mahanine (4a) from 2,7-dihydroxy-3-methylcarbazole, condensation with citral took place on the A ring, possibly at C-6 and not at C-8 as the authors suggest. By methylating the A ring hydroxy-group, condensation was forced on to the C ring and the methyl ether (4b) of mahanine resulted¹² (Scheme 2).

6-(3-Methylbuta-1,3-dienyl)indole^{5a} has been synthesized.¹³



Reagents: i, CH_2N_2 ; ii, citral-pyridine

Scheme 2

Non-isoprenoid Tryptamines.—A study¹⁴ of the effect of time of day, moisture stress, and frosting on the constituents of *Phalaris tuberosa* showed how the relative concentrations of N_bN_b -dimethyltryptamine, 5-methoxy- and 5-hydroxy- N_bN_b -dimethyltryptamine, and gramine in the leaves varied with these factors. For example the tryptamines were present in greater concentration in the morning than at other times.

The roots of *Desmodium tiliaefolium* were shown¹⁵ to contain, as well as two tetrahydroisoquinoline and five β -phenylethylamine bases, tryptamine, abrine, and hypaphorine. The leaves and roots of *Desmodium gyrans* contain¹⁶ N_bN_b -dimethyltryptamine and its N_b -oxide and bufotenine as well as an uncharacterized β -carboline and uncharacterized β -indolylalkanamines. 6-Canthinone has been isolated¹⁷ from the root and stem bark of *Zanthoxylum ordifolium*. Brevicolline^{5c} can be degraded¹⁸ to 6-nitroharman by successive nitration, to yield a mixture of 6- and 8-mono- and 6,8-dinitro-derivatives, and then side-chain oxidation and decarboxylation of the 6-nitro-derivative.

¹¹ D. P. Chakraborty, S. N. Ganguly, P. N. Maji, and A. R. Mitra, *Chem. and Ind.*, 1973, 322.

¹² F. Anwer, R. S. Kapil, and S. P. Popli, *Experientia*, 1972, **28**, 769.

¹³ H. Ishii, Y. Murakami, T. Furuse, H. Takeda, and N. Ikeda, *Tetrahedron Letters*, 1973, 355.

¹⁴ J. D. Williams, *Austral. J. Agric. Res.*, 1972, **23**, 611 (*Chem. Abs.*, 1972, **77**, 111 458).

¹⁵ S. Ghosal and R. S. Srivastava, *Phytochemistry*, 1973, **12**, 193.

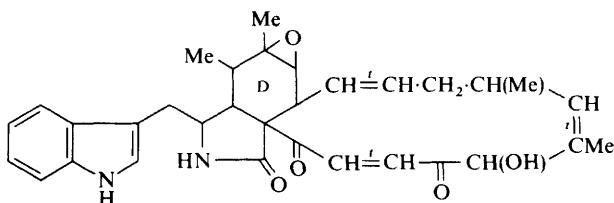
¹⁶ S. Ghosal, V. K. Mazumder, and R. Mehta, *Phytochemistry*, 1972, **11**, 1863.

¹⁷ S. K. Talapatra, S. Dutta, and B. Talapatra, *Phytochemistry*, 1973, **12**, 729.

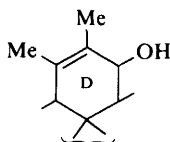
¹⁸ T. I. Shirshova, I. V. Terent'eva, P. A. Vember, and G. V. Lazur'evskii, *Khim. geterotsikl. Soedinenii*, 1972, 987 (*Chem. Abs.*, 1972, **77**, 140 396).

A Caribbean sponge, *Polyfibrospongia maynardii*, contains¹⁹ 5,6-dibromotryptamine and 5,6-dibromo-*N*_b-methyltryptamine.

Three isomeric metabolites, C₃₂H₃₆N₂O₅, of *Chaetomium globosum*,^{5d} named chaetoglobosins A, B, and C, have been examined.²⁰ Only the first two, (5) and (6), which are yellow, have been given structures so far and these are based principally on a detailed n.m.r. analysis. Chaetoglobosin A is transformed by treatment with triethylamine into a mixture of chaetoglobosin B and the colourless chaetoglobosin C.

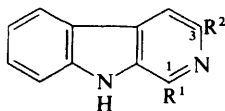


Chaetoglobosin A (5)

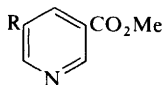


Chaetoglobosin B (6)

In continuation^{9b} of McLean's examination of the alkaloidal constituents of the bark of *Nauclea diderrichii* the structures for several further alkaloids have been settled.²¹ Thus harman (7a), 3-methoxycarbonylharman (7b), 1-methoxycarbonylnorharman (7c), and the corresponding amide (7d), which, however, may well be an artefact from the ester, are present^{21a} as well as pyridines^{21a} (8a—d) and other indole bases (see p. 292^{21b,c}).



- (7) a; R¹ = Me, R² = H Harman
 b; R¹ = Me, R² = CO₂Me
 c; R¹ = CO₂Me, R² = H
 d; R¹ = CONH₂, R² = H



- (8) a; R = MeCH(OMe)
 b; R = MeCH(OH)
 c; R = MeCH(NH₂)
 d; R = CH₂:CH

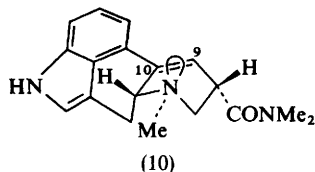
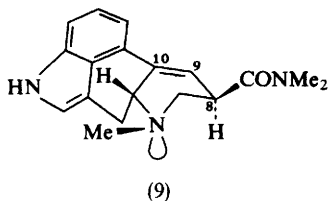
¹⁹ G. E. Van Lear, G. O. Morton, and W. Fulmor, *Tetrahedron Letters*, 1973, 299.

²⁰ S. Sakita, K. Yoshihira, S. Natori, and H. Kuwano, *Tetrahedron Letters*, 1973, 2109.

²¹ (a) S. McLean and D. G. Murray, *Canad. J. Chem.*, 1972, **50**, 1478; (b) D. G. Murray, A. Szokolai, and S. McLean, *ibid.*, p. 1486; (c) S. McLean and D. G. Murray, *ibid.*, p. 1496.

2 Isoprenoid Tryptamine and Tryptophan Alkaloids

Non-terpenoid Alkaloids.—With the aid of a 220 MHz n.m.r. study the conformation of D-lysergic acid dimethylamide has been deduced²² to be as is shown in (9). The conformation of D-isolysergic acid dimethylamide is probably best represented by (10). In both cases ring D is in a half-chair and the N_b -methyl and the C-8-amide functions are ψ -equatorial. It is hypothesized that the marked difference in biological activity between the epimeric lysergic and isolysergic acid derivatives is due to the orientation of the N_b -lone pair, which is oriented α in the former and β in the latter.



9,10-Dihydrolysergic acid derivatives undergo²³ Mannich condensation with formaldehyde-piperidine at the indole α -position. The catalytic reduction of the 9,10-double bond in ergocristine has been described.²⁴

A revision of the formulation (11) proposed^{25b,9c} earlier for clavicipitic acid has been suggested,^{25a} mainly on the basis of the structure of the product of its reaction with acetic anhydride. In the newly reported^{25a} work the acid was obtained as a pair of stereoisomers from *Claviceps fusiformis*, with or without the feeding of ethionine. The isomers had identical u.v. and mass spectra and could not be interconverted by the action of ammonia or heat; they were used as a pair for structural investigations. A trimethyl derivative, claimed^{25b} earlier, could not be obtained in the present work by treatment with diazomethane; di- and mono-methyl derivatives were said to be formed but no data are presented for them. Treatment of clavicipitic acid with acetic anhydride-methanol gave a product whose structure seems firmly established as (12). The key structural features which come from the n.m.r. analysis [see data on (12)] are the two methyl groups on a double bond and the coupled C-9 vinylic and C-10 benzylic protons, which specify the presence and location of the seven-membered hetero-ring. On the basis of this degradation product, structure (13) is now proposed for clavicipitic acid itself.

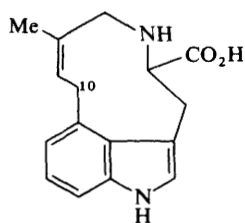
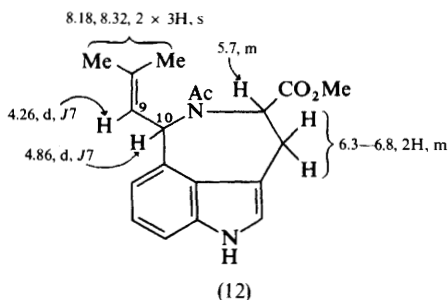
It is possible to conceive of a sequence whereby the amide (12) might be formed from a structure (11) by ring-opening and reclosure. It is to be noted that the earlier work adduced evidence that the two hydrogen atoms at C-10 which come from mevalonate were both still present in the metabolite when an appropriately

²² K. Bailey and A. A. Grey, *Canad. J. Chem.*, 1972, **50**, 3876.

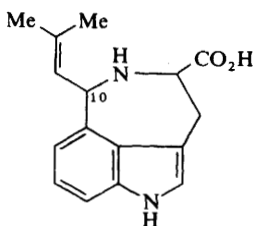
²³ L. Bernardi and A. Temperilli, *Chimica e Industria*, 1972, **54**, 998.

²⁴ H. Cousse, G. Mouzir, and B. Bonnaud, *Bull. Soc. chim. France*, 1972, 3131.

²⁵ (a) G. S. King, P. G. Mantle, C. A. Szczyrbak, and E. S. Waight, *Tetrahedron Letters*, 1973, 215; (b) J. E. Robbers and H. G. Floss, *ibid.*, 1969, 1857.

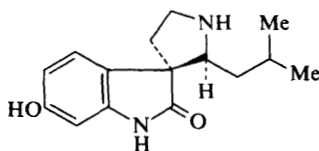
Clavicipitic acid^{25b} (11)

(12)

Clavicipitic acid^{25a} (13)

tritiated mevalonate was fed. The problem of differentiating between the two possibilities would seem to be easily resolvable by n.m.r. measurements on the natural product itself; neither group of workers reports such measurements! The n.m.r. spectrum of the trimethyl derivative claimed in the earlier note is reported,^{25b} but only to the extent of one signal, namely the vinylic hydrogen signal and then without comment on its multiplicity. No comment was made^{25b} on the presence or otherwise of two C-methyl group signals as opposed to one C-methyl and one C:C-CH₂N signal in the spectrum of this trimethyl derivative.

From the root bark of *Eleagnus commutata* has been obtained²⁶ the isopentyl 6-hydroxytryptamine oxindole (14); the structure was established by an X-ray analysis.



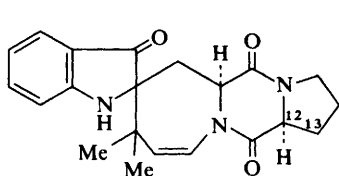
(14)

Full details of the isolation and structural elucidation of the toxic metabolites of *Aspergillus ustus* have been given.²⁷ Besides the two compounds mentioned^{5e} in last year's Report, three other variations on the theme have now been identified,

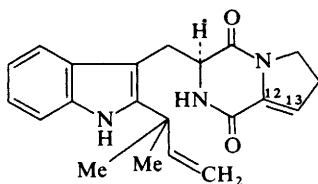
²⁶ M. N. G. James and G. J. B. Williams, *Canad. J. Chem.*, 1972, **50**, 2407.

²⁷ P. S. Steyn, *Tetrahedron*, 1973, **29**, 107.

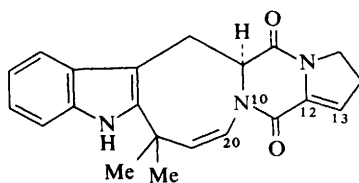
namely 12,13-dihydroaustamide (15), 12,13-dehydropoly-2-(1',1'-dimethylallyl)-tryptophyldiketopiperazine (= 12,13-dehydrobrevianamide E) (16), and 10,20-dehydro-12,13-dehydropoly-2-(1',1'-dimethylallyl)tryptophyldiketopiperazine (17).



(15)

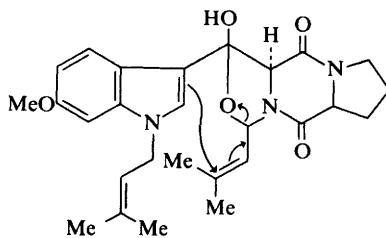


(16)



(17)

In the light of speculations^{28a} that the 'inverted' α,α -dimethylallyl residues at the indole α -position in such compounds as the austamides and echinulin are formed by an inversion-migration from initial N_a - γ,γ -dimethylallyl intermediates, it is significant that the major metabolite of *Penicillium lanosum*, lanosulin, recently isolated, has been ascribed^{28b} the structure (18), in which just such an N_a - γ,γ -dimethylallyl group is present. It is interesting to note in passing the alternative possibility, illustrated in this same metabolite, that the 'inverted' dimethylallyl unit could be delivered to the indole α -position by an intramolecular S_N2' attack from an initial N_b - γ,γ -dimethylallyl intermediate, with nitrogen [or oxygen, as suggested by arrows on (18)] as leaving group.



(18)

²⁸ (a) A. J. Birch and K. R. Farrar, *J. Chem. Soc.*, 1963, 4277; G. Casnati and A. Pochini, *Chem. Comm.*, 1970, 1328. (b) D. T. Dix, J. Martin, and C. E. Moppett, *J.C.S. Chem. Comm.*, 1972, 1168.

Monoterpenoid Alkaloids.—*Yohimbine-Corynantheine-Heteroyohimbine (and Related Oxindoles) Group.* Tetrahydroalstonine has been isolated from the leaves of *Amsonia tabernaemontana*^{29a} and the leaves and stems of *Uncaria bernaysii*^{29b} and its 4R-N₆-oxide from the stems of the same species of *Uncaria*^{29c} from which the roxburghines were isolated. Both 4R- and 4S-N₆-oxides of akuammigine were also isolated in this study^{29c} and akuammigine itself was isolated from *U. bernaysii*.^{29b} It may be useful to note that the C-3 hydrogen in N₆-oxides in this series gives a signal in the n.m.r. downfield from the main aliphatic hydrogen envelope and thus locatable, whether it is oriented equatorial or axial. In the corresponding bases it has long been recognized that an equatorial C-3 hydrogen is necessary for the signal to be downfield. Dihydrocorynantheol was isolated from *Amsonia tabernaemontana*^{29a} and trunk bark of *Ochrosia confusa*;^{29d} demethoxycarbonylgeissoschizine and geissoschizal were detected^{29e} in extracts of young seedlings of *Strychnos nux vomica*. Serpentine was obtained^{29f} from *Catharanthus ovalis* and reserpiline, isoreserpiline, 10,11-dimethoxypicrapphylline, and ochroposinine from the bark of *Ochrosia vieillardii*.^{29g} A yohimbine and a heteroyohimbine carrying A-ring hydroxy- and methoxy-groups respectively were obtained^{29h} from root and trunk bark of *Rauwolfia suaveolens* and hirsutine and mitrajavine from the leaves of *Mitragyna hirsuta*.²⁹ⁱ Pleiocarpamine was found in the bark of *Alstonia spectabilis*^{29j} and of *A. glabriflora*^{29j} and in the aerial bark of *A. muelleriana*^{29k} and 2,7-dihydropleiocarpamine in the last mentioned species. This indoline had previously been obtained only as a degradation product. The oxindoles rauvoxine and carapanaubine were isolated^{29d} from *O. confusa* and the N₆-oxides of isopteropodine, pteropodine, speciophylline, and uncarine F from *U. bernaysii*.^{29b}

A brief review³⁰ of the thirty or so alkaloids of *Mitragyna* takes as its starting point the arousal of interest in this group by the reported physiological effects of extracts—the leaves of *M. speciosa* for example were chewed as an opium substitute—and show how this has led to structural and stereochemical studies. Tissue cultures of *Rauwolfia caffra*, *R. verticillata*, and *R. serpentina* have been examined;³¹ cultures of the seeds and roots of the last mentioned gave the highest yields of alkaloids. Following reports that reserpine causes marked inhibition of growth, especially of certain tumours, experiments have now shown³² that it inhibits the incorporation of thymidine into liver DNA.

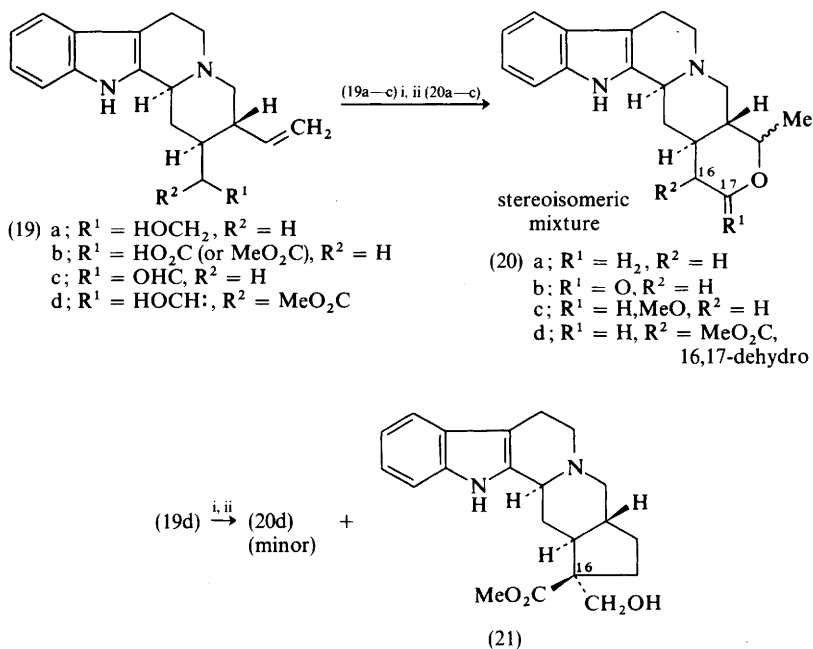
²⁹ (a) J. M. Panas, A. M. Morfaux, L. Olivier, and J. Le Men, *Ann. pharm. franç.*, 1972, 30, 273; (b) J. D. Phillipson and S. R. Hemingway, *Phytochemistry*, 1973, 12, 1481; (c) L. Merlini, G. Nasini, and J. D. Phillipson, *Tetrahedron*, 1972, 28, 5971; (d) J. Bruneton and A. Cavé, *Phytochemistry*, 1972, 11, 2618; (e) S. I. Heimberger and A. I. Scott, *J.C.S. Chem. Comm.*, 1973, 217; (f) N. Langlois and P. Potier, *Phytochemistry*, 1972, 11, 2617; (g) J. Bruneton, T. Sevenet, and A. Cavé, *ibid.*, p. 3073; (h) S. P. Majumder, J. Poisson, and P. Potier, *ibid.*, 1973, 12, 1167; (i) J. D. Phillipson, P. Tantivatana, E. Tarpo, and E. J. Shellard, *ibid.*, p. 1507; (j) N. K. Hart, S. R. Johns, and J. A. Lambertson, *Austral. J. Chem.*, 1972, 25, 2739; (k) D. E. Burke, G. A. Cook, J. M. Cook, K. G. Haller, H. A. Lazer, and P. W. Le Quesne, *Phytochemistry*, 1973, 12, 1467.

³⁰ E. J. Shellard, *Nadbítka 'Herba Polonica'*, 1972, 18, 147.

³¹ A. G. Vollosovich, L. A. Nikolaeva, and T. R. Zharko, *Rast. Resur.*, 1972, 8, 331 (*Chem. Abs.*, 1972, 77, 111 529).

³² B. Hach, P. Mitznegg, and F. Heim, *Experientia*, 1972, 28, 1418.

Experiments³³ (Scheme 3) designed to effect formation of a hetero-ring E from model compounds (19a–c) and from demethylcorynantheine (19d) by intramolecular oxymercuration were successful in the models, but led predominantly to a five-membered carbocyclic product (21) when the enolic system in demethylcorynantheine reacted at C-16 and not at oxygen. In the total syntheses of (\pm)-ajmalicine and others, summarized last year,^{5f} just such a cyclization was successful in producing a bicyclic intermediate comprising the D and E rings, with the heterocyclic ring E being formed in good yield. It is not clear what is responsible for this difference.



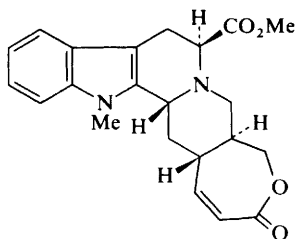
Reagents: i, $\text{Hg}(\text{OAc})_2\text{-AcOH}$ or $\text{Hg}(\text{OAc})_2\text{-MeOH-HNO}_3$; ii, NaBH_4

Scheme 3

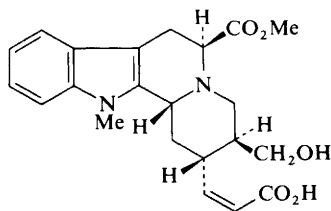
Two more cranberry alkaloids,³⁴ cannagunines B and C, have been given structures (22) and (23). Like that^{5g} for cannaguine (= demethoxycarbonyl-cannagunine B) the evidence available is, in this Reporter's view, far from decisive. Cannagunine B can be converted into cannagunine C by basic hydrolysis. The transformation of cannagunine C of structure (23) into a keto-ester of structure (24), by reaction with sodium hydride, seems, to say the least, unlikely.

³³ (a) L. Djakouré, F. X. Jarreau, R. Goutarel, and M.-M. Janot, *Compt. rend.*, 1972, 274, C, 1520; (b) M.-M. Janot, L. Djakouré, F. X. Jarreau, and R. Goutarel, *ibid.*, p. 2077.

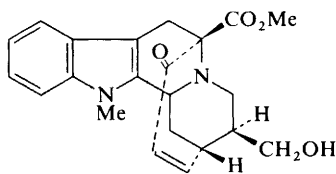
³⁴ K. Jankowski, *Experientia*, 1973, 29, 519.



? Cannagunine B (22)



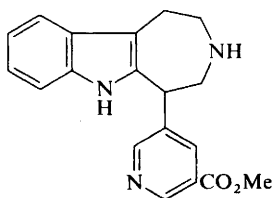
? Cannagunine C (23)



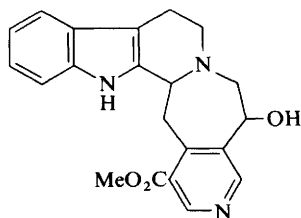
(24)

As well as the bases mentioned above^{21a} (see p. 286) six alkaloids^{21b} which contain an indole and an aromatic pyridine unit have been obtained from *Nauclea diderrichii* as well as an alkaloid,^{21c} $C_{21}H_{26}N_2O_4$, and a high molecular weight amorphous alkaloid which may be a glycoside. There is considerable doubt as to whether the alkaloids are not artefacts produced by the action of ammonia used in work-up.

The structure of naucleidine was settled earlier.^{9b} Nauclederine is considered to be (25), not giving mass-spectral peaks typical of a tetrahydro- β -carboline and having a base peak at $M - C_2H_4N$. Quite reasonable, but less fully proved, is structure (26) for nauclechine. The order of the three substituents on the pyridine ring rests, at present, on justifiable reference to the pyridines (see p. 286) and other alkaloids obtained from the plant.



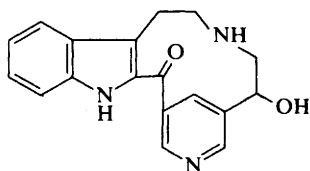
Nauclederine (25)



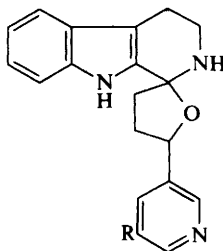
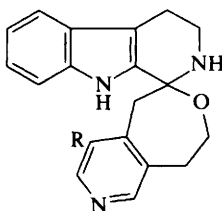
Nauclechine (26)

Nauclexine has been given a working structure (27), on the basis of u.v. and mass spectra and reasonable analogy. The two further alkaloids, one of which does and the other does not carry a pyridine-ring ester, have been tentatively

assigned structures (28a and b) which have a different type of skeleton. Granted the acknowledged^{21b} complexity of the n.m.r. spectra it would seem that formulations such as (29a and b), which would be structurally consistent with the other bases in the plant, should not yet be discarded.



Nauclexine (27)

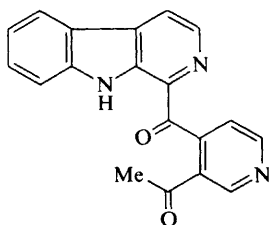
(28) a; R = MeO₂C
b; R = H(29) a; R = MeO₂C
b; R = H

It can be seen^{21c} that all the alkaloids so far assigned firm structures are composed of a tryptamine unit and a pyridine unit comprising nitrogen and either a full C₁₀-secologanin unit, as in (26), or moieties in which all or part of the side-chains are not present. The pyridines (see p. 286) isolated from the plant can also be defined as modified secologanin derivatives though in none of those so far isolated is there a pyridine C-4 substituent.

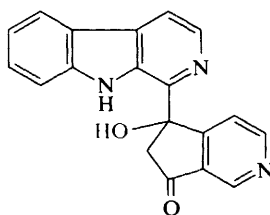
The root alkaloids of *Pauridiantha callicarpoides*³⁵ and the leaf bases of *Strychnos angustiflora*³⁶ can also be structurally analysed in this same general way. Pauridianthine (30),³⁵ pauridianthinine (31),³⁵ and angustidine (32a)³⁶ all lack one carbon of a secologanin unit whereas angustoline (33)³⁶ and angustine (32b)³⁶ have the complete C₁₀-unit. It is to be noted that the *S. angustiflora* alkaloids could be obtained whether or not ammonia was used in the extraction procedure.

³⁵ J.-L. Pousset, A. Bouquet, A. Cavé, A. Cavé, and R.-R. Paris, *Compt. rend.*, 1971, **272**, C, 665.

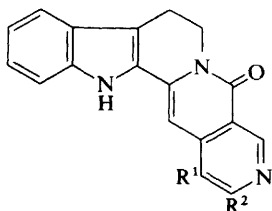
³⁶ T. Y. Au, H. T. Cheung, and S. Sternhell, *J.C.S. Perkin I*, 1973, 13.



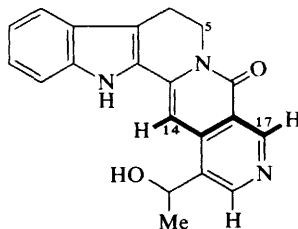
Pauridianthine (30)



Pauridianthine (31)

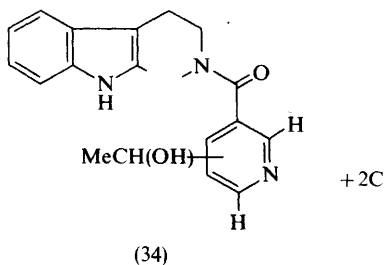


- (32) a; $R^1 = H, R^2 = Me$ Angustidine
 b; $R^1 = CH_2=CH, R^2 = H$ Angustine



Angustoline (33)

Structure determination for these highly unsaturated alkaloids is generally readily accomplished with the aid of n.m.r. spectroscopy and this indeed was the case with the present group; the use of long-range coupling to settle the final details is noteworthy. Thus in the spectrum of angustoline, the $MeCH(OH)$ group, two pyridine α -protons, one also *ortho* to a carbonyl function, one other olefinic proton singlet, and two triplets for the ethanamine bridge protons, together with the typical 2,3-disubstituted indole signals, taken with the neutrality of N_b (no change in chemical shift of the C-5-hydrogens in CF_3CO_2H solvent) gave a partial structure (34). The observation of long-range coupling between the hydrogen atoms at C-14 and at C-17 completed the elucidation.

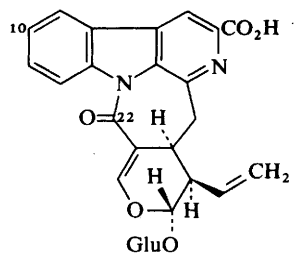


(34)

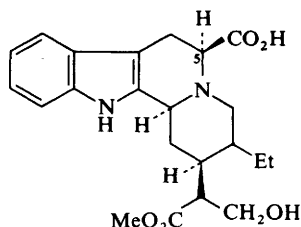
In continuation of his studies of *Adina* alkaloids Brown has shown that the 10β -D-glucosyloxy-derivative of vincoside lactam⁵⁸ occurs³⁷ in fresh shoots of

³⁷ R. T. Brown and W. P. Blackstock, *Tetrahedron Letters*, 1972, 3063.

Adina rubescens and the N_a , C-22 lactam (35)^{38a} of 10-desoxycordifoline in heartwood. Isolated in the form of their methyl ester tetra-acetates, 5 α -carboxystrictosamide and 5 α -carboxyvincoside lactam^{5g} were obtained^{38b} from *A. cordifolia*. Adirubine^{38c} from *A. rubescens* is another in the small but steadily growing group of indole alkaloids which retain the carboxy-group of precursor tryptophan. It has been given the structure (36) largely on the grounds of a careful mass-spectral comparison of adirubine with lithium aluminium hydride (and deuteride) reduction products and with dihydrositsirikine derivatives: it is 5 α -carboxy-18,19-dihydrositsirikine.



10-Desoxycordifoline lactam (35)



Adirubine (36)

Demethoxycarbonyl-3,14-dihydrogambirtannine occurs³⁹ in the leaves of *Ochrosia lifuana* and *O. miana*.

The use of the Madelung ring synthesis to build up an indolylquinuclidine system has been demonstrated⁴⁰ and used to prepare desvinylcinchonamine^{40b} and both (\pm)- and ($-$)-forms of dihydrocinchonamine (37). Scheme 4 shows the indole-ring-forming steps, starting with the preformed quinuclidine precursor,^{40c} in the synthesis^{40a} of dihydrocinchonamine. Elaboration of the intermediate (38) was by standard methods.

trans-Yohimbone (39) can be prepared⁴¹ by building the E ring on to the N_a -benzylketone (40) (Scheme 5). In a similar but more elaborate way the complete D/E ring system for yohimbone was neatly prepared from *N*-methyl-4-piperidone; from this intermediate (41) Stork developed syntheses⁴² of (\pm)-yohimbine (42), (\pm)- β -yohimbine, and (\pm)- ψ -yohimbine. The synthesis of (\pm)-yohimbine is detailed in Scheme 6. The formation of the C ring was effected by regioselective mercuric acetate dehydrogenation of (43).^{5f}

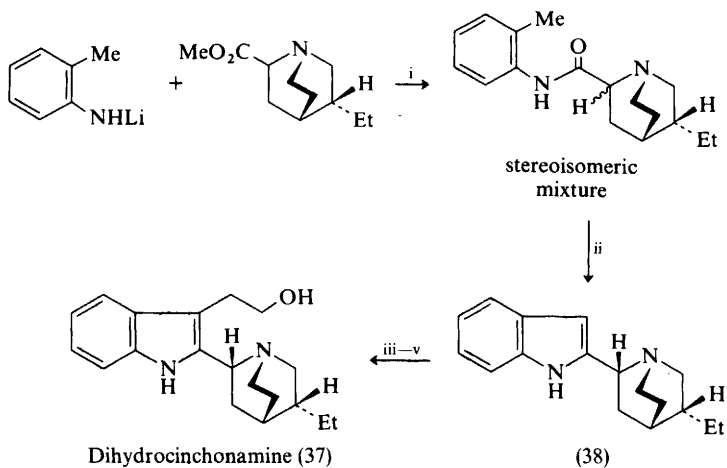
³⁸ (a) R. T. Brown and S. B. Fraser, *Tetrahedron Letters*, 1973, 841; (b) W. P. Blackstock, R. T. Brown, C. L. Chapple, and S. B. Fraser, *J.C.S. Chem. Comm.*, 1972, 1006; (c) R. T. Brown, C. L. Chapple, and G. K. Lee, *ibid.*, p. 1007.

³⁹ N. Peube-Locou, M. Plat, and M. Koch, *Phytochemistry*, 1973, 12, 199.

⁴⁰ (a) G. Grethe, H. L. Lee, and M. R. Uskoković, *Synth. Comm.*, 1972, 55; (b) R. L. Augustine and S. F. Wanat, *ibid.*, p. 63; (c) M. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Amer. Chem. Soc.*, 1971, 93, 5904.

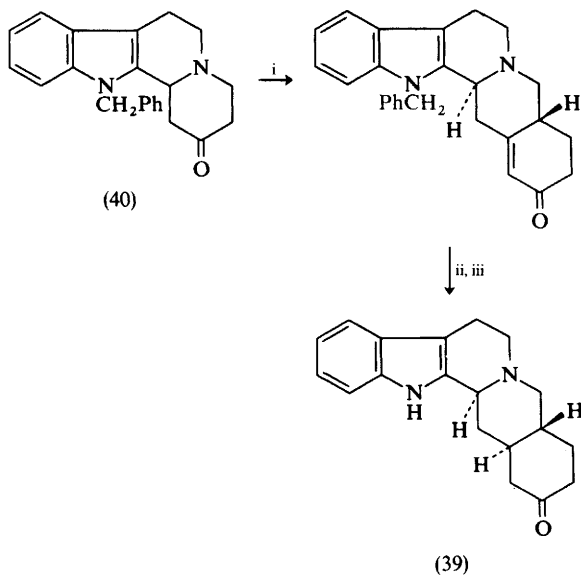
⁴¹ K. Mori, I. Takemoto, and M. Matsui, *Agric. and Biol. Chem. (Japan)*, 1972, 36, 2605 (*Chem. Abs.*, 1973, 78, 97 847).

⁴² G. Stork and R. Nath Guthikonda, *J. Amer. Chem. Soc.*, 1972, 94, 5109.



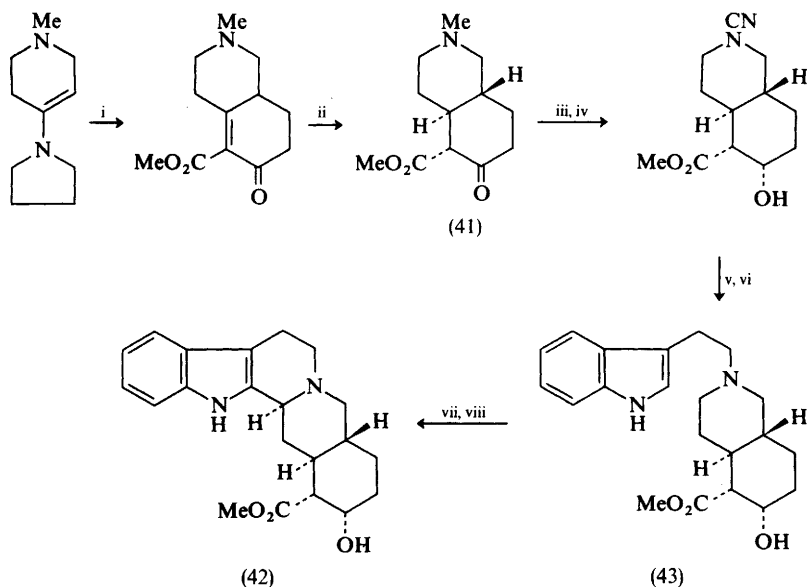
Reagents: i, heat; ii, NaNH_2 , 250°C ; iii, $(\text{COCl})_2$; iv, EtOH ; v, LiAlH_4

Scheme 4



Reagents: i, $\text{MeCO}\cdot\text{CH}\cdot\text{CH}_2$; ii, Na-Bu'OH ; iii, oxidation

Scheme 5

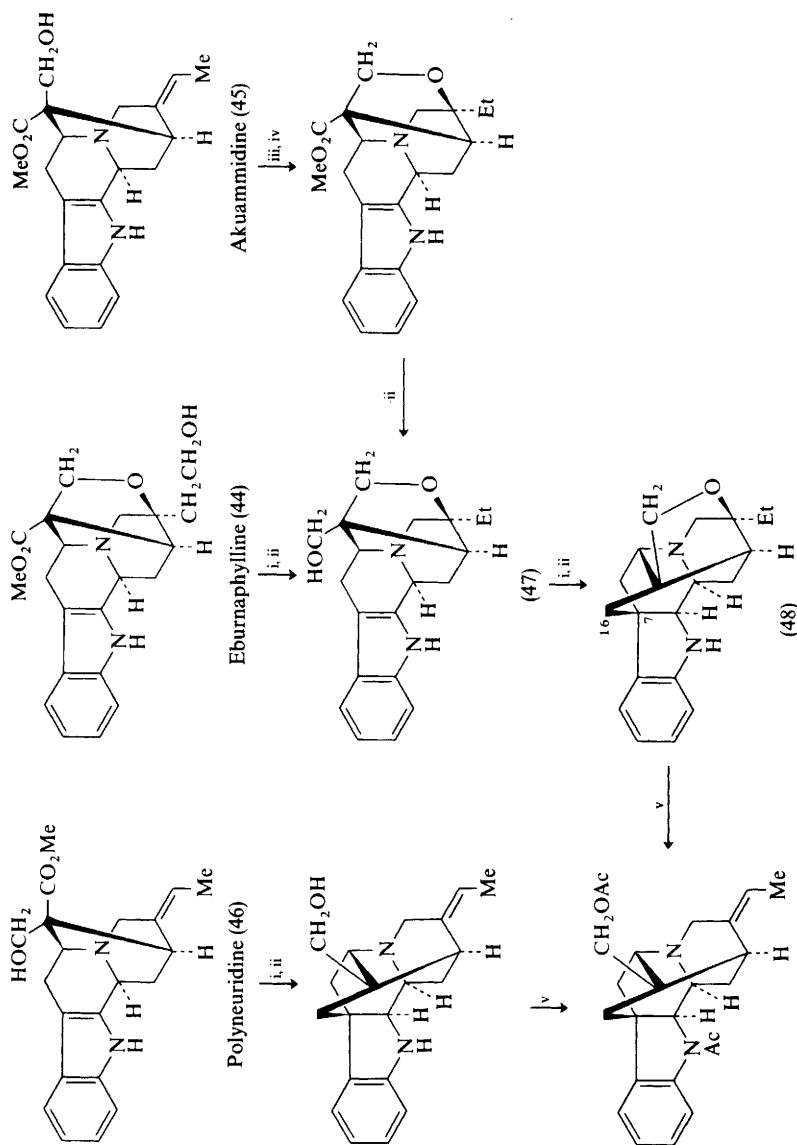


Reagents: i, $\text{CH}_2\text{:CHCOCH}_2\text{CO}_2\text{Me-PhH-MeOH-heat}$; ii, $-78^\circ\text{C-Li-NH}_3\text{-4Bu'OH}$; iii, $\text{H}_2\text{-Pt-AcOH-r.t.}$; iv, CNBr-PhH-r.t. ; v, $\text{Zn-AcOH-100}^\circ\text{C}$; vi, $\beta\text{-indolyl-CH}_2\text{CH}_2\text{Br-K}_2\text{CO}_3\text{-MeOH}$; vii, $\text{Hg(OAc)}_2\text{-edta}$; viii, NaBH_4

Scheme 6

Sarpagine-Ajmaline-Picraline Group. Akuammidine has been isolated from *Alstonia boonei* leaves,^{43a} *Amsonia tabernaemontana*,^{29a} and *Aspidosperma quebracho-blanco* leaves,^{43b} normacusine B was obtained from the trunk bark of *Tabernaemontana brachyantha*^{43c} and *Rauwolfia suaveolens*^{29h} and detected in *Strychnos nux vomica*.^{29e} polyneuridine is present in *R. suaveolens*.^{29h} Quebrachidine occurs in *A. quebracho-blanco*,^{43b} *Alstonia spectabilis*,^{29j} and *A. muelleriana*.^{29k} Anhydrovobasindiol was obtained from *T. brachyantha*.^{43c} *R. suaveolens* also contains^{29h} suaveoline, lochnerine, tetraphyllicine, ajmaline, and N_a -norajmaline; *A. spectabilis* also contains^{29j} vincamajine and N_a -methylsarpagine. Details^{43d} have been given of structural work on raucaffricine.^{10e} Picrinine occurs in the leaves of *Alstonia macrophylla*^{43e} and of *A. scholaris*.^{43f} The C-16 epimer

⁴³ (a) G. Croquelois, N. Kunesch, M. Debray, and J. Poisson, *Plant Med. Phytotherap.*, 1972, **6**, 122 (*Chem. Abs.*, 1972, **77**, 98 778); (b) R. L. Lyon, H. H. S. Fong, N. R. Farnsworth, and G. H. Svoboda, *J. Pharm. Sci.*, 1973, **62**, 218; (c) M. B. Patel, L. Thompson, C. Miet, and J. Poisson, *Phytochemistry*, 1973, **12**, 451; (d) M. A. Khan and A. M. Ahsan, *Pakistan J. Sci. Ind. Res.*, 1972, **15**, 30 (*Chem. Abs.*, 1973, **78**, 30 046); (e) A. Banerji, M. Chakraborty, and B. Mukherjee, *Phytochemistry*, 1972, **11**, 2605; (f) M. M. Gale, M. Maung, and Tin Tin Nu, *Union Burma J. Sci. Technol.*, 1970, **3**, 1 (*Chem. Abs.*, 1972, **77**, 111 466); (g) S. Savaskan, I. Kompiš, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1972, **55**, 2861; (h) B. Danieli, E. Bombardelli, A. Bonati, B. Gabetta, and G. Mustich, *Chimica e Industria*, 1972, **54**, 618 (*Chem. Abs.*, 1972, **77**, 101 968).



Reagents: i, TsCl ; ii, LiAlH_4 ; iii, $\text{Hg}(\text{OAc})_2$; iv, NaBH_4 ; v, Ac_2O

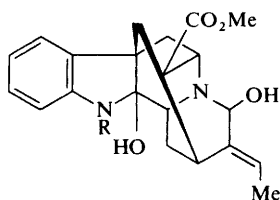
Scheme 7

of picrinine, named picralstonine, was isolated^{43e} from *A. macrophylla*, as was affinisine. The upper parts of *Vinca minor*^{43g} contain desacetylakuammiline and its 10-methoxy-derivative and the root bark of *Rauwolfia confertiflora* contains a base, raufloridine, which is 10-methoxyakuammiline itself.

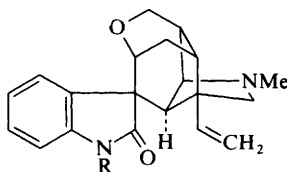
A detailed analysis⁴⁴ of root bark, stem bark, and fruit pods of *Picralima nitida* showed that there is more akuammicine in mature seeds and more ψ -akuammigine in immature seeds; the tenuous conclusion was drawn that probably ψ -akuammigine is a biogenetic precursor of akuammicine.

In a neat piece of chemistry from the Le Men-Lévy group (Scheme 7), the absolute configuration of eburnaphylline (44)^{45a} was established^{45b} by inter-conversions with both akuammidine (45) and polyneuridine (46). In the former case, the novel ether ring was introduced into akuammidine by intramolecular oxymercuration. This ether ring was stable to acetic anhydride in the alkaloid itself or, for example, in compound (47), and could not be opened; however, when the C-7—C-16 ajmaline bond was formed and this extra ring had laid strain on it, as in (48), it could be cleaved and a degradation product of polyneuridine so derived.

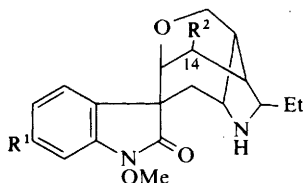
Herbadine and herbamine from the aerial parts of *Vinca herbacea* have been given⁴⁶ structures (49a) and (49b) without stereochemistry.



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



(50) a; R = H
b; R = MeO



(51) a; R¹ = H, R² = H
b; R¹ = MeO, R² = HO

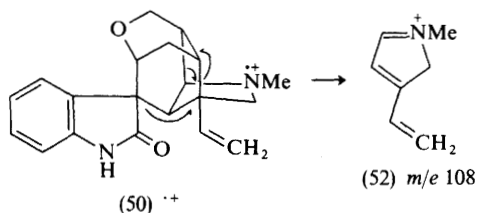
⁴⁴ B. L. Møller, L. Seedorf, and F. Nartey, *Phytochemistry*, 1972, 11, 2620.

⁴⁵ (a) A. M. Morfaux, L. Olivier, and J. Le Men, *Bull. Soc. chim. France*, 1971, 3967; (b) A. M. Morfaux, L. Le Men-Olivier, J. Lévy, and J. Le Men, *Tetrahedron Letters*, 1973, 1939.

⁴⁶ V. Yu. Vachnadze, V. M. Malikov, K. S. Mudzhiri, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, 8, 341 (*Chem. Abs.*, 1972, 77, 152 416).

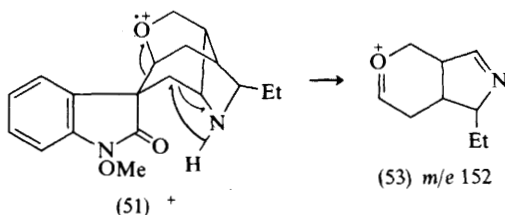
The mass-spectral fragmentation of gelsemine (50a) and gelsedine (51a) types has been analysed^{47a} and was of value in elucidating^{47b} the structures of N_4 -methoxygelsemine (= gelseverine^{5h}) (50b) and 14-hydroxygelsemine (51b), minor alkaloids of *Gelsemium sempervirens* roots.

The fragmentation of the gelsemine type is dominated by an ion at m/e 108 which is interpreted as (52) [arrows on (50)⁺ in Scheme 8]. The gelsedine skeleton

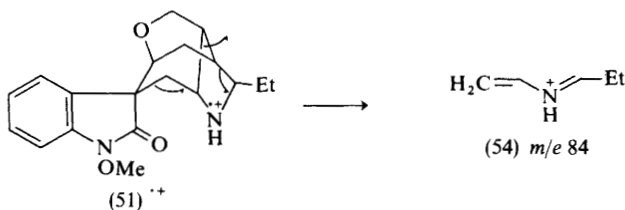


Scheme 8

fragments in the mass spectrometer to give two important ions, at m/e 152 and 84. These characteristic ions are given structures (53) and (54), postulated to arise as shown by arrows on (51)⁺ in Schemes 9 and 10 respectively.



Scheme 9



Scheme 10

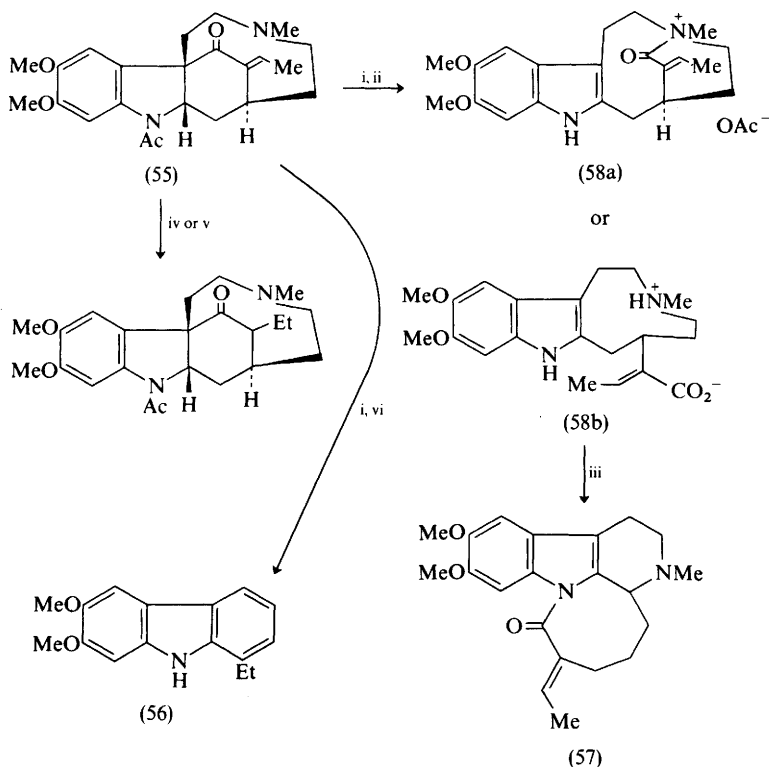
Strychnine-Akuammicine-Condyllocarpine-Ellipticine Group. Vinnervinine has been isolated from *Alstonia muelleriana*.^{29k} Ellipticine occurs in *Ochrosia confusa*;^{29d} also present in this plant were ellipticine N_b -oxide and 1,2-dihydro- and 1,2,3,4-tetrahydro-ellipticines. The bark of *Strychnos camptoneura*⁴⁸ contains

⁴⁷ (a) M. Wichtl, A. Nikiforov, S. Sponer, and K. Jentzsch, *Monatsh.*, 1973, **104**, 87; (b) M. Wichtl, A. Nikiforov, G. Schulz, S. Sponer, and K. Jentzsch, *ibid.*, p. 99.

⁴⁸ M. Koch, J. Garnier, and M. Plat, *Ann. pharm. franç.*, 1972, **30**, 299 (*Chem. Abs.*, 1972, **77**, 85 680).

the N_b -oxide of retuline and four other alkaloids not yet assigned structures. Diaboline and isostrychnine were detected in *Strychnos nux vomica*^{29e} and 19,20-dihydrocondylocarpine was isolated from *Amsonia tabernaemontana*.^{29a} The separation of strychnine and brucine by high-speed liquid-liquid chromatography has been described.⁴⁹ Spin-lattice relaxation data have been employed⁵⁰ in signal assignments in the ^{13}C n.m.r. spectrum of brucine.

It is well worth reading the description⁵¹ by Moore and Rapoport of the structural elucidation of geissovelline (55) from the bark of *Geissospermum vellosii*. Firstly the paper is a full account of the completed work and has not been preceded by a preliminary communication. Secondly both the paper itself and the work it describes, encompassing as it does extensive use of both chemical



Reagents: i, 1N-HCl-100 °C; ii, $\text{Pb}(\text{OAc})_4$ -AcOH-PhH; iii, 180 °C; iv, H_2 -Pt-AcOH; v, NaBH_4 -EtOH-NaOH; vi, 280 °C, N_2 atmosphere

Scheme 11

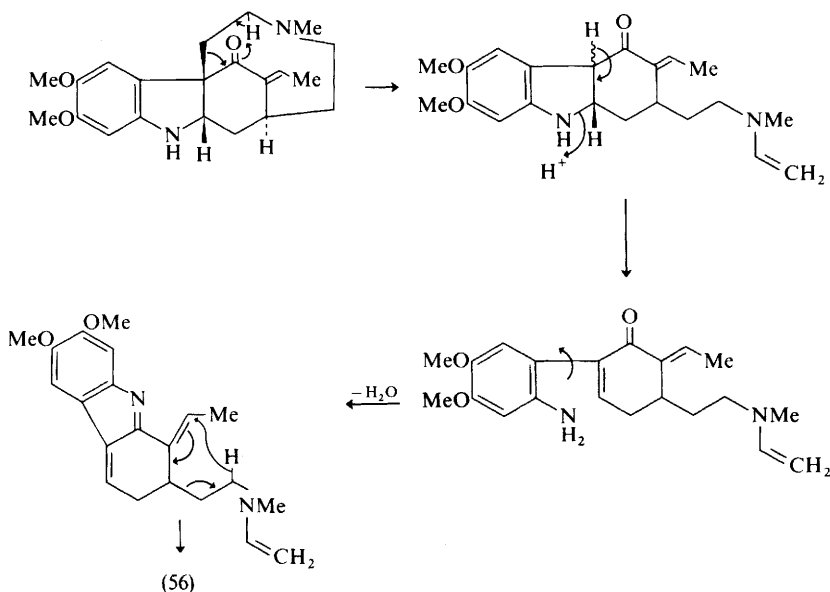
⁴⁹ Chang-Yi Wu and S. Siggia, *Analyt. Chem.*, 1972, **44**, 1499.

⁵⁰ F. W. Wehrli, *J.C.S. Chem. Comm.*, 1973, 379.

⁵¹ R. E. Moore and H. Rapoport, *J. Org. Chem.*, 1973, **38**, 215.

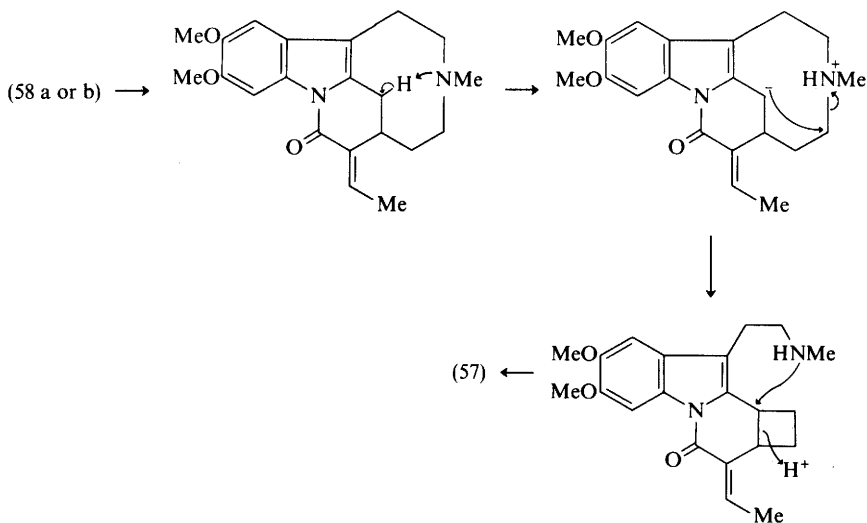
degradation and modern spectroscopy (including full ^{13}C and 300 MHz ^1H n.m.r. spectral analyses of the desacetyl alkaloid) are models at which to aim, although it must be added that, with the wealth of indole alkaloid data available, the elucidation could probably have been shortened by employing appropriate interconversions and spectral comparisons. The work contains results which must have been by no means straightforward as they actually emerged—the alkaloid has a carbon–carbon double bond which is reduced by both borohydride and lithium aluminium hydride as well as catalytically; it also undergoes several complex molecular rearrangements. Despite this, the paper unfolds the structural analysis in a beautifully clear yet intriguing fashion—the alkaloid's structure is not 'revealed' until the end of the fifth page. This Report gives (Scheme 11) some of the more exotic chemistry of geissovelline while not attempting to summarize the systematic degradations and structural arguments which are so well presented in the paper.

Pyrolysis of desacetylgeissovelline gives a carbazole (56) in 20% yield, which has a carbon skeleton which does not reflect that of the alkaloid; this has been rationalized as shown in Scheme 12. In an even more astounding rearrangement,



Scheme 12

the indole (57) resulted when desacetylgeissovelline (its dihydro-derivative gave an analogous product) was treated first with lead tetra-acetate to give a water-soluble indole, possibly (58b) [the author prefers (58a)], and this then pyrolysed at 180 °C. Scheme 13 shows the author's own rationalization of the formation of (57).



Scheme 13

Geissovelline is of a type closely related to dichotine;^{9d} whether the absolute stereochemistry is correctly represented as shown by the authors and in (55), which would place it in an enantiomeric relationship with dichotine and condylocarpine, is not yet known.

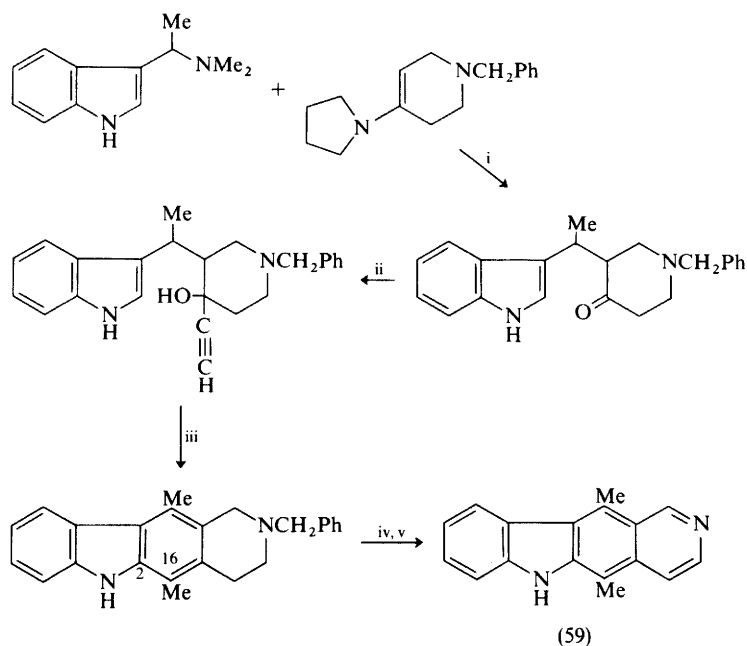
A sequence in a model series^{52a} later developed into a synthesis of the alkaloid itself^{52b} is one of two new approaches^{52b,53} reported this year to the base ellipticine (59). In Le Goffic's synthesis^{52b} (Scheme 14) α -methylgramine was used to alkylate a 4-piperidone pyrrolidine enamine and the C ring built up with a C-2—C-16 bonding step. Sainsbury's sequence⁵³ (Scheme 15) starts with an α -substituted indole and utilizes an indole β -substitution as a late step; it requires a more complex pyridine but a simpler indole as starting materials.

Eburnamine–Aspidospermine–Aspidofractine Group. The root bark of *Criocerastripladeniiflorus*^{54a,b} has yielded eight alkaloids which include 14,15-dehydrovincamine and its 12-methoxy-derivative, 14,15-dehydro-16-epivincamine, 14,15-dehydro-16-methoxycarbonyl-eburnamine, voaphylline, and tabersonine. As well as rhazinilam, aspidospermine and (–)-pyrifolidine were isolated^{43b} from *Aspidosperma quebracho blanco*. Further alkaloids of *Catharanthus ovalis*^{29f} include venalstonine, venalstonidine, and vindolinine. Tubotaiwine and its *N*_b-oxide have been isolated from the root bark of *Conopharyngia johnstonii*.^{54c} The

⁵² F. Le Goffic, A. Gouyette, and A. Ahond, (a) *Compt. rend.*, 1972, **274**, C, 1948; (b) *ibid.*, p. 2008.

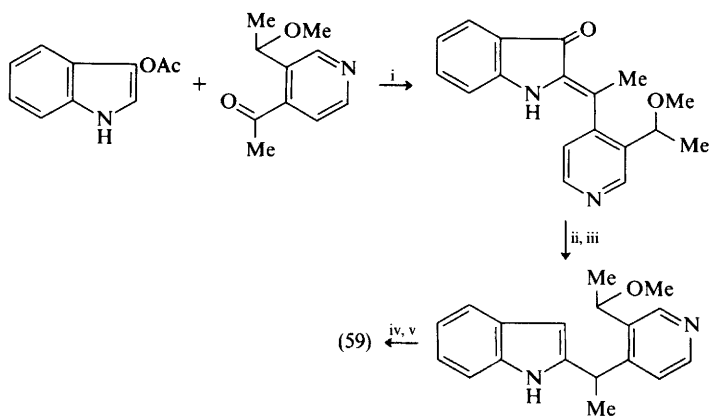
⁵³ K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264.

⁵⁴ (a) J. Bruneton, A. Bouquet, and A. Cavé, *Phytochemistry*, 1973, **12**, 1455; (b) J. Bruneton, A. Cavé, and A. Cavé, *Tetrahedron*, 1973, **29**, 11 1; (c) M. Pinar, U. Renner, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1972, **55**, 2972; (d) B. Zsádon, J. Tamás, and M. Szilasi, *Chem. and Ind.*, 1973, 229.



Reagents: i, dioxan-heat; ii, $\text{HC}\equiv\text{CNa-NH}_3\text{liq.}$; iii, $\text{HCO}_2\text{H-heat}$; iv, $\text{Na-NH}_3\text{liq.}$; v, Pd/C-decalin-heat

Scheme 14

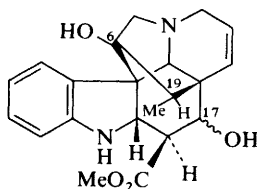


Reagents: i, aq. NaOH ; ii, NaBH_4 ; iii, $\text{H}^+ (-\text{H}_2\text{O})$; iv, 60% HBr-heat ; v, adsorb on silica gel-r.t.

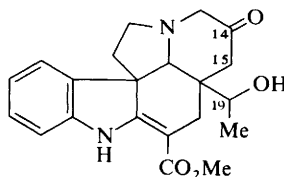
Scheme 15

leaves of *Amsonia tabernaemontana* have yielded^{54d} as well as vincamine and 6,7-dehydrovincamine the two 3-*epi*-analogues; also from the leaves of this plant were obtained^{29a} (+)-vincadifformine, (+)-aspidospermidine and its *N*_a-formyl and 1,2-dehydro-derivatives, and quebrachamine. The location of vincamine and related alkaloids in the stalks and leaves of *Vinca minor* has been identified⁵⁵ as the latex tubes and vacuoles of hyperdermal parenchymatic cells.

Melobaline, a trace of 19-*epi*melobaline, and baloxine are alkaloids isolated from the leaves of *Melodinus balansae*.⁵⁶ Melobaline and baloxine were assigned structures (60) and (61) respectively very largely on the grounds of their mass-spectral fragmentation. Thus the tertiary hydroxy-group in melobaline (= 6,17-dihydroxyvindolicine) was evidently not on the piperidine ring and had therefore to be at C-6. The carbonyl oxygen in baloxine (= 14-ketominovincinine) was mass-spectrally located on the piperidine ring; differentiation between C-14 and C-15 carbonyl possibilities was based on the absence of intramolecular hydrogen-bonding to the C-19 hydroxy-group, to be anticipated had the carbonyl group been at C-15.



Melobaline (60)



Baloxine (61)

Full details of Saxton's successful eburnamine synthesis, summarized^{9e} previously, have now been given.⁵⁷ Continuing interest in this ring system is evidenced by the two independent but similar stereoselective syntheses^{58a,b} of (±)-vincamine (62) published this year and summarized in Scheme 16. Both Szántay^{58a} and Potier^{58b} employed as starting material the tetracyclic enamine (63),^{58c} which was utilized in this way in an earlier synthesis of eburnamonine.^{58c}

The 20-desethyl-20-*iso*-aspidospermine ring system can be produced^{59a} in one step (Scheme 17) when the amide (64) is treated with boron trifluoride, re-collecting the mechanistically entirely analogous step in the synthesis of vindorosine described last year.⁵⁴ Intermediates similar to (64), but without the amide function, have of course been previously exploited by Wenkert in syntheses of the A-D rings of tetrahydro-β-carboline alkaloids.^{59b}

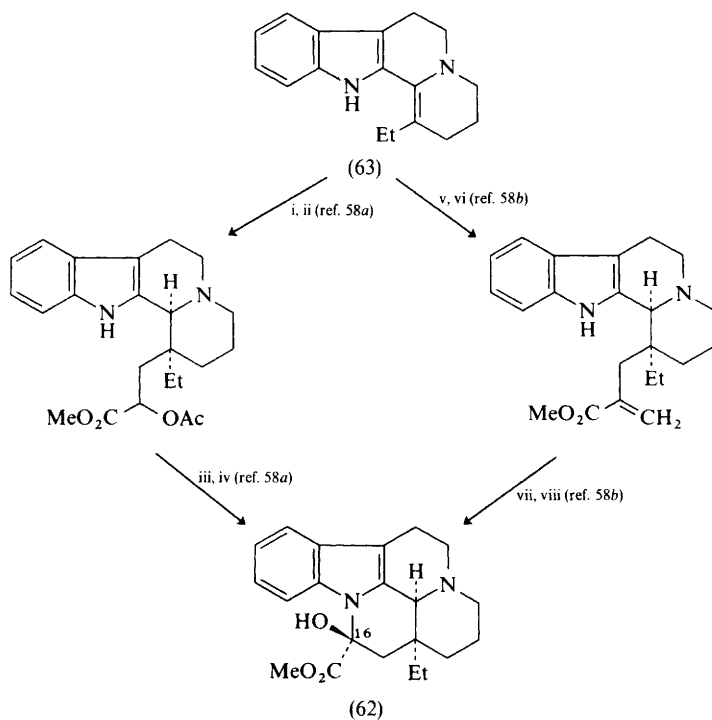
⁵⁵ G. Verzar-Petri, Postep Dziedzinie Leku Rosl. Pr. Ref. Dosw. Wygloszone Symp., ed. F. Kaczmarek, 1970, p. 115 (*Chem. Abs.*, 1973, **78**, 55 378).

⁵⁶ M. H. Mehri, M. Koch, M. Plat, and P. Potier, *Bull. Soc. chim. France*, 1972, 3291.

⁵⁷ K. H. Gibson and J. E. Saxton, *J.C.S. Perkin I*, 1972, 2776.

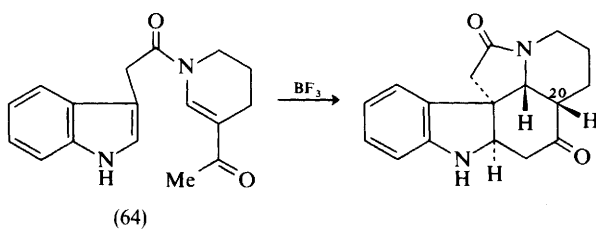
⁵⁸ (a) Cs. Szántay, L. Szabó, and Gy. Kalász, *Tetrahedron Letters*, 1973, 191; (b) C. Thal, T. Sevenet, H. P. Husson, and P. Potier, *Compt. rend.*, 1972, **275**, C, 1295; (c) E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, 1965, **87**, 1580.

⁵⁹ (a) E. Wenkert, J. S. Bindra, and B. Chauncy, *Synth. Comm.*, 1972, **2**, 285; (b) E. Wenkert, *Accounts Chem. Res.*, 1968, **1**, 78.



Reagents: i, $\text{CH}_2=\text{C}(\text{OAc})\text{CO}_2\text{Me}$; ii, H_2 -Pd-MeOH; iii, MeONa-MeOH; iv, Ag_2CO_3 -celite-PhH-heat; v, $\text{BrCH}_2\text{C}(\text{CO}_2\text{Me})=\text{CH}_2$; vi, NaBH_4 ; vii, OsO_4 ; viii, HIO_4

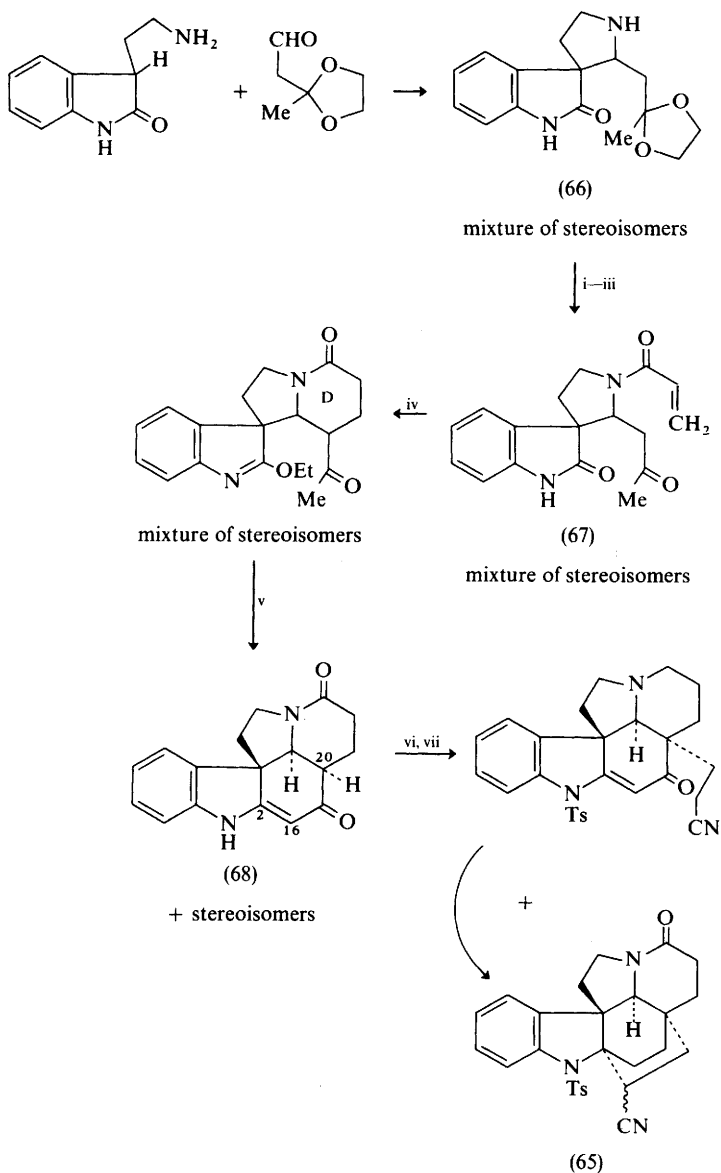
Scheme 16



Scheme 17

Ban's group has achieved the first total synthesis⁶⁰ (Scheme 18) of the aspidofractinine skeleton [as in (65)]. The aspidospermine skeleton was constructed^{60a} first from the tryptamine oxindole condensation product (66); this of itself is a

⁶⁰ (a) Y. Ban, T. Ohnuma, M. Nagai, Y. Sendo, and T. Oishi, *Tetrahedron Letters*, 1972, 5023; (b) T. Ohnuma, T. Oishi, and Y. Ban, *J.C.S. Chem. Comm.*, 1973, 301.

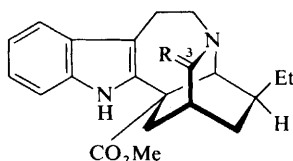


Reagents: i, $\text{ClCH}_2\text{CH}_2\text{COCl}$; ii, $\text{H}^+ - \text{H}_2\text{O}$; iii, $\text{NaOH} - \text{EtOH} - \text{CH}_2\text{Cl}_2$; iv, $\text{Et}_3\text{O}^+ \text{BF}_4^- - (\text{CH}_2\text{Cl})_2$, 65°C ; v, $\text{NaH} - \text{DMSO} - \text{heat}$; vi, $\text{TsCl} - \text{NaH}$; vii, $\text{CH}_2=\text{CHCN} - \text{Bu}'\text{OK} - \text{Bu}'\text{OH} - \text{DMSO}$

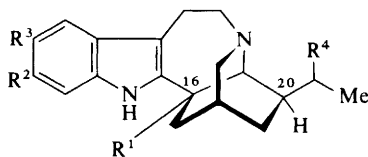
Scheme 18

novel route to the pentacyclic system. Treatment of (67) with triethyloxonium borofluoride resulted not only in the formation of an iminoether unit at N_a but also in closure of the D ring. This produced an intermediate in which the C-2—C-16 bond could now be made.* This gave (68), having electrophilic character at C-2 and the potential for enolate nucleophilicity at C-20, thus allowing a double Michael condensation to effect^{60b} insertion of the bridge and the formation of the sixth ring.

Ibogamine Group. Voacangine has been isolated from the leaves of *Alstonia boonei*.^{4,3a} Two new alkaloids in this group are 3-oxocoronaridine (69a) and 3-(2-ketopropyl) coronaridine (69b) from a sample of *Ervatamia coronaria*.⁶¹ The structure of (69b) is extremely interesting, possessing as it does an 'extra' three-carbon unit; because of this a more exhaustive structural proof should be provided. The structure at the moment is based principally on mass-spectral fragmentation evidence.



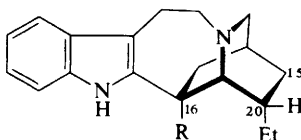
(69) a; R = O
b; R = H, CH₂COMe



	R ¹	R ²	R ³	R ⁴	
(70) a;	MeO ₂ C	H	H	H	16S,20S (-)-Coronaridine
b;	MeO ₂ C	MeO	MeO	H	16S,20S (-)-Conopharyngine
c;	MeO ₂ C	MeO	H	HO	16S,20R (-)-Isovoacristine
d;	MeO ₂ C	MeO	H	H	16S,20S (-)-Isovoacangine
e;	MeO ₂ C	H	MeO	H	16S,20S (-)-Voacangine
f;	H	H	H	H	16R,20S (-)-Ibogamine
g;	H	H	MeO	H	16R,20S (-)-Ibogaine
h;	H	MeO	H	H	16R,20S (-)-Tabernanthine
i;	H	H	MeO	HO	16R,20R (-)-Iboxygaine
j;	MeO ₂ C	H	H	HO	16S,20R (-)-Heyneanine

* See ref. 10d for a failure to achieve an analogous cyclization to make the akuammicine skeleton.

⁶¹ G. delle Monache, I. L. D'Albuquerque, F. delle Monache, and G. B. Marini-Bettolo, *Atti Accad. naz. Lincei, Rend. Classe Sci., fis., mat., nat.*, 1972, **52**, 375 (*Chem. Abs.*, 1973, **78**, 40 468).

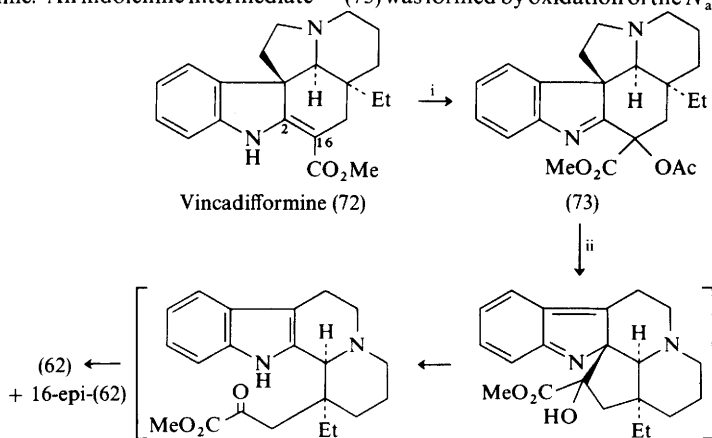


- (71) a; R = MeO₂C 15,20-dehydro 16R (+)-Catharanthine
 b; R = MeO₂C 16R,20S (+)-Dihydrocatharanthine
 c; R = H 16S,20S (+)-Epi-ibogamine

In a reversal of the previous view it has now been shown^{62a} by Trojanek that the iboga alkaloids are not all in the same enantiomeric series. Thus previous extrapolations based on the established absolute stereochemistry of cleavamine methiodide, chemically derived from catharanthine, are not justified. Studies of their c.d. spectra have now clearly shown that the large majority of known iboga bases are in a series enantiomeric with catharanthine. Formulae (70a-j) and (71a-c) show the details for the alkaloids and derivatives in the two series which were examined.^{62a} An X-ray analysis^{62b} of (+)-coronaridine hydrobromide has confirmed the assignment for this base.

Details⁶³ have been given of a synthesis of desethylbogamine, which served as a model for the synthesis of ibogamine summarized^{9f} previously.

Skeletal Rearrangements and Interconversions. In extension of their earlier work^{10b} French workers have succeeded⁶⁴ in converting (Scheme 19) vincadifformine (72) into a mixture of vincamine (62) (main product) and 16-epivincamine. An indolenine intermediate^{10b} (73) was formed by oxidation of the N_a-C-2-



Reagents: i, Pb(OAc)₄; ii, aq. AcOH-NaOAc

Scheme 19

⁶² (a) K. Blaha, Z. Koblikova, and J. Trojanek, *Tetrahedron Letters*, 1972, 2763; (b) J. P. Kutney, K. Fuji, A. M. Treasurywala, J. Fayos, J. Clardy, A. I. Scott, and C. C. Wei, *J. Amer. Chem. Soc.*, 1973, **95**, 5407.

⁶³ P. Rosenmund, W. H. Haase, J. Bauer, and R. Frische, *Chem. Ber.*, 1973, **106**, 1459.

⁶⁴ G. Hugel, J. Lévy, and J. Le Men, *Compt. rend.*, 1972, **274**, C, 1350.

—C-16 enamine system of the starting material with the introduction of oxygen at C-16 and this was then rearranged by treatment with aqueous acetic acid–sodium acetate.

The first note^{65a} in a series of four^{65a–d} maintains that the remaining three constitute a ‘complete vindication’ for observations, reported⁶⁶ in 1968. These claimed then that rearrangement of (–)-tabersonine to a mixture of (±)-catharanthine (12% yield) and ψ -catharanthine (28%) and of (+)-stemmadenine to (±)-tabersonine (12%), (±)-catharanthine (9%), and ψ -catharanthine (16%) could be effected by heating each substrate in refluxing acetic acid. These claims could later^{67a,9g,5j} not be reproduced, despite extensive efforts, by British and French workers, although in the case of catharanthine the formation of allocatharanthine and derivatives by rearrangements of a different type was uncovered^{67a,5j,9g} and this is now acknowledged and has been repeated.^{65d}

The three notes^{65b–d} describe new work by the Yale group: rearrangements of 19,20-dihydrostemmadenine acetate (74), 19,20-dihydroprekuaammicine acetate (75), stemmadenine acetate (76), 19,20-dihydroprecondylocarpine acetate (77), and allocatharanthine (78), none of which is carried out by heating in refluxing acetic acid, are described (Scheme 20). All proceed in minute yields and all, save one with dihydroprekuaammicine acetate, were effected by the pyrolysis of the substrate or its hydrochloride on a silica gel surface at 150 °C; one rearrangement of dihydroprekuaammicine acetate was procured by heating in methanol at 80 °C. Neither the results of the rearrangements nor the other experiments described^{65b–d} bear on the question of the validity of the originally reported acetic acid rearrangements of tabersonine and stemmadenine; in fact nowhere does this group of papers claim specifically to have successfully repeated the earlier disputed experiments; in this Reporter’s view this makes the claim^{65a} for ‘complete vindication’ totally unjustified and consequently the accompanying innuendo of the ‘prologue’^{65a} unscientific and distasteful.

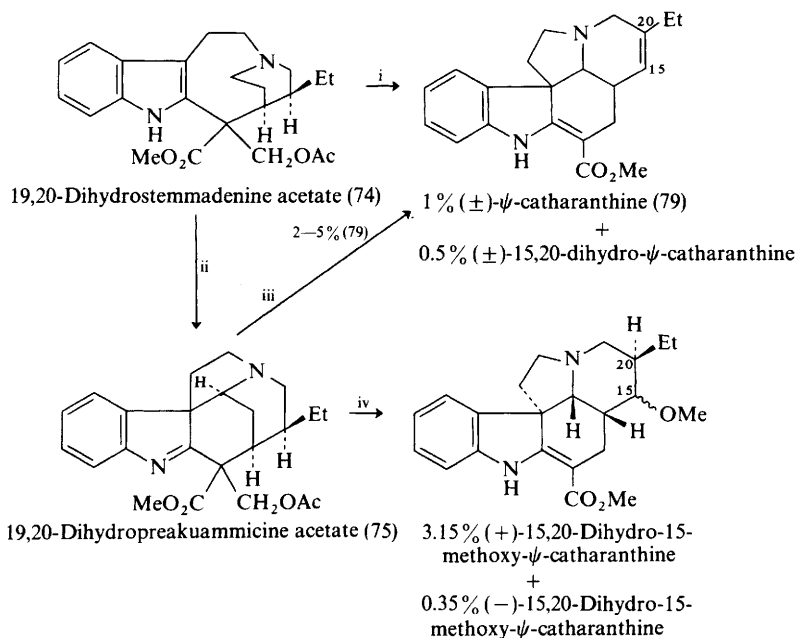
In a rebuttal,^{67b} Brown, Poisson, and Smith point out the total illogicality of a claim^{65a} for ‘complete vindication’ for reported⁶⁶ acetic acid rearrangements giving products in appreciable yields (see above), which is based on later results^{65b–d} with different substrates rearranged in very small yields under different conditions. They also comment that catharanthine could not possibly have been obtained in yields of 12 and 9% since this alkaloid is converted into other compounds to the extent of >99% after treatment with refluxing acetic acid for periods less than those specified.⁶⁶

The new experimental results reported^{65b–d} are summarized in full in Schemes 20–22. The yields and such experimental details as have so far been given are

⁶⁵ (a) A. I. Scott, *J. Amer. Chem. Soc.*, 1972, **94**, 8262; (b) A. I. Scott and C. C. Wei, *ibid.*, p. 8263; (c) *ibid.*, p. 8264; (d) *ibid.*, p. 8266.

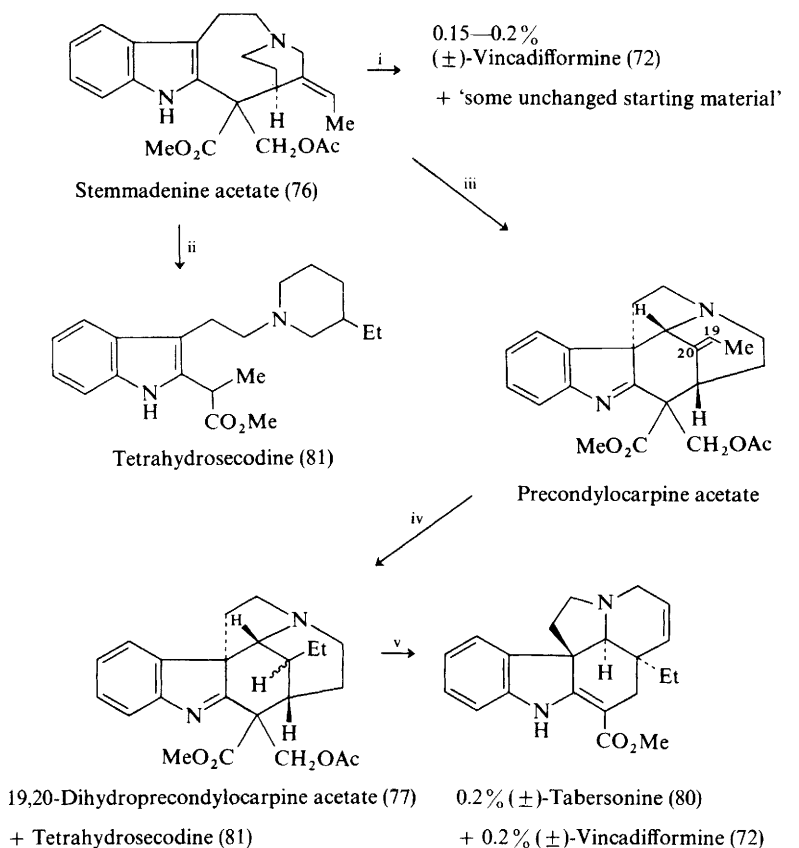
⁶⁶ A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 945.

⁶⁷ (a) R. T. Brown, J. S. Hill, G. F. Smith, K. S. J. Stapleford, J. Poisson, M. Muquet, and N. Kunesch, *Chem. Comm.*, 1969, 1475; M. Muquet, N. Kunesch, and J. Poisson, *Tetrahedron*, 1972, **28**, 1363; R. T. Brown, J. S. Hill, G. F. Smith, and K. S. J. Stapleford, *ibid.*, 1971, **27**, 5217; (b) R. T. Brown, G. F. Smith, and J. Poisson, *J. Amer. Chem. Soc.*, 1973, **95**, 5778.

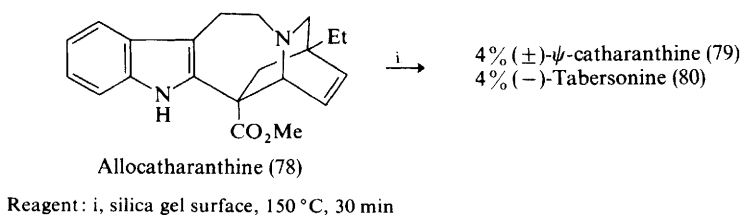
Scheme 20^{65b}

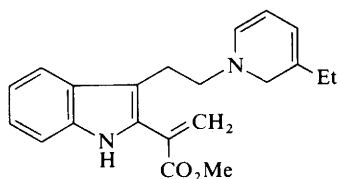
reproduced in detail. The experiments with dihydrostemmadenine acetate (74) and dihydropreakuammicine acetate (75) demonstrated the conversion of the stemmadenine–akuamma skeleton into the ψ -catharanthine (79) system (Scheme 20): stemmadenine acetate (76) and 19,20-dihydroprecondylocarpine acetate (77) rearrangements (Scheme 21) showed the transformation of stemmadenine–condylocarpine skeleta to the natural aspidosperma system, tabersonine (80) and vincadifformine (72) being formed; finally it was shown (Scheme 22) that the unnatural ring system of allocatharanthine (78) could be rearranged to the unnatural ψ -catharanthine (79) and the natural aspidosperma ring system of tabersonine (80).

The results are of course interesting in themselves and, if they should prove to be reproducible, support a view that dehydrosecodines of the two types, (Sec A) and (Sec B), may serve as intermediates in rearrangements of these substrates and under the conditions described (Schemes 20–22). However, the newly presented results^{65b–d} are neither useful as a basis for viable synthetic processes nor, for the most part, are they carried out under conditions even remotely like those existing in living plants, which might more easily permit their direct extrapolation as laboratory models for the processes believed to be involved in the biosynthesis of the various indole alkaloid structural types.

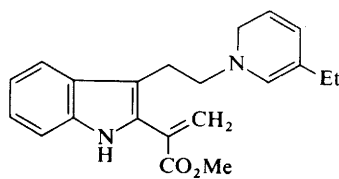


Reagents: i, hydrochloride salt–silica gel surface, 150 °C, 25 min; ii, H₂–Pt (75% yield); iii, 'platinum catalysed oxidation' (no yield given); iv, 'reduction' (no yield given); v, silica gel surface, 150 °C, 25 min

Scheme 21^{6.5c}Scheme 22^{6.5d}



Dehydrosecodine (Sec A)

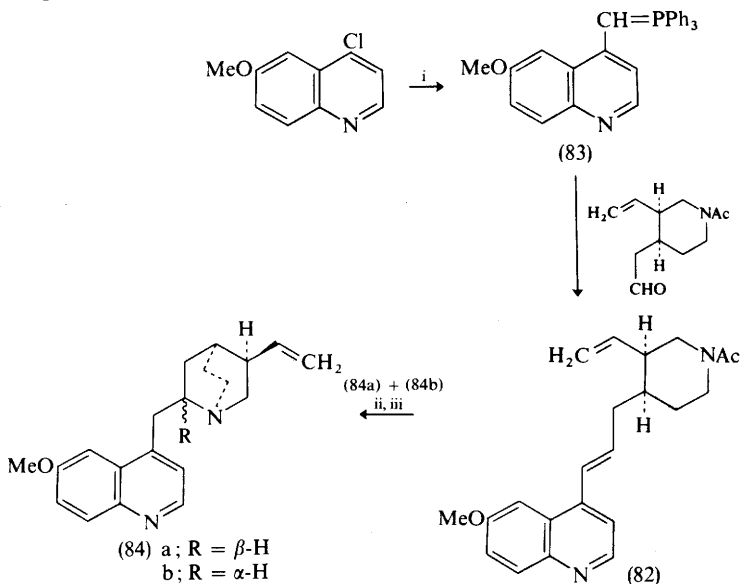


Dehydrosecodine (Sec B)

3 Biogenetically Related Quinoline Alkaloids

The leaves of the olive tree and of privet contain⁶⁸ cinchonine, dihydrocinchonine, and cinchonidine, which had all previously only been obtained from *Cinchona* and *Remijia* species and from *Strychnos pseudo-quina*. Camptothecin (85) and the new 9-methoxycamptothecin were isolated⁶⁹ from all parts of *Mappia foetida*.

An alternative means has been described⁷⁰ for the preparation of 1-(4-piperidylmethyl)-2-(4-quinolyl)ethylene intermediates, such as (82), which are central to the recently developed syntheses^{9h} of, for example, desoxyquinine and desoxyquinidine and therefrom quinine and quinidine. In this variation the crucial intermediate is prepared *via* a phosphonium ylide (83), in turn readily synthesizable from a quinoline carrying a good leaving group at C-4 by nucleophilic displacement with methylenetriphenylphosphorane. Scheme 23 shows how the



Reagents: i, $2\text{Ph}_3\text{P}=\text{CH}_2$; ii, hydrolysis; iii, spontaneous cyclization

Scheme 23

⁶⁸ G. Schneider and W. Kleinert, *Planta Med.*, 1972, **22**, 109 (*Chem. Abs.*, 1973, **78**, 33 857).

⁶⁹ T. R. Govindachari and N. Viswanathan, *Indian J. Chem.*, 1972, **10**, 453.

⁷⁰ E. C. Taylor and S. F. Martin, *J. Amer. Chem. Soc.*, 1972, **94**, 6218.

route was used to make desoxyquinine (84a) and desoxyquinidine (84b), Uskoković's intermediate providing the aliphatic moiety.

Using an analogous sulphonium ylide it was shown⁷⁰ that this approach could be used to shorten appreciably the synthesis of 1-(4-piperidylmethyl)-2-(4-quinolyl)ethylene oxides, as employed in Uskoković's refined synthesis^{5k} which gave quinine and quinidine directly; unfortunately so far only 4-chloroquinoline itself has been converted into a sulphonium ylide; (\pm)-cinchonine and (\pm)-cinchonidine were synthesized in this way.

Preliminary communications on three more total syntheses⁷¹⁻⁷³ of (\pm)-camptothecin (85) have been published since the last Report, which summarized^{5l} the first four. In two^{71,73} the D/E ring system is built up on an A/B/C tricyclic foundation, and in the third⁷² the C/D rings and the carbon substituents for the E ring were completed first. Japanese workers⁷¹ chose the quinoline lactam (86a)^{71b} as a starting point, building a 4-methoxy-2-pyridone ring on to it as a first stage [\rightarrow (87)]. Although Vilsmeier formylation of (87) took place as desired at C-16, the resulting formyl derivative proved unstable to the conditions which had been developed in a model series for the elaboration of the E ring; this problem was avoided by selectively reducing the B ring as a prelude to the elaboration of the E ring lactone. This involved, after formylation at C-16, an interesting displacement of methoxy from the 4-position of the 2-pyridone with the anion of di-*t*-butyl malonate. Subsequent steps were straightforward but did of course require the inclusion of a B ring re-aromatization step (Scheme 24).

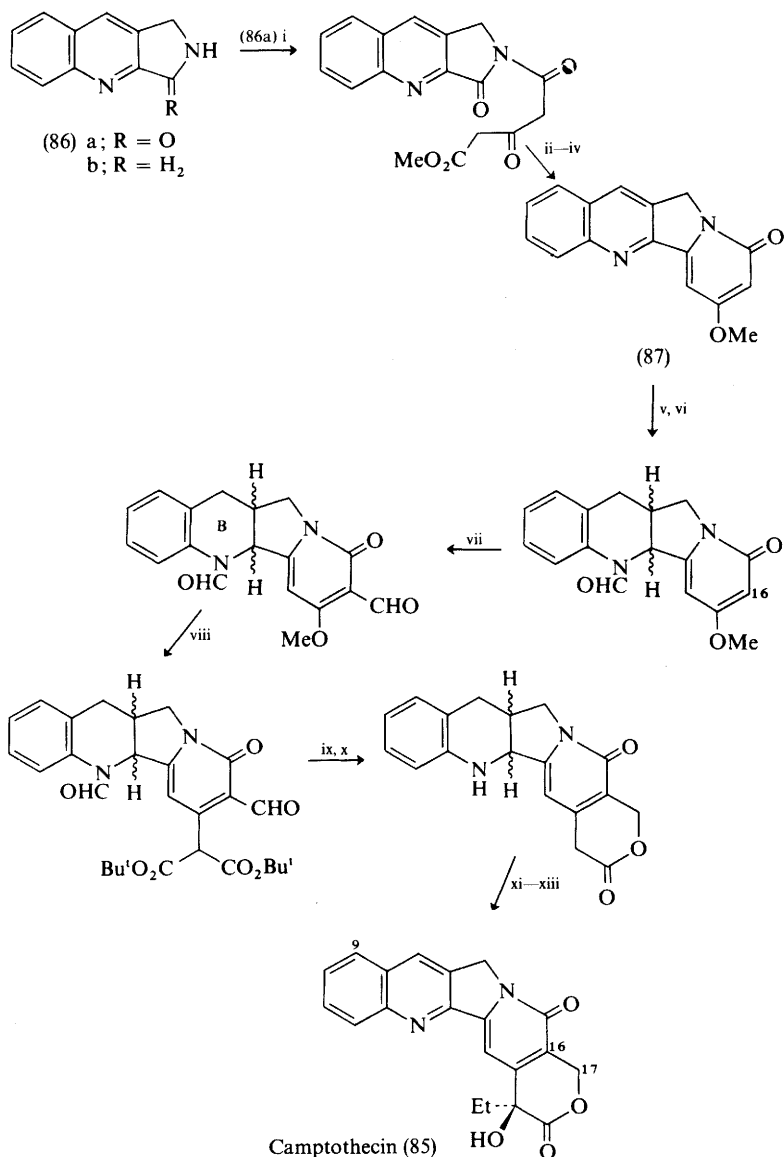
The original plan for the route shown in Scheme 25 had as a theme the possibility of utilizing a substituted furan to carry the essential features of the future ring E in a masked form. However, this plan was somewhat thwarted at a late stage by the unexpected failure to achieve the straightforward furan ring-opening required for release of the desired functionalities. The synthesis was, however, carried through to completion, though of course by a rather longer route than had originally been hoped for and certainly with more steps than is suggested by the fifteen 'synthetic operations from furfural' by which the synthesis is described.⁷³ Furfural was first converted into the masked aldehydo-diacid (88). Attachment to the A/B/C/ nucleus was followed by opening of the furan ring [\rightarrow (89)], unfortunately with loss of one carbon which it had been hoped would be C-17 of the final product. Several further steps were then necessary to complete the synthesis.

Rapoport's neat route^{72a,b} employs the nipecotic acid-acetic anhydride rearrangement^{72c} applied to the bicyclic nipecotic acid (90)^{72b} to give the methylene piperidone (91). The remaining carbons necessary for the E ring were neatly introduced *via* a Claisen rearrangement [(92) \rightarrow (93)]. These and the remaining steps in this synthesis are detailed in Scheme 26.

⁷¹ (a) T. Sugawara, T. Toyoda, and K. Sasakura, *Tetrahedron Letters*, 1972, 5109; (b) T. Sugawara, T. Toyoda, K. Sasakura, and T. Hidaka, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1971.

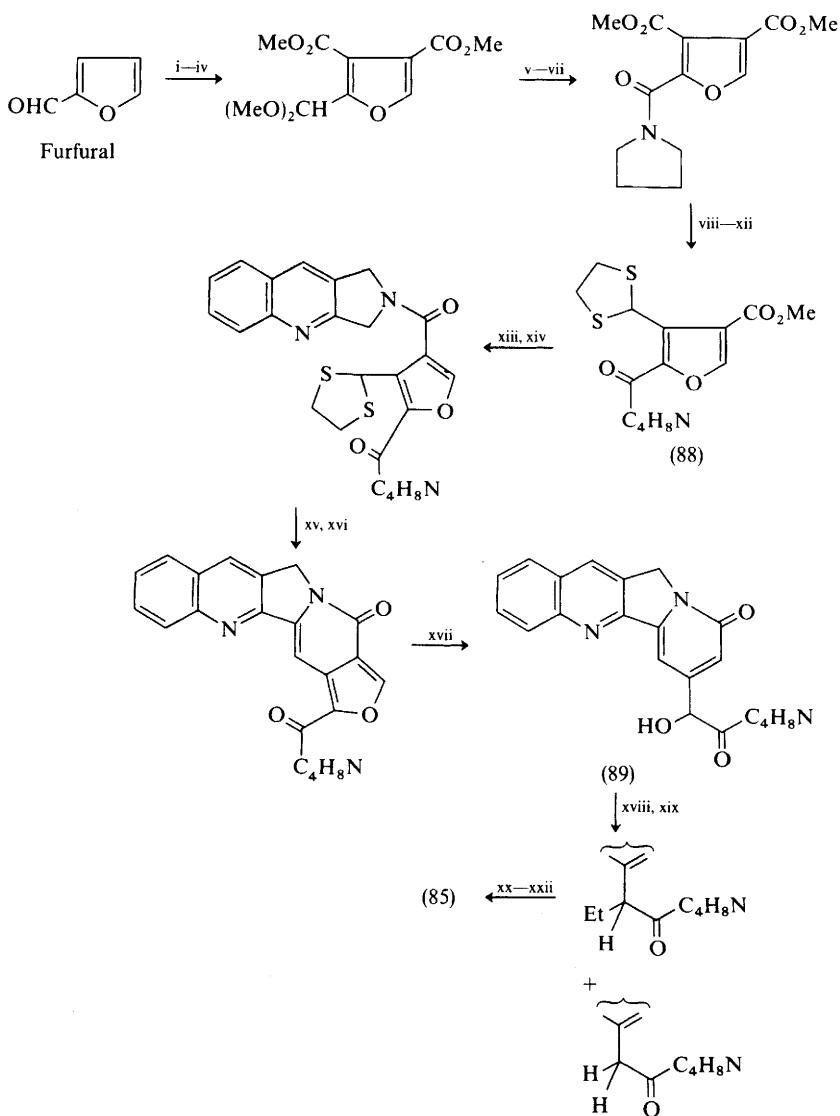
⁷² (a) C. Tang and H. Rapoport, *J. Amer. Chem. Soc.*, 1972, **94**, 8615; (b) J. J. Plattner, R. D. Glocs, and H. Rapoport, *ibid.*, p. 8613; (c) M. L. Rueppel and H. Rapoport, *ibid.*, p. 3877.

⁷³ A. S. Kende, T. J. Bentley, R. W. Draper, J. K. Jenkins, M. Joyeux, and I. Kubo, *Tetrahedron Letters*, 1973, 1307.



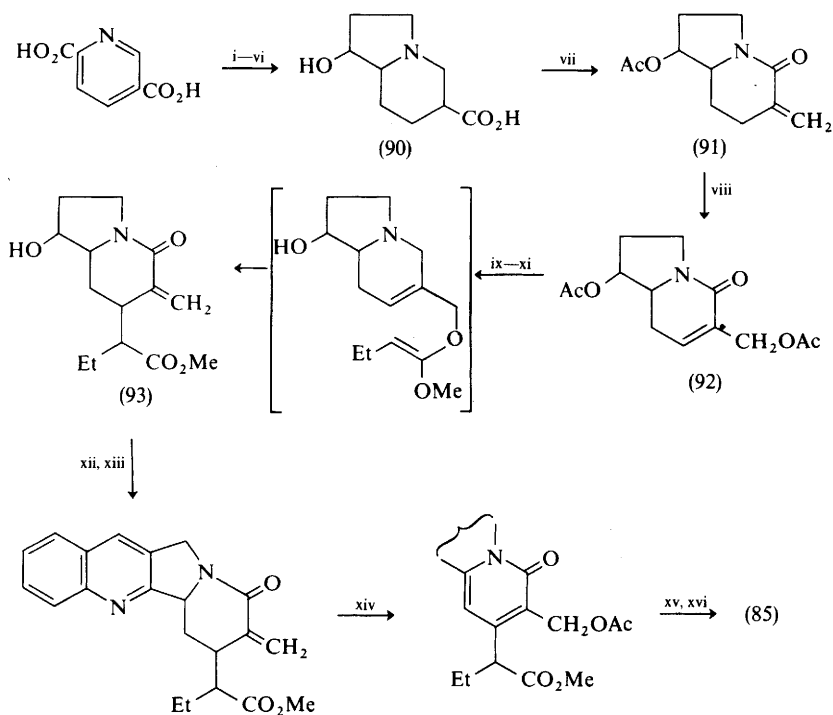
Reagents: i, MeO₂C·CH₂CO·CH₂CO₂Me, 140 °C; ii, MeCN-piperidine-heat; iii, conc. HCl, 150 °C (-CO₂); iv, Me₂SO₄-K₂CO₃-Me₂CO-heat; v, H₂-Pt-HCl-MeOH; vi, HCO₂H-heat; vii, DMF-POCl₃; viii, CH₂(CO₂Bu')₂-NaH-dioxan-heat; ix, NaBH₄; x, conc. HCl-r.t.; xi, DDQ-dioxan-heat; xii, EtBr-NaH-DMF; xiii, O₂-Et₃N-copper acetate-DMF-MeOH

Scheme 24



Reagents: i, MeOH-H⁺; ii, MeO₂C:C:C:CO₂Me; iii, H₂-Pd/C; iv, 190 °C (-CH₂:CH₂); v, Jones oxidation; vi, SOCl₂; vii, pyrrolidine; viii, OH⁻, 0 °C; ix, LiBH₄; x, CH₂N₂; xi, Collins oxidation; xii, HSCH₂CH₂SH; xiii, KOH; xiv, (86b)-β-morpholinoethyl cyclohexyl carbodi-imide metho-*p*-tosylate; xv, HgO-BF₃; xvi, AcOH-KOAc; xvii, alkaline hydrolysis; xviii, SOCl₂-DMF; xix, LiEt₃Cu-THF, 0 °C; xx, MeOH-H₂SO₄-r.t.-5 days; xxi, paraformaldehyde-H₂SO₄; xxii, oxidation

Scheme 25



Reagents: i, H_2 -Ni; ii, MeOH-HCl ; iii, $\text{BrCH}_2\text{CH}_2\text{CO}_2\text{Me}$; iv, Dieckmann; v, 6N-HCl - 105°C ; vi, NaBH_4 , 0°C ; vii, Ac_2O , 145°C ; viii, SeO_2 - AcOH , 70°C ; ix, $\text{MeOH-K}_2\text{CO}_3$ -r.t. (\rightarrow diol); x, excess $(\text{MeO})_3\text{C-CH}_2\text{CH}_2\text{Me}$ -catalytic amount EtCO_2H ; xi, K_2CO_3 - MeOH (to hydrolyse small amount of ester formed); xii, $\text{DCC-DMSO-H}_3\text{PO}_4$ -r.t.; xiii, *o*-aminobenzaldehyde *p*-toluidine Schiff base (Friedlander quinoline synthesis); xiv, SeO_2 - AcOH , 80°C ; xv, $12\text{N-H}_2\text{SO}_4$ -glyme, 50°C ; xvi, O_2 - CuCl_2 -DMF

Scheme 26

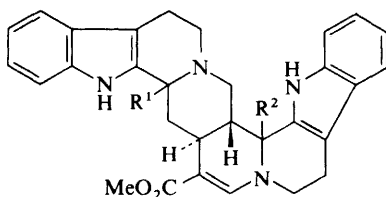
4 Bisindole Alkaloids

Alstonia spectabilis and *A. glabrifolia* contain^{29j} villalstonine; the former also has macralstonidine and the latter macralstonine and alstophylline. Des- N'_a -methylanhydromacralstonine was obtained from *A. muelleriana*.^{29k} Ochrolifuanine and 19,20-dihydro-ochrolifuanine were isolated^{29d} from *Ochrosia confusa*. An X-ray analysis of the di-iodide of C-curarine has confirmed⁷⁴ the structure. Vobtusine and an alkaloid of undefined structure, ditabersonine, were obtained^{54a} from *Crioceris dipladeniiflorus*, voacordine and an isomer from *Tabernaemontana brachyantha*,^{43c} and vindolicine, vinblastine, leurosine, and catharine from *Catharanthus ovalis*.^{29f}

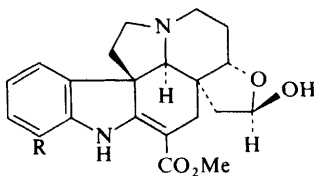
⁷⁴ N. D. Jones and W. Nowacki, *J.C.S. Chem. Comm.*, 1972, 805.

Verticillium tenerum has given⁷⁵ a dimer, 11 α ,11' α -dihydroxychaetocin, which carries four hydroxy-groups corresponding to both the two in chaetocin and the two in verticillin.^{10c} N.m.r. analysis has shown⁷⁶ that roxburghines D and E are epimeric only at C-19; the relative stereochemistry for the four isomers B—E can now be summarized (94a–d).

As well as vobtusine and goziline, the phenolic 17'-*O*-desmethylvobtusine was isolated⁷⁷ from the leaves of *Hedranthera barteri*. Also obtained in this study were hedrantherine (95a) and 17-hydroxyhedrantherine (95b), two new aspidosperma alkaloids of particular interest in that they represent structurally the 'top half' of the vobtusine type of bis-alkaloid, hitherto not found as a monomeric alkaloid.



- (94) a; R¹ = α -H, R² = β -Me Roxburghine B
 b; R¹ = α -H, R² = α -Me Roxburghine C
 c; R¹ = β -H, R² = α -Me Roxburghine D
 d; R¹ = β -H, R² = β -Me Roxburghine E



- (95) a; R = H Hedrantherine
 b; R = HO 12-Hydroxyhedrantherine

In a review⁷⁸ in the first of these Reports, Gorman *et al.* suggested structure (96) for serpentinine on the basis of a detailed n.m.r. and mass-spectral analysis and pointed out that further evidence would be necessary to settle the structure. Now an X-ray analysis⁷⁹ of the dihydrobromide dihydrate has settled some questions

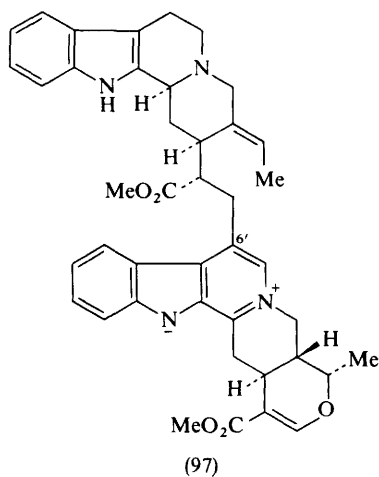
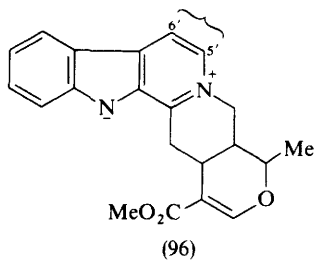
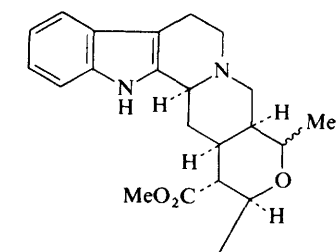
⁷⁵ D. Hauser, H. R. Loosli, and P. Niklaus, *Helv. Chim. Acta*, 1972, **55**, 2182.

⁷⁶ C. Cistano, L. Merlini, R. Mondelli, and G. Nasini, *J.C.S. Chem. Comm.*, 1972, 785.

⁷⁷ J. Naranjo, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1972, **55**, 1849.

⁷⁸ A. A. Gorman, M. Hesse, H. Schmid, P. G. Waser, and W. H. Hopff, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London 1971, vol. 1, p. 287.

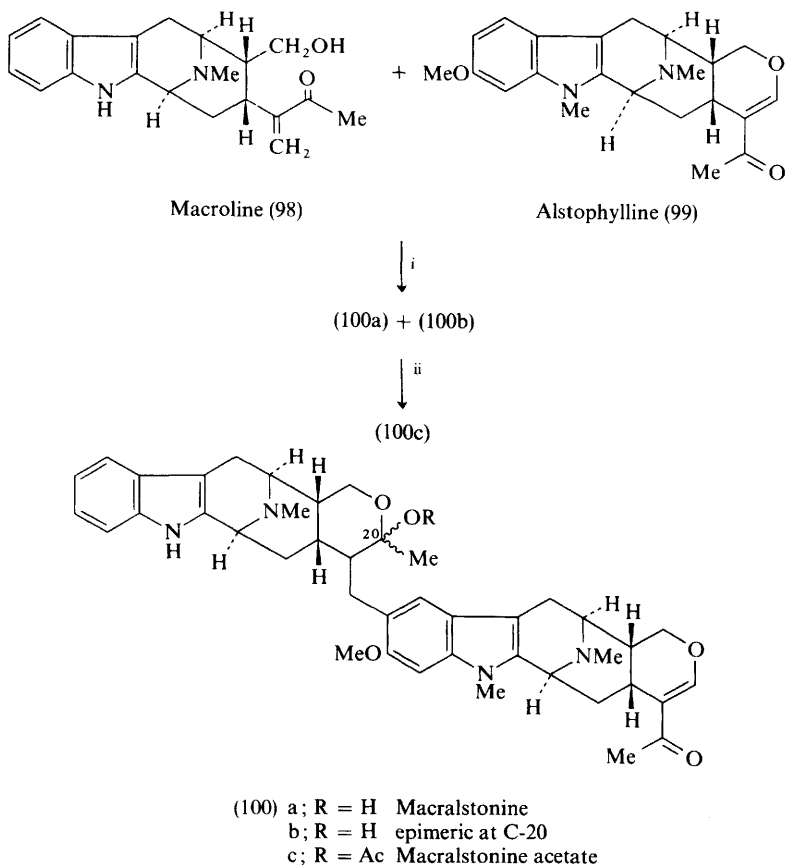
⁷⁹ H. Irie, K. Ishizuka, S. Kawashima, N. Masaki, K. Osaki, T. Shingu, S. Uyeo, H. Kaneko, and S. Naruto, *J.C.S. Chem. Comm.*, 1972, 871.



and brought to light others. Thus the attachment of the 'upper-half' at C-6' is confirmed in the structure (97) now demonstrated; Gorman *et al.* deduced that the attachment should be either C-5' or C-6'. However, the formula now given to the alkaloid contains one less oxygen atom than was originally believed to be present by both Japanese and Anglo-Swiss workers. No comment is made on this discrepancy in the present note.⁷⁹ The oxygen 'missing' is from the upper half, and the conclusion now is that the upper half is tetra- and not penta-cyclic. The

n.m.r. data available⁷⁸ can be accounted for in terms of (97). However, it is difficult to see how the borohydride (deuteride) tetrahydro-derivatives, which seemed to have molecular ions corresponding to tetrahydro-(96) and not tetrahydro-(97), could have been formed.

Details have been given⁸⁰ of the investigations which led to the partial syntheses^{5m} of villalstonine and alstonisidine. A similar line of approach by Le Quesne's group has now resulted in the partial synthesis⁸¹ of macralstonine (100a) from its component 'halves' macroline (98) and alstophylline (99) (Scheme 27).



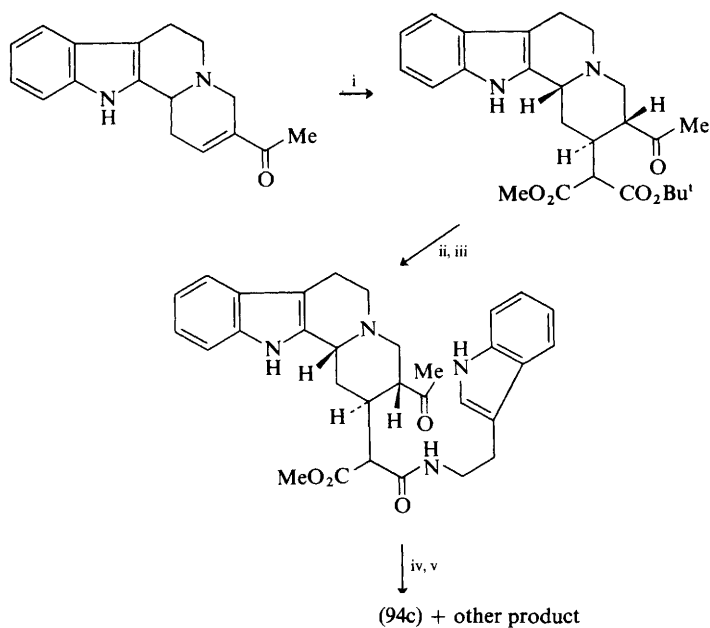
Reagents: i, 0.2N-HCl-r.t.-120 h; ii, Ac_2O

Scheme 27

⁸⁰ D. E. Burke, J. M. Cook, and P. W. Le Quesne, *J. Amer. Chem. Soc.*, 1973, **95**, 546.

⁸¹ D. E. Burke, C. A. De Markey, P. W. Le Quesne, and J. M. Cook, *J.C.S. Chem. Comm.*, 1972, 1346.

Winterfeldt has adapted his synthetic approach, which has previously successfully led to heteroyohimbine⁹ⁱ and camptothecin^{5d} types, to provide the first synthesis⁸² of (\pm)-roxburghine D. This is outlined in Scheme 28.

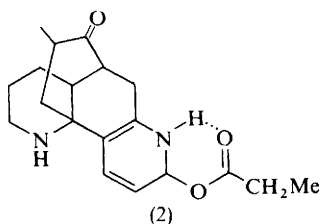
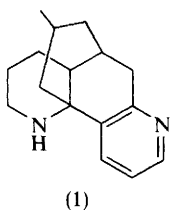


Reagents: i, $\text{CH}_2(\text{CO}_2\text{Me})\text{CO}_2\text{Bu}^t$; ii, $\text{CF}_3\text{CO}_2\text{H}$; iii, β -indolyl- $\text{CH}_2\text{CH}_2\text{NH}_2$ -dicyclohexyl carbodi-imide; iv, H^+ ; v, Bu_2AlH -glyme, 0°C

Scheme 28

⁸² H. Riesner and E. Winterfeldt, *J.C.S. Chem. Comm.*, 1972, 786.

The first example of a lycodine-type (1) alkaloid isolated from other than a Lycopodiaceae species has been reported.¹ Gymnamine obtained from *Gymnema sylvestre* (Asclepiadaceae) was assigned structure (2) on the basis of spectroscopic evidence and chemical conversion into lycodine (1). The biogenetic relationship of gymnamine to β -obscurine-type alkaloids was noted.

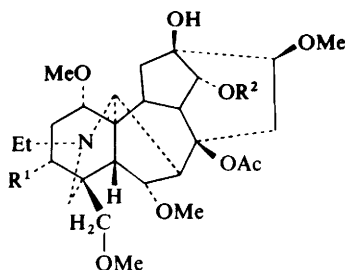


¹ G. S. Rao, J. E. Sinsheimer, and H. M. McIlhenny, *Chem. and Ind.*, 1972, 537.

1 Introduction

The diterpenoid alkaloids continue to attract considerable interest. New bases have been reported from *Aconitum karakolicum*, *A. excelsum*, *Delphinium dictyocarpum*, and *D. bicolor*, and a new diterpenoid alkaloid, anopterine, has been isolated from a species of Escalloniaceae.

Czechoslovakian workers re-examined the alkaloid constituents of *Aconitum ferox* Wall.¹ from which pseudaconitine had previously been obtained,² and found seven alkaloids, four of which were identified as pseudaconitine (1), bikhaconitine (2), chasmaconitine (3), and indaconitine (4).



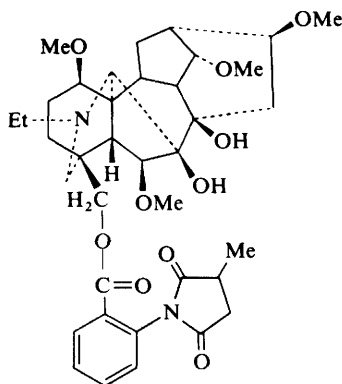
- Pseudaconitine (1) $R^1 = OH$; $R^2 = \text{veratroyl}$
 Bikhaconitine (2) $R^1 = H$; $R^2 = \text{veratroyl}$
 Chasmaconitine (3) $R^1 = H$; $R^2 = \text{benzoyl}$
 Indaconitine (4) $R^1 = OH$; $R^2 = \text{benzoyl}$

A study of the curare-like neuro-muscular effects of the total alkaloids from *Delphinium grandiflorum* L., *D. triste* Fisch., and *D. crassifolium* Schrad. has been published.³ This activity was especially pronounced in the alkaloid fraction from *D. crassifolium*. Methyl-lycoctonine (5) has been identified by paper and thin-layer chromatography as a component of the alkaloid mixtures obtained from all three species.

¹ A. Klásek, V. Šimánek, and F. Šantavý, *Lloydia*, 1972, 35, 55.

² C. R. A. Wright and A. P. Luff, *J. Chem. Soc.*, 1878, 33, 151.

³ M. N. Mats, *Rast. Resur.*, 1972, 8, 249 (*Chem. Abs.*, 1972, 77, 79 509).



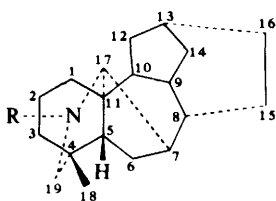
Methyl-lycoctonine (5)

Structural investigations of diterpenoid alkaloids include extensive use of n.m.r. and mass spectral analyses; a comprehensive ^{13}C n.m.r. study of a series of alkaloids possessing the lycoctonine-type skeleton has been reported.

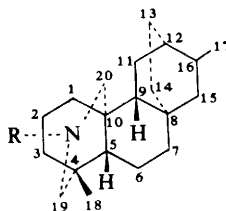
Published work on alkaloids of the *Daphniphyllum* genus included structural reports on daphniphyllidine, yuzurimine, yuzurimine-A, yuzurimine-B, daphniphyllidone, and the results of the crystallographic analyses of daphnilactones-A⁴ and -B.⁵ Two biogenetic studies on the *Daphniphyllum* alkaloids have appeared.^{6,7}

Among the synthetic studies reported were some preliminary investigations utilizing the atisane-aconane rearrangement step of the proposed biosynthetic interconversion of these alkaloid skeletons. Wiesner and co-workers have published a new annelation approach to the synthesis of the diterpenoid ring A³⁴ and an aziridine rearrangement in the synthesis of ring-B-bridged diterpenoids.³⁵

The numbering systems of the lycoctonine, atisine, and veatchine skeletons are indicated in structures (A), (B), and (C), respectively.



Lycoctonine skeleton (A)



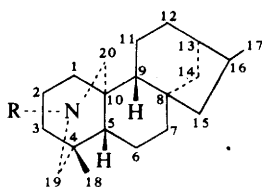
Atisine skeleton (B)

⁴ K. Sasaki and Y. Hirata, *J.C.S. Perkin II*, 1972, 1411.

⁵ K. Sasaki and Y. Hirata, *Acta Cryst.*, 1972, **B29**, 547.

⁶ K. T. Suzuki, S. Okuda, H. Niwa, M. Toda, Y. Hirata, and S. Yamamura, *Tetrahedron Letters*, 1973, 799.

⁷ H. Niwa, Y. Hirata, K. T. Suzuki, and S. Yamamura, *Tetrahedron Letters*, 1973, 2129.

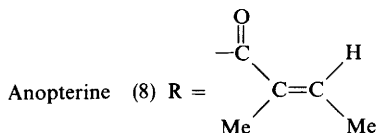
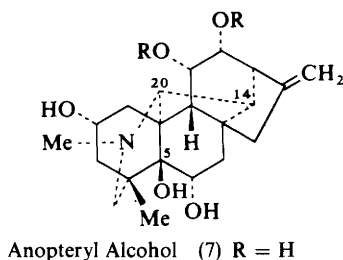
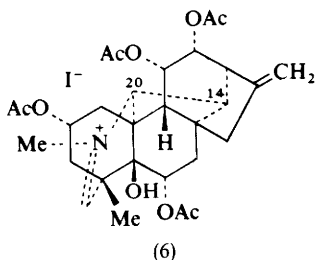


Veatchine skeleton (C)

2 Structural and Chemical Investigations

C₂₀ Diterpenoid Alkaloids.—*Anopterine*. The first diterpenoid alkaloid isolated from the family Escalloniaceae has been reported by Australian workers.⁸ Anopterine, C₃₁H₄₃NO₇, m.p. 222–223 °C, was isolated as the major alkaloid from the leaves and bark of *Anopterus macleayanus* F. Muell. (Queensland) and was also isolated from *Anopterus glandulosus* Labill. (Tasmania). Alkaline hydrolysis of anopterine affords tiglic acid and anopteryl alcohol, C₂₁H₃₁NO₅.

An X-ray crystallographic structure analysis of the methiodide of the tetra-acetyl derivative of anopteryl alcohol determined its structure to be the azomethine (6), the indicated absolute stereochemistry being assigned from Bijvoet measurements. From chemical and spectroscopic data, anopteryl alcohol and anopterine were assigned structures (7) and (8), respectively. Formation of the azomethine bond in (6) during the slow reaction with methyl iodide was attributed to oxidation by iodine and/or oxygen. The locations of the tigloyloxy-groups in anopterine were assigned on the basis of n.m.r. data.

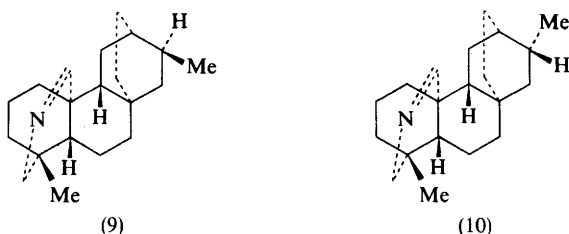


In addition to the discovery of a diterpenoid alkaloid in a different botanical family, this base is of particular interest because of the unique C-14–C-20 linkage in the basic veatchine skeleton. Similar bonds are not unusual in alkaloids of

⁸ W. A. Denne, S. R. Johns, J. A. Lamberton, A. McL. Mathieson, and H. Soares, *Tetrahedron Letters*, 1972, 2727.

the atisine class.⁹ Moreover, the hydroxyl function at C-5 does not occur in any of the diterpenoid alkaloids previously reported.

Vakatisine. Singh and Singh have published some preliminary studies on the structure of vakatisine, $C_{22}H_{34}NO_2Cl$ (chloride salt, m.p. $308^\circ C$),¹⁰ one of the major alkaloids previously isolated from *Aconitum palmatum* Don.¹¹ Selenium dehydrogenation afforded a neutral fraction, from which seven hydrocarbons were isolated, and a basic fraction, from which two epimeric bases $C_{20}H_{31}N$ were obtained. Two of the hydrocarbons were identified as 6-ethyl-1-methylphenanthrene and 6-ethyl-1,7-dimethylphenanthrene, confirmed by comparisons with authentic samples of these compounds. The epimeric bases (9) and (10) were identical with the imines previously isolated from the selenium dehydrogenation products of deoxydihydroatisine.¹²



The n.m.r. and i.r. spectral analyses of vakatisine indicate the presence of an azomethine bond, a tertiary methyl group, and an exocyclic methylene group. On the basis of these data, vakatisine was assumed to possess an atisine-type skeleton.

Carbon-13 Nuclear Magnetic Resonance Studies.—Jones and Benn have demonstrated the utility of ^{13}C n.m.r. studies in structure elucidation of diterpenoid alkaloids.^{13,14} The ^{13}C n.m.r. spectra of lycoctonine (11), deoxylycoctonine (12), deoxymethylenelycoctonine (13), browniine (14), isotalatizidine (15), delphonine (16), lycoctonal (17), and their corresponding hydrochloride or perchlorate salts were examined using decoupling techniques and additivity relationships. Self-consistent assignments of almost all the resonances were made and are summarized in correlation diagrams.¹⁴

For these alkaloids, the ^{13}C shifts for the heteroatom-substituted carbons were generally downfield of 50 p.p.m., while those for carbons that were not substituted with heteroatoms were in most cases upfield. The shifts of the

⁹ S. W. Pelletier and L. H. Keith in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1970, Vol. 12, p. 174.

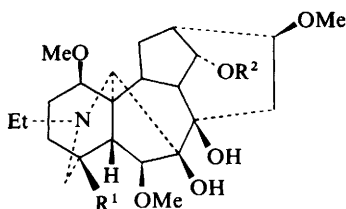
¹⁰ N. Singh and A. Singh, *Indian J. Chem.*, 1972, **10**, 953.

¹¹ N. Singh and A. Singh, *J. Indian Chem. Soc.*, 1965, **42**, 49.

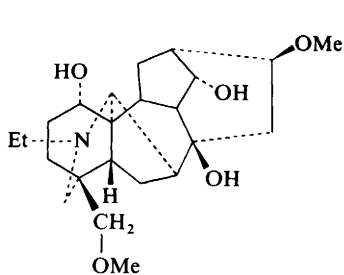
¹² S. W. Pelletier and P. C. Parthasarathy, *J. Amer. Chem. Soc.*, 1965, **87**, 777.

¹³ A. J. Jones and M. H. Benn, *Tetrahedron Letters*, 1972, 4351.

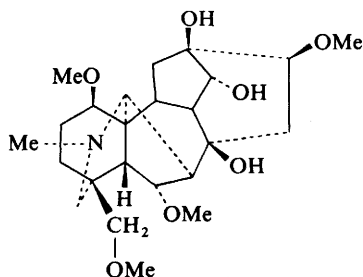
¹⁴ A. J. Jones and M. H. Benn, *Canad. J. Chem.*, 1973, **51**, 486.



- | | |
|----------------------------|---|
| Lycoctonine | (11) $R^1 = \text{CH}_2\text{OH}$; $R^2 = \text{Me}$ |
| Deoxylycoctonine | (12) $R^1 = R^2 = \text{Me}$ |
| Deoxymethylene-lycoctonine | (13) $R^1 = \text{H}$; $R^2 = \text{Me}$ |
| Browniine | (14) $R^1 = \text{CH}_2\text{OMe}$; $R^2 = \text{H}$ |
| Lycoctonal | (17) $R^1 = \text{CHO}$; $R^2 = \text{Me}$ |



Isotalatizidine (15)



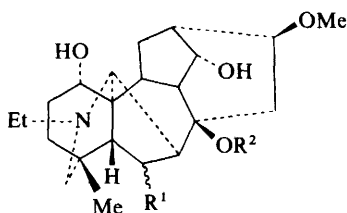
Delphonine (16)

quaternary carbon atoms were in a constant pattern except in cases of major substitution differences.

Delphinium Alkaloids.—*Alkaloids from Delphinium bicolor.* Application of this n.m.r. data base was demonstrated in the structure determinations of two alkaloids isolated in small amounts from *Delphinium bicolor* Nutt.^{13,14} Alkaloid A, $\text{C}_{25}\text{H}_{39}\text{NO}_6$, non-crystalline (HI salt: m.p. $> 240^\circ\text{C}$), was shown to contain a tertiary methyl, an *N*-ethyl, an acetoxy-, two methoxy-, and two hydroxy-groups by i.r. and n.m.r. studies. The acetoxy-group was demonstrated to be at C-8 by a pyrolysis study in glycerol,¹⁵ with the generation of acetic acid being monitored by n.m.r. examination. Base B, $\text{C}_{22}\text{H}_{35}\text{NO}_5$, m.p. $190\text{--}191^\circ\text{C}$, contains a tertiary methyl, an *N*-ethyl, a methoxy-, and hydroxy-groups. Comparisons of the ^{13}C shifts for alkaloids A and B and their hydrochloride salts with those of deoxylycoctonine and isotalatizidine were used to assign structures (18) and (19), respectively, to these bases.

Alkaloids from Delphinium dictyocarpum: *Dictyocarpine*, Base of Mol. Wt. 453, and Base of Mol. Wt. 541. In studies of the alkaloids of *Delphinium dictyocarpum*, Yunusov and co-workers have isolated from the aerial portions of the plants

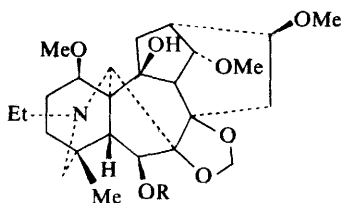
¹⁵ L. H. Keith and S. W. Pelletier, *J. Org. Chem.*, 1968, **33**, 2497.



(18) $R^1 = \text{OMe}$; $R^2 = \text{Ac}$

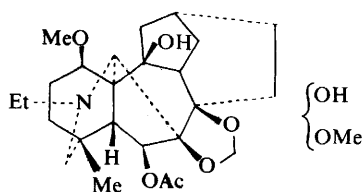
(19) $R^1 = \text{OH}$; $R^2 = \text{H}$

methyl-lycoctonine (5), deltaline (eldeline) (20), deltamine (eldelidine) (21), and a new alkaloid dictyocarpine, $\text{C}_{26}\text{H}_{39}\text{NO}_8$, m.p. 210–212 °C.¹⁶ On the basis of chemical and spectral studies and comparisons with the analogous data of deltaline, the partial structure (22) was proposed for dictyocarpine.

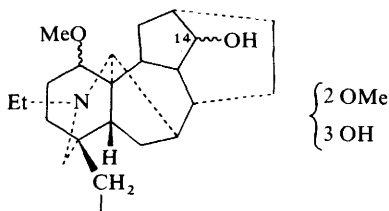


Deltaline (Eldeline) (20) $R = \text{Ac}$

Deltamine (Eldelidine) (21) $R = \text{H}$



Dictyocarpine (22)



(23)

Chloroform extraction of the roots of *D. dictyocarpum* afforded 1.83% total alkaloids, from which methyl-lycoctonine, lycoctonine, and two new bases were isolated. A partial structure (23) for one of these alkaloids, which was amorphous, mol. wt. 453, was derived from spectral and chemical analyses. Acetylation with acetic anhydride–pyridine afforded a diacetate, demonstrating that two of the hydroxy-groups are probably secondary, with one being located at C-14 on the basis of the n.m.r. data. The preliminary i.r. and n.m.r. spectral data for the

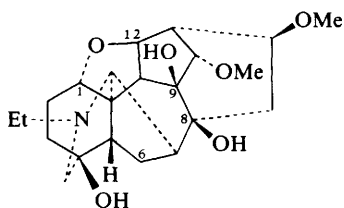
¹⁶ A. S. Narzullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, 8, 498 (*Chem. Abs.*, 1973, 78, 1990).

second base, also amorphous, mol. wt. 541, indicate it to be a benzoyl ester containing an *N*-ethyl, three methoxy-, and several hydroxy-groups.

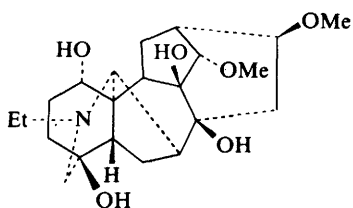
Excelsine. This new alkaloid, $C_{22}H_{33}NO_6$, m.p. 103–105 °C, has been isolated from the roots of *Aconitum excelsum* (*Leucostomum*), and structure (24) has been proposed from chemical and spectral data.¹⁷

Acetylation of excelsine with acetic anhydride–toluene-*p*-sulphonic acid yielded a triacetate, while acetyl chloride produced a tetra-acetate. Excelsine was reduced with Raney catalyst to afford lapaconidine (25), but was not reduced with Adams' catalyst, sodium borohydride, or lithium aluminium hydride.

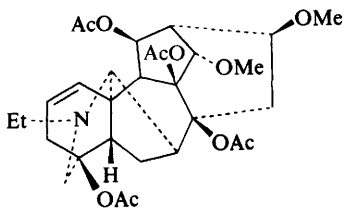
On warming (24) hydrochloride with aqueous hydrochloric acid, two epimers $C_{22}H_{34}NO_6Cl$ were obtained. Treatment of this mixture with sulphuric acid resulted in a crystalline product, $C_{22}H_{33}NO_6$. This compound formed a tetra-acetate derivative whose structure was proposed to be (26) on the basis of spectral analyses.



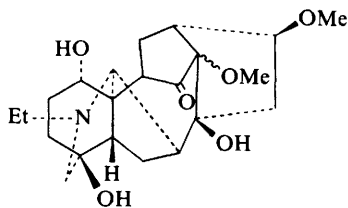
Excelsine (24)



Lapaconidine (25)



(26)



(27)

Oxidation of excelsine with Kiliani reagent afforded a compound $C_{22}H_{31}NO_6$, containing a carbonyl function in a five-membered ring. Since lapaconidine yielded (27) under similar conditions,¹⁸ this product probably results from cleavage of the C-8–C-9 diol system.

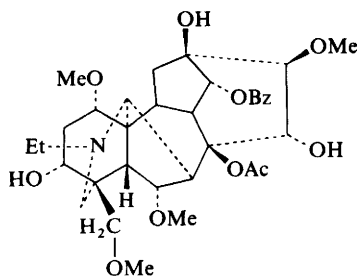
Treatment of excelsine with periodic acid at room temperature gave a product, $C_{22}H_{33}NO_6$, with an oxocyclopentyl group. Model studies indicated that an

¹⁷ V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, **9**, 129 (*Chem. Abs.*, 1973, **78**, 159 947).

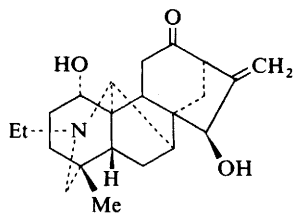
¹⁸ V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 639 (*Chem. Abs.*, 1971, **74**, 76 573).

oxygen bridge between C-1 and C-6 is improbable; therefore, an ether linkage between C-1 and C-12 was proposed.

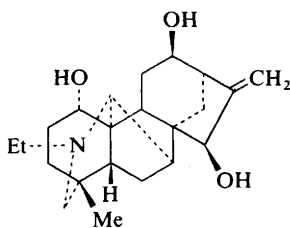
Alkaloids from *Aconitum karakolicum*.—*Aconifine*, *Karakoline*, and *Karakolidine*. From tubers of *Aconitum karakolicum* collected in the Terskei Ala-Tau ranges of the Kirghiz S.S.R. have been isolated aconitine (28), songorine (29), napelline (30), a base $C_{19}H_{22}N_2O_3$, m.p. 120—122 °C, and a new alkaloid, aconifine, $C_{34}H_{47}NO_{12}$, m.p. 195—196 °C.¹⁹ Comparisons of the n.m.r., i.r., and mass spectra of aconifine with those of aconitine, deltamine, delphelatine, and dictyocarpine allowed assignment of the partial structure (31) to aconifine.



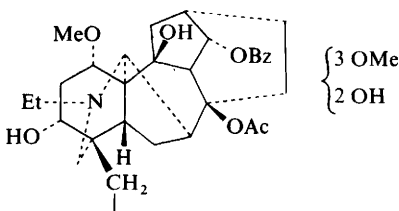
Aconitine (28)



Songorine (29)



Napelline (30)



Aconifine (31)

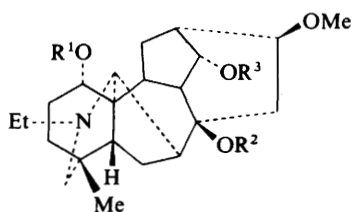
The roots of *A. karakolicum* growing in the Kungei Ala-Tau range of the Kirghiz S.S.R. afforded an alkaloid fraction containing songorine, napelline, and three new bases: karakoline, $C_{22}H_{35}NO_4$, m.p. 183—184 °C; karakolidine, $C_{22}H_{35}NO_5$, m.p. 222—224 °C; and one of m.p. 159—160 °C.^{19–21} Detailed chemical and spectral studies of karakoline have determined its structure as (32).²¹ On acetylation with acetic anhydride–pyridine, karakoline afforded a diacetate, while heating with acetyl chloride gave a triacetyl derivative. Oxidation

¹⁹ M. N. Sultankhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, **9**, 127 (*Chem. Abs.*, 1973, **78**, 159 946).

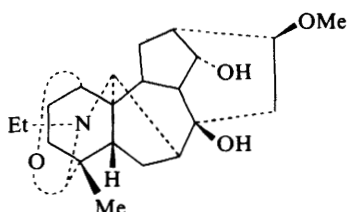
²⁰ M. N. Sultankhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 399 (*Chem. Abs.*, 1972, **77**, 161 996).

²¹ M. N. Sultankhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, **9**, 199 (*Chem. Abs.*, 1973, **79**, 32 152).

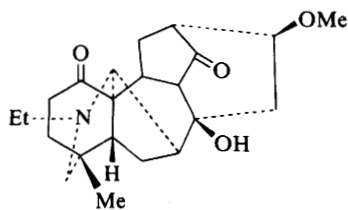
of (32) with permanganate resulted in the formation of an internal carbinolamine ether (33), which was easily converted into the original base on hydrogenation with Adams' catalyst. Oxidation of karakoline with chromic anhydride afforded a dihydro-product, assigned structure (34) on the basis of i.r. absorptions for oxocyclopentyl and oxocyclohexyl groups. These reactions confirm the presence of an α -hydroxy-group at C-1. Pyrolysis of triacetylkarakoline followed by saponification of the reaction product gave acetyldemethylisopyrokarakoline (35), confirmed by spectral and chemical investigations. Hydrogenation of (35) over platinum catalyst gave (36), which formed the triacetate (37). The apparently anomalous failure of the acetate group in (35) to be hydrolysed was substantiated by study of the saponification of diacetylkarakoline (38), diacetylaltatizidine (39), and tetra-acetyl-lappaconidine (40). In the time necessary for the complete hydrolysis of the acetates of (39) and (40), diacetylkarakoline gave equal amounts



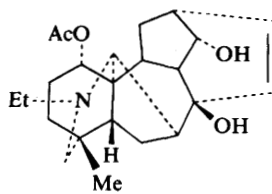
Karakoline (32) $R^1 = R^2 = R^3 = H$
 (38) $R^1 = R^3 = Ac; R^2 = H$
 (41) $R^1 = Ac; R^2 = R^3 = H$
 (42) $R^1 = R^3 = Bz; R^2 = Ac$



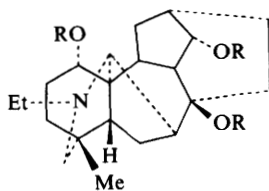
(33)



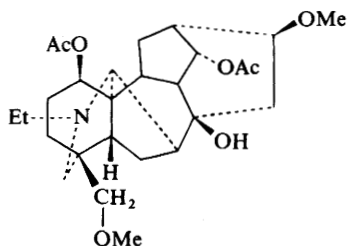
(34)



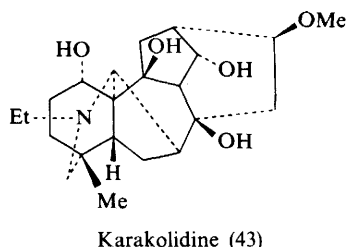
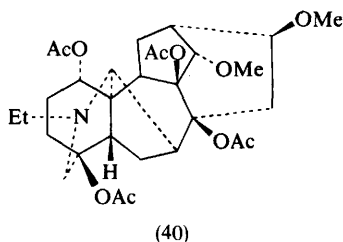
(35)



(36) $R = H$
 (37) $R = Ac$



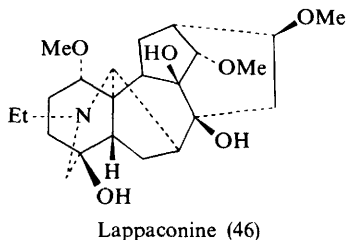
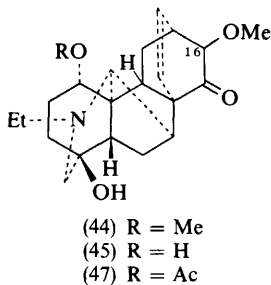
(39)



of starting material and the monoacetate (41). This resistance to hydrolysis was attributed to steric hindrance. The dibenzoylacetyl derivative (42) of karakoline was prepared, and analysis of its mass spectrum allowed the assignment of the methoxy-group to C-16.

Karakolidine also formed an internal α -carbinolamine ether on oxidation with permanganate, characteristic of an α -hydroxy-group at C-1.¹⁹ Oxidation of karakolidine with Kiliani reagent afforded didehydrokarakoline, $C_{22}H_{21}NO_5$, with carbonyl functions in five- and six-membered ring systems, as indicated by the i.r. spectrum. Pyrolysis of the tetra-acetate of karakolidine followed by saponification gave pyrokarakolidine, which was isomerized to isopyrokarakolidine by heating in methanolic HCl. This well-known pyrolysis-rearrangement is characteristic of alkaloids possessing a lycotonine-type skeleton with a tertiary acetate at C-8 and a methoxy-group at C-16. From these chemical transformations and spectral analyses, structure (43) for karakolidine can be deduced.

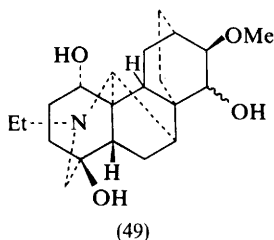
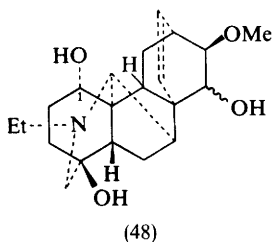
Sulphuric Acid Rearrangement Products of Lappaconine and Lapaconidine.—Additional evidence for the proposed structures of (44) and (45), the sulphuric acid rearrangement products of lappaconine (46)²² and lapaconidine (25),²³ respectively, has been presented.²⁴ The attempted hydrogenolysis of the methoxy-



²² V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, 6, 583 (*Chem. Abs.*, 1971, 74, 42 527).

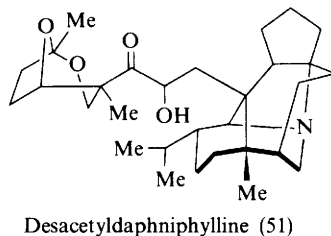
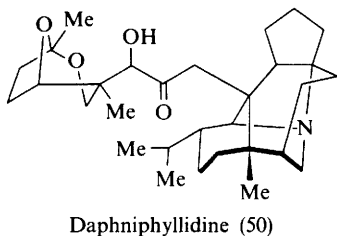
²³ V. A. Tel'nov, M. S. Yunusov, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, 7, 622 (*Chem. Abs.*, 1972, 76, 99 877).

²⁴ V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 9, 130 (*Chem. Abs.*, 1973, 78, 159 948).



group at C-16 in anhydromethanol-lapaconidine (45) with zinc powder in glacial acetic acid resulted in the formation of monoacetate (47) in quantitative yield. Reduction of (45) with sodium borohydride afforded (48), while hydrogenation over Adams' catalyst gave the tetrahydro-compound (49). The mass spectral data for these compounds were compared, and the ion at $M - 31$ was assigned to loss of the methoxy-group at C-16, and not from C-1 as was previously reported for anhydromethanol-lapaconidine.²³

Daphniphyllum Alkaloids.—*Daphniphyllidine*. The structure of daphniphyllidine, $C_{30}H_{47}NO_4$, m.p. 264°C, has been determined from chemical and spectral evidence to be (50).²⁵ This alkaloid was isolated from the leaves and bark of *Daphniphyllum macropodum* Miquel and was previously identified as Alkaloid D.²⁶ As chemical proof of structure, daphniphyllidine was correlated with desacetyldaphniphylline (51). Treatment of (51) with sodium methoxide-methanol under reflux gave (50) in 50% yield. The authors postulate that daphniphyllidine is formed from desacetyldaphniphylline by either a 1,2-hydride shift or through an enediol intermediate.



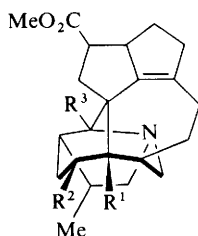
Yuzurimine, Yuzurimine-A, and Yuzurimine-B. A full report of structural work on these alkaloids isolated from *Daphniphyllum macropodum* Miquel has appeared.²⁷ The structure of yuzurimine (52) had been previously determined by an X-ray crystallographic study of its hydrobromide derivative,²⁸ and the structures of yuzurimine-A (53) and yuzurimine-B (54) were proposed on the basis

²⁵ M. Toda, H. Niwa, Y. Hirata, and S. Yamamura, *Tetrahedron Letters*, 1973, 797.

²⁶ M. Toda, H. Irikawa, S. Yamamura, and Y. Hirata, *Nippon Kagaku Zasshi* [J. Chem. Soc. Japan], 1970, 91, 103.

²⁷ H. Irikawa, S. Yamamura, and Y. Hirata, *Tetrahedron*, 1972, 28, 3727.

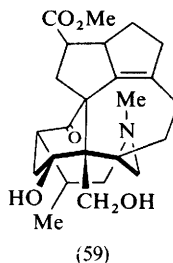
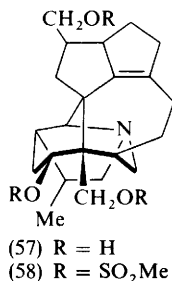
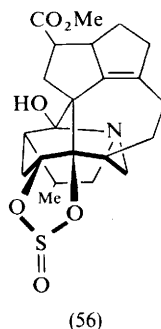
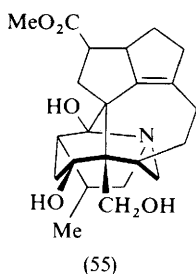
²⁸ H. Sakurai, N. Sakabe, and Y. Hirata, *Tetrahedron Letters*, 1966, 6309.



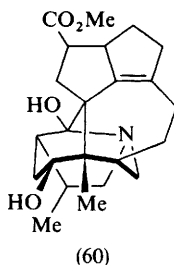
- Yuzurimine (52) $R^1 = \text{CH}_2\text{OAc}$; $R^2 = \text{OAc}$; $R^3 = \text{OH}$
 Yuzurimine-A (53) $R^1 = \text{Me}$; $R^2 = \text{OAc}$; $R^3 = \text{OH}$
 Yuzurimine-B (54) $R^1 = \text{CH}_2\text{OH}$; $R^2 = R^3 = \text{H}$

of spectral comparisons with yuzurimine.²⁹ Some interesting chemical reactions of these compounds with additional spectral data were reported in the latest publication.²⁷

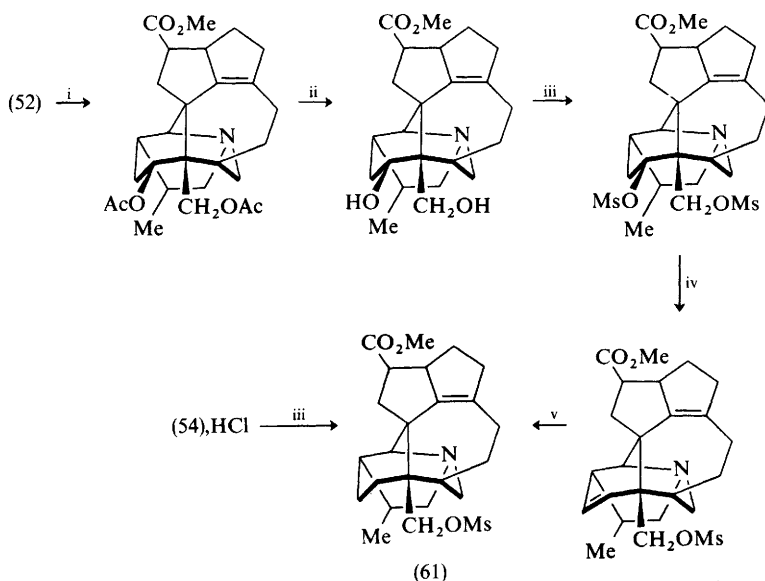
The reaction of desacetylyuzurimine (55) with thionyl chloride in pyridine afforded the sulphite (56). Reduction of (52) with lithium aluminium hydride gave the triol (57), which formed a trimesylate (58) on treatment with methanesulphonyl chloride. Reduction of the latter compound with lithium aluminium hydride yielded the original triol. Treatment of yuzurimine methiodide with methanolic base gave the keto-amine (59).



²⁹ H. Sakurai, H. Irikawa, S. Yamamura, and Y. Hirata, *Tetrahedron Letters*, 1967, 2883.



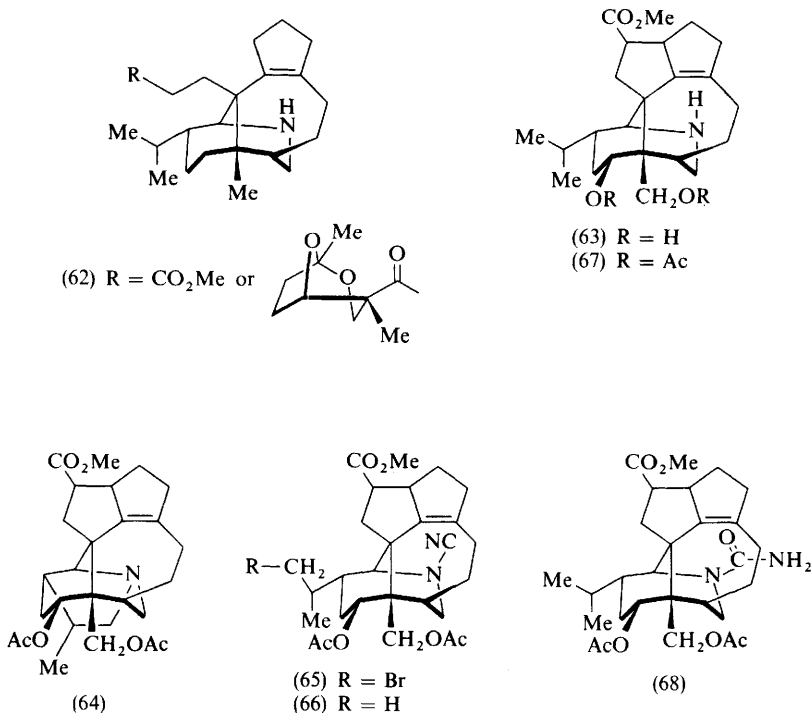
Yuzurimine-A (desacetoxy-yuzurimine) was hydrolysed with 10% HCl-MeOH to yield desacetylyuzurimine-A (macrodaphniphyllamine) (60). The structure of yuzurimine-B was confirmed by the conversion of yuzurimine into the mesylate (61) of yuzurimine-B as described in Scheme 1.



Reagents: i, Zn, HOAc; ii, 7% HCl, MeOH; iii, MsCl, pyridine; iv, LiCl, DMF, Δ ; v, H_2 , PtO_2 .

Scheme 1

In support of the proposed biogenetic intermediate (62) for the compounds daphniphylline, yuzurimine, methyl homosecodaphniphyllate, and daphni-lactone-B, yuzurimine was chemically transformed into the related compound (63). The reaction of deoxyyuzurimine (64) with cyanogen bromide afforded (65). Reduction of (65) with sodium borohydride in DMSO yielded the cyanamide (66), which was refluxed with acetic acid saturated with hydrogen chloride to

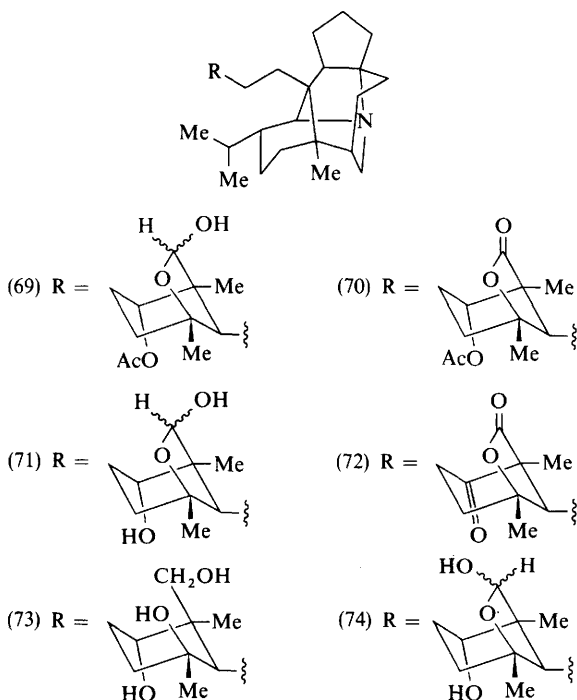


give (67) (49%) and (68) (19%). Alkaline hydrolysis of (67) gave (63). In addition to radioactive labelling studies, work is continuing on the isolation of minor components to elucidate further the biosynthetic pathways for this group of alkaloids.

Daphmacropodine. Nakano, Hasegawa, and Saeki have determined the structure of this alkaloid, isolated from *D. macropodum* Miquel, to be (69) by its conversion into daphmacrine (70).³⁰ Daphmacropodine, $\text{C}_{32}\text{H}_{51}\text{NO}_4$, m.p. 214°C , gave (71) on mild alkaline hydrolysis. Oxidation of (71) hydrochloride with Jones' reagent afforded the keto-lactone (72). Reduction of daphmacropodine or daphmacrine with lithium aluminium hydride yielded a mixture of (73) and (74), with (74) differing from (71), presumably in the stereochemistry of the hemiacetal hydroxy-group. Oxidation of (69) with Jones' reagent resulted in a compound whose hydrobromide salt was identical with daphmacrine hydrobromide. The structure of daphmacrine had been previously established by an X-ray crystallographic study.³¹

³⁰ T. Nakano, M. Hasegawa, and Y. Saeki, *J. Org. Chem.*, 1973, **38**, 2404.

³¹ C. S. Gibbons and J. Trotter, *J. Chem. Soc. (B)*, 1969, 840.



3 Diterpenoid Alkaloid Synthesis

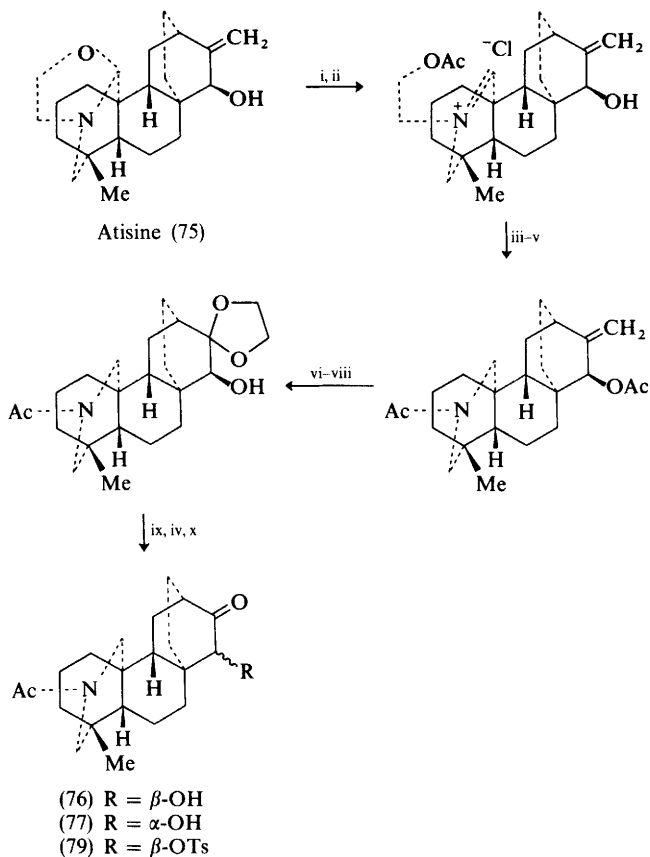
Atisane–Aconane Conversions.—Johnson and Overton have approached the synthesis of the lycotoline–aconitine alkaloids through the conversion of the atisane skeleton into the aconitine skeleton by utilizing reactions to effect a proposed key step in the biosynthetic pathway.³²

Atisine (75) was converted into the epimeric ketols (76) and (77) as outlined in Scheme 2. Acetolysis of (76) or (77) gave only (78). However, preparative gas-phase pyrolysis of the β -tosylate (79) afforded the desired keto-olefin (80) in 77% yield. Under the same pyrolytic conditions, the α -tosylate gave only (78). The regiospecificity of the rearrangement–elimination of (79) to (80) was explained on the basis that the most favourable configuration for the concerted process is that in which the C–H and C–O bonds to be broken are 1,3-diaxial and antiperiplanar to the bond migrating from the intermediate carbon atom.

The solvolysis of the tosylate (81) derived from levopimaric acid as a model for the atisane–aconane conversion has been reported by Ayer and Deshpande.³³ Levopimaric acid was converted into the keto-acid (82) by the addition of α -acetoxyacrylonitrile followed by alkali work-up. This keto-acid was reduced

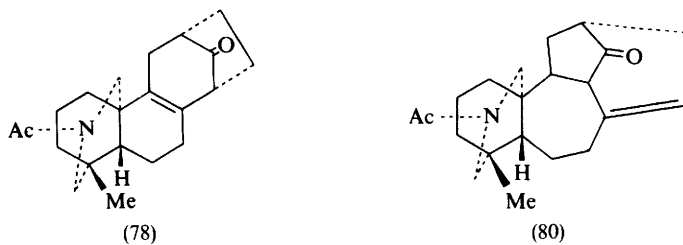
³² J. P. Johnson and K. H. Overton, *J.C.S. Perkin I*, 1972, 1490.

³³ W. A. Ayer and P. D. Deshpande, *Canad. J. Chem.*, 1973, **51**, 77.

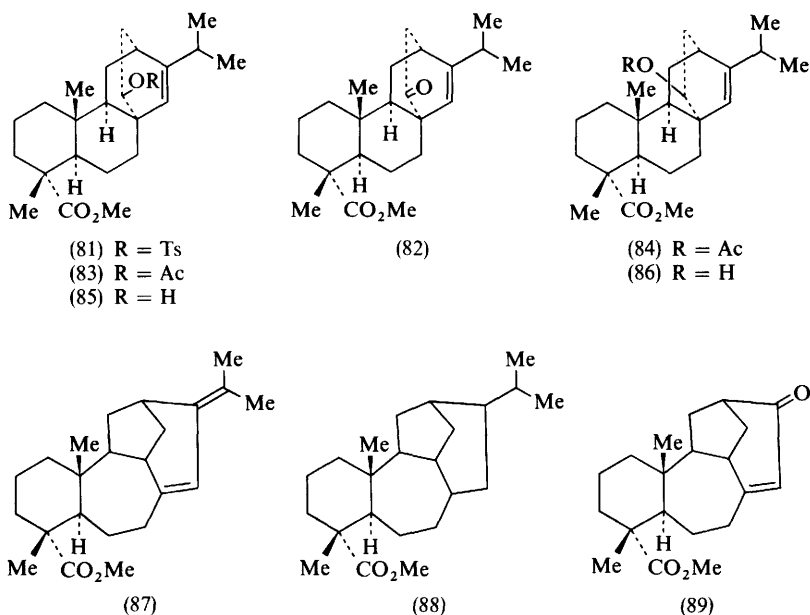


Reagents: i, HCl; ii, Ac_2O ; iii, KOH, CHCl_3 ; iv, NaBH_4 ; v, Ac_2O , pyridine; vi, OsO_4 , aq. dioxan, NaIO_4 ; vii, Na_2CO_3 , $\text{MeOH-H}_2\text{O}$; viii, Ethylene glycol, TsOH; ix, CrO_3 , pyridine; x, aq. AcOH.

Scheme 2



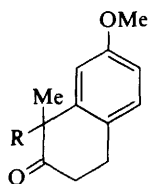
with sodium borohydride, and the crude product was esterified with diazo-methane, then acetylated to afford a mixture of acetoxy-esters (83) and (84) in a ratio of 3:4. These compounds were separated by chromatography on alumina. Hydrolysis of the acetoxy-compounds gave the alcohols (85) and (86). The tosylate (81) was prepared, and chromatography over silica gel produced the desired rearrangement to (87) in 70% yield, along with (85) in yields of



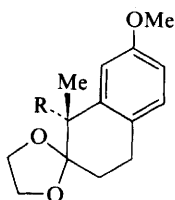
15–20%. Solvolysis in hot acetic acid–sodium acetate afforded (87) in 40% yield and (83) in 12% yield. Hydrogenation of (87) over Adams' catalyst gave (88), while low-temperature ozonolysis resulted in a 10% yield of the conjugated ketone (89).

Annulation Procedure for the Synthesis of the Diterpenoid Ring A.—Wiesner and co-workers have developed an annulation procedure for the construction of the A-ring system in diterpenoid synthesis.³⁴ Starting with 7-methoxy-2-tetralone, methylation by the Stork procedure yielded (90), which was treated with sodium hydride and benzyl chloromethyl ether to give (91). The ketal of (91) was hydrogenated with palladium on calcium carbonate to the alcohol (92). Oxidation with chromium trioxide–pyridine afforded the aldehyde (93), which was immediately treated with an excess of the Grignard reagent prepared from 5-bromopent-1-ene to yield the epimeric alcohols (94) and (95). Methylation with sodium hydride and methyl iodide gave (96) and (97), which were separable by

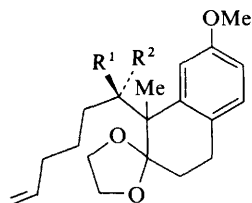
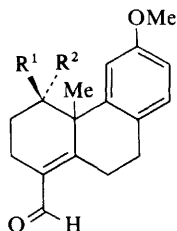
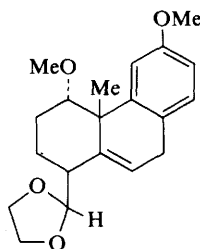
³⁴ K. Wiesner, R. Vlahov, and K. Muzika, *Tetrahedron Letters*, 1973, 2309.



(90) R = H

(91) R = CH₂OCH₂Ph(92) R = CH₂OH

(93) R = CHO

(94) R¹ = H; R² = OH(95) R¹ = OH; R² = H(96) R¹ = H; R² = OMe(97) R¹ = OMe; R² = H(98) R¹ = H; R² = OMe(99) R¹ = OMe; R² = H

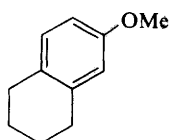
(100)

chromatography on silica gel. The aldehydes (98) and (99) were prepared by the hydroxylation of the double bond with osmic acid-sodium chlorate, periodic acid cleavage to the keto-aldehyde, and treatment with aqueous methanolic bicarbonate. Acetalization of (98) gave (100). The C-5-C-6 double bond serves as an active function for the introduction of oxygen groups at C-6. This type of intermediate should be of general utility in diterpenoid syntheses.

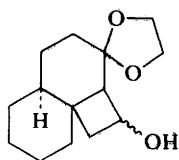
Model Studies for the Synthesis of c/d Ring Systems of the Delphinine-type Alkaloids.—A new synthetic route for the construction of the c/d ring system of delphinine-type alkaloids has been investigated in a model series based on previous syntheses of the atisine system.³⁵ Starting from methoxytetralin (101), the previously reported³⁶ allene adduct (102) was prepared, and this rearranged to the hydroxy-ketone (103). This compound was methylated with sodium hydride-methyl iodide, and the resulting methoxy-ketone (104) was converted into (105) by refluxing with *t*-butyl perbenzoate and cuprous bromide in benzene. Reduction of (105) with lithium aluminium hydride afforded (106), which underwent a pyro-isopyro-type rearrangement to (107) when heated with glacial acetic acid and toluene-*p*-sulphonic acid. Compound (107) possesses the BCD ring system of the diterpenoid alkaloids. Extensions of these methods to the previously prepared intermediate (108) would afford the total carbon skeleton

³⁵ K. Wiesner, T. Y. R. Tsai, K. Huber, and S. Bolton, *Tetrahedron Letters*, 1973, 1233.

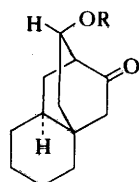
³⁶ R. W. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 1966, 4645.



(101)

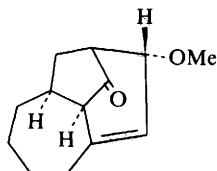


(102)

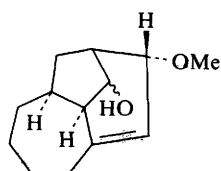


(103) R = H

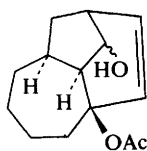
(104) R = Me



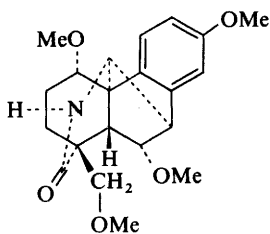
(105)



(106)



(107)



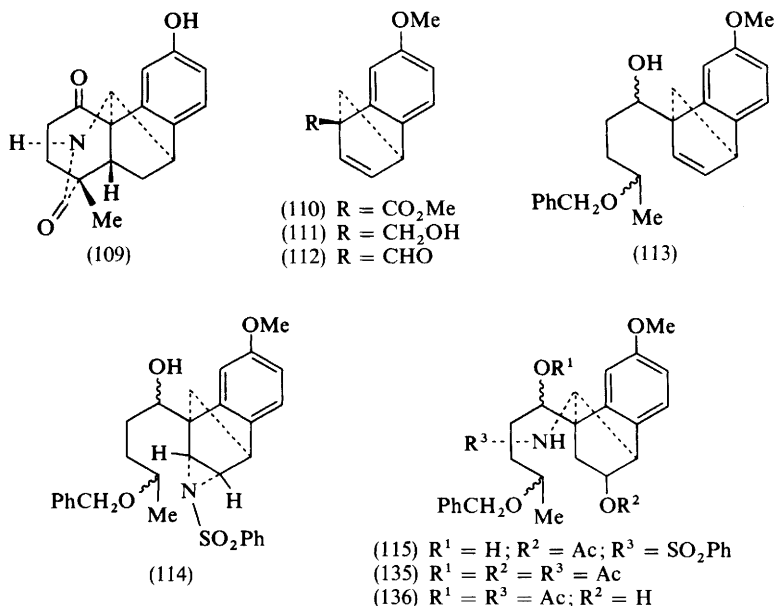
(108)

of the ring-B-bridged C_{19} -diterpenoid alkaloids, with only modifications of the various oxygen functionalities necessary for the completion of the total synthesis of these alkaloids.

Syntheses Directed towards Songorine.—In synthetic studies of ring-B-bridged diterpenoids, with the synthesis of songorine (29) as one immediate goal, the New Brunswick group has developed a more efficient synthesis of the pentacyclic songorine intermediate (109).³⁷

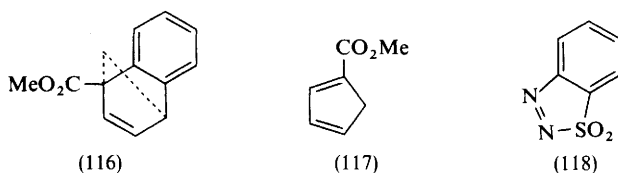
Starting from (110), reduction with lithium aluminium hydride afforded (111), which was converted into the aldehyde (112) by oxidation with NN' -dicyclohexylcarbodi-imide–dimethyl sulphoxide–pyridine in benzene. Treatment of (112) with Grignard reagent from 1-bromo-3-benzyloxybutane gave a mixture of diastereoisomers (113). The mixture was converted into the unstable aziridines (114) by reaction with benzenesulphonyl azide. This reaction and subsequent

³⁷ K. Wiesner, Pak-tsun Ho, D. Chang, Y. K. Lam, C. S. J. Pan, and W. Y. Ren, submitted for publication. We wish to thank Professor Wiesner for a pre-publication copy of the manuscript.



rearrangement to (115) are key steps in this synthetic scheme, and the general synthetic utility of this method was studied in detail.

Previous work had shown that benzenesulphonylaziridine derivatives of benzobicycloheptenes underwent acetolytic rearrangement to yield the desired bridged amine intermediates.³⁸ Five benzobicycloheptene derivatives were prepared to study the influence of the substitution patterns on the direction of the aziridine rearrangement.³⁹ The ester (116) was synthesized by the addition



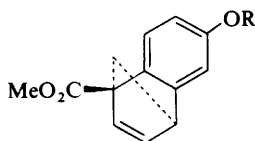
of (117) to (118). The preparation of (110), an intermediate in a songorine synthesis, has previously been reported⁴⁰ and reviewed.⁴¹ Compounds (119) and (120) were prepared using these identical methods from (121), which was obtained by the base-catalysed condensation of *m*-methoxyacetophenone with glyoxylic

³⁸ K. Wiesner and A. Philipp, *Tetrahedron Letters*, 1966, 1467.

³⁹ K. Wiesner, Pak-tsun Ho, R. C. Jain, S. F. Lee, S. Oida, and A. Philipp, *Canad. J. Chem.*, 1973, **51**, 1448.

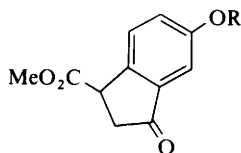
⁴⁰ Pak-tsun Ho, S. Oida, and K. Wiesner, *J.C.S. Chem. Comm.*, 1972, 883.

⁴¹ S. W. Pelletier and S. W. Page, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3, Ch. 13.



(119) R = Me

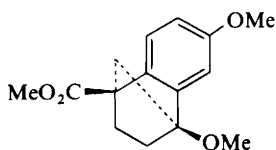
(120) R = Ms



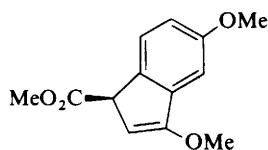
(121) R = H

(122) R = Me

(123) R = Ms

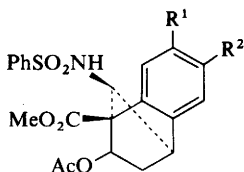
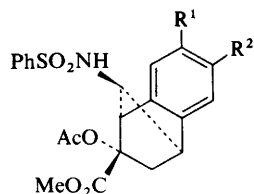


(124)

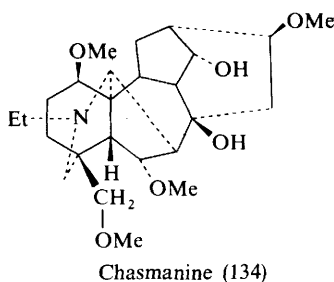
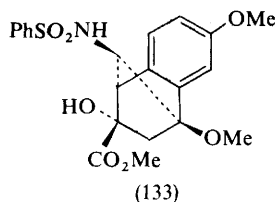
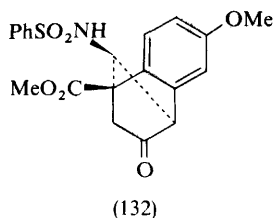


(125)

acid followed by cyclization with aluminium chloride. This phenol was methylated with dimethyl sulphate-potassium carbonate to yield (122), or mesylated with methanesulphonyl chloride in pyridine to the mesyloxy-keto-ester (123), and these compounds were transformed into (119) and (120), respectively. For the preparation of (124), the keto-ester (122) was converted into the enol ether (125) by reaction with trimethyl orthoformate-HCl. Addition of maleic anhydride and bisdecarboxylation of the resulting adduct gave (124). These derivatives were converted into the corresponding benzenesulphonylaziridines by reaction with benzenesulphonyl azide. Addition in all cases resulted exclusively in an *exo*-aziridine. The aziridine from (116) underwent acetolysis in glacial acetic acid at 100 °C to afford (126) and (127) in a ratio of 94 : 6. The aziridine from (110) was unstable and was acetolized at room temperature to give exclusively (128). Acetolysis of the aziridine from (119) gave only (129), while the analogous mesyloxy-aziridine resulted in (130) and (131), 90 : 10, with an overall yield of

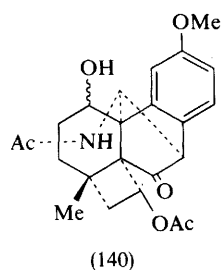
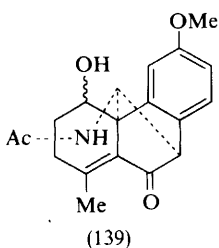
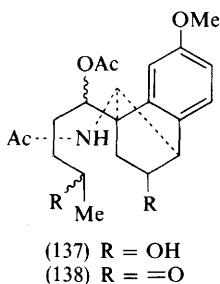
(126) R¹ = R² = H(128) R¹ = OMe; R² = H(130) R¹ = H; R² = OMs(127) R¹ = R² = H(129) R¹ = H; R² = OMe(131) R¹ = H; R² = OMs

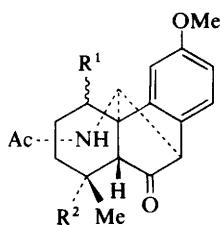
52.5%. The aziridine from (124) was immediately acetolysed to form (132) and (133), 70 : 30, in an overall yield of 86%. This compound is an intermediate for the synthesis of the alkaloid chasmanine (134). The product ratios were explained on the basis of the influences of the methoxycarbonyl-group and the



substituents of the aromatic ring: the *p*-methoxy-group had a greater directing influence than the methoxycarbonyl group, while the effects of the mesyloxy-group were similar to those of a hydrogen atom. In (110) the effects of the *p*-methoxy-group and the methoxycarbonyl group were additive, while in (119) the former completely dominated.

The diastereoisomers (115) were reduced with lithium aluminium hydride, and the product was acetylated with acetic anhydride-pyridine to yield (135). Partial hydrolysis afforded (136), which was converted into (137) by hydrolysis. Oxidation with chromium trioxide in pyridine gave the epimeric ketones (138). Refluxing (138) with methanolic potassium carbonate effected an aldol condensation, yielding (139). Photoaddition of vinyl acetate gave the epimers (140), which were saponified with methanolic potassium hydroxide. Enol acetylation with sodium acetate and acetic anhydride gave (141). Osmic acid-periodate oxidation to the aldehydes (142), followed by Jones' oxidation and esterification with diazomethane, afforded (143). Alkaline hydrolysis





(141) $R^1 = \text{OAc}$; $R^2 = \text{CH}=\text{CHOAc}$

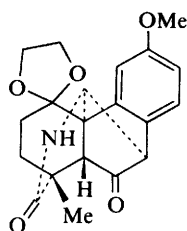
(142) $R^1 = \text{OAc}$; $R^2 = \text{CHO}$

(143) $R^1 = \text{OAc}$; $R^2 = \text{CO}_2\text{Me}$

(144) $R^1 = \text{OH}$; $R^2 = \text{CO}_2\text{Me}$

(145) $R^1 = \text{O}$; $R^2 = \text{CO}_2\text{Me}$

(146) $R^1 = \text{—} \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{—} \end{array} \text{—}$; $R^2 = \text{CO}_2\text{Me}$



(147)

(1% aqueous KOH in methanol) of (143) yielded (144). Subsequent Jones' oxidation to (145) and ketalization resulted in (146). Refluxing (146) with methanolic sodium hydroxide afforded the lactam (147). Wolff-Kishner reduction and treatment of the ketal with HBr and acetic acid gave the desired intermediate (109). The overall yield from (90) to (109) was 7.8%.

Steroidal Alkaloids of the Apocynaceae, Buxaceae, and Asclepiadaceae and of the *Salamandra-Phyllobates* Group

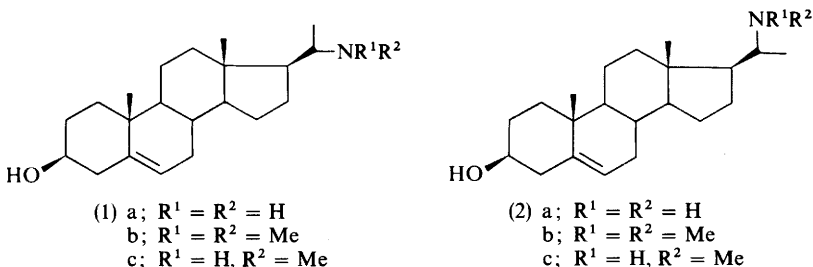
BY F. KHUONG-HUU AND R. GOUTAREL

This chapter is concerned with the steroidal alkaloids of the Apocynaceae and Buxaceae and with the steroidal alkaloids isolated from plants of other botanical families and from animals (batrachotoxins, salamander alkaloids).

1 Alkaloids of the Apocynaceae: The *Holarrhena* and *Paravallaris* Alkaloids

Steroidal Alkaloids and Amines.—*Phytochemistry.* Eight previously known alkaloids have been extracted from the bark of *Holarrhena mitis*, an Apocynaceae species from Ceylon: conessine, isoconessimine, holafebrine, holarrhenine, holadienine, konkurchine, holarrhimine, and *N*-3-methylholarrhimine. The holarrhimine-type alkaloids have been isolated in 30% yield.¹

Synthesis, Reactions, and Transformations of Steroidal Amines. Holafebrine (1a) was methylated with a large excess of formaldehyde in MeOH under reflux followed by NaBH₄ reduction to give irehine (1b). Analogous methylations were performed with (1c), (2a), and (2c). This method gave better results than the classical Eschweiler-Clarke methylation.²

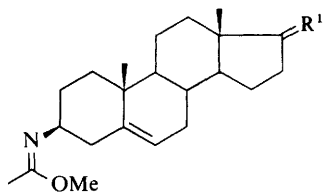


The 3- β -amino-steroid imidates (3) have been obtained from the amides (4a) with methyl fluorosulphonate. By reduction with NaBH₄, the imide (3a) gave the secondary amine (4b). With sodium amalgam, the imidates (3) afforded the

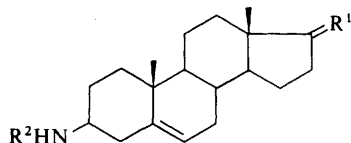
¹ G. P. Wannigama and A. Cavé, *Ann. pharm. franç.*, 1972, **30**, 535.

² B. L. Sondengam, H. J. Hentchoya, and G. Charles, *Tetrahedron Letters*, 1973, 261.

corresponding primary amines (4c; R^1 as in 3a—3d); this affords a method for cleaving an amide function, in the presence of reducible groups, under mild conditions.³

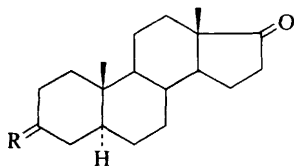


- (3) a; $R^1 = \alpha\text{-H}, \beta\text{-C}_8\text{H}_{17}$
 b; $R^1 = \alpha\text{-H}, \beta\text{-COMe}$
 c; $R^1 = \text{O}$
 d; $R^1 = \text{H}_2$

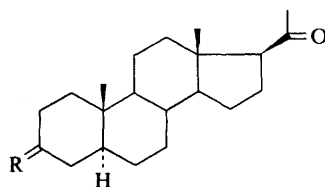


- (4) a; $R^2 = \text{Ac}$
 b; $R^1 = \alpha\text{-H}, \beta\text{-C}_8\text{H}_{17}; R^2 = \text{Et}$
 c; $R^2 = \text{H}$

The reductive amination, with NaBH_3CN and ammonium acetate, mono-methylamine, or dimethylamine, of steroidal ketones has been studied. With the diketones (5a) and (6a), the epimeric 3-amino-derivatives (5b), (5c), (5d), (6b), (6c), and (6d), were selectively obtained. A mechanism in which the slow step is enamine formation was proposed.⁴



- (5) a; $R = \text{O}$
 b; $R = \begin{smallmatrix} \text{H} \\ \diagup \quad \diagdown \\ \text{NH}_2 \end{smallmatrix}$
 c; $R = \begin{smallmatrix} \text{H} \\ \diagup \quad \diagdown \\ \text{NHMe} \end{smallmatrix}$
 d; $R = \begin{smallmatrix} \text{H} \\ \diagup \quad \diagdown \\ \text{NMe}_2 \end{smallmatrix}$



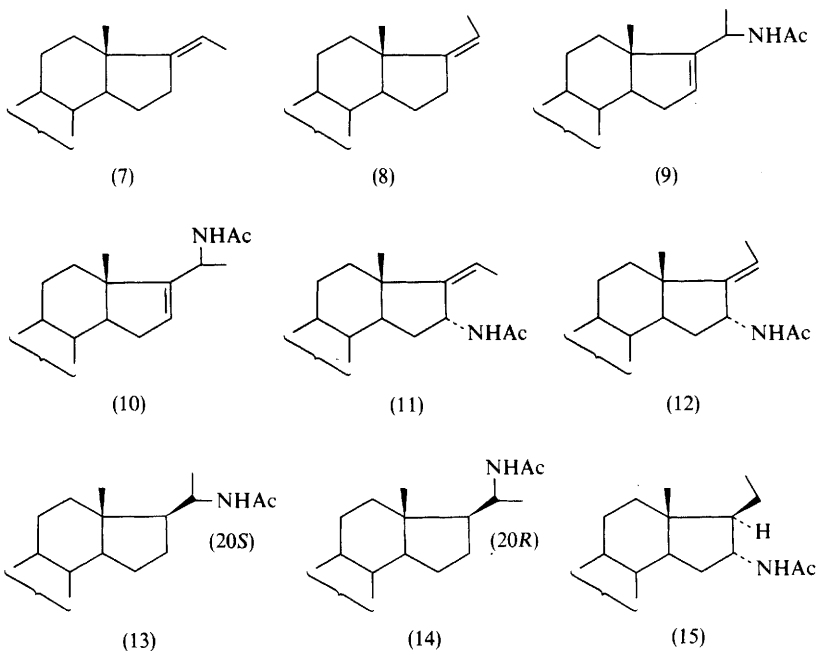
- (6) a; $R = \text{O}$
 b; $R = \begin{smallmatrix} \text{H} \\ \diagup \quad \diagdown \\ \text{NH}_2 \end{smallmatrix}$
 c; $R = \begin{smallmatrix} \text{H} \\ \diagup \quad \diagdown \\ \text{NHMe} \end{smallmatrix}$
 d; $R = \begin{smallmatrix} \text{H} \\ \diagup \quad \diagdown \\ \text{NMe}_2 \end{smallmatrix}$

By the action of acetonitrile in the presence of mercuric nitrate, followed by NaBH_4 reduction, the isomeric olefins 5α -pregn-17-ene (*E*) (7) and 5α -pregn-17-ene (*Z*) (8) led to the allylic amides (9)—(12). Catalytic hydrogenation of (9) and (10) gave the known (20*S*)-acetamido- 5α -pregnane (13) and (20*R*)-acetamido- 5α -pregnane (14) respectively. Catalytic hydrogenation of (11) and (12) led to (15).⁵

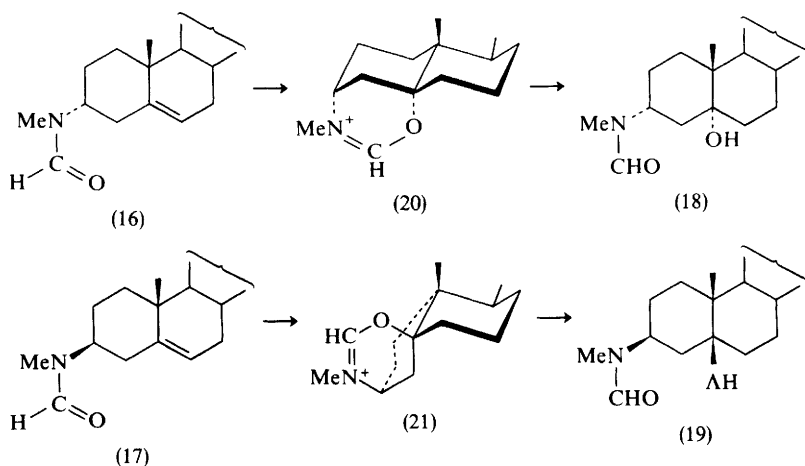
³ S. Julia and R. J. Ryan, *Compt. rend.*, 1972, **274**, C, 1207.

⁴ M. H. Boutigue and R. Jacquesy, *Bull. Soc. chim. France*, 1973, 750.

⁵ B. Delpech and Q. Khuong-Huu, *Tetrahedron Letters*, 1973, 1533.

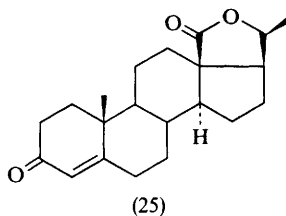
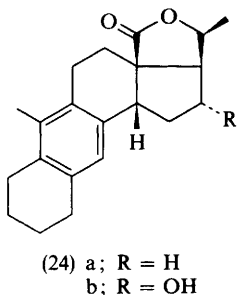
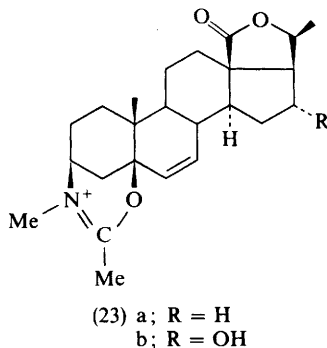
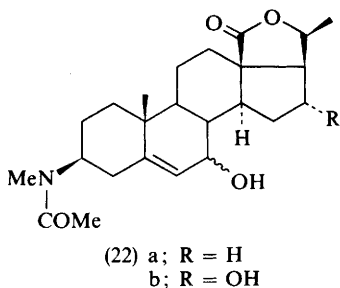


With trifluoroacetic acid, the 3α - and 3β -amido- Δ^5 steroidal derivatives (16) and (17) gave derivatives (18) and (19), by stereospecific introduction of a hydroxy-function at position 5. The dihydro-oxazinium intermediates (20) and (21) were isolated as the perchlorates and identified by an n.m.r. study.⁶



⁶ A. Ahond, A. Cavé, C. Kan-Fan, and P. Potier, *Bull. Soc. chim. France*, 1970, 3624.

Rearrangement of 7 α - and 7 β -hydroxy-*N*-acetylparavallarine (22a) and of 7 α - and 7 β -hydroxy-*N*-acetylparavallaridine (22b) into anthracene steroidal analogues has been reported.⁷ Reaction of (22a) and (22b) with trifluoroacetic acid at room temperature gave the dihydro-oxazinium intermediates (23a) and (23b). On raising the temperature to 60°C, derivatives (24a) and (24b) were formed. Structures were based on n.m.r. studies and corroborated by preparation of (24a) from (25) with acetyl bromide in propan-2-ol according to Mazur's procedure.⁸ The 14- β H configuration of (24a) and (24b) is that observed in other anthrasteroid rearranged products.

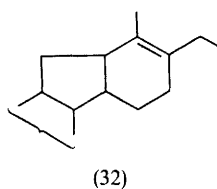
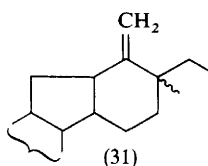
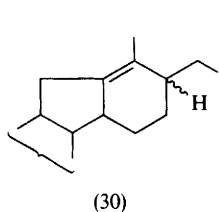
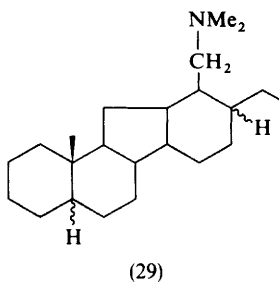
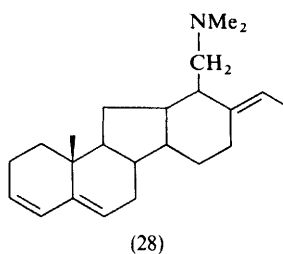
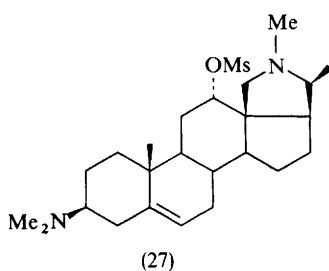
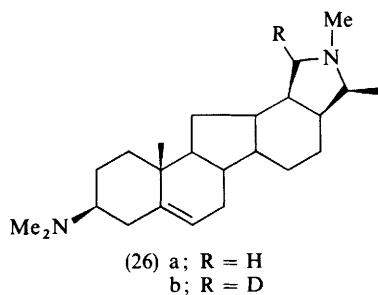


Further converging data were afforded for the structure of c-nor-D-homoconessine (26a), the rearranged product from holarrhenine mesylate (27) with hydrides.⁹ Mass and n.m.r. spectra of (26a) and (26b) gave arguments for deuterium incorporation at position 18 in (26b). Degradation reactions of (26a) were also studied. A modified Hofmann degradation (potassium *t*-butoxide in DMF) on the methiodide from (26a) gave the triene (28) with a 17(20)-double bond. The hydrogenation product (29) (mixture of diastereoisomers) was subjected to a quaternization followed by a Hofmann degradation giving a mixture of isomers (30)–(32).

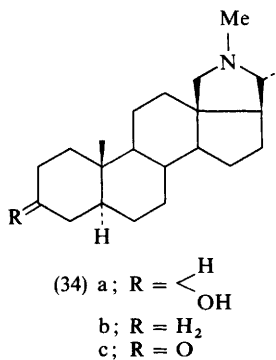
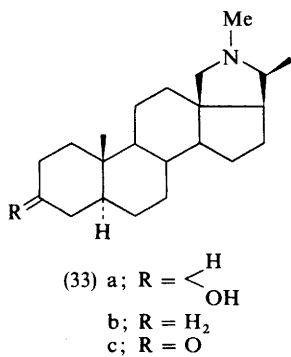
⁷ G. Massiot, A. Cavé, H. P. Husson, and P. Potier, *Tetrahedron Letters*, 1973, 29.

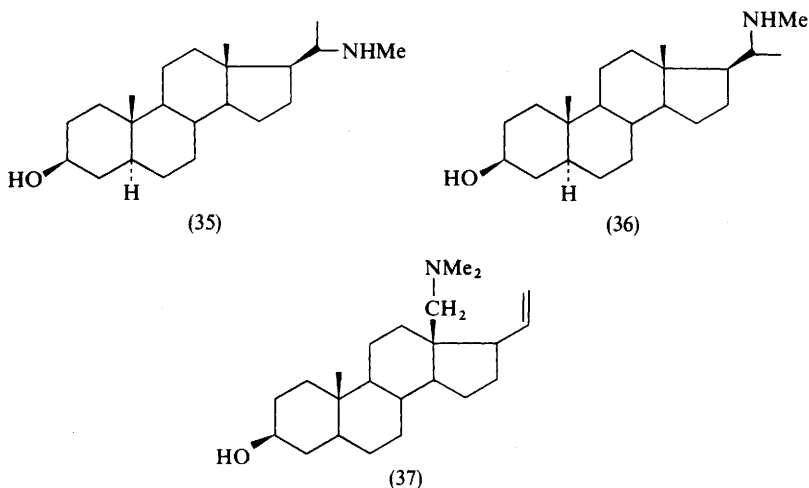
⁸ J. Libman and Y. Mazur, *Chem. Comm.*, 1971, 730.

⁹ G. Van de Woude and L. Van Hove, *Bull. Soc. chim. belges*, 1973, **82**, 31; cf. *Tetrahedron Letters*, 1972, 1305, reviewed in Volume 3 of this Report.



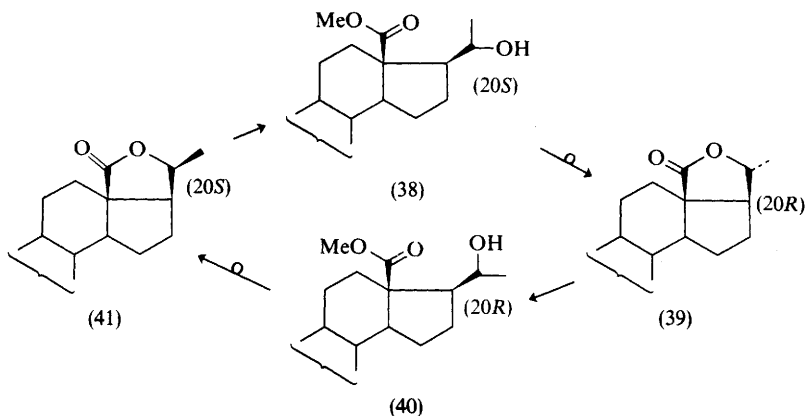
3 β -Hydroxyconanine (33a) and 3 β -hydroxyheteroconanine (34a) have been obtained by a Hofmann–Loeffler reaction effected with 3 β -hydroxy-20 α -methylamino-5 α -pregnane (35) and 3 β -hydroxy-20 β -methylamino-5 α -pregnane





(36), respectively.¹⁰ From (33a) and (34a), conanine (33b) and *heteroconanine* (34b), conan-3-one (33c) and *heteroconan*-3-one (34c) were prepared. Reductive amination of (33c) and (34c) has been effected. Hofmann degradation of (33a) and (34a) gave the known 18-dimethylamino-5 α -pregn-20-en-3 β -ol (37). Optical rotation data, R_f values, n.m.r. assignments, and mass spectra were given.

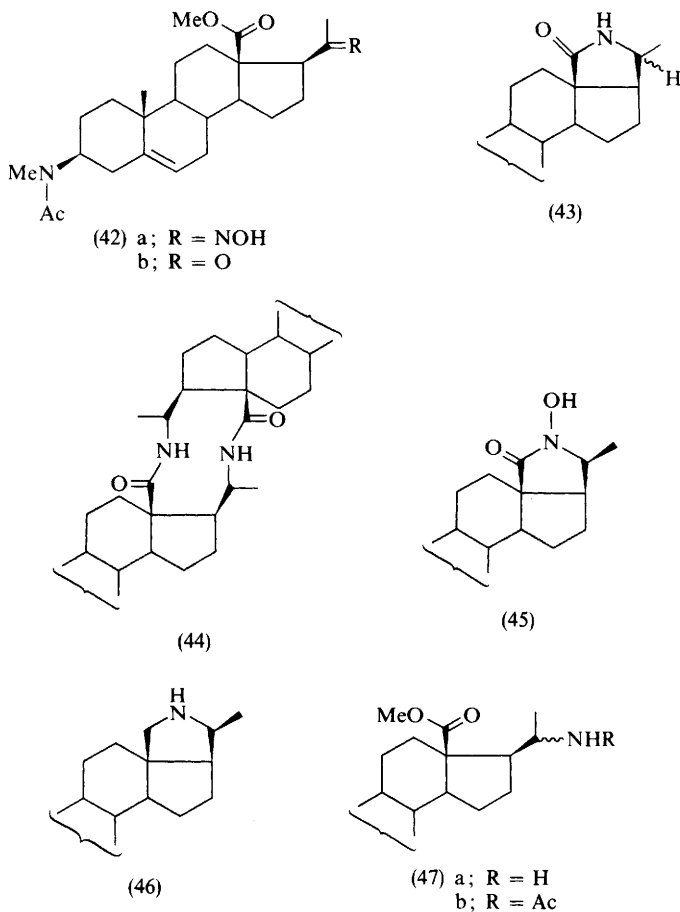
Intramolecular reactions of 18-methoxycarbonyl-steroids with an oxygenated or nitrogen function at C-20 have been studied.¹¹ The ester-(20*S*)-alcohol (38) when treated with toluene-*p*-sulphonyl chloride gave the (20*R*)-lactone (39), by intramolecular reaction with inversion of the configuration at C-20. On the other hand, the ester-(20*R*)-alcohol (40) with toluene-*p*-sulphonyl chloride led to the (20*S*)-lactone (41).



¹⁰ G. Van de Woude and L. Van Hove, *Bull. Soc. chim. belges*, 1973, **82**, 49.

¹¹ J. Einhorn, C. Monneret, and Q. Khuong-Huu, *Bull. Soc. chim. France*, 1973, 303.

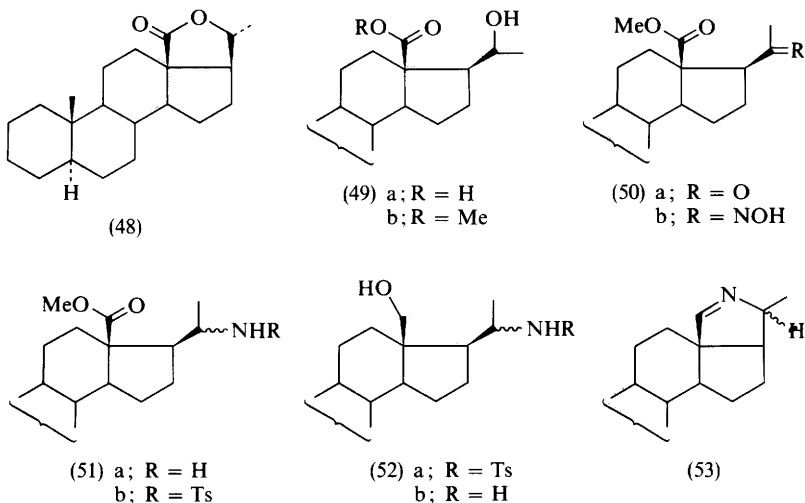
Under reducing conditions, the ester-oxime (42a) led to various products according to the reducing agents used. With lithium in ethylamine, the (20*S*)-lactam (43) was obtained; with zinc in acetic acid, the keto-ester (42b), the (20*S*)-lactam (43), and the bis-steroid (44) were formed; the (20*S*)-hydroxamic acid (45) was formed when LiBH_4 was used, and the (20*S*)-pyrrolidine (46) was obtained with LiAlH_4 reduction. Only catalytic hydrogenation gave the (20*R*)- and (20*S*)-amines (47a) from (42a).



Cyclizations were also observed by reduction of 18-methoxycarbonyl-20-amino- or acetamido-steroids. With LiAlH_4 , the (20*S*)- and (20*R*)-amino-esters (47a) gave the (20*S*)- and (20*R*)-lactams (43), respectively, also obtained from the (20*S*)- and (20*R*)-acetamido-esters (47b) when treated with sodium in propanol. These results were discussed,¹¹ and have been used for a synthesis of

18(N) steroidal Δ^1 -pyrrolines with (20*S*) and (20*R*) configuration¹² and for a synthesis of conessidine.¹³

The lactone (48) obtained starting from (20*R*)-hydroxy-5 α -pregnane was hydrolysed to (49a). Oxidation of (49b) gave the ketone (50a), which was converted into an oxime (50b). Catalytic hydrogenation of (50b) gave a mixture of (20*R*)- and (20*S*)-amines (51a). The tosylates (51b) were separated and reduced to the corresponding (20*R*)- and (20*S*)-tosylamino-alcohols (52a). Detosylation was effected by lithium in ethylamine and the (20*R*) and (20*S*) Δ^1 -pyrrolines (53) were obtained by oxidation of the corresponding alcohols (52b).¹²



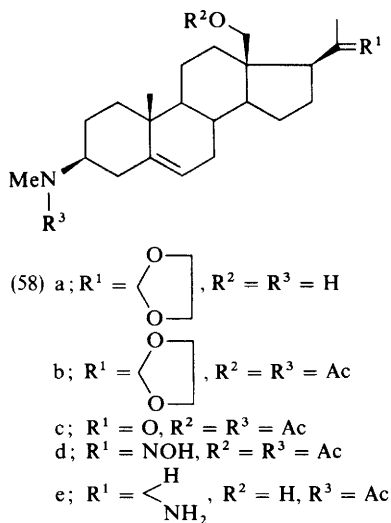
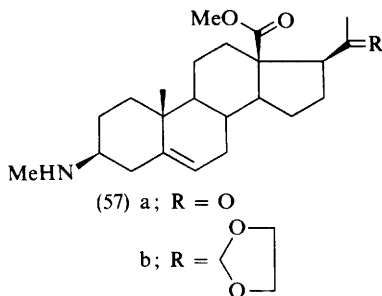
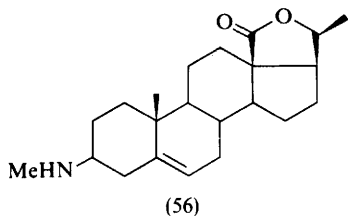
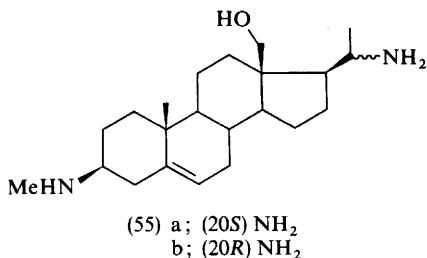
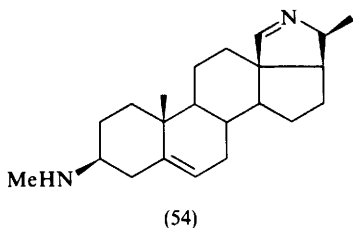
Conessidine (54) and *N*-3-methylholarrhimine (55a) and its (20*R*) epimer (55b) have been synthesized starting from paravallarine (56).¹³ The ethylene ketal (57b) from the ketone (57a) was reduced to the alcohol (58a). After acetylation, the ketal group was removed and the keto-group was converted into its oxime (58d). Reduction with sodium of (58d), followed by lithium-ethylamine reduction to remove the *N*-3-acetyl group of (58e), afforded the (20*S*)- and the (20*R*)-amines (55a) and (55b), which were separated. Oxidation of (55a) gave conessidine (54).

Δ^1 -Pyrrolines of the (20*R*)- and (20*S*)-18(N)-*N*-demethylconenine (53) have also been prepared starting from the 18-iodo-derivative (59), which was obtained by $\text{Pb}(\text{OAc})_4$ -iodine reaction with (20*R*)-hydroxy-compound.¹⁴ Oxidation of (59) gave the iodo-ketone (60) which gave the acetal (61) when treated with MeOH-silver acetate. Opening of the acetal function with hydroxylamine acetate afforded the oxime-alcohol (62), which was reduced to the (20*S*)- and

¹² J. Einhorn, C. Monneret, and Q. Khuong-Huu, *Bull. Soc. chim. France*, 1973, 296.

¹³ J. Einhorn, C. Monneret, and Q. Khuong-Huu, *Bull. Soc. chim. France*, 1973, 301.

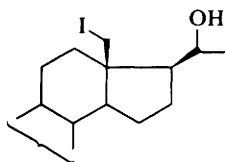
¹⁴ C. Monneret, J. Einhorn, P. Choay, and Q. Khuong-Huu, *Compt. rend.*, 1973, **275**, C, 221.



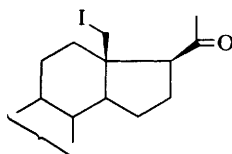
(20*R*)-amino-alcohols (52b). Separation of the amino-alcohols followed by oxidation gave the corresponding (20*S*) and (20*R*) Δ^1 -pyrrolines (53).

The 14 β -H configuration of isoconessine (63a), the acid isomerization product of conessine, has been definitively established.¹⁵ With sulphuric acid at 0 °C,

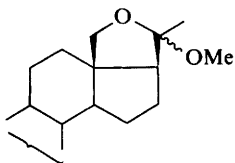
¹⁵ J. Thierry, F. Frappier, M. Pais, F. X. Jarreau, and R. Goutarel, *Bull. Soc. chim. France*, 1972, 4573.



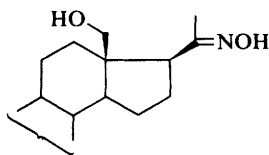
(59)



(60)

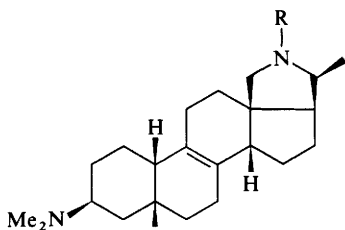
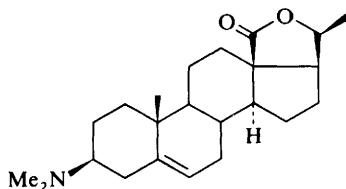


(61)

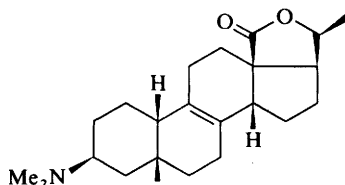


(62)

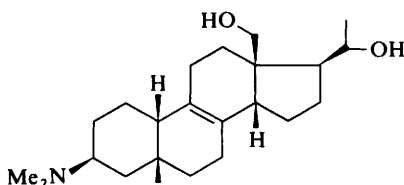
N-methylparavallarine (64) led to iso-*N*-methylparavallarine (65) as the only product, which was reduced to the diol (66). Oxidation of (66) with silver carbonate afforded a mixture of (65) and (67). Opening of the acetal ring of (67) with hydroxylamine acetate gave the oxime-alcohol (68a). Beckmann rearrangement of (68b) led to the 17 β -acetamido-derivative (69). Oxidation of (69), followed by a Wolff-Kishner reduction, gave (70) which in turn was deaminated to give the known 3 β -dimethylamino-5-methyl-19-nor-5 β ,10 β ,14 β -androst-8-en-17-one(71). On the other hand, reduction of the oxime-alcohol (68a) gave the epimeric amines (72), which were oxidized to the (20*S*)- and (20*R*)- Δ^1 -pyrrolines (73). The (20*S*)- Δ^1 -pyrroline (73a) was isolated and reduced to (63b), which was methylated to give isoconessine (63a).

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

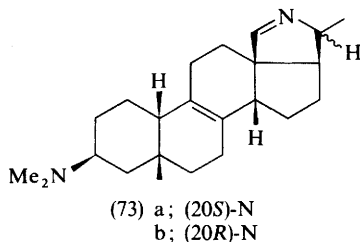
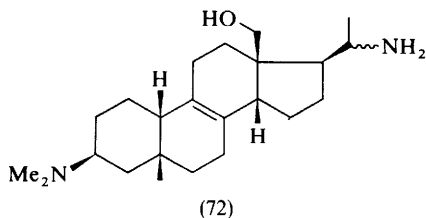
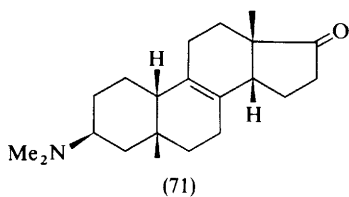
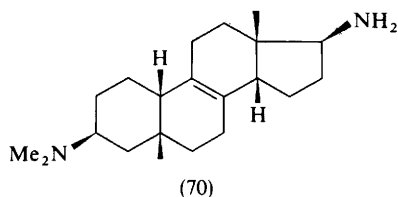
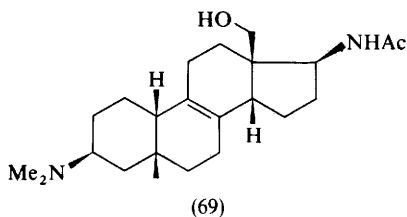
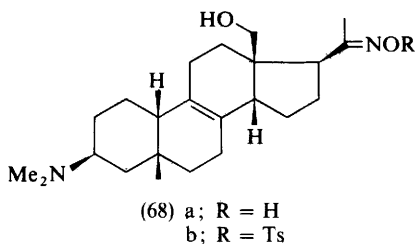
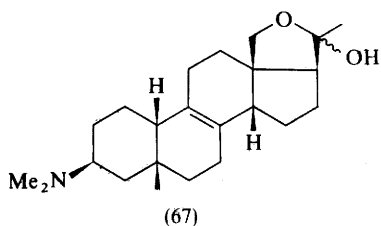
(64)



(65)

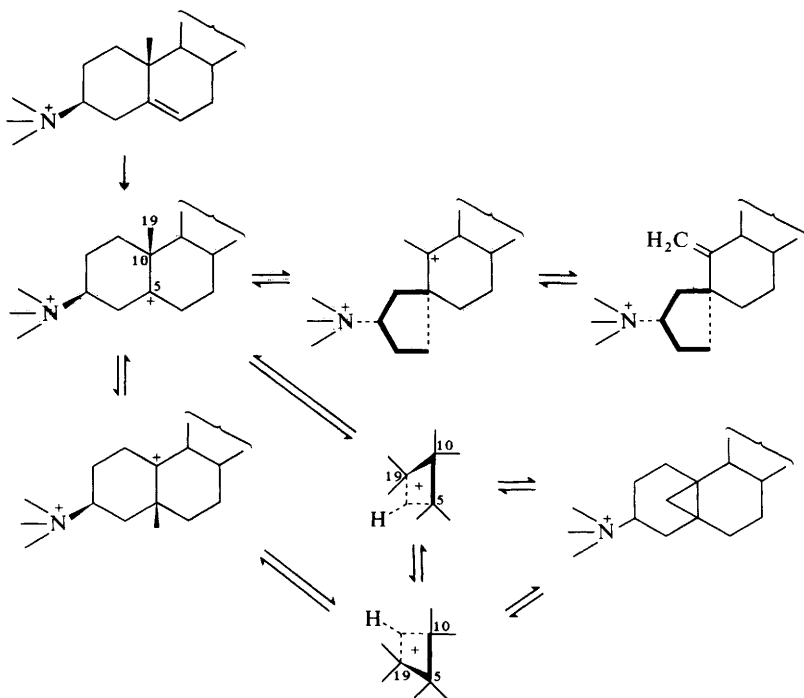


(66)



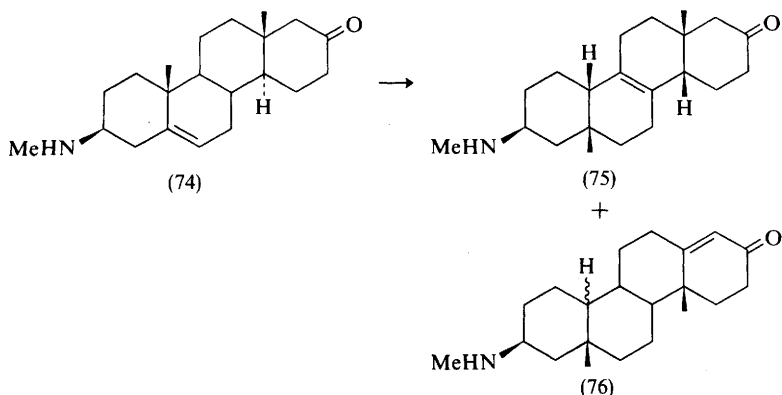
3 β -Amino- Δ^5 -steroids (namely methylholaphylline and conessine) were skeletally isomerized in D₂SO₄ with deuteration of the 19-methyl group as indicated by mass spectroscopy and ¹H and ¹³C n.m.r. studies. But a 3 α -amino- Δ^5 -steroid (holamine) did not deuteriate in the 19-methyl group during isomerization in D₂SO₄. A mechanism involving migration of the C-1—C-10 bond and forming a C-10 cation which equilibrates the 19-methyl group was discussed and compared with a cyclopropyl cation mechanism (Scheme 1).¹⁶

¹⁶ M. M. Janot, F. Frappier, J. Thierry, G. Lukacs, F. X. Jarreau, and R. Goutarel, *Tetrahedron Letters*, 1972, 3499.

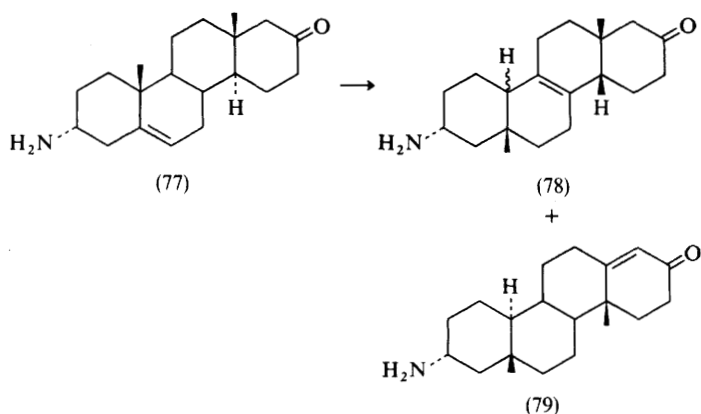


Scheme 1

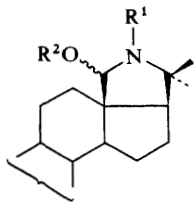
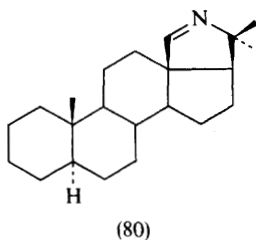
The backbone rearrangement of 3β -methylamino-D-homo-androst-5-en-7-one (74) in sulphuric acid at 0°C gave the derivatives (75) and (76). Under the same conditions, 3α -amino-D-homo-androst-5-en-7-one (77) afforded (78) and (79). These results showed that a 'directing effect' was not observed.¹⁷



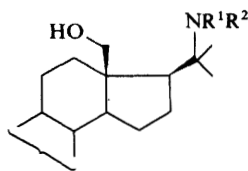
¹⁷ F. Frappier, J. Boivin, and F. X. Jarreau, *Compt. rend.* 1972, **274**, C, 2190.



The preparation of 18,20-substituted derivatives of 20-methyl-5 α -pregnane starting from the imine (80) has been studied.¹⁸ With benzoyl chloride, the imine (80) afforded the benzamido-methanols (81a) epimeric at position 18, which were reduced with NaBH₄ to derivative (82a). The amine (82c) was prepared by saponification of (82a) or by hydrogenolysis of the benzylamine (82d). With acetic anhydride in pyridine, the imine (80) afforded the acetamido-methanols (81b), which were reduced to derivative (82b). Properties of the amido-methanols (81) have also been studied.¹⁸



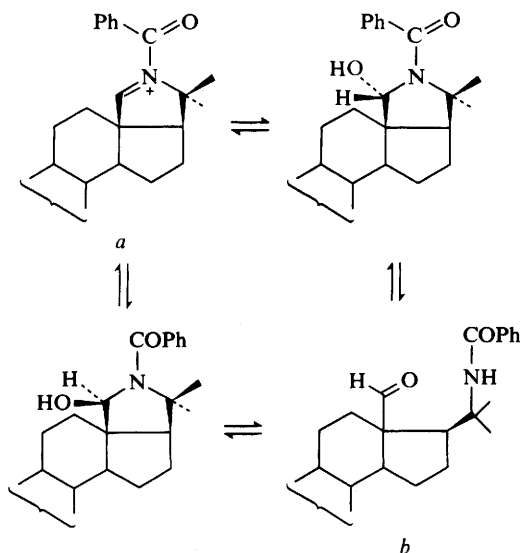
- (81) a; R¹ = CPh, R² = H
 b; R¹ = COMe, R² = H
 c; R¹ = CPh, R² = Me
 d; R¹ = COMe, R² = Me



- (82) a; R¹ = CPh, R² = H
 b; R¹ = COMe, R² = H
 c; R¹ = R² = H
 d; R¹ = CH₂Ph, R² = H
 e; R¹ = Me, R² = H
 f; R¹ = R² = Me

¹⁸ J. P. Alazard and X. Lusinchi, *Bull. Soc. chim. France*, 1972, 3267; cf. *Compt. rend.*, 1970, 271, C, 1386, reviewed in Volume 2 of this Report.

The epimeric benzamido-methanols (81a) are in equilibrium and an n.m.r. study led to the assignment of the 18β -H structure for the most stable isomer. This epimerization could occur through the ring-closed immonium ion *a* or through the open aldehydic form *b* (Scheme 2).



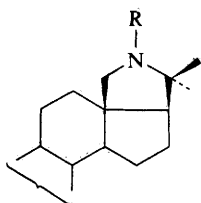
Scheme 2

With methanol, in neutral or acidic medium, the amido-methanols (81a) and (81b) gave the methoxylated forms (81c) and (81d), the immonium ion *a* being an intermediate (Scheme 2).

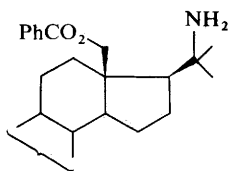
By reduction with LiAlH_4 , the benzamido-methanols (81a) afforded the benzylamine (83a), the secondary amine (83b), and the imine (80), the formation of which could be explained by aerial oxidation in the presence of the mixed hydride. The c.d. measurement indicated a conanine-like configuration for the nitrogen atom of 20-methylconanine (83c).

The acid hydrolysis of the benzamido-alcohol (82a) was effected. With $\text{N-H}_2\text{SO}_4$, the benzamido-alcohol (82a) gave the amino-ester (84), the amino-alcohol (82c), and the ether (85). This last was formed by $\text{S}_{\text{N}}2$ substitution of the C-20 amide function by the C-18 hydroxy-group, favoured by the presence at position 20 of a tetrasubstituted carbon. Under more acidic conditions ($9\text{N-H}_2\text{SO}_4$), the ether (85) was formed in 76% yield.

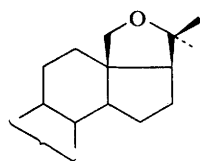
By treatment with toluene-*p*-sulphonic acid in an aprotic solvent (CH_2Cl_2), the benzamido-alcohol (82a) afforded (84) and the tetrahydro-oxazepine (86), which was hydrolysed by acids to (84). On the other hand, the formation of the ether (85) was not observed on acid treatment of the acetamido-alcohol (82b). These results were discussed.



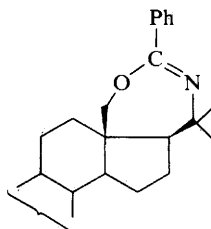
(83) a; R = CH₂Ph
 b; R = H
 c; R = Me



(84)



(85)

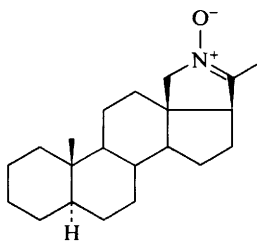


(86)

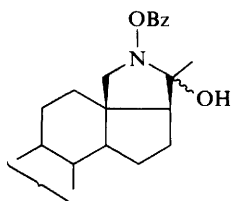
Upon methylation according to the Eschweiler-Clarke method, the amino-alcohol (82a) led to the monomethylated amine (82e), the dimethylated amine (82f), and the ether (85), which was formed from the tertiary amine (82f). The ether (85) was also obtained by iodomethylation of (82f).

The action of benzoyl and toluene-*p*-sulphonyl chlorides on the steroidal nitron (87) has been studied.¹⁹ The nitron (87) reacted with benzoyl chloride at room temperature in aqueous NaOH to give a mixture of the benzamido-methanols (88) epimeric at position 20, which in refluxing benzene or chloroform gave the imine (89). The latter was reduced to (90a) which in turn was hydrolysed to (90b) then methylated to (90c). Without base, a complex mixture was obtained.

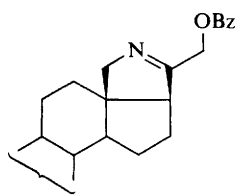
With toluene-*p*-sulphonyl chloride in the presence of base, the nitron (87) gave the oxaziridine (91). In the absence of base, the chloro-derivative (92) was obtained, which was converted into (89) by sodium benzoate in hexamethylphosphorotriamide.



(87)

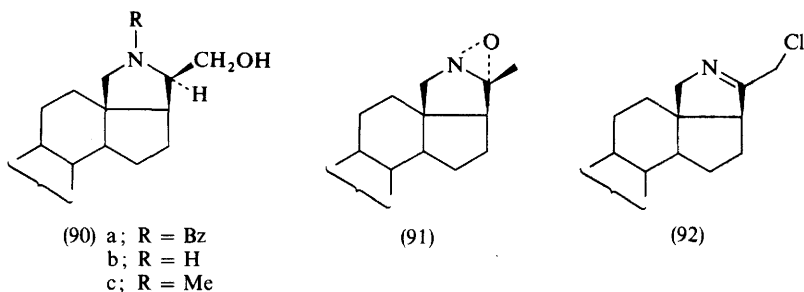


(88)

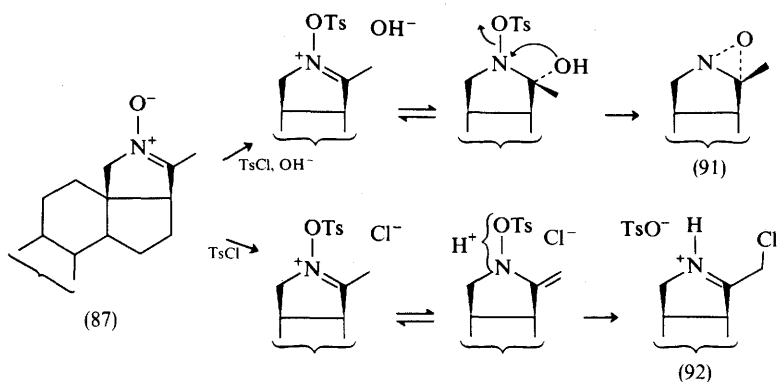


(89)

¹⁹ J. P. Alazard, B. Khemis, and X. Lusinch, *Tetrahedron Letters*, 1972, 4795.



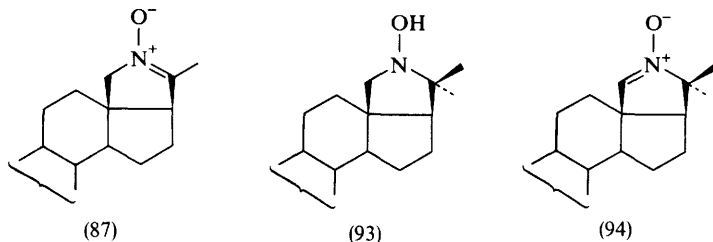
The difference between the reactivities of benzoyl chloride and toluene-*p*-sulphonyl chloride toward (87) was attributed to the different natures of the benzoyl and toluene-*p*-sulphonyl groups and to the differences in basicity of the medium (Scheme 3).



Scheme 3

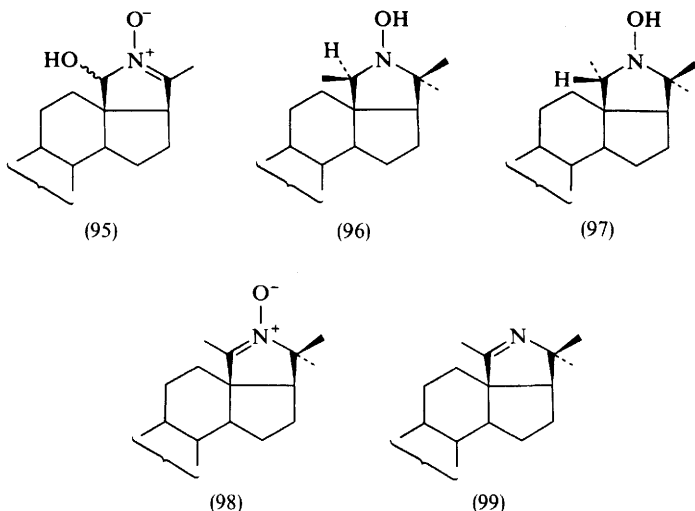
The action of methyl magnesium iodide on steroidal nitrones and α -hydroxynitrones, derivatives of conanine, has been investigated.²⁰

With methyl magnesium iodide, the 20(N)-nitrone (87) gave the 20-methylhydroxylamine (93), which could be oxidized to the 20-methyl-18(N)-nitrone (94). The latter was reduced with NaBH_4 to (93).

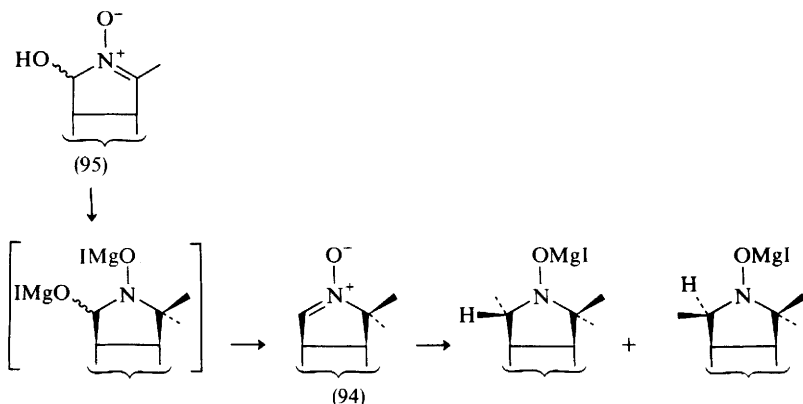


²⁰ J. P. Alazard and X. Lusinchi, *Bull. Soc. chim. France*, 1973, 1814.

Under the same conditions, the α -hydroxy-20(N)-nitron (95) afforded the 18 β ,20-dimethylhydroxylamine (96), the 20-methyl-18(N)-nitron (94), and 18,20-dimethyl-18(N)-nitron (98); the 18 α ,20-dimethylhydroxylamine (97), also formed,



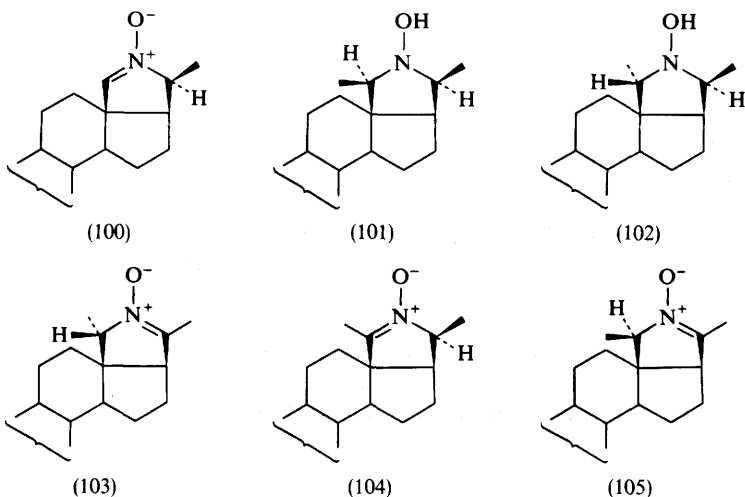
was unstable and gave (98) during work-up. The 18,20-dimethylhydroxylamines (96) and (97) were formed by action of methyl magnesium iodide on the 20-methyl-18(N)-nitron (94) formed *in situ* (Scheme 4).



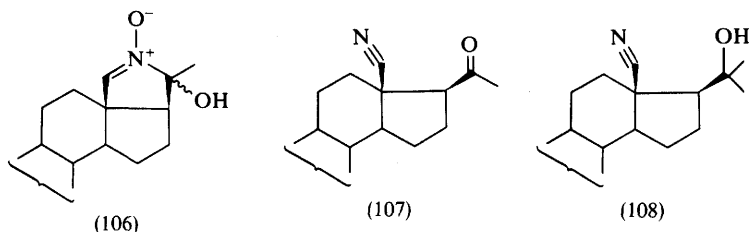
Scheme 4

With an excess of methyl magnesium iodide in refluxing benzene, the 20-methyl-18(N)-nitron (94) afforded the 18,20-dimethyl-18(N)-nitron (98) and its deoxygenation product, the imine (99); a second methyl group was not introduced at C-18.

With methyl magnesium iodide, the 18(N)-nitron (100) gave the 18-methyl-hydroxylamines (101) and (102); the latter, the main product of the reaction, was unstable and led to the 18 α -methyl-20(N)-nitron (103) and the 18-methyl-18(N)-nitron (104) which were isolated. By oxidation, the 18 β -methylhydroxylamine (101) gave the 18 β -methyl-20(N)-nitron (105). N.m.r. studies led to these structural assignments.



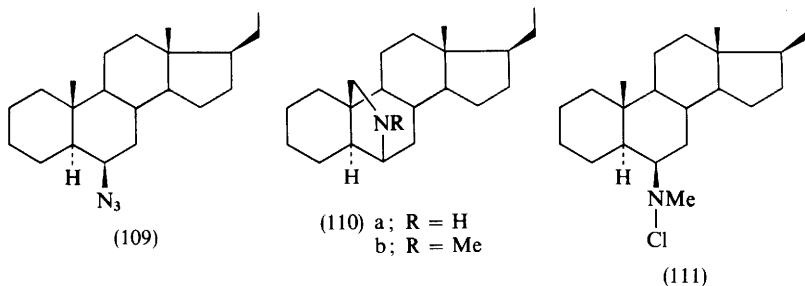
With the Grignard reagent the 20-hydroxy-18(N)-nitron (106) afforded the nitriles (107) and (108).



The 18-methyl-18(N)-nitron (104) did not react with methyl magnesium iodide, whereas the 18 α -methyl-20(N)-nitron (103) gave (97) and (98) and the 18 β -methyl-20(N)-nitron (105) afforded the hydroxylamine (96) in good yield. These various results are discussed.

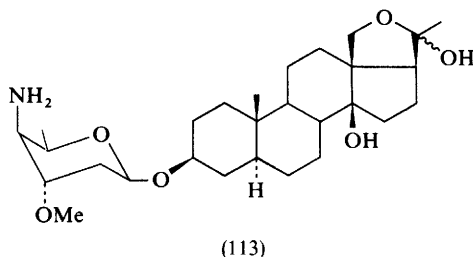
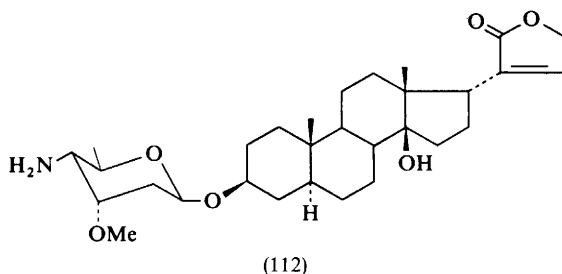
Photochemistry. A successful 1,5 hydrogen abstraction by a nitrene intermediate followed by cyclization into a pyrrolidine ring has been effected, by irradiation of a steroidal azide.²¹ Thus, irradiation of 6 β -azido-5 α -pregnane (109) in cyclohexane gave 5 α -pregnan-6-one (27%), 6-aza-B-homo-5 α -pregn-6-ene (35%),

²¹ A. Pancrazi, Q. Khuong-Huu, and R. Goutarel, *Tetrahedron Letters*, 1972, 5015.

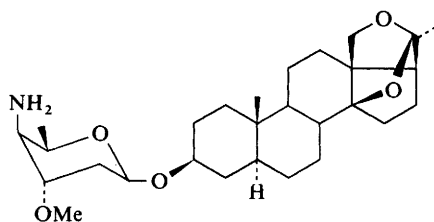


7-aza-B-homo-pregn-6-ene (25%), and 6 β ,19-imino-5 α -pregnane (110a) (6%). Methylation of (110a) led to (110b), which in turn was obtained by a Hofmann–Loeffler–Freitag reaction with the chloramine (111).

Aminoglycosteroids.—Holarosine B (112) and holantosines E (113) and F (114) have been isolated from *Holarrhena antidysenterica* leaves.²² Holarosine B (112) is the β -D-glycoside of D-holosamine with allouzarigenin. Holantosines E (113) and F (114) are β -D-glycosides of a new amino-sugar, D-holacosamine, 4-amino-4-deoxysarmentose, with (respectively) holantogenin and anhydroholantogenin. The structure of D-holacosamine was established by mass and n.m.r. measurements and corroborated by partial synthesis starting from methyl- α -D-glucopyranoside.

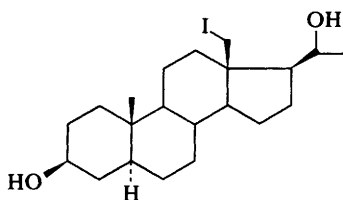


²² R. Goutarel, C. Monneret, P. Choay, I. Kaboré, and Q. Khuong-Huu, *Carbohydrate Res.*, 1972, **24**, 297.

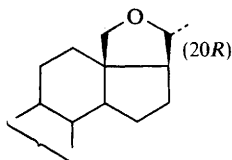


(114)

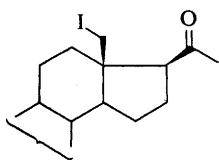
Better yields could be obtained for holantogenin synthesis with the isolation of the 18-iodo-derivative (115), an intermediate of the hypiodite reaction.²³ With base, (115) gave the (20R)-oxiran (116); the iodo-ketone (117) with silver acetate in MeOH afforded the acetal (118), which was reduced to the (20S)-oxiran (119). The acetal (118) was an intermediate for holantogenine synthesis.



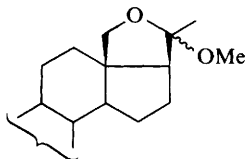
(115)



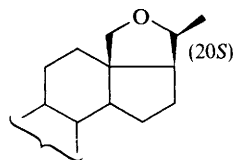
(116)



(117)



(118)



(119)

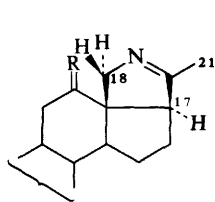
Mass and N.M.R. Spectra.—It was noted that the relative intensity of peaks m/e 71 and $M - 15$ was rather different in conanine and heteroconanine derivatives: in the latter the loss of the 21-methyl group was favoured over the fragmentation of the pyrrolidine ring, whereas in the former both processes seemed to occur to a comparable extent.¹⁰

The steroidal 12-substituted imines (120) and nitrones (121) showed, in their n.m.r. spectra, 5J coupling constants between protons at C-18 and protons at C-17 or C-21.²⁴ With specifically deuteriated products, it was shown that 18α -H was coupling with 21-H and not with 17-H, while 18β -H was coupling both with

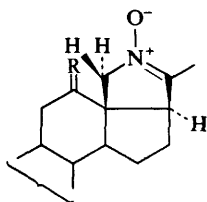
²³ P. Choay, C. Monneret, and Q. Khuong-Huu, *Bull. Soc. chim. France*, 1973, 1456.

²⁴ G. Lukacs, G. Roblot, P. Milliet, and X. Lusinchi, *Compt. rend.*, 1972, **275**, C, 291.

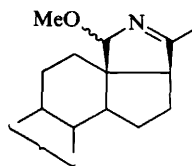
21-H and 17-H. A 4J coupling constant between protons at C-21 and C-17 was noted in derivative (121). These results have been used for the determination of the stereochemistry of the methoxylated imines (122)²⁴ and for the structural assignments of the nitrones (103)–(105).²⁰



(120)



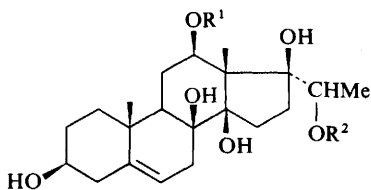
(121)



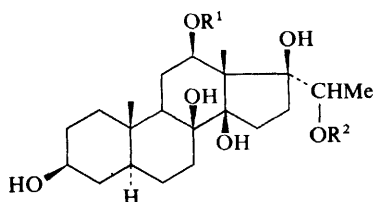
(122)

2 Alkaloids of the Asclepiadaceae

Constituents of *Marsdenia rostrata* (Asclepiadaceae) were isolated and identified.²⁵ The sample from the Toonumbar State Forest in Northern New South Wales contained anabasine and two new steroidal ester alkaloids, rostratine (123) and dihydrorostratine (124). They were identified as *O*-acetyl-*O*-nicotinoylsarcostin and *O*-acetyl-*O*-nicotinoyldihydrosarcostin. The sample from the South Coast of New South Wales yielded the two new ester alkaloids and a number of neutral polyhydroxypregnane aglycones, but no anabasine.



(123) $R^1 = \text{COMe}$
 $R^2 = \text{nicotinoyl}$



(124) $R^1 = \text{COMe}$
 $R^2 = \text{nicotinoyl}$

3 Salamandra Alkaloids

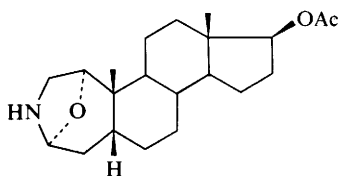
Syntheses in the field of *Salamandra* alkaloids have recently been published.

A practical and stereoselective synthesis of (125), the key compound to samandarine-type alkaloids, has been effected.²⁶ The hydroxymethylene derivative of 17 β -hydroxy-5 β -androstane-3-one (126) was treated with an equimolar amount of methyl toluene-*p*-thiosulphate in boiling ethanol in the presence of potassium acetate according to Autrey and Scullard's procedure. The product isolated after acetylation was 17 β -acetoxy-2 β -methylmercapto-androstan-3-one

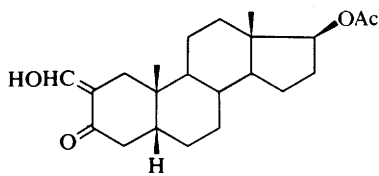
²⁵ R. E. Summons, J. Ellis, and E. Gellert, *Phytochemistry*, 1972, **11**, 3335.

²⁶ Y. Shimizu, *Tetrahedron Letters*, 1972, 2919.

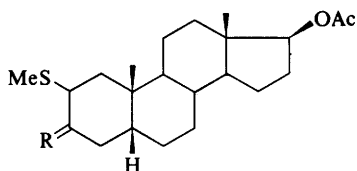
(127a). Reaction of (127a) with hydroxylamine hydrochloride in pyridine afforded the oxime (127b), which was submitted to the Beckmann fragmentation to give a seco-nitrile product (128a). Removal of the methylmercapto-group afforded the methylene derivative (128b). Epoxidation of (128b) gave the epoxide (129). The anti-Markownikoff opening of (129) with NaN_3 gave the azide (130). Treatment of (130) with an excess of NaBH_4 in refluxing propan-2-ol gave, in one step, the compound (125) in about 60% yield. It was speculated that this reaction proceeded *via* formation of the cyclic amidine *a* or imino-ester *b* which, subjected to NaBH_4 reduction, suffered concomitant cyclization to the rigid oxazolidine ring.



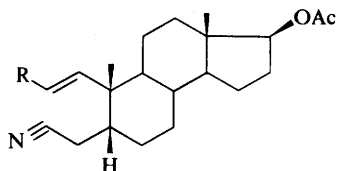
(125)



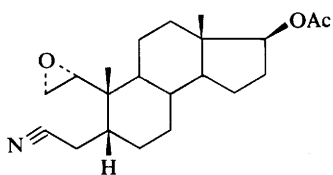
(126)



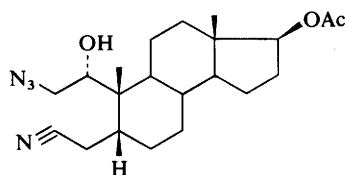
(127) a; R = O
b; R = NOH



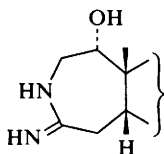
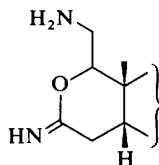
(128) a; R = SMe
b; R = H



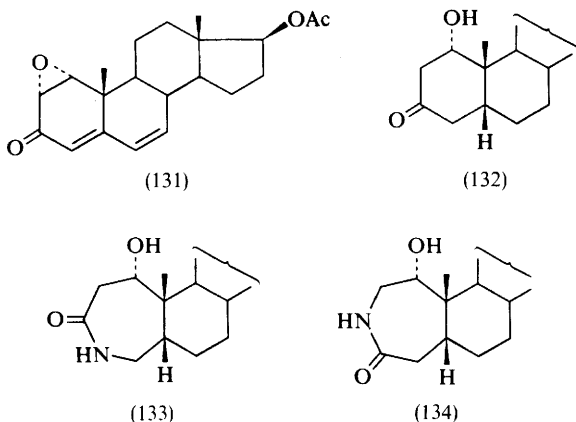
(129)



(130)

*a**b*

A biogenetically modelled synthesis of compound (125) has also been published.²⁷ Monoepoxidation of 17 β -acetoxyandrosta-1,4,6-trien-3-one gave the 1 α ,2 α -epoxide (131), which was hydrogenated to afford 17 β -acetoxy-1 α -hydroxy-5 β -androstan-3-one (132). A Schmidt reaction on (132) gave a mixture of lactams (133) and (134) which could be separated, thus providing (134) which was reduced with lithium-ethylamine-2-methylpropan-2-ol to derivative (125).



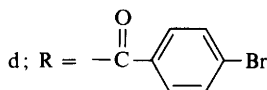
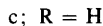
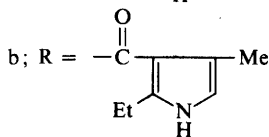
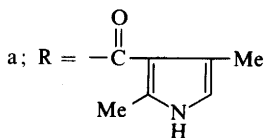
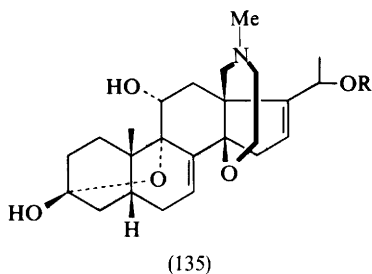
4 *Phyllobates* Alkaloids

Batrachotoxin (135a), homobatrachotoxin (135b) (previously named isobatrachotoxin), batrachotoxinin A (135c), and pseudo-batrachotoxin of unsolved structure, were isolated in 1963 by Witkop *et al.*²⁸ from the skin of the Colombian poison arrow frog *Phyllobates aurotaenia* (previously referred to as *Phyllobates bicolor*). They were also found in *Phyllobates vittatus* from Costa Rica.^{28a,f} Investigation of batrachotoxin was handicapped by the paucity of material and by its lability. The structure (135c) of batrachotoxinin A was determined by an X-ray analysis of the *p*-bromobenzoate (135d).^{28c,e} Batrachotoxinin A is 3 α ,9 α -epoxy-14 β O,18*N*-[ep(oxyethano-*N*-methylimino)]-5 β -pregna-7,16-diene-3 β ,11 α ,20 α -triol.

The structures of batrachotoxin and homobatrachotoxin were deduced from their physico-chemical properties. A strong positive Ehrlich test indicated the presence of a pyrrole moiety. U.v., i.r., n.m.r., and mass-spectroscopic data afforded evidence that batrachotoxin and homobatrachotoxin were, respectively,

²⁷ M. H. Benn and R. Shaw, *J.C.S. Chem. Comm.*, 1973, 288.

²⁸ (a) F. Märki and B. Witkop, *Experientia*, 1963, **19**, 329; (b) J. W. Daly, B. Witkop, P. Bommer, and K. Biemann, *J. Amer. Chem. Soc.*, 1965, **87**, 124; (c) T. Tokuyama, J. W. Daly, B. Witkop, I. L. Karle, and J. Karle, *J. Amer. Chem. Soc.*, 1968, **90**, 1917; (d) T. Tokuyama, J. W. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, 1969, **91**, 3931; (e) I. L. Karle and J. Karle, *Acta Cryst.*, 1969, **B25**, 428; (f) B. Witkop, *Experientia*, 1971, **27**, 1121.



dimethylpyrrolicarboxylate and ethylmethylpyrrolicarboxylate esters of batrachotoxinin A (135c), as corroborated by hydrolysis of batrachotoxin giving batrachotoxinin A. The position of the alkyl substituents of the pyrrole moiety was determined by n.m.r. spectroscopy. Batrachotoxin was shown to be batrachotoxinin A-(20S)-2,4-dimethylpyrrole-3-carboxylate and homobatrachotoxin to be batrachotoxinin A-(20S)-2-ethyl-4-methylpyrrole-3-carboxylate. This structural assignment was confirmed by the partial synthesis of batrachotoxin by acylation of the allylic-(20S)-hydroxy-group of batrachotoxinin A with the mixed anhydride prepared from 2,4-dimethylpyrrole-3-carboxylic acid and ethyl chloroformate.^{28d}

Partial synthesis of batrachotoxinin A (135c) has been carried out by Wehrli *et al.*²⁹ Batrachotoxinin A was characterized by the presence of the steroidal skeleton of a 14 β O,18N-[ep(oxyethano-N-methylimino)] function, a 3 β ,11 α -dihydroxy-3 α ,9 α -oxido-system, two Δ^7 and Δ^{16} double-bonds, and a (20S)-hydroxy-function. Introduction of these functional groups was separately studied and syntheses of various model compounds were previously described.

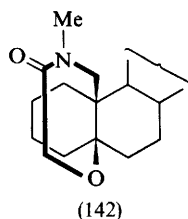
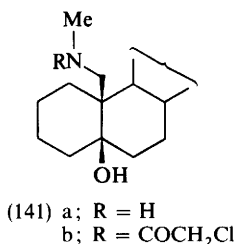
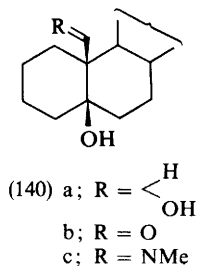
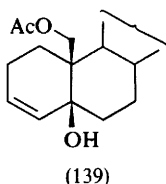
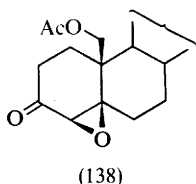
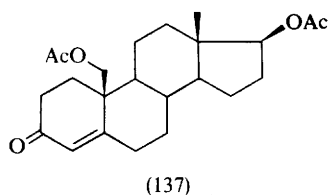
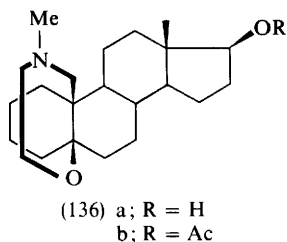
5 β ,19-[Ep(oxyethano-N-methylimino)]-17 β -acetoxysteroid (136a) was first obtained.³⁰ Epoxidation of the ketone (137) gave the epoxy-ketone (138) which, upon treatment with hydrazine hydrate,³¹ afforded the allylic alcohol (139). After hydrogenation and partial saponification, oxidation with silver carbonate³² of the primary hydroxy-group of (140a) led to the aldehyde (140b). With methylamine, the imine (140c) was obtained and reduced with NaBH₄ to the amine (141a). Acylation of (141a) with chloroacetyl chloride afforded the amide (141b)

²⁹ R. Imhof, E. Gössinger, W. Graf, L. Berner-Fenz, H. Berner, R. Schaufelberger, and H. Wehrli, *Helv. Chim. Acta*, 1973, **56**, 139; cf. H. Wehrli, *Chimia (Switz.)*, 1973, **27**, 21; R. Imhof, E. Gössinger, W. Graf, H. Berner, L. Berner-Fenz, and H. Wehrli, *Helv. Chim. Acta*, 1972, **55**, 1151.

³⁰ H. Berner, L. Berner-Fenz, R. Binder, W. Graf, T. Grütter, G. Pascual, and H. Wehrli, *Helv. Chim. Acta*, 1970, **53**, 2252; cf. H. Wehrli, *Chimia (Switz.)*, 1969, **23**, 403.

³¹ P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, 1961, **26**, 3615.

³² M. Fetizon and M. Golfier, *Compt. rend.*, 1968, **267**, C, 900.



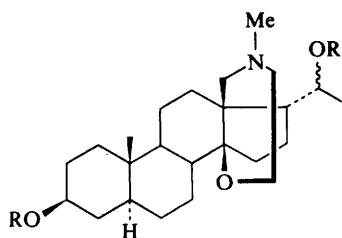
which, upon treatment with base, gave the lactam-ether (142). Reduction with LiAlH_4 of (142) afforded (136a), characterized as *O*-acetyl derivative (136b).

Preparation of $14\beta\text{O}, 18\text{N}$ -[ep(oxyethano-*N*-methylimino)]-20 ξ , 3β -diacetoxy- $5\alpha, 17\alpha$ -pregnane (143) was then performed.³³ The keto-acetate (144) prepared by ring-opening of 3β -acetoxy-18-hydroxy- 5α -pregnan-20-one (18—20 hemiacetal) was hydroxylated in position 14β by classical methods,³⁴ via the epoxy-compound (145), to give (146). Reduction with $\text{Li}[\text{Al}(\text{Bu}'\text{O})_3\text{H}]$ of (146) led to a mixture of the (20*S*) and (20*R*) alcohols (147a). Acetylation followed by partial hydrolysis afforded the diol (147c), which was oxidized to (148a). With methylamine the methylamine (148b) was obtained and reduced after 20-*O*-acetylation to the amine (149a). Acylation with chloroacetyl chloride of (149a) gave (149b) which, with base, led to the lactam (150). Reduction of (150) afforded the compound (143a), characterized as *O*-acetyl derivative (143b). This sequence: aldehyde (148a) \rightarrow *N*-methyl-imine (148b) \rightarrow *N*-methyl-amine (149a) \rightarrow chloroacetamido

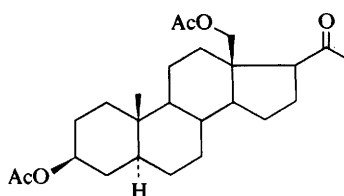
³³ L. Berner-Fenz, H. Berner, W. Graf, and H. Wehrli, *Helv. Chim. Acta*, 1970, **53**, 2258.

³⁴ Pl. A. Plattner, L. Ruzicka, H. Heussler, and E. Angliker, *Helv. Chim. Acta*, 1947, **30**, 385.

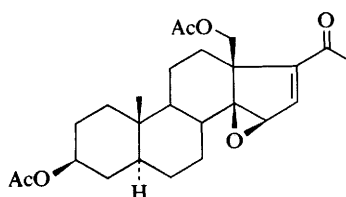
derivative (149b) \rightarrow lactam-ether (150) was also used for introduction of the 14,18-bridged ring on other model compounds: 3-*O*-methyl-17 α -20 ξ -tetrahydrobatrachotoxinin A (151a) and 3-*O*-methyl-20 ξ -7,8-dihydrobatrachotoxinin A (152).



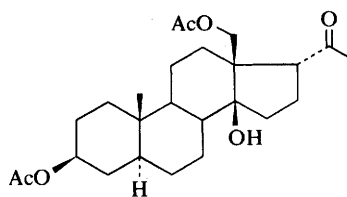
(143) a; R = H
b; R = Ac



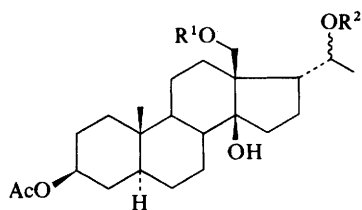
(144)



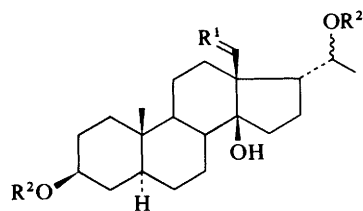
(145)



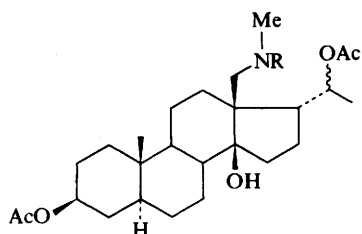
(146)



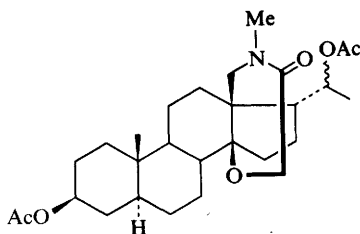
(147) a; R¹ = R² = H
b; R¹ = R² = Ac
c; R¹ = H, R² = Ac



(148) a; R¹ = O, R² = Ac
b; R¹ = NMe, R² = H

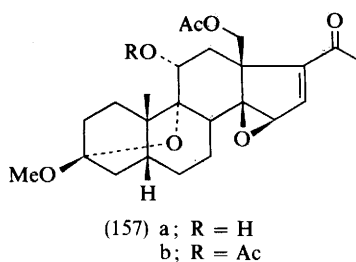
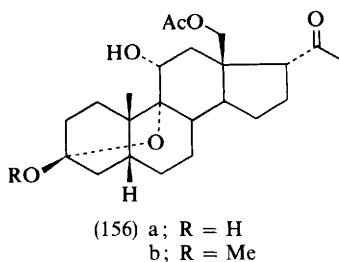
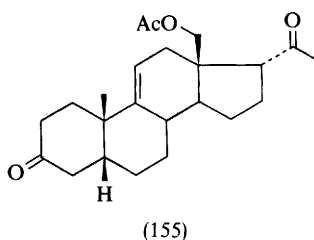
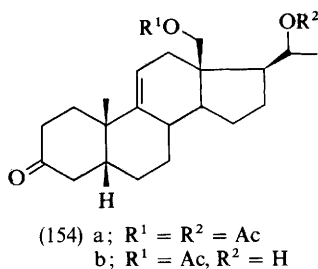
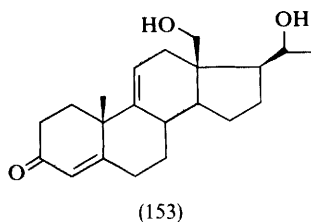
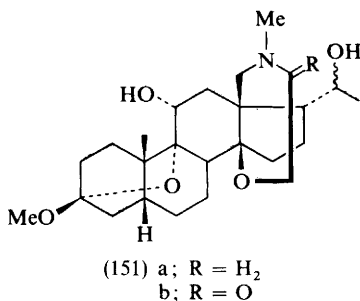


(149) a; R = H
b; R = COCH₂Cl



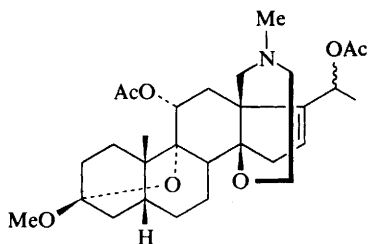
(150)

For the synthesis of 3-*O*-methyl-17 α ,20 ξ -tetrahydrobatrachotoxinin A (151a), introduction of the 3 β ,11 α -dihydroxy-3 α ,9 α -oxido-system was first effected.³⁵ Partial deacetylation of (154a), prepared from (153), gave the monoacetyl derivative (154b), which was then oxidized to the diketone (155). Osmylation of the Δ^9 -double-bond afforded the hemiacetal (156a) which gave, with MeOH, the 3-*O*-methyl derivative (156b). Then, after hydroxylation at position 14 β by classical methods, the epoxide (157a) being an intermediate, the 14,18-bridged ring was introduced according to the reaction sequence previously described, leading to the lactam-ether (151b), which was finally reduced to (151a).

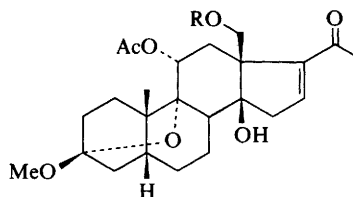


³⁵ W. Graf, H. Berner, L. Berner-Fenz, E. Gössinger, R. Imhof, and H. Wehrli, *Helv. Chim. Acta*, 1970, **53**, 2267.

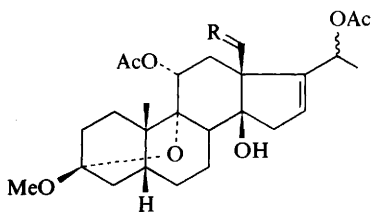
(20*S*)- and (20*R*)-7,8-dihydrobatrachotoxinin A (152) have also been synthesized.³⁶ The epoxy-ketone (157a), previously prepared, was acetylated and the diacetate (157b) gave the tertiary alcohol (158a) by catalytic hydrogen transfer (cyclohexane–Pd catalyst). The aldehyde (159a) was obtained by oxidation of (158b) with CrO_3 in pyridine–methylene chloride. Reduction with di-isobutyl-lithium aluminium hydride at -78°C of the 20-keto-group of the dimethylacetal (159b) led to the (20*S*)- and (20*R*)-alcohols (160a). Removal of the protective group gave the aldehyde (160b), which in turn was transformed into a mixture of (20*S*)- and (20*R*)-7,8-dihydrobatrachotoxinin A (152) as previously described.



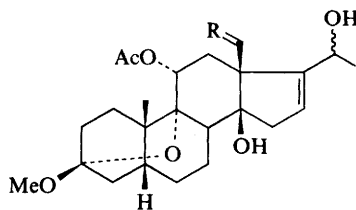
(152) a; (20*S*)-OAc
b; (20*R*)-OAc



(158) a; R = Ac
b; R = H



(159) a; R = O
b; R = $\begin{matrix} \text{OMe} \\ \diagup \quad \diagdown \\ \text{OMe} \end{matrix}$



(160) a; R = $\begin{matrix} \text{OMe} \\ \diagup \quad \diagdown \\ \text{OMe} \end{matrix}$
b; R = O

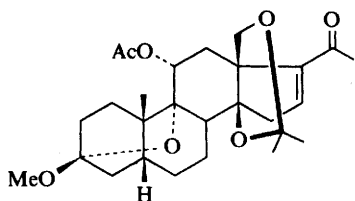
An alternative route giving better yield and leading to (152a) and to (152b) has been described.³⁷

The acetonide (161), prepared starting from (158b), was reduced with NaBH_4 at -30°C to the (20*S*)- and (20*R*)-alcohols (162a) and (163a) [ratio (163):(162) = 1:4] which were separated and acetylated. After removal of the acetonide group, oxidation of (164a) and (165a) with dimethyl sulphoxide–acetic anhydride³⁸ gave the aldehydes (164b) and (165b), having a 14 β -*O*-methylthiomethyl group. The imines (164c) and (165c) were reduced to the amines (166a) and (167a). After acylation with chloroacetyl chloride, the methylthiomethyl ether was

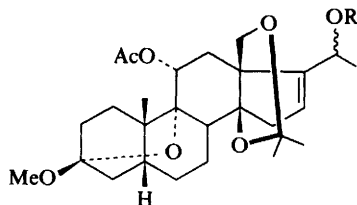
³⁶ W. Graf, E. Gössinger, R. Imhof, and H. Wehrli, *Helv. Chim. Acta*, 1971, **54**, 2789.

³⁷ W. Graf, E. Gössinger, R. Imhof, and H. Wehrli, *Helv. Chim. Acta*, 1972, **55**, 1545.

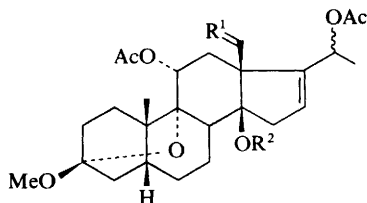
³⁸ J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 1967, **89**, 2416.



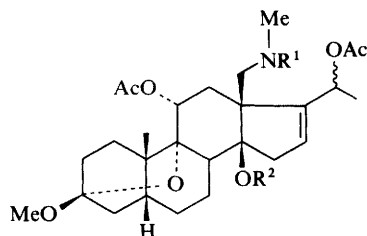
(161)



(162) (20*S*)-OR a; R = H
b; R = Ac
(163) (20*R*)-OR a; R = H
b; R = Ac



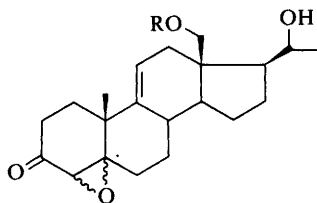
(164) (20*S*)-OAc a; R¹ = $\begin{matrix} \text{H} \\ \text{OH} \end{matrix}$; R² = H
b; R¹ = O; R² = CH₂SMe
c; R¹ = NMe; R² = CH₂SMe
(165) (20*R*)-OAc a; R¹ = $\begin{matrix} \text{H} \\ \text{OH} \end{matrix}$; R² = H
b; R¹ = O; R² = CH₂SMe
c; R¹ = NMe; R² = CH₂SMe



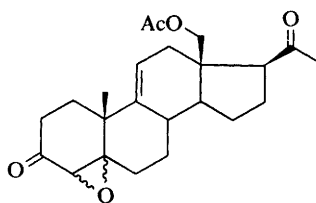
(166) (20*S*)-OAc a; R¹ = H, R² = CH₂SMe
b; R¹ = COCH₂Cl, R² = CH₂SMe
c; R¹ = COCH₂Cl, R² = H
(167) (20*R*)-OAc a; R¹ = H, R² = CH₂SMe
b; R¹ = COCH₂Cl, R² = CH₂SMe
c; R¹ = COCH₂Cl, R² = H

hydrolysed with acid and the (20*S*)- and (20*R*)-dihydrobatrachotoxinin A (152a) and (152b) were obtained starting from (166c) and (167c) as previously described.

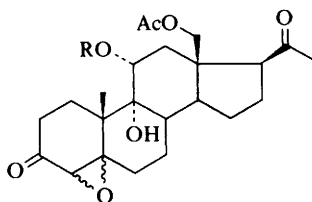
Synthesis of batrachotoxinin A has finally been carried out;³⁹ the remaining problem was the introduction of the 7(8)-double bond, *via* a 7 α -hydroxy-function.³⁹ The ketone (153), previously described, was converted by H₂O₂ oxidation into the 4,5-oxides (168a), which underwent partial acetylation and oxidation to the 20-ketone (169). This was submitted to osmylation and acetylation to give (170b). The conjugated ketone (171) was obtained from (170b) with Zn or NaI in acetic acid. Dehydration with DDQ of (171) led to the conjugated dienone (172), which underwent epoxidation to the 6,7-oxide (173). Reductive opening to the 7 α -alcohol (174) was performed by catalytic hydrogen transfer (Pd on BaSO₄-cyclohexene). Catalytic hydrogenation of (174) led to the semi-acetal (175a) which was converted into (175b). After acetylation of the 7-alcohol, a series of reactions led to the 14 β ,15 β -epoxide (176), which underwent catalytic hydrogen transfer to give (177a), hydrolysed to the 14,18-diol (177b). The acetonide (178) was reduced to the (20*S*)-allyl alcohol (179a) in 60% yield, which was acetylated. The lactam-ether (183a) was obtained from the 14,18-diol (180) according to the reactions previously described: oxidation with DMSO-Ac₂O to the aldehyde (181a), condensation with methylamine and reduction of the 18-methylimino-product (181b) to the amine (182a), *N*-chloroacetylation and acid treatment to give (182c), and base cyclization to (183a). Hydrolysis of (183a) gave (183b), which was acetylated to the 11 α ,20(*S*)-diacetyl compound (183c). Dehydration with thionyl chloride in pyridine [to (184)] followed by reduction afforded 3-*O*-methylbatrachotoxinin A, which was converted on acid treatment into batrachotoxinin A (135c).



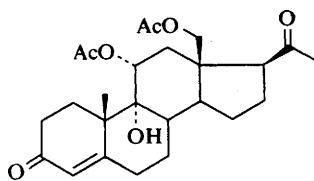
(168) a; R = H
b; R = Ac



(169)

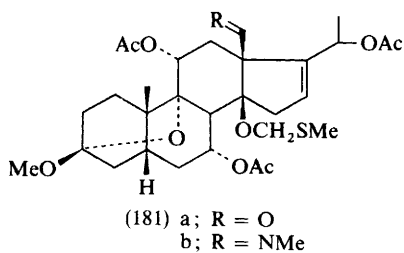
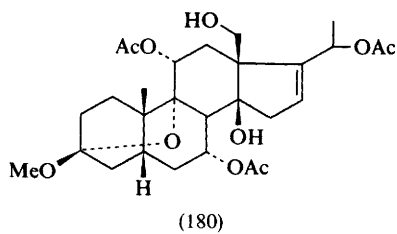
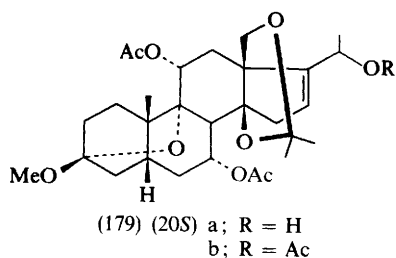
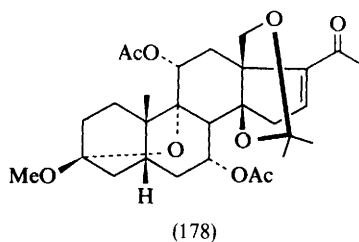
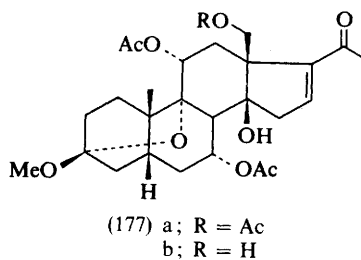
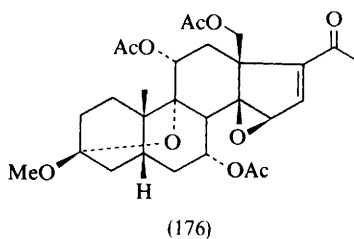
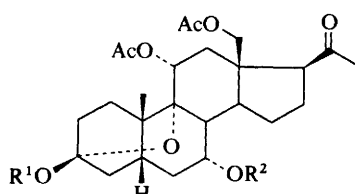
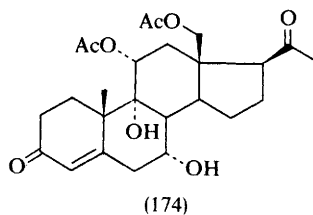
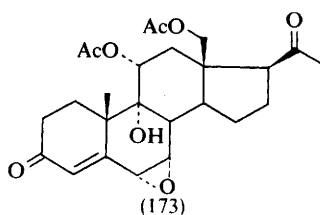
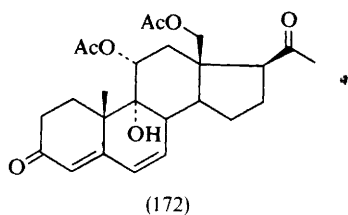


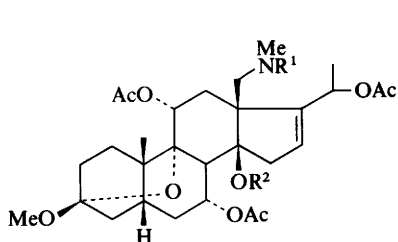
(170) a; R = H
b; R = Ac



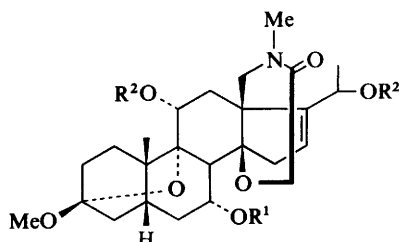
(171)

³⁹ R. Imhof, E. Gössinger, W. Graf, W. Schnüriger, and H. Wehrli, *Helv. Chim. Acta*, 1971, **54**, 2775.

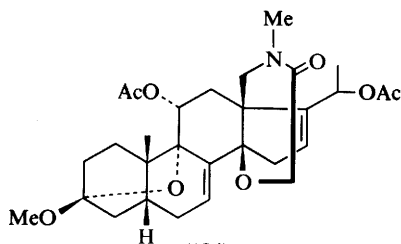




- (182) a; $R^1 = H, R^2 = CH_2SMe$
 b; $R^1 = COCH_2Cl, R^2 = CH_2SMe$
 c; $R^1 = COCH_2Cl, R^2 = H$

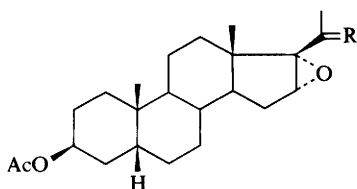


- (183) a; $R^1 = R^2 = Ac$
 b; $R^1 = R^2 = H$
 c; $R^1 = H, R^2 = Ac$

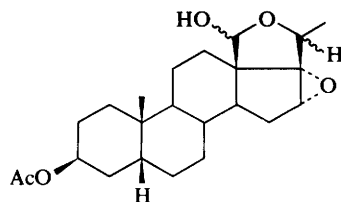


(184)

On the other hand, synthesis of compound (185), having a homomorpholinone ring, has been performed.⁴⁰ 3β -Acetoxy- $16\alpha,17$ -epoxy- 5β -pregnan-20-one (186a) was reduced to the alcohols (186b) which underwent cyclization to the semiacetal (187); this was then oxidized with DMSO- SO_3 pyridine complex⁴¹ to the keto-aldehyde (188). Reductive opening of the $16\alpha,17\alpha$ -oxide followed by selective reduction of the 20-ketone afforded the semiacetal (189), which was then oxidized to the keto-lactone (190). Bromination and dehydrobromination performed on (190) led, after reduction of the 16-ketone and epoxidation of the Δ^{14} -double bond, to the $14\beta,15\beta$ -oxide (191). Reduction with $LiAlH_4$ afforded the pentol



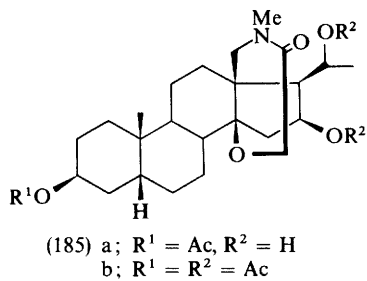
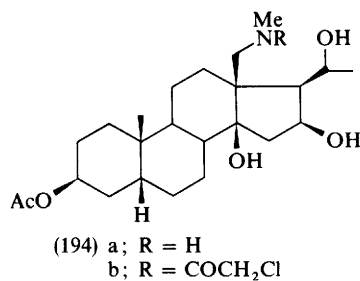
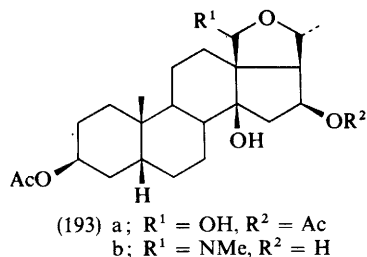
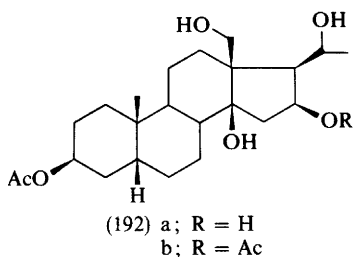
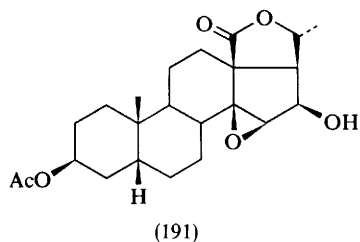
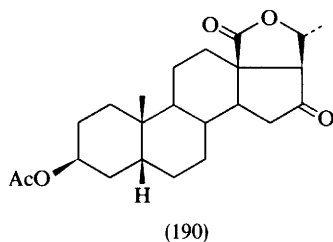
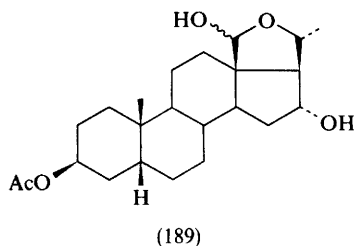
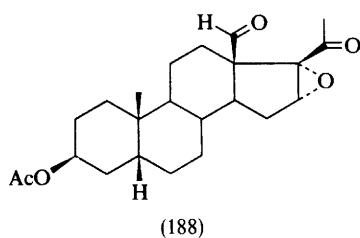
- (186) a; $R = O$
 b; $R = \begin{matrix} H \\ < \\ OH \end{matrix}$



(187)

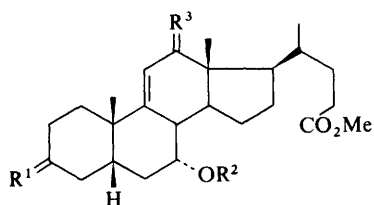
⁴⁰ U. Kerb, H. D. Berndt, U. Eder, R. Wiechert, P. Buchschacher, A. Furlenmeier, A. Fürst, and M. Müller, *Experientia*, 1971, **27**, 759.

⁴¹ J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, 1967, **89**, 5505.



(192a). Protection of the 14,18-diol as acetonide, acetylation of 3 β - and 16 β -alcohols, removal of the acetonide, and selective oxidation of the primary hydroxy-function of (192b) gave the semiacetal (193a). With methylamine, the *N*-methylaminoepoxy derivative (193b) was obtained and reduced to the *N*-methylaminotriol (194a). Cyclization to (185) was carried out, *via* the chloro-acetamido-derivative (194b).

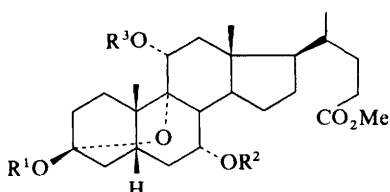
The ABC ring system of batrachotoxinin has also been synthesized, starting from cholic acid.⁴² Cholic acid was transformed by the method of Fieser into the diacetate (195a). Desulphurization of the corresponding ethylene dithioketal afforded the olefin-ester (195b). Selective removal of the C-3 acetate group followed by oxidation gave (195c). Osmylation of the Δ^9 -double bond afforded the semiacetal (196a); this was hydrolysed to the $7\alpha,11\alpha$ -diol semiacetal (196b) which readily formed acetal (196c) upon treatment with acidic methanol. Selective acetylation of the 11α -alcohol and dehydration of (196d) with phosphoryl chloride in pyridine led to the desired methyl 3β -methoxy- $3\alpha,9\alpha$ -oxido- 11α -acetoxy- Δ^7 -cholenate (197).



(195) a; $R^1 = \begin{smallmatrix} \text{H} \\ \diagup \\ \text{OAc} \end{smallmatrix}$ $R^2 = \text{Ac}$, $R^3 = \text{O}$

b; $R^1 = \begin{smallmatrix} \text{H} \\ \diagup \\ \text{OAc} \end{smallmatrix}$ $R^2 = \text{Ac}$, $R^3 = \text{H}_2$

c; $R^1 = \text{O}$, $R^2 = \text{Ac}$, $R^3 = \text{H}_2$

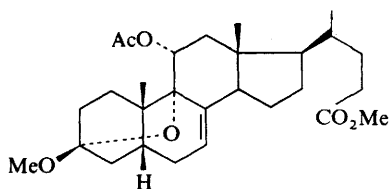


(196) a; $R^1 = R^3 = \text{H}$, $R^2 = \text{Ac}$

b; $R^1 = R^2 = R^3 = \text{H}$

c; $R^1 = \text{Me}$, $R^2 = R^3 = \text{H}$

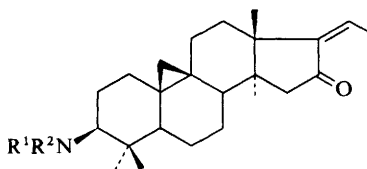
d; $R^1 = \text{Me}$, $R^2 = \text{H}$, $R^3 = \text{Ac}$



(197)

5 Alkaloids of the Buxaceae

The isolation of buxene (198a) and methylbuxene (198b) from *Buxus sempervirens* and their relationship with buxeneone have been described.⁴³



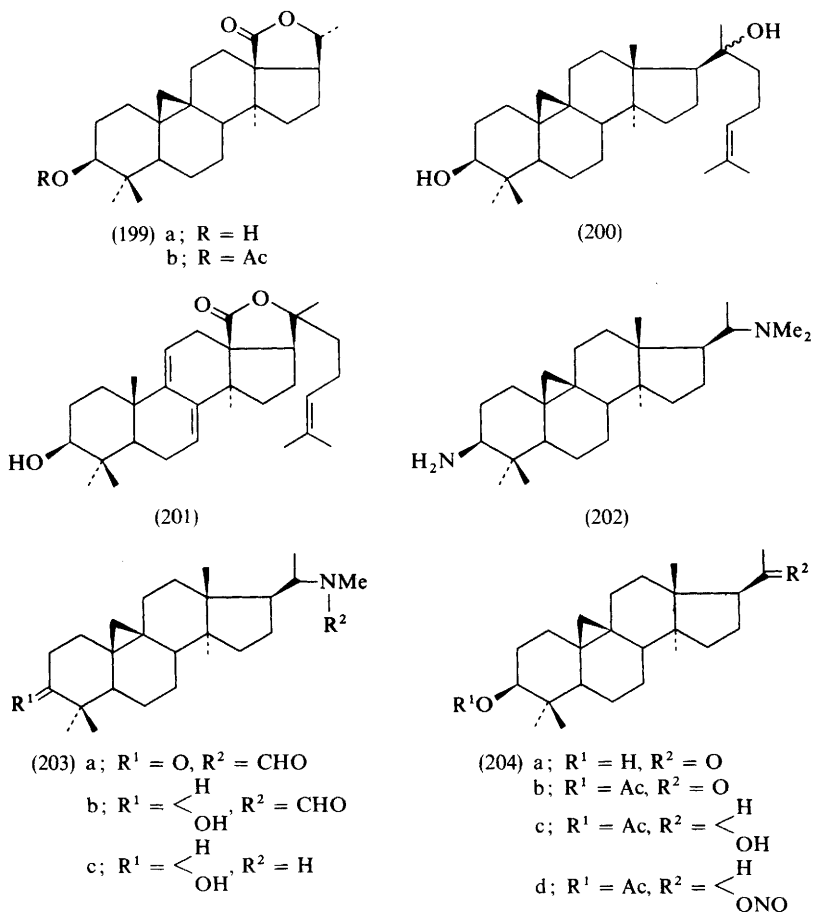
(198) a; $R^1 = \text{H}$, $R^2 = \text{CO}_2\text{Et}$

b; $R^1 = \text{Me}$, $R^2 = \text{CO}_2\text{Et}$

⁴² R. Schumaker and J. F. W. Keana, *J.C.S. Chem. Comm.*, 1972, 622.

⁴³ W. Doepke and R. Haertel, *Biochem. Physiol. Alkaloide*, Fourth Internat. Symposium, 1969, (published in 1972), ed. K. Mothes, p. 451.

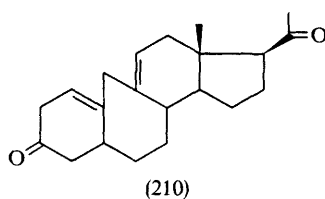
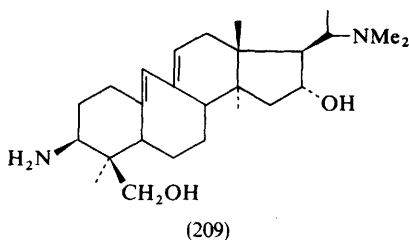
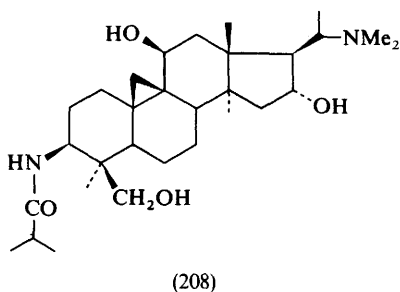
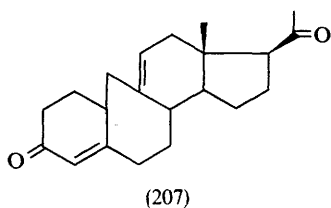
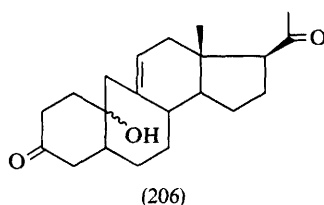
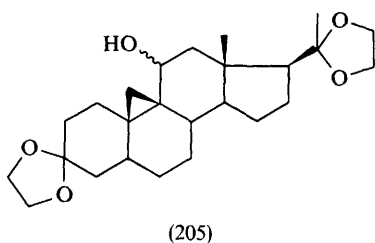
The lactone (199a) and the tertiary alcohol (200), potential intermediates for the synthesis of the holothurinogenin (201)⁴⁴ were prepared from cycloprotobuxine F (202).⁴⁵ Thus, oxidation of (202) with ruthenium tetroxide afforded the 3-oxo-20-(formylmethylamino) derivative (203a), which was reduced to (203b), and hydrogenolysed to the methylamino-derivative (203c). Deamination gave the 20-oxo-compound (204a), which was treated with the Grignard reagent of 1-bromo-4-methylpent-3-ene to give the tertiary alcohol (200). On the other hand, acetylation of (204a) gave the 3-acetoxy-derivative (204b), which was reduced to the (20*R*)-alcohol (204c). Irradiation of the (20*R*)-nitrite (204d) afforded the 18-oximino-(20*R*)-hydroxy-compound; this was subsequently oxidized to the lactone (199b), which was hydrolysed to (199a).



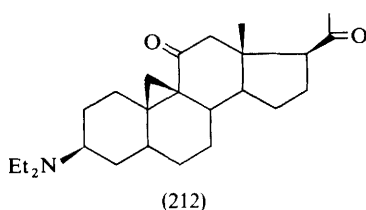
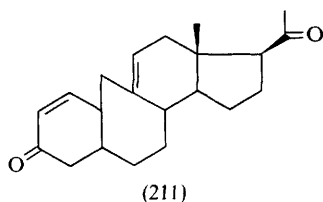
⁴⁴ G. Habermehl and G. Volkwein, *Toxicon*, 1971, 9, 319.

⁴⁵ A. Milliet, M. J. Magdeleine, and F. Khuong-Huu, *Compt. rend.*, 1972, 275, C, 335.

The 9 β ,19-cyclo-11-oxo-steroid system showed a marked difference in reactivity compared with the corresponding triterpenoid derivatives.⁴⁶ 11 β - and 11 α -hydroxy-9,19-cyclo-5 α ,9 β -pregnane-3,20-dione bis(ethylene ketal) (205) underwent ring opening in acidic medium to give (206) and (207) in contrast to *Buxus* alkaloid (208) which gave the 9(10 \rightarrow 19)-*abeo*-pregnane-9(11),10(19)-diene (209). Under more acidic conditions dienes (210) and (211) were also formed. No product of the conjugated diene-type was detected under a variety of conditions using (205) and (206). Hydride reduction of a series of steroidal 11-oxo-amines such as (212) also proceeded to a different extent than in the triterpenoid alkaloids; no reduction of the 11-ketone to a methylene group was observed. These results are rationalized on the basis of significant differences in molecular conformations between the steroid and triterpenoid series.



⁴⁶ S. M. Kupchan, J. W. A. Findlay, P. Hackett, and R. M. Kennedy, *J. Org. Chem.*, 1972, 37, 2523.



6 Biological Notes

The structures and biogenetic relations of 18 steroidal alkaloids and steroidal alkaloidal glycosides from species of Solanaceae, Apocynaceae, Buxaceae, and Liliaceae have been reviewed.⁴⁷

Positively inotropic cardenolide aminodeoxyglycosides were prepared.⁴⁸

3-Aminocorda-4,20(22)-dienolides⁴⁹ and 3-(alkylamino)card-20(22)-enolides,⁵⁰ useful as cardiostimulant drugs, have been synthesized, and 3 α - and 3 β -amino-3-deoxydigitoxigenin prepared.⁵¹

The ΔpK , the difference between the first and second basicity constants, of the four isomeric pregn-5-ene-3,20-diamines (IDA and its isomers) increases as their ability to stabilize DNA against heat decreases. Thus the heat-stabilizing function may be controlled by the distance between the amine groups. A relation between ΔpK and the distance between the amine functions was also established, confirming that the Bjerrum electrostatic relation applies even to functions that are relatively widely separated.⁵²

Pharmacology of batrachotoxin has been investigated.^{28f,53} The effects of batrachotoxin in a variety of systems can be explained as either a direct or an indirect consequence of the depolarization of electrically excitable membranes. Batrachotoxin irreversibly increases the permeability of membranes to Na⁺ and is a valuable tool for studying ion transport in electrogenic membranes.

Synthesis of some model C-20- and C-22-azacholanic acids as potential regulators of steroid biosynthesis and metabolism has been carried out, starting from 17 β -amino-3 β -hydroxypregn-5-ene and (20S)- and (20R)-amino-3 β -hydroxypregn-5-ene, respectively.⁵⁴

⁴⁷ K. Schreiber, *Biochem. Physiol. Alkaloide*, Fourth Internat. Symposium, 1969, ed. K. Mothes, Kurt. Akad. Verlag, Berlin, 1972, p. 435.

⁴⁸ W. Meyer zu Reckendorf and H. Machleidt, *Ger. Offen.*, 1 903 901 (*Chem. Abs.*, 1970, 73, 131 274x).

⁴⁹ U. Stache and W. Fritsch, *Ger. Offen.*, 2 053 117 (*Chem. Abs.*, 1972, 77, 102 042x).

⁵⁰ U. Stache and W. Fritsch, *Ger. Offen.*, 2 051 204 (*Chem. Abs.*, 1972, 77, 102 043y).

⁵¹ L. Sawlewicz, E. Weiss, H. H. A. Linde, and K. Meyer, *Helv. Chim. Acta*, 1972, 55, 2452.

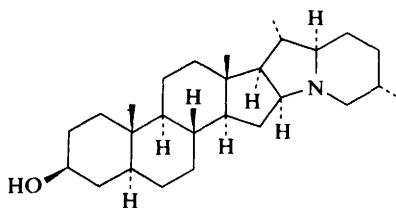
⁵² J. P. Mazaleyrat, A. Tchapla, and Q. Khuong-Huu, *Compt. rend.*, 1973, 276, C, 611.

⁵³ E. X. Albuquerque, J. W. Daly, and B. Witkop, *Science*, 1972, 172, 995.

⁵⁴ D. L. Venton, F. Kohen, and R. E. Counsell, *J. Medicin. Chem.*, 1973, 16, 571.

1 Solanum Alkaloids

The stereochemistry of the indolizidine skeleton of the solanidanes has been deduced from an *X*-ray analysis of demissidine (1) hydroiodide.¹ The analysis which led to this important result has been refined without affecting the previously reported results.²



(1)

Compounds of the 22,26-epiminocholestane type are key intermediates in the synthesis of alkaloids of the spirosolane and solanidane series, and this skeletal type is apparent in naturally occurring steroidal bases.^{3,4} As part of a general study⁵⁻⁷ of the synthesis, stereochemistry, and chemistry of these compounds, 22,26-epimino-5 α -cholestan-3 β ,16 α ,20-triols and their derivatives have been examined.⁸ Hydrogenation of (2)⁶ gave (3) as a major product together with a low yield of the C-25 isomer (5). The C-16 acetoxy-function in each case was labile to column chromatography on silica. Both (3) and (5) gave *OON*-triacetates.

22,26-Epiminocholestane derivatives without a C-20 hydroxy-group gave *N*-chloro-derivatives the o.r.d. curves of which show⁹ a positive Cotton effect

¹ E. Höhne, K. Schreiber, H. Ripperger, and H.-H. Worch, *Tetrahedron*, 1966, **22**, 673.

² E. Höhne, *J. prakt. Chem.*, 1972, **314**, 371.

³ K. Schreiber, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1968, vol. 10, p. 1.

⁴ R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1973, vol. 3, p. 279.

⁵ K. Schreiber and G. Adam, *Annalen*, 1963, **666**, 155.

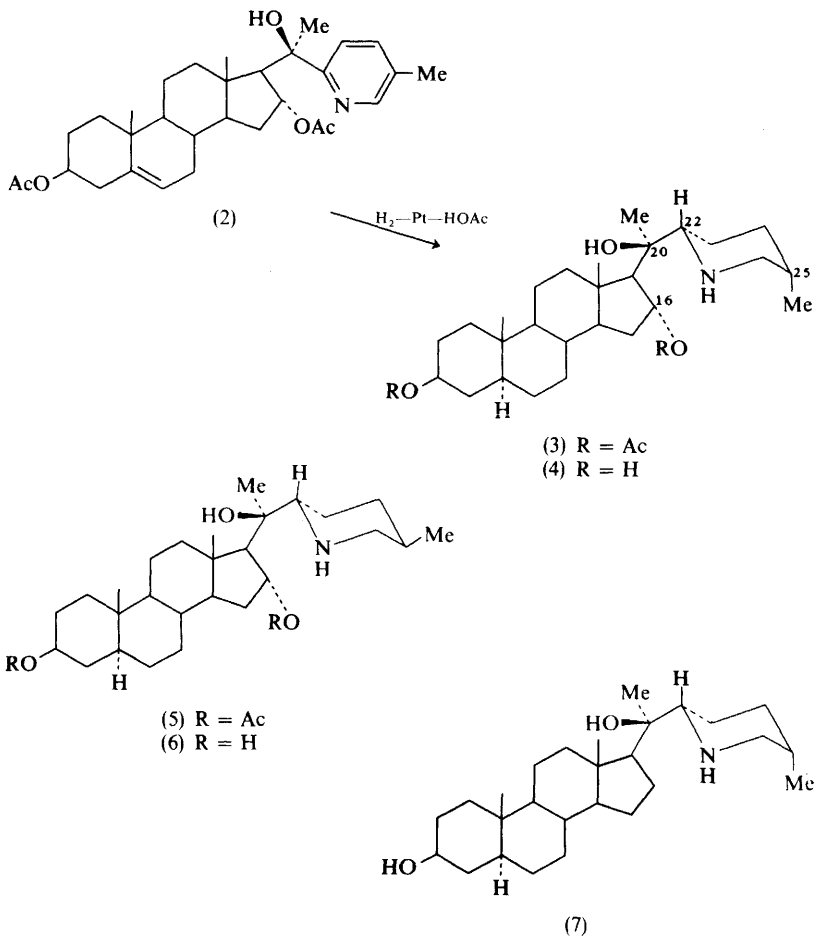
⁶ K. Schreiber and G. Adam, *Annalen*, 1963, **666**, 176.

⁷ K. Schreiber and G. Adam, *Tetrahedron*, 1964, **20**, 1707.

⁸ G. Adam, D. Voigt, and K. Schreiber, *Tetrahedron*, 1971, **27**, 2181.

⁹ H. Ripperger, K. Schreiber, and G. Snatzke, *Tetrahedron*, 1965, **21**, 727.

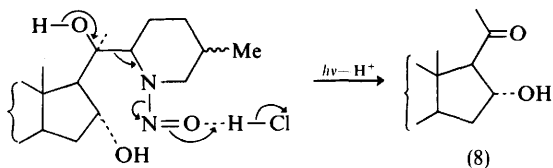
between 260 and 280 nm if the configuration at C-22 is *R* and a negative effect if it is *S*. The *N*-chloro-derivatives of (3) and (4) both show a positive Cotton effect in this region, but the triol (4) is proven to be of *S* configuration at C-22 by *X*-ray analysis of its crystalline hydroiodide.¹⁰ It was noted later that the *N*-chloro-derivative of (20*R*,22*S*,25*S*)-22,26-epimino-5 α -cholestan-3 β ,20-diol (7) also gave rise to a positive Cotton effect; the constitution and configuration of (7) were established by *X*-ray analysis of its hydroiodide.¹¹ Thus it seems that the effect is general for C-20 hydroxy-compounds. It may be noted that analogous molecular rotation differences were observed in all these cases.



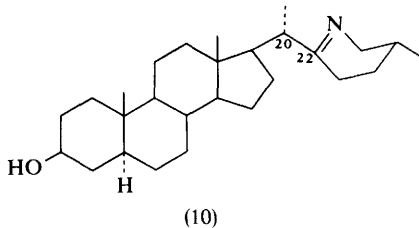
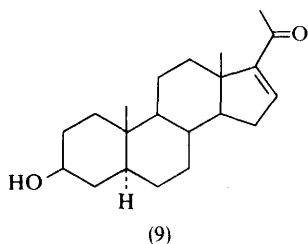
¹⁰ E. Höhne, I. Seidel, G. Adam, D. Voigt, and K. Schreiber, *J. prakt. Chem.*, 1971, **313**, 51.

¹¹ E. Höhne, I. Seidel, G. Adam, D. Voigt, and K. Schreiber, *Tetrahedron*, 1973, **29**, 747.

In contrast to the photolytic cyclization of *N*-nitroso-22,26-epimino-5 α -cholestan-3 β ,16 β -diols to spirostan alkaloids,¹² irradiation of the *N*-nitroso-derivative of (4) in ethanolic hydrochloric acid gave 3 β ,16 β -dihydroxy-5 α -pregnan-20-one (8) in high yield.⁸ The only other product obtained was (4). Similar results were obtained with the *N*-nitroso-derivative of (6). A reasonable mechanism for this aberrant process was proposed (Scheme 1). The *N*-chloro-derivative of (4) underwent analogous fragmentation with sodium methoxide and photolytically in trifluoroacetic acid. In the base-catalysed reaction (9) was also obtained.



Scheme 1



The negative-ion mass spectra¹³ of a series of 22,26-epimino-cholestanes with various substituents and degrees of unsaturation have been recorded.¹⁴ Besides a prominent $M - 1$ peak the characteristic mode of fragmentation is generally the same as with conventional mass spectrometry: cleavage between C-20 and C-22 (with charge retention on the steroidal fragment). However, $\Delta^{22(N)}$ -compounds, e.g. solacongostidine (10), show as the result of ion-molecule collision with nitrogen a most prominent $M + 14$ peak, and fragmentation across the C-20—C-22 bond was not apparent. In all cases examined, peaks corresponding to loss of water were observed and for *N*-acetates loss of CH_3CO .

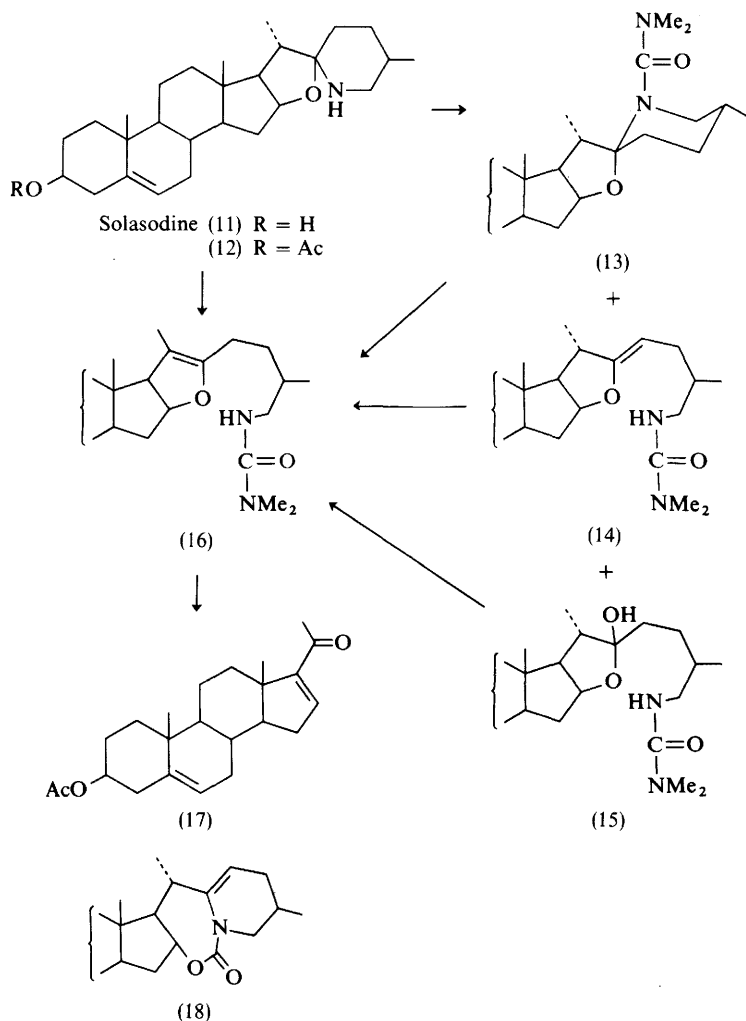
A simple conversion of solasodine (11) into (17) in high yield is relevant to the production of hormones. This has been achieved by reaction of the *ON*-diacetate of (11) with acid followed by oxidation and hydrolysis.¹⁵ An alternative method, which is comparably convenient and high yielding, involves the reaction of

¹² G. Adam and K. Schreiber, *Tetrahedron*, 1966, **22**, 3591; G. Adam, Habilitationsschrift, Univ. Halle, 1967.

¹³ M. V. Ardenne, K. Steinfelder, and R. Tümmeler, 'Elektronenanlagerungs-Massenspektrographie organischer Substanzen', Springer-Verlag, Berlin, 1971.

¹⁴ G. Adam, K. Schreiber, R. Tümmeler and K. Steinfelder, *J. prakt. Chem.*, 1971, **313**, 1051.

¹⁵ Y. Sato, N. Ikekawa, and E. Mosettig, *J. Org. Chem.*, 1960, **25**, 783.

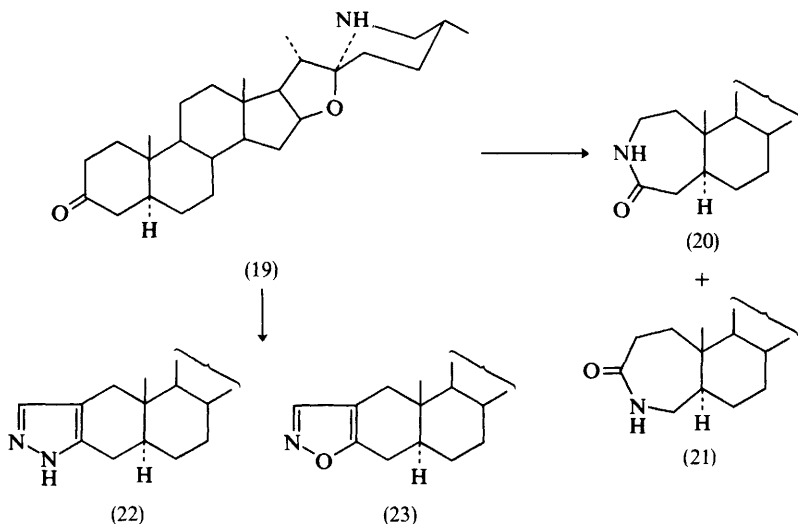


O-acetylsolasodine (12) with phosgene in basic medium.¹⁶ In triethylamine, to which dimethylamine was later added, three products were obtained, (13)—(15), of which (15) was formed in least amount. Each of these products was readily transformed into (16) by treatment with glacial acetic acid. Reaction of (12) with phosgene and dimethylamine in pyridine, on the other hand, gave (16) directly and (18). Oxidation of the furostadiene derivative (16) with chromic acid in aqueous acetic acid, followed by hydrolysis with aqueous acetic acid to remove the acyloxy side-chain, gave (17). Of the two routes to (17) with phosgene,

¹⁶ Y. Sato and M. Nagai, *J. Org. Chem.*, 1972, 37, 2629.

reaction in triethylamine followed by treatment of the mixed products with acetic acid to give (16) was recommended.

Methods for preparing the isomeric lactams (20) and (21) from 5 α -solasodan-3-one (19) have been compared.¹⁷ Optimum conditions for the Beckmann rearrangement of the oxime of (19) were obtained using toluene-*p*-sulphonic acid in pyridine and the two products were obtained in equal amounts. Reaction of (19) in a Schmidt reaction with trichloroacetic acid and sodium azide, on the other hand, gave lactams (20) and (21) in a 3:1 ratio. Lithium aluminium hydride reduction gave the corresponding diazasteroids, A-homo-2a-aza-5 α -solasodane and A-homo-3a-aza-5 α -solasodane.



Reaction of (19) with ethyl formate in the presence of sodium methoxide followed by treatment with hydrazine or hydroxylamine gave (22) and (23), respectively.¹⁸

Dehydration of solasodine (11) and 5 α -dihydrosolasodine with a range of dehydrating agents gave the same products, (24) and (25) respectively, in varying yields.¹⁹

Solasonine, solamargine, and β -solamargine have been isolated from *Solanum transcaucasicum* during the fruit bearing stage,²⁰ and the former two alkaloids also from *S. pinnatum*²¹ together with a glucose- and rhamnose-containing

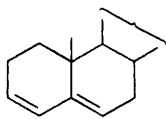
¹⁷ G. N. Romachenko, M. I. Goryaev, and M. P. Irismetov, *Izvest. Akad. Nauk Kazakh. S.S.R., Ser. khim.*, 1972, **22**, 67 (*Chem. Abs.*, 1972, **77**, 102 015).

¹⁸ M. I. Goryaev, M. P. Irismetov, and G. N. Romachenko, *Izvest. Akad. Nauk Kazakh. S.S.R., Ser. khim.*, 1973, **23**, 70 (*Chem. Abs.*, 1973, **78**, 136 522).

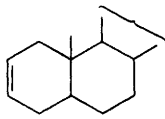
¹⁹ M. I. Goryaev, G. N. Romachenko, and M. P. Irismetov, *Izvest. Akad. Nauk Kazakh. S.S.R., Ser. khim.*, 1972, **22**, 83 (*Chem. Abs.*, 1973, **78**, 84 645).

²⁰ S. M. Aslanov, *Khim. prirod. Soedinenii*, 1972, **8**, 132 (*Chem. Abs.*, 1972, **77**, 72 556).

²¹ A. Urzúa and B. K. Cassels, *Phytochemistry*, 1972, **11**, 3548.



(24)



(25)

glycoside of solasodine which is probably the same as a partial hydrolysis product²² of solamargine. Solamargine and β -solamargine have been identified as new alkaloids in the fruits of *S. xanthocarpum*.²³ The first examination of *S. icanum* carried out has revealed that solasodine is a constituent of unripe fruits.²⁴ Solasodine and solanidine have been isolated from *Cestrum purpureum*, but *C. aurantiacum* and *C. diurnum* were devoid of alkaloid.²⁵

The root bark of *S. laciniatum* has been found to contain the solasodine (11), glycosides, solamargine, solasonine, solaradixine, solashabanine and solaradinine.²⁶ The constitution of solaradixine was found to be solasonine plus β -D-glucose²⁷ (solasonine is a solasodine glycoside of L-rhamnose, D-glucose, and D-galactose).²⁸

Quantitative determination of the sugar content of solashabanine and solaradinine showed that they were constituted as follows: solashabanine: 1 mole of D-galactose, 1 mole of L-rhamnose, and 3 moles of D-glucose; solaradinine: 1 mole of D-galactose, 1 mole of L-rhamnose, and 4 moles of D-glucose.²⁹ Enzymic cleavage of solashabanine with β -glucosidase gave solasonine, whereas solaradinine gave solaradixine with loss in each case of two D-glucose moieties. The results of periodate oxidation suggested that the additional glucose units were not attached to the D-glucose molecules already present in the glycosides or to rhamnose in position 3.

2 *Veratrum* Alkaloids

The polyester derivatives of the alkamines germinine (27) and protoverine (28), isolated from the *Veratrum* genus,³⁰ are clinically useful hypotensive agents.³¹ Detailed structural and stereochemical assignments have been made for the alkamines, based on extensive degradative studies,³⁰ but conclusive proof of

²² R. Kuhn and I. Löw, *Chem. Ber.*, 1955, **88**, 289.

²³ G. Kusano, J. Beisler, and Y. Sato, *Phytochemistry*, 1973, **12**, 397.

²⁴ D. V. Zaitschek and R. Segal, *Lloydia*, 1972, **35**, 192.

²⁵ M. S. Karawya, A.-F. M. Rizk, F. M. Hammouda, A. M. Diab, and Z. F. Ahmed, *Acta Chim. Acad. Sci. Hung.*, 1972, **72**, 317 (*Chem. Abs.*, 1972, **77**, 58 861).

²⁶ P. Bite, M. M. Shabana, L. Jókay, and L. Pongrácz-Sterk, *Acta Chim. Acad. Sci. Hung.*, 1970, **63**, 343.

²⁷ L. Ferenczy, M. M. Shabana, and P. Bite, *Acta Chim. Acad. Sci. Hung.*, 1970, **65**, 101.

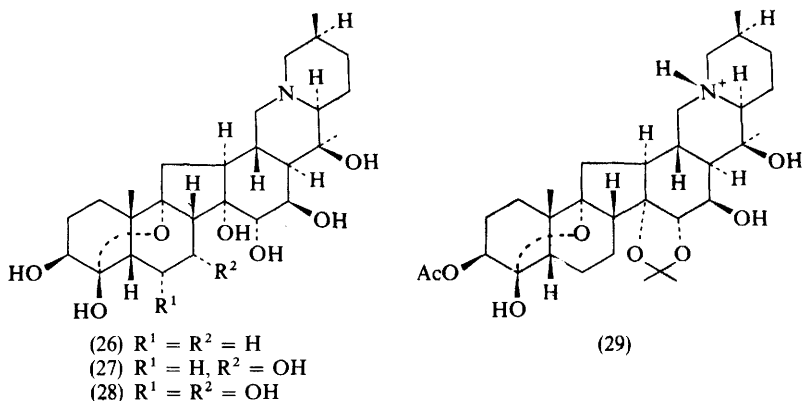
²⁸ K. Schreiber, in ref. 3, p. 18.

²⁹ P. Bite and M. M. Shabana, *Acta Chim. Acad. Sci. Hung.*, 1972, **73**, 361 (*Chem. Abs.*, 1972, **77**, 111 578); P. Bite and M. M. Shabana, *Magyar Kém. Folyóirat*, 1972, **78**, 221 (*Chem. Abs.*, 1972, **77**, 31 536).

³⁰ S. M. Kupchan and A. W. By, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1968, vol. 10, p. 193.

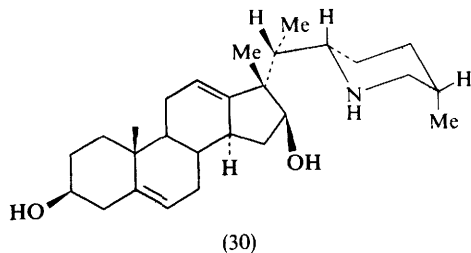
³¹ S. M. Kupchan and W. E. Flacke, in 'Antihypertensive Agents', ed. E. Schlittler, Academic Press, New York, 1967, Chapter 12.

the correctness of these assignments was lacking. Recent *X*-ray diffraction analysis of the structure of zygacine acetonide hydroiodide (29), however, confirms unambiguously the stereochemistry (26) for zygadenine and, as a consequence, the correctness of structures (27) and (28) for germine and protoverine.³²



The structure and stereochemistry of veralkamine was defined as (30) with the aid of chemical and spectroscopic data³³ and an *X*-ray analysis of its hydroiodide.³⁴ Unusual in the structure of veralkamine is the absence of the 18-methyl group and in fact veralkamine was the first plant steroid lacking this substituent to be reported.

Perhydrogenation of veralkamine gave a tetrahydro-derivative (31) which could be converted into the ketone (32).³³ The hydrogenation introduced a new asymmetric centre at C-13. Correlation of the o.r.d. measurements for the ketone (32) with the possibilities for the configuration at C-13 and the conformation of ring c, led to the conclusion that in (32) the hydrogen at C-13 was α and that ring c was a boat.³⁵ *X*-Ray analysis of the hydroiodide of tetrahydro-veralkamine allowed the structure and stereochemistry to be confirmed as (31)

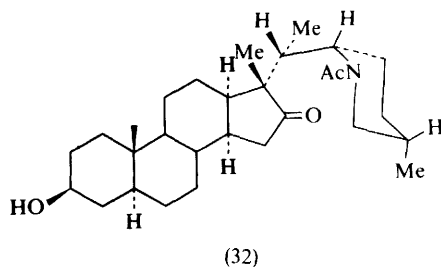
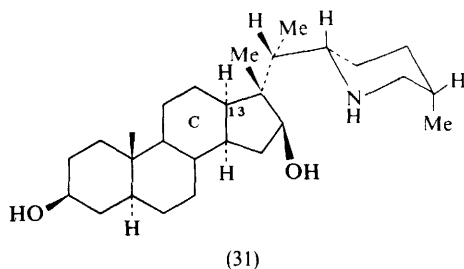


³² R. F. Bryan, R. J. Restivo, and S. M. Kupchan, *J.C.S. Perkin II*, 1973, 386.

³³ J. Tomko, A. Vassová, G. Adam, and K. Schreiber, *Tetrahedron*, 1968, **24**, 4865.

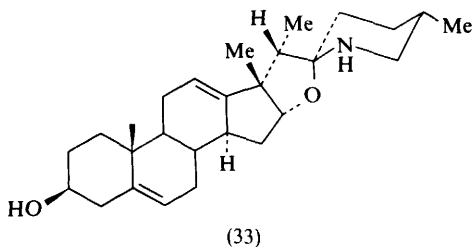
³⁴ E. Höhne, G. Adam, K. Schreiber, and J. Tomko, *Tetrahedron*, 1968, **24**, 4875.

³⁵ E. Höhne, I. Seidel, G. Adam, K. Schreiber, and J. Tomko, *Tetrahedron*, 1972, **28**, 4019.



and it was apparent from the results that, for tetrahydroveralkamine, ring c exists simultaneously in the chair and boat conformations in a ratio of 2:1 in the crystalline state.³⁵

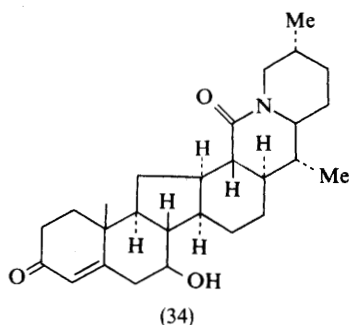
A structure (33) related to that of veralkamine (30), and with similar stereochemistry, has been assigned³⁶ to veramine³⁰ on the basis of spectroscopic data on the alkaloid and its acetylation and hydrogenation derivatives and by stereochemical correlation with tomatidine and solasodine and their derivatives.



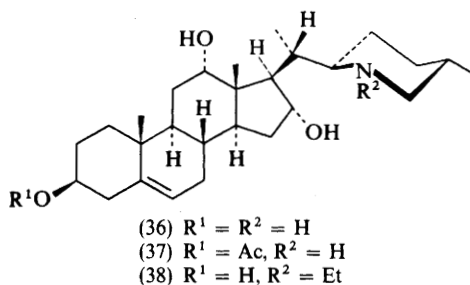
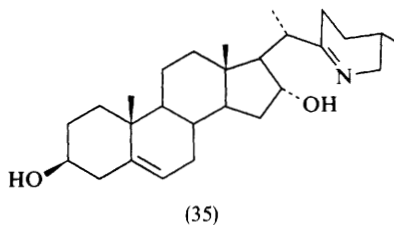
A new alkaloid, veralodine, extracted from the above-ground parts of *Veratrum album* subsp. *lobelianum* has been assigned the structure (34).³⁷

³⁶ G. Adam, K. Schreiber, J. Tomko, Z. Voticky, and A. Vassová, in *Biochem. Physiol. Alkaloids*, Fourth Internat. Symposium, ed. K. Mothes, 1969, p. 453 (*Chem. Abs.*, 1972, **77**, 114667). This book, which was published in 1972, seems to be unavailable in Britain, and may be out of print.

³⁷ K. Samikov, R. Shakirov, S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 770 (*Chem. Abs.*, 1973, **78**, 108 218).

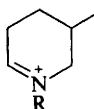


Two glycosidic alkaloids with a normal steroid skeleton have been isolated recently from *V. grandiflorum*. The structure of a major component obtained after hydrolysis was assigned as (35).³⁸ Two further alkaloids³⁹ with a similar skeleton have also been isolated from this plant, and called baikeine (36) and baikeidine (37) after the Japanese name for this plant: 'baikeiso'. A normal steroidal skeleton for baikeine was apparent from the methyl resonances in its n.m.r. spectrum. Baikeine gave both a mono-*N*-acetate and a tetra-acetate. Lithium aluminium hydride reduction of the mono-*N*-acetate yielded *N*-ethylbaikeine (38) from which a triacetate could be formed. It followed that baikeine contained a secondary amine function and three hydroxy-groups. The mass spectral fragmentation of these baikeine derivatives revealed that the



³⁸ K. Kaneko, M. Watanabe, Y. Kawakoshi, and H. Mitsunashi, *Tetrahedron Letters*, 1971, 4251; R. B. Herbert in ref. 4, p. 293.

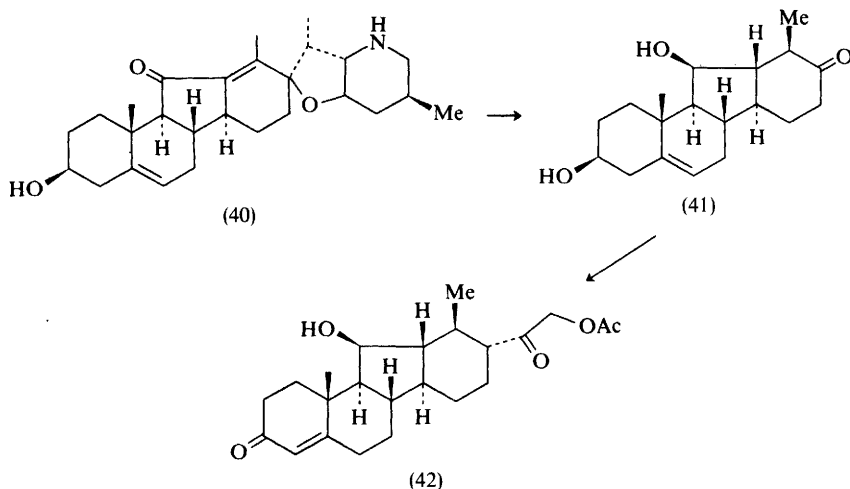
³⁹ I. Iwai and M. Yoshimura, *Tetrahedron Letters*, 1972, 2961.



(39) R = H, Ac, or Et

amine function of baikeine was contained in a methyl-piperidine ring; the fragments lost corresponded to (39). Changes in molecular rotation and in the chemical shift values for the 18- and 19-methyl groups associated with saturation of the double bond, deduced to be trisubstituted from the n.m.r. spectrum of baikeine, suggested that the double bond was Δ^5 . A triketone was obtained by Jones oxidation of *N*-ethylbaikeine (38), one carbonyl function of which was $\alpha\beta$ -unsaturated. From this and a positive Liebermann-Burchard reaction for (36), one hydroxy-group of baikeine was assigned to C-3. Further experiments allowed partial delineation of the position and stereochemistry of the other two hydroxy-groups. Baikeidine could not be obtained pure, but, from the correlations which could be made between its acetyl derivatives and those of baikeine, its structure followed as 3-acetylbaikeine. Because further chemical experiments were prevented by the lack of material, an *X*-ray crystallographic analysis of a baikeine derivative (*N*-ethylbaikeine hydrobromide) was undertaken which established the structure of baikeine as (36).

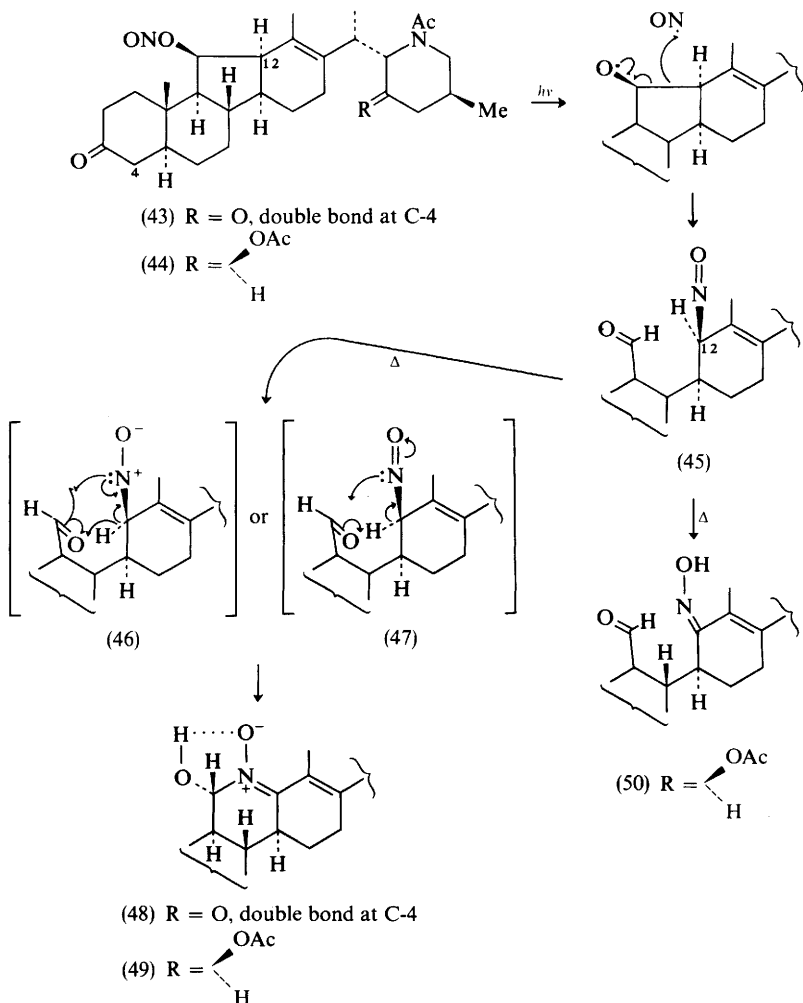
A continuing interest in modified steroids with enhanced or more specific pharmacological properties has led to the synthesis of C-nor-D-homo-17-epicorticosterone-21-acetate (42).⁴⁰ The starting point for the synthesis was the readily available *Veratrum* alkaloid jervine (40) which could be converted *via* (41)⁴¹ into (42), in a multi-step sequence.



⁴⁰ T. Masamune and T. Orito, *Bull. Chem. Soc. Japan*, 1972, **45**, 1888.

⁴¹ T. Masamune, A. Murai, and S. Numata, *Tetrahedron*, 1969, **25**, 3145.

Irradiation of (43) in toluene or carbon tetrachloride yields the nitron (48) in a novel reaction.⁴² Photolysis of (44) results in the formation of the analogous nitron (49),⁴³ under similar conditions. In THF or piperylene, however, (50) is produced in addition to a little (49). This compound is analogous to an intermediate proposed⁴² for the photolysis of (43) but it did not give (49) under either photolytic or thermolytic conditions. Evidence was then adduced by photolysing (44) under different conditions, which showed that the nitroso-aldehyde (45)



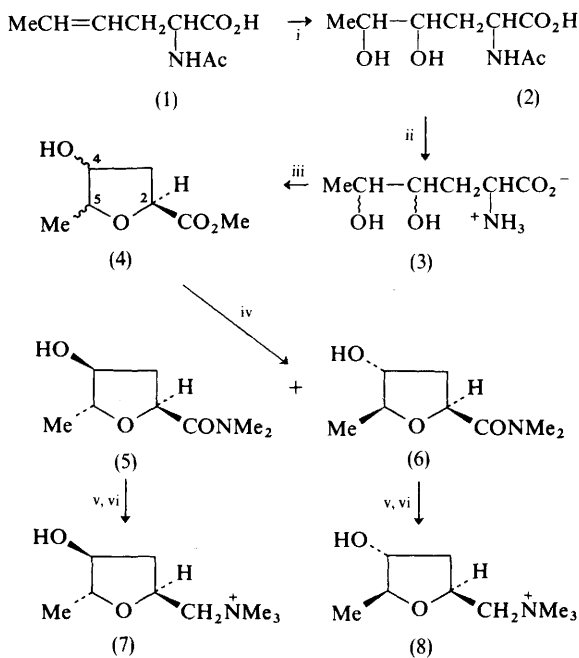
⁴² H. Suginome, N. Sato, and T. Masamune, *Tetrahedron*, 1971, 27, 4863; R. B. Herbert, in ref. 4, p. 298.

⁴³ H. Suginome, T. Mizuguchi, and T. Masamune, *J.C.S. Chem. Comm.*, 1972, 376.

was an intermediate and that its ring closure was a ground-state reaction. Formation of a single nitron (49) with an α -hydroxy-group followed from the assumption that the configuration of C-12 in (44) is retained in (45) and that hydrogen transfer is as shown in (46) or (47).

1 Muscarine Alkaloids

An efficient and convenient synthesis of L-(+)-allomuscarine (7) and L-(+)-muscarine (8) has been devised (Scheme 1).¹ The advantages of the new approach are as follows: enzymatic resolution is achieved at the *N*-deacylation step [(2) → (3)] and nitrous acid deamination proceeds with retention of configuration at C(2) [(3) → (4)]. To complete the synthesis, previously developed methods were used. Treatment of ester (4) with dimethylamine gave a mixture of all the four



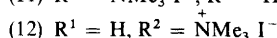
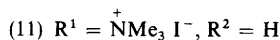
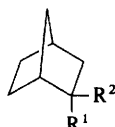
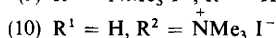
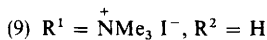
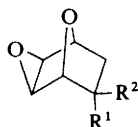
Reagents: i, HCO_3H ; ii, Hog kidney acylase, pH 8; iii, $\text{HNO}_2\text{-MeOH}$; iv, Me_2NH , 100°C ; v, $\text{LiAlH}_4\text{-Et}_2\text{O}$; vi, $\text{MeI-Et}_2\text{O}$.

Scheme 1

¹ J. Whiting, Y. K. Au-Young, and B. Belleau, *Canad. J. Chem.*, 1972, **50**, 3322.

possible stereoisomers resulting from chirality at C(4) and C(5). However, since mainly *trans*-(1) was used, predominantly *erythro*-diols (2) should have been produced, and these in turn would be expected to give amides (5) and (6) as the major products. In fact, amides (5) and (6) accounted for 65% (1 : 1) of the total product of the amidolysis reaction and these were then converted into L-(+)-allomuscarine (7) and L-(+)-muscarine (8), respectively. The structure of (7) was established by 220 MHz n.m.r. spectroscopy with the exception of the C(4)-C(5)-relative configuration. The relative configurations shown for (7) and (8) were established by studies of their biological activity. Whereas (7) showed very weak activity (similar to that of D,L-allomuscarine), the isomer (8) was twice as potent as acetylcholine. Since only the natural alkaloid, L-(+)-muscarine, shows such high activity, the configuration (8) is assigned to one of the final products. The other product (7) is assigned the *allo*-configuration on the basis of the weak activity and the mechanistic rationale mentioned previously for the steps (1) \rightarrow (2) \rightarrow (3).

The *endo*- and *exo*-7-oxabicyclo[2,2,1]heptane derivatives (9) and (10) have been synthesized for the purpose of studying muscarinic activity.² A comparison of the activities of (9) and (10) with those of the corresponding *endo*- and *exo*-bicyclo[2,2,1]heptane derivatives (11) and (12) was made, and it was shown that of all these compounds only the *exo*-isomer (12) had marginal muscarine-like activity.



2 Imidazole Alkaloids

Recommendations of official methods for the analysis of pilocarpine (13) are available.³

The isolation of pilocarpine by silica-gel chromatographic⁴ and ion-exchange counter-current⁵ methods has been described.

Hydrolysis of bleomycin A₂, a complex antibiotic possessing a variety of heterocyclic appendages,⁶ gives L-*erythro*- β -hydroxyhistidine (14).⁷ The structure

² W. L. Nelson, D. R. Allen, and F. F. Vincenzi, *J. Pharm. Sci.*, 1972, **61**, 1640.

³ E. Smith, *J. Assoc. Offic. Analyt. Chemists*, 1972, **55**, 248.

⁴ V. Massa, P. Susplugas, and C. Taillade, *J. Pharm. Belg.*, 1973, **28**, 69 (*Chem. Abs.*, 1972, **77**, 156 626e).

⁵ E. S. Vysotskaya, Yu. V. Shostenko, and S. Kh. Mushinskaya, *Tr. Voronezh. Gos. Univ.*, 1969, **72**, 220 (*Chem. Abs.*, 1972, **77**, 156 309h).

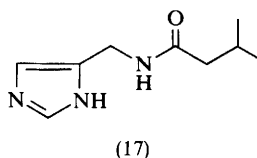
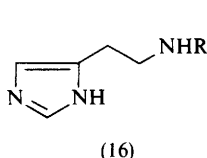
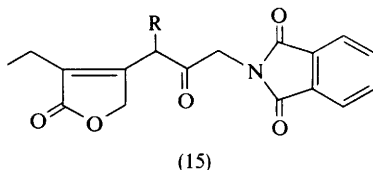
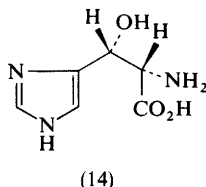
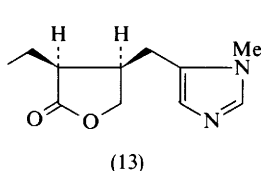
⁶ T. Takita, T. Yoshioka, Y. Muraoka, K. Maeda, and H. Umezawa, *J. Antibiot.*, 1971, **24**, 795.

⁷ G. Koyama, H. Nakamura, Y. Muraoka, T. Takita, K. Maeda, H. Umezawa, and Y. Iitaka, *J. Antibiot.*, 1973, **26**, 109.

and stereochemistry of (14) have been established by an X-ray crystallographic analysis.

Treatment of 2-ethyl-3-alkoxycarbonylmethylbut-2-enolide with phthaloylglycyl chloride in the presence of sodium ethoxide gives compound (15; R = CO₂Me), which upon thermolysis provides (15; R = H), a potential precursor for pilocarpine (13).⁸

Aberrant alkaloid biosynthesis in *Dolichothele sphaerica*, which normally produces dolichotheline (16; R = COCH₂CHMe₂) by a combination of histamine and isovaleroyl-CoA, has been demonstrated.⁹ Using the appropriate radio-labelled carboxylic acid precursors, it has been shown that the unnatural alkaloids *N*-isocaproylhistamine (16; R = COCH₂CH₂CHMe₂) and 4-[(isovaleroylamino)methyl]imidazole (17) but not the *N*-benzoyl-, *N*-isobutyryl-, and *N*-isovaleroyl-*N*-isopropyl-histamines are produced in *D. sphaerica*. Such studies may be important in yielding new, potentially biologically active compounds and in providing more insight into enzymatic specificity of alkaloid biosynthesis.



Detailed spectroscopic studies of *d*-pilocarpine (13) and its quaternary ammonium salts have been described.¹⁰ Studies of ring-chain tautomerism in imidazole and annelated imidazole systems may be of general interest.¹¹

⁸ A. V. Chumachenko, E. N. Zvonkova, and R. P. Evstigneeva, *Zhur. org. Khim.*, 1972, **8**, 1100 (*Chem. Abs.*, 1972, **77**, 61 476w).

⁹ H. Rosenberg and A. G. Paul, *J. Pharm. Sci.*, 1973, **62**, 403.

¹⁰ A. Ben-Bassat and D. Lavie, *Israel J. Chem.*, 1972, **10**, 385.

¹¹ L. M. Alekseeva, E. M. Peresleni, Yu. N. Sheinker, P. M. Kochergin, A. N. Krasovskii, and B. V. Kurmaz, *Khim. geterotsikl. Soedinenii*, 1972, 1125 (*Chem. Abs.*, 1972, **77**, 139 322q).

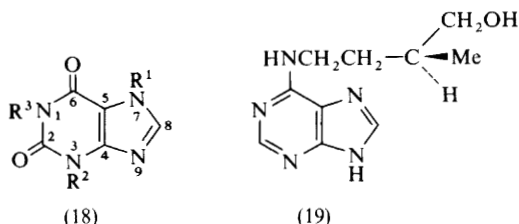
Kinetics of complexation of pilocarpine with $[\text{Cr}(\text{NCS})_4(\text{py})_2]^-$ have been determined¹² and the thermal stability of the reineckate salt of pilocarpine has been investigated.¹³

Ocular penetration of pilocarpine nitrate in the rhesus monkey has been observed.¹⁴

3 Purine Alkaloids

Caffeine (18; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$) has been identified in the leaves of *Coffea arabica*, *C. canephora*, *C. excelsa*, *C. liberica*, and *C. salvatrix*¹⁵ and in Paraguay Tea (*Ilex paraguariensis*).¹⁶

The (S) absolute configuration of (–)-dihydrozeatin (19), a unique saturated isoprenylated adenine from *Lupinus luteus*, has been established by o.r.d. studies of synthetic material prepared from 6-chloropurine and (S)-2-methyl-4-aminobutan-1-ol oxalate.¹⁷



Association constants between caffeine and a number of chemical species have been measured.¹⁸ π -Complexation has been inferred from these as well as from n.m.r. spectral studies. Investigations concerning the tautomerism, protonation, and methylation of mono-, bis-, and tris-methylthiopurine derivatives previously described (see Vol. 3 of these Reports) have been extended.¹⁹ Ring-chain tautomerism phenomena in C(8)-S-acylated purine and theophylline systems have been studied as a function of solvent polarity.¹¹ The complex (caffeine) $[\text{Cr}(\text{CNS})_4(\text{py})]$ has been prepared.¹² The kinetics of the reaction between purine and hydroxide ion have been studied by an ultrasonic attenuation technique.²⁰ The electrochemical reduction of purine has been studied in detail.²¹

¹² J. Zsako, D. Oprescu, Cs. Varhelyi, and I. Ganescu, *Zhur. neorg. Khim.*, 1972, **17**, 3242 (*Chem. Abs.*, 1973, **78**, 48 800y).

¹³ J. Masse, J. Rambaud, S. Alberola, and F. Sabon, *Trav. Soc. Pharm. Montpellier*, 1972, **32**, 215 (*Chem. Abs.*, 1972, **77**, 33 849x).

¹⁴ C. F. Asseff, R. L. Weisman, S. M. Podos, and B. Becker, *Amer. J. Ophthalmol.*, 1973, **75**, 212 (*Chem. Abs.*, 1972, **77**, 119 078g).

¹⁵ R. R. Paris, *Compt. rend.*, 1972, **275**, D, 1617.

¹⁶ C. L. Franck de Soldi, *Rev. Fac. Agron., Univ. Nac. La Plata*, 1972, **48**, 1 (*Chem. Abs.*, 1973, **78**, 109 496c).

¹⁷ T. Fujii and N. Ogawa, *Tetrahedron Letters*, 1972, 3075.

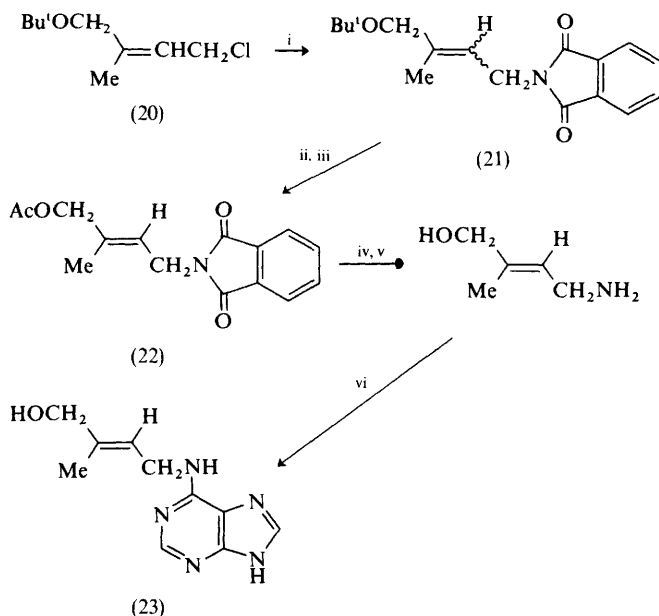
¹⁸ I. Horman and R. Viani, *J. Food Sci.*, 1972, **37**, 925.

¹⁹ U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Neiman, *J. C. S. Perkin I*, 1973, 793.

²⁰ M. Brennan and K. Kustin, *J. Phys. Chem.*, 1972, **76**, 2838.

²¹ P. J. Elving, S. J. Pace, and J. E. O'Reilly, *J. Amer. Chem. Soc.*, 1973, **95**, 647.

An efficient synthesis of *trans*-zeatin (23), a very active cell-division stimulant²² (see Vol. 3 of these Reports), has been announced (Scheme 2).²³ In this scheme, the initial step [(20) → (21), Gabriel synthesis] leads to a mixture of *cis*- and *trans*-isomers of (21) from which the latter can be separated in 51% yield. However, the remaining steps, including the interesting ether → ester exchange (21) → (22), proceed efficiently to provide an overall 27% yield of *trans*-zeatin (23).



Reagents: i, potassium phthalimide–DMF; ii, separate; iii, AcOTs–MeCN; iv, NaOMe–MeOH; v, N_2H_4 –EtOH, room temp.; vi, 6-Cl-purine– Et_3N – Bu^nOH , reflux.

Scheme 2

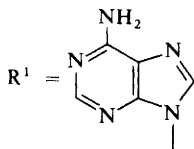
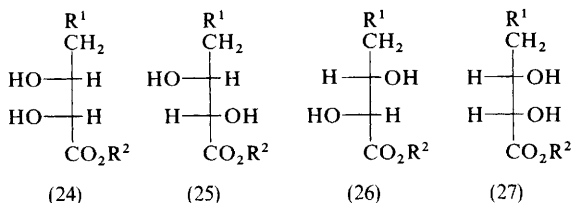
The synthesis of a number of geometric and positional zeatin isomers and their corresponding 9- β -D-ribofuranosyl derivatives has been reported.²⁴ The availability of these compounds allowed the establishment of structure–biological activity correlations. In this connection, it is of interest to note that raphanatin, which structurally is a zeatin glucoside that is different from synthetic 9- β -D-glucopyranosylzeatin, has been shown to be a metabolite of zeatin in *Raphanus sativus* (radish).²⁵

²² D. S. Letham, *Ann. Rev. Plant Physiol.*, 1967, **18**, 349.

²³ J. Corse and J. Kuhnle, *Synthesis*, 1972, 618.

²⁴ R. Y. Schmitz, F. Skoog, A. J. Playtis, and N. J. Leonard, *Plant Physiol.*, 1972, **50**, 702.

²⁵ C. W. Parker, D. S. Letham, D. E. Cowley, and J. K. MacLeod, *Biochem. Biophys. Res. Comm.*, 1972, **49**, 460.



The recognition of significant hypocholesterolemic activity of eritadenine (24), isolated from *Lentinus edodes*, has prompted further synthetic work on this alkaloid and its analogues.^{26,27} Treatment of the acetonide of eritadenine methyl ester (24; $\text{R}^2 = \text{Me}$) with barium hydroxide resulted in an *erythro* \rightarrow *threo* epimerization to give the corresponding acetonide of D-*threo*-eritadenine (25; $\text{R}^2 = \text{H}$).²⁶ The acetonide of (25; $\text{R}^2 = \text{Me}$) could also be prepared by treatment of the brosylate of 2,3-*O*-isopropylidene-D-threonate with the sodium salt of adenine. An attempt to use a similar approach for the preparation of L-*threo*-eritadenine (26; $\text{R}^2 = \text{H}$) failed. Thus an alternative, albeit lengthier, route was devised (Scheme 3). Finally, the synthesis of L-eritadenine (27; $\text{R}^2 = \text{H}$) was simply achieved (Scheme 4) by a route starting with L-erythrrolactone acetonide (28), which was readily available in two steps from L-rhamnose. A by-product of the condensation reaction between (28) and adenine was the 3-substituted isomer (29). Scheme 4 has been analogously applied to the synthesis of the eritadenine (24; $\text{R}^2 = \text{H}$) using the optical antipode of (28) as starting material.²⁷ It is of some interest to note that (6-amino-9H-purin-9-yl)-3-hydroxybutyric acid has been identified as an intermediate in the biosynthesis of eritadenine in *L. edodes*.²⁸ Finally, a number of analogues of eritadenine have been prepared by the route outlined in Scheme 3 for evaluation of their structure-activity relationships.²⁹

No diminution of synthetic activity in this area appears to be imminent. A facile synthesis of some relatively rare 7-aryltheophylline derivatives (31) from uracil precursors (30) by treatment with nitrosobenzene in refluxing acetic anhydride has been reported.³⁰ 8-Cyanomethyltheophylline (33; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_2\text{CN}$) was prepared starting with the 2-cyanoethylaminouracil derivative (32; $\text{R} = \text{CH}_2\text{CH}_2\text{CN}$).³¹ Consecutive nitrosation and dehydrative cyclization

²⁶ M. Hashimoto, Y. Saito, H. Seki, and T. Kamiya, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1374.

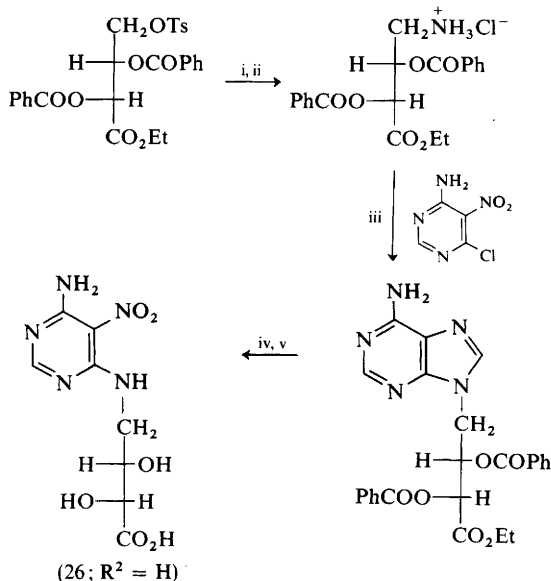
²⁷ T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *J. Heterocyclic Chem.*, 1972, **9**, 359.

²⁸ H. Itoh, T. Morimoto, K. Kawashima, and I. Chibata, *Experientia*, 1973, **29**, 271.

²⁹ M. Hashimoto, Y. Saito, H. Seki, and T. Kamiya, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1186.

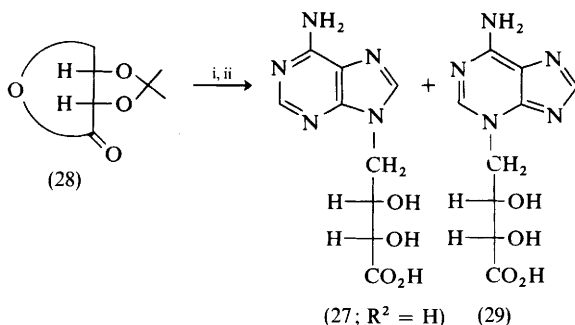
³⁰ E. C. Taylor and F. Yoneda, *J. Org. Chem.*, 1972, **37**, 4464.

³¹ A. Rybar and L. Stibranyi, *Coll. Czech. Chem. Comm.*, 1972, **37**, 2630.



Reagents: i, NaN₃-DMSO; ii, H₂, Pd/C, HCl-EtOH; iii, Et₃N-EtOH, room temp.; iv, H₂, Pd/C, HCO₂H; v, 1N-NaOH.

Scheme 3



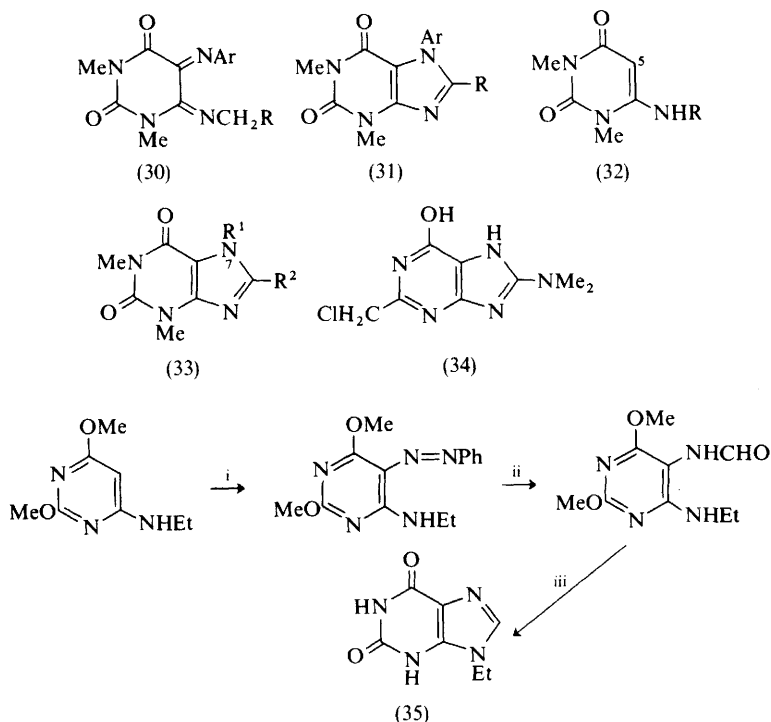
Reagents: i, adenine-Na₂CO₃-DMF, reflux; ii, 10% HOAc.

Scheme 4

of the latter gives (33; R¹ = H, R² = CH₂CN), which can be further converted into a variety of alkylated derivatives (33; R¹ = alkyl, R² = CH₂CN). A new 8-aminopurine synthesis proceeds by nitrosation of the uracil (32; R = H) to give the corresponding 5-nitroso-derivative, which when subjected to the Vilsmeier reaction (POCl₃, DMF) directly yields compound (33; R¹ = H, R² = NMe₂) in good yield.³² On the other hand, treatment of 6-amino-4-hydroxy-2-methyl-5-nitrosopyrimidine under the same conditions gave the product of cyclization and

³² F. Yoneda, T. Matsumura, and K. Senga, *J. C. S. Chem. Comm.*, 1972, 606.

side-chain halogenation (34). A new unambiguous route to 9-ethylxanthine (35) has been developed (Scheme 5).³³ A new nitration–cyclization sequence on the uracil (32; $R = \text{CH}_2\text{Ph}$) provides the 7-oxide of 8-phenyltheophylline (33; $R^1 = \text{H}$, $R^2 = \text{Ph}$) (65%), which may be reduced to (33; $R^1 = \text{H}$, $R^2 = \text{Ph}$) by treatment with DMF.³⁴



Reagents: i, $\text{PhN}_2^+ \text{Cl}^-$, HOAc, pH 5–5.5; ii, $\text{Zn-HCO}_2\text{H-H}_2\text{O}$, 55 °C; iii, $\text{HCO}_2\text{H-HCONH}_2$, reflux.

Scheme 5

New 7-substituted theophylline derivatives which have been prepared recently include [33; $R^1 = (\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{COPh}$, $R^2 = \text{H}$],³⁵ [33; $R^1 = \text{CH}_2\text{CH}(\text{OH})\text{-Et}$, $R^2 = \text{H}$],³⁶ [33; $R^1 = \beta\text{-L-fucopyranosyl}$, $R^2 = \text{H}$],³⁷ [33; $R^1 = (\text{CH}_2)_2\text{NCS}$, $R^2 = \text{alkyl}$],³⁸ and [33; $R^1 = (\text{CH}_2)_2\text{NHCOC}(\text{Me})=\text{CH}_2$, $R^2 = \text{H}$].³⁹ New

³³ M. Israel, M. M. Berman, and N. Muhammad, *Org. Prep. Proced. Int.*, 1972, **4**, 83.

³⁴ F. Yoneda and Y. Sakuma, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 448.

³⁵ R. Szebeni, K. Harsanyi, and D. Korbonits, *Magyar Kém. Folyóirat*, 1972, **78**, 605 (*Chem. Abs.*, 1973, **78**, 72 068m).

³⁶ M. Eckstein and J. Zajackowska, *Farmaco, Ed. Sci.*, 1973, **28**, 250 (*Chem. Abs.*, 1973, **78**, 147 919a).

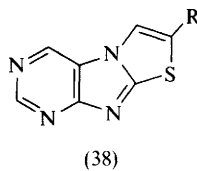
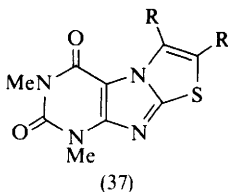
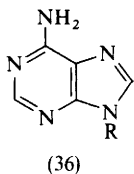
³⁷ K. Antonakis, *Carbohydrate Res.*, 1972, **24**, 229.

³⁸ A. Rybar, L. Stibranyi, and M. Uher, *Coll. Czech. Chem. Comm.*, 1972, **37**, 3936.

³⁹ K. Kondo, Y. Hisaoka, and K. Takemoto, *Chem. Letters*, 1973, 125.

9-substituted purine derivatives include [36; R = (CH₂)₂NHCOC(Me)=CH₂],³⁹ [36; R = CH₂CH(NH₂)CO₂H],⁴⁰ and [36; R = Me, Et, CH₂Ph, or (CH₂)₂Ph].⁴¹ The last report⁴¹ describes a modification of an alkylation procedure which gives predominantly 9-substituted products. Synthesis of the 8-substituted theophylline derivatives (33; R¹ = Me, R² = CH₂CO₂H)⁴² and [33; R¹ = H, R² = SCH(R)-COR]^{43,44} along conventional lines has been reported. Compounds of the type [33; R¹ = H, R² = SCH(R)COR] have been cyclized to produce saturated and unsaturated derivatives of the thiazolo[2,3-*f*]theophylline system (37).⁴³⁻⁴⁵ The corresponding thiazolo[2,3-*f*]purines (38) have been analogously obtained.⁴³ Interestingly, the presence of a 6-amino-substituent in the otherwise similar purine precursor gave the isomeric thiazolo[3,2-*e*]adenines (39).⁴⁶

A large number of 2,8-disubstituted and 2-substituted amino- and amino-acid-derivatives of 3,7-dimethylhypoxanthine (40) have been synthesized.⁴⁷ In the purine series, 2,6-diamino-,⁴⁸ 8- and 2-[bis(aziridino)phosphinamido]-,⁴⁹ and diaziridinylphosphinyl⁵⁰ derivatives have become available. In addition, a variety of alkylthio-, methoxy-, and dimethylamino-substituted purines have been prepared in order to test structural requirements for their use as amplifying agents for the antibiotic phleomycin in its action against *Escherichia coli*.⁵¹ *N*-9-Glycosyl derivatives of 6-chloropurine have been synthesized.⁵²



⁴⁰ M. Lidaks, J. Sluke, and S. Poritere, *Khim. geterotsikl. Soedinenii*, 1972, 1561 (*Chem. Abs.*, 1973, **78**, 43 427x).

⁴¹ T. Fujii, S. Sakurai, and T. Uematsu, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1334.

⁴² L. A. Gutorov and E. S. Golovchinskaya, *Khim.-Farm. Zhur.*, 1972, **6**, 20 (*Chem. Abs.*, 1972, **77**, 126 574y).

⁴³ M. I. Yurchenko, B. V. Kurmaz, and P. M. Kochergin, *Khim. geterotsikl. Soedinenii*, 1972, 996 (*Chem. Abs.*, 1973, **78**, 43 424u).

⁴⁴ H. Uno, A. Irie, and K. Hino, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2603.

⁴⁵ H. Uno, A. Irie, and K. Hino, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 256.

⁴⁶ H. Uno, A. Irie, and K. Hino, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 34.

⁴⁷ L. A. Gutorov and E. S. Golovchinskaya, *Khim.-Farm. Zhur.*, 1972, **6**, 13 (*Chem. Abs.*, 1972, **77**, 126 573x); I. M. Ovcharova and E. S. Golovchinskaya, *ibid.*, 1973, **7**, 3 (*Chem. Abs.*, 1973, **78**, 97 600s).

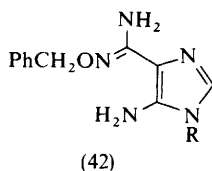
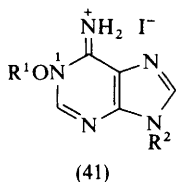
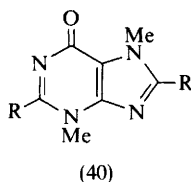
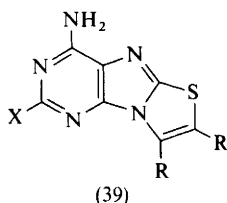
⁴⁸ V. S. Kuznetsov and A. L. Remizov, *Khim. geterotsikl. Soedinenii*, 1972, 1430 (*Chem. Abs.*, 1973, **78**, 43 423t); G. S. Tret'yakova, N. N. Nedel'kina, and V. M. Cherkasov, *Ukrain. khim. Zhur.*, 1972, **38**, 602 (*Chem. Abs.*, 1973, **78**, 16 123p).

⁴⁹ V. S. Korsunskii and E. S. Golovchinskaya, *Khim.-Farm. Zhur.*, 1972, **6**, 28 (*Chem. Abs.*, 1972, **77**, 88 447z).

⁵⁰ I. M. Ovcharova and E. S. Golovchinskaya, *Khim.-Farm. Zhur.*, 1973, **7**, 17 (*Chem. Abs.*, 1973, **78**, 159 560q).

⁵¹ D. J. Brown, R. L. Jones, A. M. Angyal, and G. W. Grigg, *J. C. S. Perkin I*, 1972, 1819.

⁵² M. Fuertes, G. Garcia-Munoz, F. G. De las Heras, R. Madronero, M. Stud, and M. Rico, *Tetrahedron*, 1972, **28**, 4099.



The chemistry of purine derivatives continues to attract substantial effort. Dealkylation of 1-alkoxy- and 1-benzyloxy-adenine derivatives (41; $R^1, R^2 = \text{Me}$ or CH_2Ph) to give the corresponding *N*-oxides by a variety of nucleophilic agents has been reported.⁵³ Furthermore, the 1-benzyloxy-compound (41; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$ or CH_2Ph) upon successive treatment with Raney nickel and phenylhydrazine in acid solution gave the imidazole (42; $R = \text{H}$ or CH_2Ph).⁵⁴ Treatment of 5-benzylamino-1,3-dimethyluracil (43) with 4-amino-6-chloro-2-methylpyrimidine (44) in excess *N*-nitrosodimethylamine gives a mixture of the dimethylaminopyrimidine (46) and 8-phenyltheophylline (33; $R^1 = \text{H}$, $R^2 = \text{Ph}$) in 76% and 84% yields, respectively (Scheme 6).⁵⁵ Presumably this unusual reaction is initiated by nitrosation of the uracil (43) to give (45), which then ring-closes to the theophylline derivative (33; $R^1 = \text{H}$, $R^2 = \text{Ph}$). The dimethylamine thus generated serves to displace halogen in (44) to give (46). 3-Acetoxy-8-methylxanthine (47; $R^1 = \text{Ac}$, $R^2 = \text{Me}$) undergoes facile rearrangement in aqueous solution at room temperature to 8-(hydroxymethyl)xanthine (48; $R = \text{OH}$). By-products are 3-hydroxy-8-methyl-xanthine (47; $R^1 = \text{H}$, $R^2 = \text{Me}$) and 8-methylxanthine (48; $R = \text{H}$).⁵⁶ A radical mechanism has been suggested for the formation of (48; $R = \text{H}$). In contrast to 3-acetoxyxanthine (47; $R^1 = \text{Ac}$, $R^2 = \text{H}$), which undergoes reaction with a variety of nucleophiles to yield 8-substituted xanthines, the 3-acetoxy-8-methyl derivative (47; $R^1 = \text{Ac}$, $R^2 = \text{Me}$) gives only (48; $R = \text{OH}$) under the same conditions. The theobromine-8-acetic acid (49; $R = \text{CO}_2\text{H}$) was converted into the bromo-derivative (49; $R = \text{Br}$) by the Hunsdiecker reaction; (49; $R = \text{H}$) could be directly chlorinated with SO_2Cl_2 to give (49; $R = \text{Cl}$).⁵⁷ Both derivatives were converted into the cor-

⁵³ T. Fujii, T. Itaya, and S. Moro, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 958.

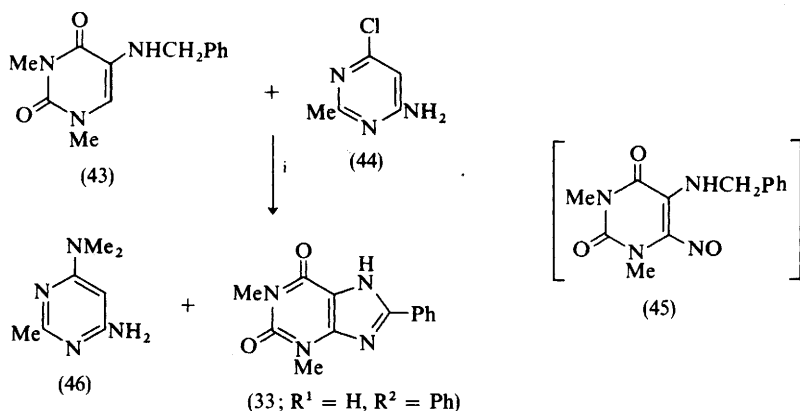
⁵⁴ T. Fujii, T. Itaya, and S. Moro, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1818.

⁵⁵ F. Yoneda, K. Senga, and S. Nishigaki, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2063.

⁵⁶ D. R. Sutherland and G. B. Brown, *J. Org. Chem.*, 1973, **38**, 1291.

⁵⁷ H. M. Nour El-Din, M. Y. Ebeid, and S. T. Hassib, *Bull. Fac. Pharm., Cairo Univ.*, 1971, **90**, 53 (*Chem. Abs.*, 1973, **78**, 159 562s).

responding amino-compounds (49; $R = NR_2^1$) with secondary amines. 8-Bromo-derivatives of caffeine, theobromine, and theophylline have been prepared in good yield by direct bromination of the appropriate methylxanthines.⁵⁸



Reagents: i, Me_2NNO , 175 °C.

Scheme 6

The pyrazolo[4,3-*b*]pyrimidines (50) have been synthesized and shown to exhibit useful cytokinin antagonist activity.⁵⁹ A number of 1-deazapurines (51),^{60,61} 7-deazapurines (52),⁶² and 7-deazatheophyllines (53)⁶³ have been prepared, some by novel synthetic reactions.

Standardized solvent systems and colour reagents for the paper-chromatographic separation of purine derivatives are available.⁶⁴ A combined t.l.c.–fluorescence spectroscopic method for the determination of caffeine, theobromine, and theophylline has been developed.⁶⁵ These three alkaloids may also be cleanly separated by application of high-speed liquid chromatography.⁶⁶ Iodine⁶⁷ and iodine tribromide⁶⁸ complexes of purine bases have been studied.

⁵⁸ M. Eckstein, M. Gorczyca, and A. Zejc, *Acta Pharm. Jugoslav.*, 1972, **22**, 133 (*Chem. Abs.*, 1973, **78**, 72 070f).

⁵⁹ F. Skoog, R. Y. Schmitz, R. M. Bock, and S. M. Hecht, *Phytochemistry*, 1973, **12**, 25.

⁶⁰ C. Temple, jun., B. H. Smith, R. D. Elliott, and J. A. Montgomery, *J. Medicin. Chem.*, 1973, **16**, 292.

⁶¹ J. E. Schelling and C. A. Saleminck, *Rec. Trav. chim.*, 1972, **91**, 650.

⁶² D. H. Kim and A. A. Santilli, *Tetrahedron Letters*, 1972, 2301.

⁶³ K. Senga, S. Nishigaki, M. Higuchi, and F. Yoneda, *Chem. and Pharm. Bull (Japan)*, 1972, **20**, 1473.

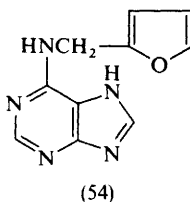
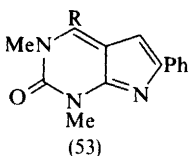
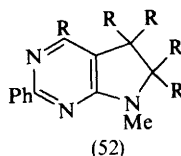
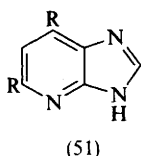
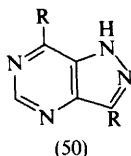
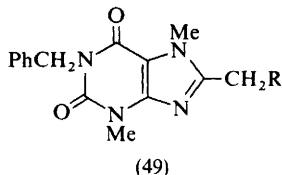
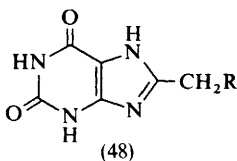
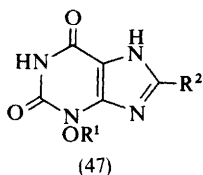
⁶⁴ L. Reio, *J. Chromatog.*, 1972, **68**, 183.

⁶⁵ M. T. Cuzzoni and G. Gazzani, *Farmaco, Ed. Prat.*, 1972, **27**, 564 (*Chem. Abs.*, 1973, **78**, 28 013r).

⁶⁶ C.-Y. Wu and S. Siggia, *Analyt. Chem.*, 1972, **44**, 1499.

⁶⁷ M. S. Sunova, B. Kakac, and M. Semonsky, *Cesk. Farm.*, 1972, **21**, 397 (*Chem. Abs.*, 1973, **78**, 102 050u).

⁶⁸ I. I. Dozorova and G. A. Melent'eva, *Farmatsiya (Moscow)*, 1972, **21**, 43 (*Chem. Abs.*, 1972, **77**, 156 355v).



Caffeine and related alkaloids exhibit antimutagenic or cytostatic effects on human blood lymphocytes in culture.⁶⁹ The interesting proposal has been advanced that the lack of mutagenic activity of these compounds in man may be due to the fact that the antimutagenic threshold is the same as the mutagenic threshold, thus not allowing the reproduction of the mutant cells which are produced. A number of other pharmacological effects of natural and synthetic compounds have been investigated.⁷⁰ Injection of kinetin (54) appears to alter the morphological character and lower the alkaloid production in *Papaver somniferum*.⁷¹

4 *Securinega* Alkaloids

This group has recently been reviewed.⁷²

The interesting tetrahydro-1,2-oxazine structure (55) has been assigned to phyllantidine, which was originally isolated from *Phyllanthus discoides* and more

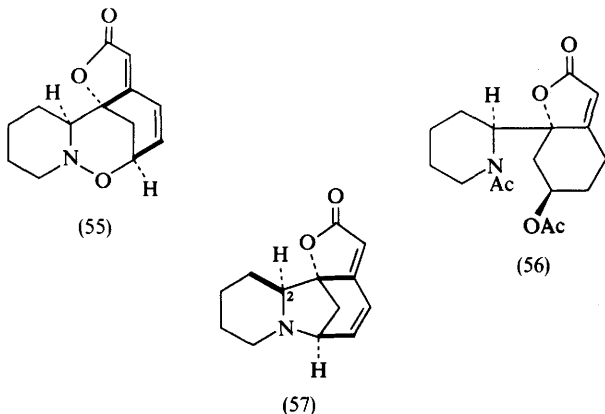
⁶⁹ J. Timson, *Mutat. Res.*, 1972, **15**, 197 (*Chem. Abs.*, 1972, **77**, 84 051t).

⁷⁰ E. Y. Tong, E. E. Bittar, S. S. Chen, and B. G. Danielson, *Experientia*, 1972, **28**, 1031; H. Schnack and N. Stefanelli, *Aktuel. Ber. Geb. Verdau.-Stoffwechselkr., Verh. Tag. Deut. Ges. Verdau.-Stoffwechselkr.* 25th 1969, ed. R. Ammon, Georg Thieme, Stuttgart, 1971, 159 (*Chem. Abs.*, 1973, **78**, 79 625z); G. Niebch and Fr. Schneider, *Z. Naturforsch.*, 1972, **27b**, 675; J. A. Montgomery, H. J. Thomas, and K. Hewson, *J. Medicin. Chem.*, 1972, **15**, 1189.

⁷¹ P. Gracza and G. Verzar-Petri, *Postep Dziedzine Leku Rosl., Pr. Ref. Dosw. Wygloszone Symp.* 1970, p. 182, ed. F. Kaczmarek, Inst. Przem. Zielarskiego, Poznan, Poland, 1972 (*Chem. Abs.*, 1973, **78**, 53 889p).

⁷² V. A. Snieckus in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1973, Vol. 14, p. 425.

recently found in *Securinega suffruticosa*.⁷³ Its structure rests on spectral data and its degradation to the easily recognizable⁷² *NO*-diacetyl derivative (56). It can also be readily synthesized in high yield by treatment of allosecurinine (57) with hydrogen peroxide. This reaction is essentially a Meisenheimer rearrangement and undoubtedly proceeds *via* the *N*-oxide of (57). (For a related example, see Ch. 2, Section 4 of this volume). Since the absolute stereochemistry of allosecurinine had been previously determined, structure (55) also represents the absolute stereochemistry of phyllantidine. The distribution of securinine [C(2)-epimer of (57)] in the shoots and leaves of European *S. suffruticosa* has been analysed.⁷⁴



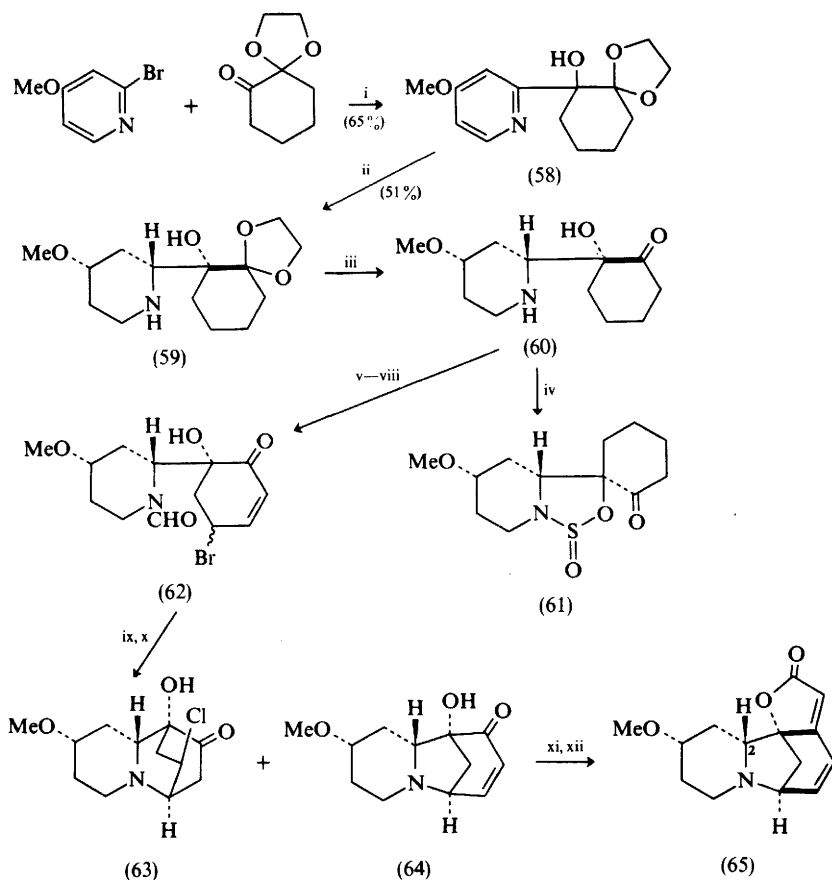
A synthesis of 2-episecuritinine (65), which is a C(2)-epimer of the naturally occurring alkaloid securitinine, has been achieved (Scheme 7).^{75,76} The logistics of this route have been previously developed in the synthesis of securinine.⁷² The readily available hydroxy-ketal (58) was catalytically reduced to give a mixture of three of the four theoretically possible diastereoisomers. That the stereochemistry of the major product is as shown in (59) was established by n.m.r. analysis of the oxathiazolidine derivative (61) that could be prepared by treatment with thionyl chloride followed by acid-catalysed hydrolysis.⁷⁵ The key ketone intermediate (60) was converted into the bromo $\alpha\beta$ -unsaturated ketone (62), which was then cyclized to give a mixture of the two tricyclic compounds (63) and (64).⁷⁶ The undesired isoquinuclidine (63) resulting from Michael addition and halogen exchange is a type of product encountered in the early degradation work on this group of alkaloids.⁷² The remaining steps to 2-episecuritinine (65) follow previously described synthetic work.⁷²

⁷³ Z. Horii, T. Imanishi, M. Yamauchi, M. Hanaoka, J. Parello, and S. Munavalli, *Tetrahedron Letters*, 1972, 1877.

⁷⁴ Ch. Younos, F. Mortier, and J. M. Pelt, *Plant. Med. Phytother.*, 1971, 5, 282.

⁷⁵ Z. Horii, T. Imanishi, T. Tanaka, I. Mori, M. Hanaoka, and C. Iwata, *Chem. and Pharm. Bull. (Japan)*, 1972, 20, 1768.

⁷⁶ Z. Horii, T. Imanishi, M. Hanaoka, and C. Iwata, *Chem. and Pharm. Bull. (Japan)*, 1972, 20, 1774.



Reagents: i, $\text{Bu}^n\text{Li}-\text{Et}_2\text{O}$, -20°C ; ii, H_2 , $\text{Rh}/\text{Al}_2\text{O}_3$, EtOH , 100°C , 140 atm.; iii, 10% HCl , 60°C ; iv, $\text{SOCl}_2-\text{C}_6\text{H}_5\text{N}$; v, HCO_2Ac , 90°C ; vi, $\text{Br}_2-\text{EtOH}-\text{CHCl}_3$ -dry HCl , 50°C ; vii, $\text{Li}_2\text{CO}_3-\text{LiBr}-\text{DMF}$, 120°C ; viii, $\text{NBS}-(\text{PhCO}_2)_2-\text{CCl}_4$; ix, 20% HCl , 90°C ; x, K_2CO_3 -wet CHCl_3 , reflux; xi, $\text{LiC}\equiv\text{COEt}-\text{Et}_2\text{O}$, -20°C ; xii, 15% H_2SO_4 -THF, reflux.

Scheme 7

5 Peptide Alkaloids

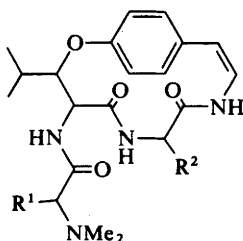
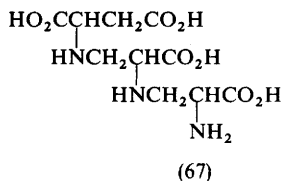
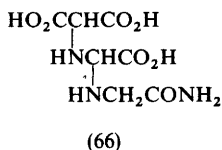
The structural elucidation, synthesis, and biological properties of some phytotoxins derived from amino-acids, *e.g.* lycomarasmine (66) and aspergillomarasmine A (67), have been reviewed.⁷⁷

Details concerning the isolation of three new alkaloids, codonocarpine, *N*-methylcodonocarpine, and an unknown of m.p. $188-189^\circ\text{C}$ and producing

⁷⁷ M. Barbier, *Phytotoxins Plant Dis., Proc. NATO Advan. Study Inst.* 1970, p. 91, ed. R. K. S. Wood, Academic Press, London, 1972 (*Chem. Abs.*, 1973, 78, 53 477c).

M^+ 479, isolated from *Codonocarpus australis*, have become available⁷⁸ (see Vol. 3 of these Reports). Another peptide alkaloid, m.p. 211–212 °C, M^+ 568, of undetermined structure, has been isolated from *Discaria crenata*.⁷⁹

Although the structures of frangulanine (68), discarine A (69), and discarine B (70), the major alkaloids isolated from *D. crenata*, had been previously established (see Vol. 3 of these Reports), the configuration of the β -aryl-serine units within these structures was left uncertain. No stereochemical conclusion could be drawn from the formation of the *threo*- α -amino- β -hydroxy-amino-acid upon acid hydrolysis because of almost certain loss of chirality at the hydroxy carbon atom under these reaction conditions. Examination of the 220 MHz n.m.r. spectrum of frangulanine(68) indicated that only an *erythro* configuration of the β -oxyleucine moiety satisfies the chemical-shift and coupling-constant information in the rigid fourteen-membered-ring environment.⁸⁰ On the basis of this analysis, the *erythro* configurations for the β -substituted serine units could be assigned also to discarine A (69), discarine B (70), and a number of other peptide alkaloids. Chemical corroboration was obtained by Birch reduction of dihydrofrangulanine followed by acid hydrolysis to yield only *erythro*- β -hydroxyleucine. The course of these steps does not affect the chiral centre of the β -oxyleucine group and thus confirms the presence of an *erythro*- β -aryloxyleucine moiety in frangulanine (68). The L configuration of the *erythro*- β -aryloxyleucine unit was established by enzymatic hydrolysis of dihydrofrangulanine.



(68) $R^1 = \text{Bu}^s$, $R^2 = \text{Bu}^i$

(69) $R^1 = \beta$ -indolylmethyl, $R^2 = \text{Bu}^s$

(70) $R^1 = \text{Bu}^s$, $R^2 = \beta$ -indolylmethyl

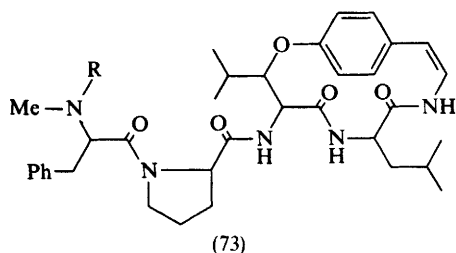
(71) $R^1 = R^2 = \text{Bu}^i$

(72) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Bu}^i$

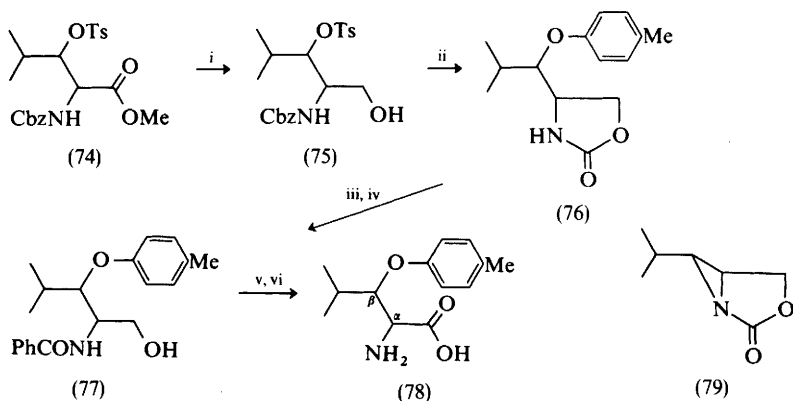
⁷⁸ N. A. Pilewski, J. Tomko, A. B. Ray, R. W. Doskotch, J. L. Beal, G. H. Svoboda, and W. Kubelka, *Lloydia*, 1972, **35**, 186.

⁷⁹ P. Pacheco, S. M. Albonico, and M. Silva, *Phytochemistry*, 1973, **12**, 954.

⁸⁰ M. Gonzalez Sierra, O. A. Mascaretti, F. J. Diaz, E. A. Ruveda, C.-J. Chang, E. W. Hagaman, and E. Wenkert, *J. C. S. Chem. Comm.*, 1972, 915.



The same conclusions concerning the configuration of the β -oxyleucine unit in the related alkaloid lasiodine B (73; R = H) were independently reached by a different group of workers using an approach of oxidative ring opening at the styryl double bond⁸¹ (for summary of preliminary work, see Vol. 3 of these Reports). Thus four successive steps [OsO_4 ; $\text{Pb}(\text{OAc})_4$; H_2 , Pd/C; and H^+] were required to obtain β -(*p*-tolylloxy)leucine (78) (Scheme 8) from acetyl-lasiodine (73; R = Ac). The *erythro* stereochemistry of (78) was deduced from the vicinal proton coupling-constant ($J_{\alpha,\beta}$) of its *NN*-dimethyl derivative and from its stereospecific synthesis (Scheme 8). Preparation of the diastereoisomeric β -hydroxyleucine derivatives (74) was achieved starting with chiral β -hydroxyleucine. The *erythro*- and *threo*-diastereoisomers (74) were separated and then were converted into *erythro*- and *threo*-(78), respectively. An interesting step in the sequence (75) \rightarrow (76) \rightarrow (77) \rightarrow (78) is the transformation of (75) into the oxazolidone (76). This step proceeds with retention of configuration, with the intervention of the aziridine intermediate (79), which could be isolated in the *threo*-series.



Reagents: i, LiAlH_4 -THF; ii, $p\text{-MeC}_6\text{H}_4\text{O}^-\text{Na}^+$, HMPT; iii, NaOH -abs. EtOH; iv, PhCOCl - NaOH - CH_2Cl_2 - PhH - H_2O ; v, Jones oxidation; vi, HOAc - HCl .

Scheme 8

⁸¹ J. Marchand, F. Rocchiccioli, M. Pais, and F. X. Jarreau, *Bull. Soc. chim. France*, 1972, 4699.

Reports concerning the isolation of five unknown alkaloids evoline, evopine, evomine, europine, and eurolin (also referred to as alkaloids A—E consecutively) from *Euonymus europaeus* were previously reviewed in the Sesquiterpenoid Alkaloid section (see Vol. 3, p. 56 of these Reports). The structures of four of these alkaloids have now been established and they have been shown to possess peptide- and tetrahydroisoquinoline-type structures.^{82,83} The previous classification, which was based on the unfortunate nomenclature and the source of alkaloids A—D, is thus in error.* On the basis of spectroscopic and chemical evidence, alkaloids A, B, and C have been identified as the known alkaloids frangulanine (68), franganine (71), and franguloline (72), respectively.⁸³ This represents the first time peptide alkaloids have been found in the Family Celastraceae. Alkaloid D has been shown to be armejavine, a simple benzylisoquinoline alkaloid. (See Chapter 8 in this volume.)

The *Lunaria* alkaloids have been briefly reviewed.^{83a} Previously proposed structures (see Vol. 1, p. 460 of these Reports) for the minor *Lunaria* bases LBX and LBZ, from *Lunaria biennis*, have been revised to (80; $R^1 + R^2 = O$) and (80; $R^1 = OH, R^2 = H$), respectively, on the basis of spectroscopic and chemical evidence.⁸⁴ That the original structure [81; $n = 3, m = 4, N(2)-C_\alpha-CH_2$ bridge] for alkaloid LBX was incorrect was clear from the comparison of its n.m.r. spectrum with that of its $[C_\alpha-^2H_2]$ derivative: the clean AB quartet at τ 4.16 and τ 3.98 in the alkaloid was absent in the deuteriated derivative. Furthermore, treatment of lunarine (81; $R^1 + R^2 = O, n = 3, m = 4$) with formaldehyde gave a compound which was found to be identical with alkaloid LBX. Alkaloid LBZ was shown to possess structure (80; $R^1 = OH, R^2 = H$) by its synthesis from lunarinol II (81; $R^1 = OH, R^2 = H, n = 3, m = 4$) and formaldehyde under acidic conditions. This fact also mitigates against the original structural proposals, that were based on mechanistic considerations for the Mannich reactions which are involved in the alkaloid interconversions. The configurations of the secondary alcohol functions in lunarinol II (81; $R^1 = OH, R^2 = H, n = 3, m = 4$) and lunarinol I (81; $R^1 = H, R^2 = OH, n = 3, m = 4$) were assigned from their n.m.r. spectra. Thus the stereochemistry at this chiral centre in alkaloid LBZ was also established. The possibility that the structures of the Mannich reaction products of lunarine and lunarinol II (and thus of alkaloids LBX and LBZ) correspond to perhydro-1,3-diazepine derivatives resulting from formaldehyde interaction across N(2) and N(3) can only be partially ruled out by hypothesizing greater strain restrictions placed upon seven-membered-ring formation. On the basis of similar evidence, a different group of workers have also proposed the same structures (80; $R^1 + R^2 = O$) and (80; $R^1 = OH, R^2 = H$) for alkaloids

* We thank Dr. J. D. Phillipson for correspondence clarifying this matter.

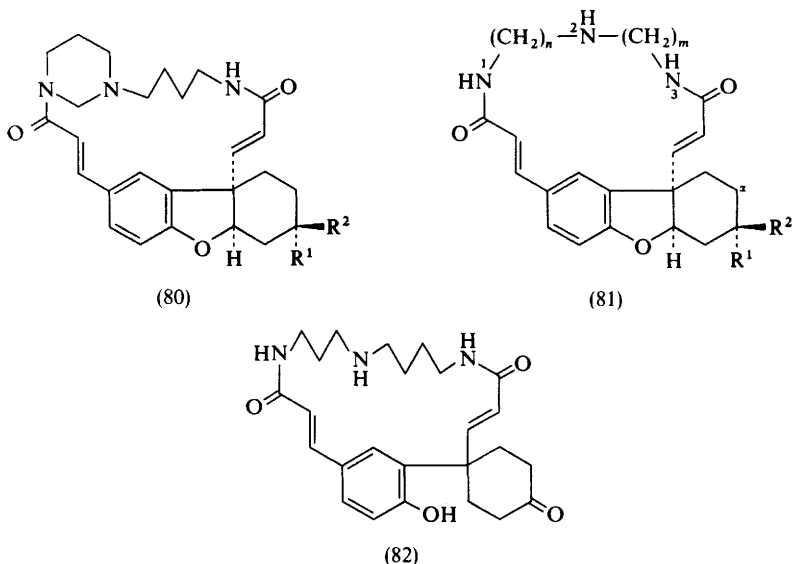
⁸² D. W. Bishay, Z. Kowalewski, and J. D. Phillipson, *J. Pharm. Pharmacol.*, 1972, **24** (Suppl.), 169P.

⁸³ D. W. Bishay, Z. Kowalewski, and J. D. Phillipson, *Phytochemistry*, 1973, **12**, 693.

^{83a} M. M. Badawi, K. Bernauer, P. Van den Broek, D. Groeger, A. Guggisberg, S. John, I. Kompis, F. Schneider, H.-J. Veith, M. Hesse, and H. Schmid, *Pure Appl. Chem.*, 1973, **33**, 81.

⁸⁴ R. W. Doskotch, E. H. Fairchild, and W. Kubelka, *Experientia*, 1972, **28**, 382.

LBX and LBZ, respectively.⁸⁵ In addition, this report details the extensive spectral and chemical work which culminated in the complete structural proposal (81; $R^1 + R^2 = O$, $n = 3$, $m = 4$) for lunarine, the major alkaloid of *L. biennis*, as well as for the minor alkaloids LBY [lunarinol II, (81; $R^1 = OH$, $R^2 = H$, $n = 3$, $m = 4$)] and numismine (82). An equally detailed report on the structural elucidation of lunaridine (81; $R^1 + R^2 = O$, $n = 4$, $m = 3$) is available.⁸⁶ The interpretation of mass-spectral fragmentation patterns of the *N*(2)-methyl derivatives (deuteriated and undeuteriated) of lunarine (81; $R^1 + R^2 = O$, $n = 3$, $m = 4$) and lunaridine was particularly useful in the structural assignments.



A number of new and biogenetically interesting alkaloids have been isolated from *Zizyphus* species by Tschesche and his co-workers.⁸⁷⁻⁹⁰ Amphibines B (83), C (84), D (85), and E (86) from *Z. amphibia* show structures which formally embody *para*-coupling of 3-hydroxyproline and styrylamine units in a phenolic ether thirteen-membered-ring framework.⁸⁷ The same structural subunit is found in mauritine A (87) and mauritine B (88), which have been isolated from *Z. mauritiana*.⁸⁸ Mucronine D (89), the major alkaloid from *Z. mucronata*, structurally

⁸⁵ C. Poupat, H. P. Husson, B. Rodriguez, A. Husson, P. Potier, and M. M. Janot, *Tetrahedron*, 1972, **28**, 3087.

⁸⁶ C. Poupat, H. P. Husson, B. C. Das, P. Bladon, and P. Potier, *Tetrahedron*, 1972, **28**, 3103.

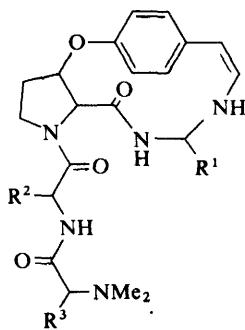
⁸⁷ R. Tschesche, E. U. Kaussmann, and H. W. Fehlhaber, *Chem. Ber.*, 1972, **105**, 3094.

⁸⁸ R. Tschesche, H. Wilhelm, and H. W. Fehlhaber, *Tetrahedron Letters*, 1972, 2609.

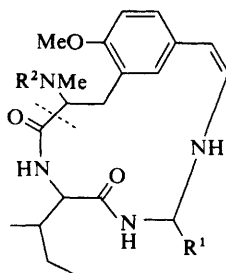
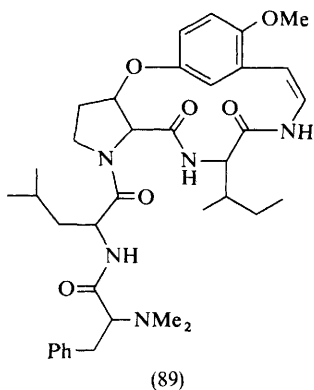
⁸⁹ R. Tschesche, S. T. David, J. Uhlendorf, and H. W. Fehlhaber, *Chem. Ber.*, 1972, **105**, 3106.

⁹⁰ H. W. Fehlhaber, J. Uhlendorf, S. T. David, and R. Tschesche, *Annalen*, 1972, **759**, 195.

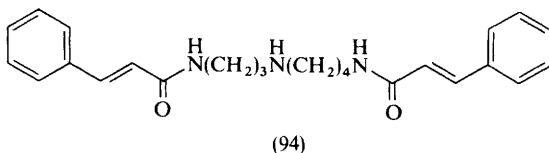
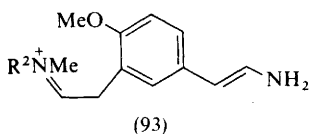
exhibits a different coupling of the 3-hydroxyproline and styrylamine moieties and, in addition, shows an aromatic methoxy-function.⁸⁹ Possibly the most interesting new alkaloids are mucronines A (90), B (91), and C (92), also obtained from *Z. mucronata*, which exhibit direct carbon-carbon interaction between amino-acid and styrylamine units rather than the phenolic ether type structure.⁹⁰ The structural elucidation of all above alkaloids followed the well-established application of n.m.r. and, in particular, mass-spectrometric methods together with hydrolytic studies. In the case of mucronines A (90), B (91), and C (92), mass-spectral fragmentation is triggered by cleavage at the site indicated (----) and follows a sequential loss of amino-acid units to give an ion at m/e 219 (93).



- (83) $R^1 = R^3 = \text{CH}_2\text{Ph}$, $R^2 = \text{Bu}^s$
 (84) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Bu}^s$, $R^3 = \text{Bu}^i$
 (85) $R^1 = R^2 = \text{Bu}^i$, $R^3 = \text{CH}_2\text{Ph}$
 (86) $R^1 = \text{Bu}^s$, $R^2 = \beta\text{-indolylmethyl}$, $R^3 = \text{Bu}^i$
 (87) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Pr}^i$, $R^3 = \text{Me}$
 (88) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Pr}^i$, $R^3 = \text{Bu}^s$



- (90) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Me}$
 (91) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$
 (92) $R^1 = \text{Bu}^i$, $R^2 = \text{Me}$



Forty years after a report of pharmacological activity of *Maytenus chuchuhuasha*, the structure of the alkaloidal component maytenine (94) has been determined.^{90a} Extensive use of spectral information, including a 270 MHz FT n.m.r. spectrum, led to the di-*trans*-cinnamoylspermidine structure (94) for maytenine. Its synthesis has also been accomplished although not reported in detail.

6 Unclassified Alkaloids and Alkaloid-containing Plants

The format of previous volumes of these Reports is followed except that secondary metabolic, nitrogen-containing products of fungal and animal origin are included.

A large number of poisonous plants of North Dakota, U.S.A., were screened and the following families showed positive tests for alkaloids: Asclepiadaceae, Asteraceae, Brassicaceae, Fabaceae, Plantaginaceae, Scrophulariaceae, and Urticariaceae.⁹¹ In an equally large screening of plants from Slavyanka mountain in Russia, evidence for new sources of alkaloids has been obtained for the following species: *Centaurea parilica* var. *incanescens*, *Convolvulus suendermannii*, *Delphinium fissum*, *Jurinea arachnoidea*, *Podanthum canescens*, *Polygala nicaensis*, and *Trachelium rumelicum* var. *chalcidicum*.⁹² A number of other new large-scale phytochemical surveys of plants which show positive evidence of contained alkaloids have been reported: India (Gujarat,⁹³ Uttar Pradesh, and Meghalaya⁹⁴ States), Malaya,⁹⁵ and Bulgaria (Belessitza Mountain and Petritch Valley,⁹⁶ Pirin Mountains.⁹⁷) The discovery of *N*-methyl-lysine in a number of

^{90a} G. Englert, K. Klinga, Raymond-Hamet, E. Schlittler, and W. Vetter, *Helv. Chim. Acta*, 1973, **56**, 474.

⁹¹ E. W. Wollmann, L. J. Schermeister, and E. G. Schmiess, *Proc. N. Dakota Acad. Sci.*, 1972, **25**, (Pt. 2), 17.

⁹² N. Stoyanov, P. Savchev, and Zh. Stefanov, *Tr. Nauchnoizsled. Khim.-Farm. Inst.*, 1972, **7**, 189 (*Chem. Abs.*, 1973, **78**, 145 225x).

⁹³ B. L. Hungund and C. H. Pathak, U.S. Forest Service, Research Paper NE 1971, No. 201, 11pp. (*Chem. Abs.*, 1972, **77**, 111 440c).

⁹⁴ L. D. Kapoor, S. N. Srivastava, A. Singh, S. L. Kapoor, and N. C. Shah, *Lloydia*, 1972, **35**, 288.

⁹⁵ K. C. Chan and L. E. Teo, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1582.

⁹⁶ P. Savchev, Zh. Stefanov, and N. Stoyanov, *Tr. Nauchnoizsled. Khim.-Farm. Inst.*, 1972, **8**, 179 (*Chem. Abs.*, 1973, **78**, 156 627f).

⁹⁷ P. Savchev, Zh. Stefanov, and N. Stoyanov, *Tr. Nauchnoizsled. Khim.-Farm. Inst.*, 1972, **8**, 163 (*Chem. Abs.*, 1973, **78**, 156 618d).

alkaloid-containing plants is of biosynthetic interest.⁹⁸ Single species in which alkaloids have been detected are listed in the Table.^{99–111}

Table Alkaloid-containing Plants

Species	Comment	Ref.
<i>Aegle marmelos</i>	Two alkaloids, A (m.p. 172–173 °C) and B (m.p. 136–137 °C); used in treatment of intestinal disease	99
<i>Cardiospermum halicacabum</i>	Alkaloid fraction shows antibacterial action	100
<i>Catesbaea spinosa</i>	Maximum alkaloid content (0.25 %) in leaves	101
<i>Crataegus monogyna</i>	Alcohol extract shows antitumour activity	102
<i>Enicostema littorale</i>	Five alkaloids; CHCl ₃ -soluble alkaloid extract has antimalarial activity and produces cardiac depression	103
<i>Kochia prostrata</i>	Traces of alkaloids	104
<i>Limnopsis loangensis</i>	Five crystalline alkaloids	105
<i>Lysichitum camtschaticense</i>	Flowers and fruits are rich in alkaloids	106
<i>Pedicularis dolichorrhiza</i> , <i>P. ludwigi</i> , <i>P. macrochila</i> , <i>P. olgae</i> , <i>P. rhinanthoides</i> , <i>P. violascens</i>	Richest source (1.18 %) is <i>P. ludwigi</i>	107
<i>Petilium raddeanum</i>	0.9 % of alkaloids	108
<i>Ritchiea fragariodora</i>	Two alkaloids and choline	109
<i>Stachys atherocalyx</i>		110
<i>Symplocarpus foetidus</i>	Rich in alkaloids	106
<i>Zanthoxylum integrifolium</i>	Alkaloids identified (?)	111

⁹⁸ E. Tyihak and D. Vagujfalvi, *Biochem. Physiol. Alkaloids, Int. Symp.*, 4th 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 133.

⁹⁹ A. Khaleque, A. K. M. M. Rahman, Kh. Md. Ismail, Md. S. Amin, and Md. W. Ali, *Sci. Res. (Dacca, Pakistan)*, 1970, **7**, 122 (*Chem. Abs.*, 1973, **78**, 1973s).

¹⁰⁰ S. D. Shukla, N. T. Modi, and B. S. Deshmankar, *Indian J. Pharm.*, 1973, **35**, 40 (*Chem. Abs.*, 1973, **78**, 119 432t).

¹⁰¹ R. C. Biswas, *Science and Culture*, 1972, **38**, 455 (*Chem. Abs.*, 1973, **78**, 133 366f).

¹⁰² A. Ulubelen and S. Kartin, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1971, **7**, 67 (*Chem. Abs.*, 1972, **77**, 72 595k).

¹⁰³ P. N. Natarajan and S. Prasad, *Planta Med.*, 1972, **22**, 42.

¹⁰⁴ V. Ya. Shishkina and E. T. Tegisbaev, *Tr. Alma.-At. Med. Inst.*, 1970, 449 (*Chem. Abs.*, 1972, **77**, 85 598p).

¹⁰⁵ A. Bouquet and A. Fournet, *Plant. Med. Phytother.*, 1972, **6**, 50.

¹⁰⁶ V. P. Konyukhov, V. S. Konyushko, and B. S. Subbotin, *Uch. Zap. Khabarovsk. Gos. Pedagog. Inst.*, 1970, **26**, 59 (*Chem. Abs.*, 1972, **77**, 149 701b).

¹⁰⁷ K. Taizhanov, S. A. Khamidkhodzhaev, E. E. Korotkova, and A. Abdusamatov, *Rast. Resur.*, 1972, **8**, 246 (*Chem. Abs.*, 1972, **77**, 79 508t).

¹⁰⁸ B. Babaev and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1972, 682 (*Chem. Abs.*, 1973, **78**, 144 837m).

¹⁰⁹ A. Cavé and R. R. Paris, *Plant. Med. Phytother.*, 1972, **6**, 66.

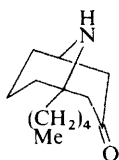
¹¹⁰ O. I. Kostyuchenko, *Farm. Zhur. (Kiev)*, 1972, **27**, 66 (*Chem. Abs.*, 1972, **77**, 58 872s).

¹¹¹ M. T. Chua, A. Maglaya, and A. C. Santos, *Philippine J. Sci.*, 1970, **99**, 205 (*Chem. Abs.*, 1973, **78**, 108 186q).

A general reference for methods of alkaloid analysis has been published.³ Other methods which may be of general applicability for analysis of alkaloids include: automated g.c.,¹¹² paper chromatography with buffered solutions,¹¹³ t.l.c.-photodensitometry,¹¹⁴ and conductometric and potentiometric titrimetry.¹¹⁵

Adalia bipunctata (Coccinellidae)

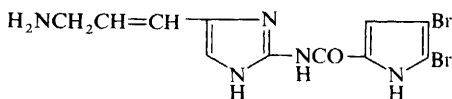
Adaline (95) is a homotropane alkaloid isolated (35 mg from 800 specimens) from *A. bipunctata*, commonly referred to as the European ladybug.¹¹⁶ The structure of adaline rests on spectral and chemical evidence and on X-ray crystallographic analysis of its hydrochloride derivative. A biogenetic relationship between adaline and the alkaloids isolated from *Coccinella* species (see below) is proposed. Adaline (95) was also obtained from *Adalia quadrimaculata* and *A. pantherina*.¹¹⁶



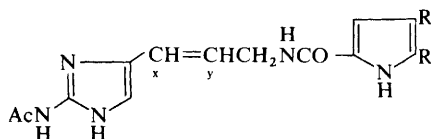
(95)

Agelas oroides

Oroidin, a bromopyrrole isolated from this marine sponge and originally assigned structure (96), has now been shown to possess structure (97; R = Br) by synthesis of its degradation product (97; R = H; x, y are saturated).¹¹⁷



(96)



(97)

¹¹² J. M. Solon, *Analyt. Instrum.*, 1972, **10**, 185 (*Chem. Abs.*, 1972, **77**, 84 081c).

¹¹³ S. N. Tewari, *J. Indian Acad. Forensic Sci.*, 1970, **9**, 69 (*Chem. Abs.*, 1972, **77**, 97 404k).

¹¹⁴ V. Massa, F. Gal, and P. Susplugas, *Int. Symp. Chromatogr. Electrophor.*, *Lect. Pap.*, 6th, 1971, p. 470 (*Chem. Abs.*, 1973, **78**, 25 964r).

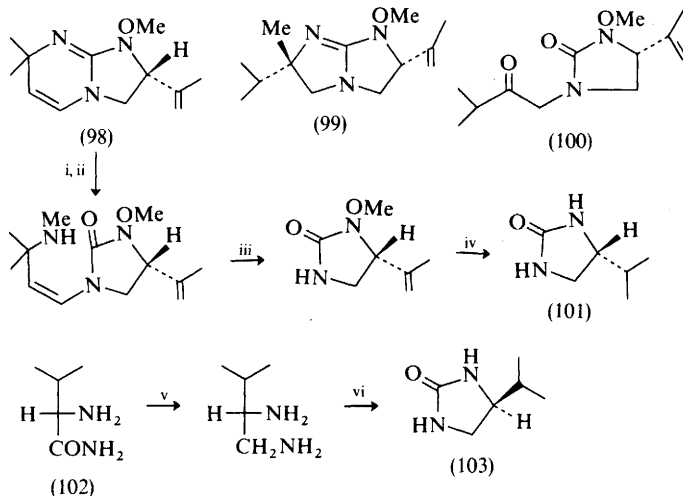
¹¹⁵ P. Cacho and F. Juan, *Rev. Acad. Cienc. Exactas, Fis. -Quim. Natur. Zaragoza*, 1972, **27**, 133 (*Chem. Abs.*, 1973, **78**, 143 532w).

¹¹⁶ B. Tursch, J. C. Braekman, D. Daloz, C. Hootele, D. Losman, R. Karlsson, and J. M. Pasteels, *Tetrahedron Letters*, 1973, 201.

¹¹⁷ E. E. Garcia, L. E. Benjamin, and R. I. Fryer, *J.C.S. Chem. Comm.*, 1973, 78.

Alchornea floribunda (Vol. 3, p. 318)

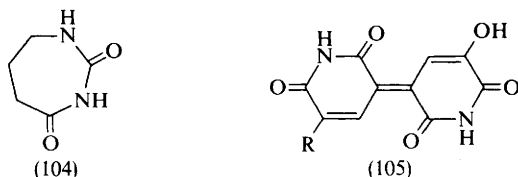
Details concerning the structural elucidation of alchorneine (98) and the new alkaloids isoalchorneine (99) and alchorneinone (100) have been reported.¹¹⁸ The absolute configuration of these alkaloids was determined by comparison of the optical rotation of (*R*)-4-isopropyl-2-imidazolidinone (101), which was obtained by degradation of alchorneine (98), with that of (*S*)-4-isopropyl-2-imidazolidinone (103), synthesized from the amide of (*S*)-(+)-valine (102) (Scheme 9).

**Scheme 9***Aniba hostmanniana* (Lauraceae)

N-[2-(4-Methoxyphenyl)ethyl]-3,4,5-trimethoxycinnamamide has been isolated.¹¹⁹ This marks the first time that an alkaloid based in part on the β -phenethylamine unit has been found in the genus *Aniba*.

Annona squamosa

Squamolone has been shown to possess the 1,3-diazepine structure (104) on the basis of spectral and chemical evidence.¹²⁰



¹¹⁸ F. Khuong-Huu, J. P. Le Forestier, and R. Goutarel, *Tetrahedron*, 1972, **28**, 5207.

¹¹⁹ O. R. Gottlieb and A. I. Da Rocha, *Phytochemistry*, 1972, **11**, 1861.

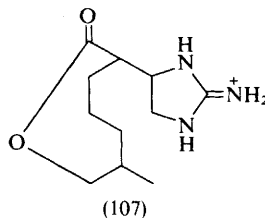
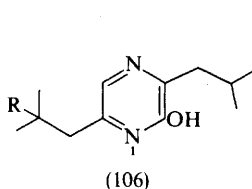
¹²⁰ T.-H. Yang and C.-M. Chen, *J. Chinese Chem. Soc. (Taipei)*, 1972, **19**, 149 (*Chem. Abs.*, 1973, **78**, 16 151w).

Arthrobacter oxidans

Nicotine blue, the pigment material isolated from *A. oxidans*, has been shown to be a mixture of two components, (105; R = OH) (80%) and (105; R = H) (20%), which could be separated by cellulose t.l.c.¹²¹ The structures were determined by u.v. and n.m.r. spectroscopy and by chemical correlations: compound (105; R = OH) was identical with authentic material while compound (105; R = H) was synthesized by autoxidation of pyridine-2,3,6-triol. Higher yields of the two components may be obtained by adding pyridine-2,3,6-triol and pyridine-2,6-diol to the culture broth, thus offering preliminary evidence for the biosynthetic pathways.

Aspergillus ochraceus (Aspergillaceae)

A new pyrazine metabolite, deoxyneo- β -hydroxyaspergillic acid (106; R = OH), has been isolated.¹²² Its structure was established by u.v., n.m.r., and mass spectral methods. The previously known neoaspergillic acid [106; R = H, N(1)-oxide] and flavacol (106; R = H) were also obtained.

*Cassia absus*

Chaksine (107) has been shown to exhibit antiarthritic effects in mice and rats.¹²³ However, long-range administration established the toxic effects of this alkaloid in both animals.

Coccinella septempunctata

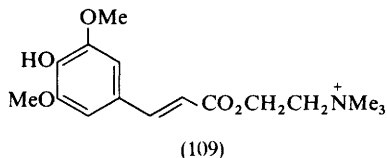
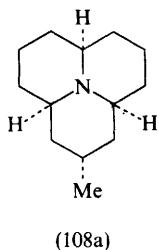
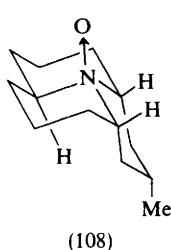
This beetle synthesizes the alkaloid coccinellin. X-Ray crystallographic analysis of the hemihydrochloride of coccinellin has now shown that one of the earlier proposed structures (108), based on spectral evidence, is correct.¹²⁴ It may be noted that the ring system of coccinellin may be found in alkaloids isolated from plant (*cf. Poranthera corymbosa* in Vol. 3 of these Reports, p. 322) and from other beetle sources (*cf. Hippodamia convergens*, *Propylaea quatuordecimpunctata*).

¹²¹ H. J. Knackmuss and W. Beckmann, *Arch. Mikrobiol.*, 1973, **90**, 167.

¹²² M. Yamazaki, Y. Maebayashi, and K. Miyaki, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2274.

¹²³ A. Qayum, K. Khanum, and G. A. Miana, *Pakistan Med. Forum*, 1971, **6**, 35 (*Chem. Abs.*, 1972, **77**, 148 526m).

¹²⁴ R. Karlsson and D. Losman, *J.C.S. Chem. Comm.*, 1972, 626.



Crambe orientalis and *C. tataria*

Sinapine (109) has been isolated from both species.¹²⁵ Other alkaloids were detected but not identified.

Datura ferox

An attempt to determine why the tissue culture of *D. ferox* does not form alkaloids was made.¹²⁶ Feeding (\pm)-[2-¹⁴C]ornithine led to the isolation of putrescine and a number of other amino-acids, including α -keto- δ -aminovalerate. Since α -keto- δ -aminovalerate forms 1-pyrroline-2-carboxylate spontaneously, it was suggested that the cultures lack the enzyme which catalyses the reaction between the latter and acetoacetic ester, thus preventing alkaloid synthesis.

Equisetum palustre

A brief review of alkaloids isolated from this species is available.^{83a}

A synthesis of (\pm)-dihydropalustramic ester (113), a key degradation product of the toxic alkaloid palustrine (115) obtained from this species (marsh horsetail), has been reported (Scheme 10).¹²⁷ The epoxy-ester (110), synthesized by a conventional route, was treated with benzylamine to give a mixture of the *threo*-*cis*- and -*trans*-piperidine derivatives (111) and (112), respectively. These were separated and each was hydrogenolysed and transesterified to give the corresponding (\pm)-*threo*-*cis*- and -*trans*-secondary amines, (113) and (114). Stereochemical assignments were made on the basis of n.m.r. evidence and lactonization experiments. The *threo*-*cis*-compound (113) was shown to be identical with the degradation product of palustrine (115). Since the (2*S*, 6*R*, 1'*S*) absolute configuration could be assigned to (113), it follows that palustrine must have the absolute stereochemistry as indicated by structure (115).

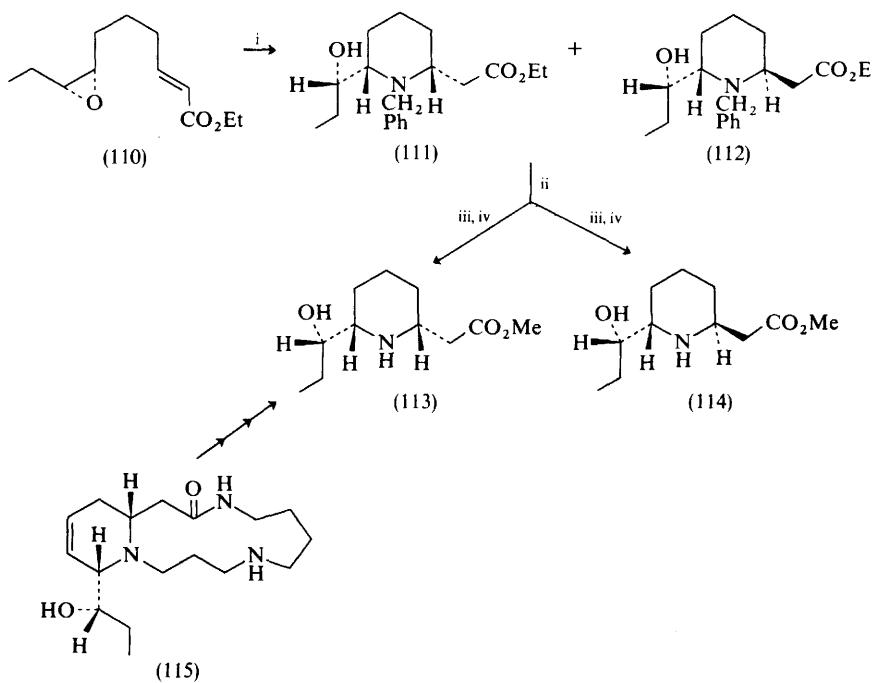
A t.l.c. method which can be used to identify palustrine (115) in *E. palustre* has been developed.¹²⁸

¹²⁵ T. Baytop and G. Ozcobek, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1971, 7, 77 (*Chem. Abs.*, 1972, 77, 72 583e).

¹²⁶ H. Elze and E. Teuscher, *Biochem. Physiol. Alkaloids, Int. Symp.*, 4th, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 239.

¹²⁷ P. Waelchli and C. H. Eugster, *Angew. Chem. Internat. Edn.*, 1973, 12, 160.

¹²⁸ L. Langhammer, K. Blaszkiewitz, and I. Kotzorek, *Deut. Apoth.-Ztg.*, 1972, 112, 1749 (*Chem. Abs.*, 1973, 78, 80 430p).



Reagents: i, PhCH₂NH₂; ii, separate (111) and (112); iii, H₂-catalyst; iv, transesterify.

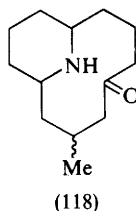
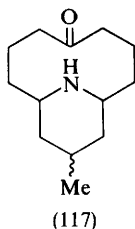
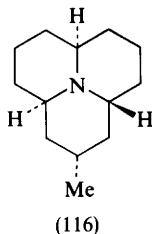
Scheme 10

Hippodamia convergens (Coleoptera, Coccinellidae)

This species (American ladybug) has yielded two alkaloids, hippodamine (116) and convergine [(117) or (118)].¹²⁹ The n.m.r. and mass spectra of hippodamine (116) were very similar to those of the known alkaloid precoccinellin (108a), thus suggesting a stereoisomeric relationship. Since the *N*-oxide and hydrochloride derivatives of hippodamine (116) do not show optical activity, hippodamine must be either a symmetrical molecule like precoccinellin (108a) or a racemic modification. ¹³C n.m.r. spectroscopy was used to eliminate the former possibility, and thus the (±)-*trans*, *cis*, *cis*-perhydro-9b-azaphenalene structure (116) was assigned to hippodamine. Convergine, an optically inactive alkaloid, showed spectral and chemical properties consistent with carbinolamine-aminoketone character. Reduction with lithium aluminium hydride gave an optically inactive compound which was identical with hippodamine (116). Thus convergine is formulated as (117) or (118) without stereochemical implications. It is to be noted that alkaloids based on the 9b-azaphenalene skeleton have now

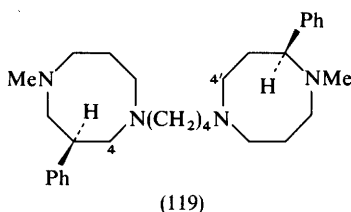
¹²⁹ B. Tursch, D. Daloz, J. M. Pasteels, A. Cravador, J. C. Braekman, C. Hootel, and D. Zimmermann, *Bull. Soc. chim. belges*, 1972, **81**, 649.

been found in a number of insects (*cf. Coccinella septempunctata, Propylaea quatuordecimpunctata*) and plants (*cf. Poranthera corymbosa* in Vol. 3 of these Reports, p. 322).



Homalium sp. and *H. pronyense* (Homaliaceae) (Vol. 3, p. 321)

Details concerning the stereospecific total synthesis of bisdihydrodeoxohomaline (119), a degradation product of the alkaloid homaline (119; 4,4'-dioxo), are now available.¹³⁰

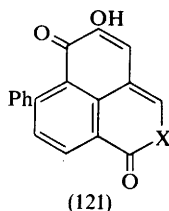
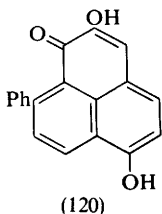


Kniphofia flavovirens, *K. foliosa*, and *K. tuckii*

The putrescine amides $\text{RNH}(\text{CH}_2)_4\text{NMe}_2$ ($\text{R} = \text{cis-4-HOC}_6\text{H}_4\text{CH}=\text{CHCO}$ and $\text{R} = \text{cis-4-MeOC}_6\text{H}_4\text{CH}=\text{CHCO}$) have been isolated and their structures have been established by spectral methods and synthesis.¹³¹

Lachnanthes tinctoria (Haemodoraceae)

This species, previously known to be rich in 9-phenylphenalenone pigments [*e.g.* (120)], has yielded the 5-oxaphenalenone (121; $\text{X} = \text{O}$) and the 5-azaphenalenone (121; $\text{X} = \text{NCH}_2\text{CH}_2\text{OH}$) derivatives.¹³² The structures were assigned on the basis of spectroscopic evidence. A biogenetic relationship between (121; $\text{X} = \text{O}$) and (121; $\text{X} = \text{NCH}_2\text{CH}_2\text{OH}$), mediated by ethanolamine, is plausible.



¹³⁰ M. Pais, R. Sarfati, and F. X. Jarreau, *Bull. Soc. chim. France II*, 1973, 331.

¹³¹ H. Ripperger, H. Budzikiewicz, and K. Schreiber, *Biochem. Physiol. Alkaloid, Int. Symp.*, 4th, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, 1972, p. 129.

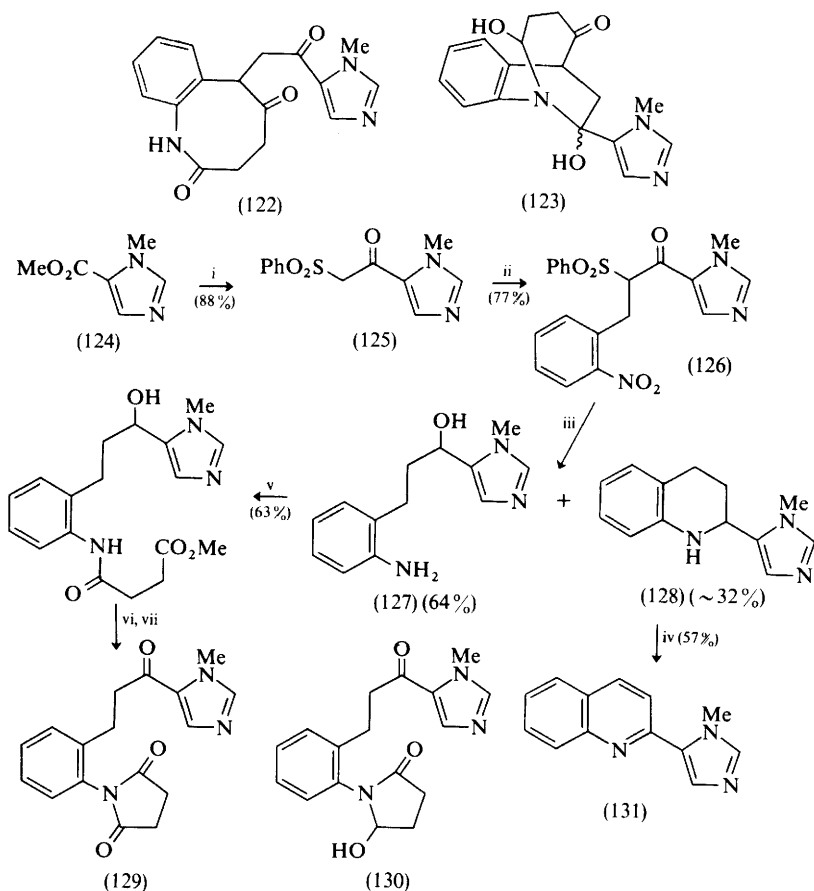
¹³² J. M. Edwards and U. Weiss, *Tetrahedron Letters*, 1972, 1631.

Leguminosae spp.

A chromatographic separation method for spherophysine, $\text{H}_2\text{NC(=NH)-NH(CH}_2)_4\text{NHCH=CHCHMe}_2$, an alkaloid found in a number of Leguminosae species, has been developed.¹³³

Macrorungia longistrobus

The previously proposed structures for dehydroisolongistrobine (122) and isolongistrobine (123), respectively, require revision to (129) and (130), respectively, as shown by total synthesis of the former alkaloid (Scheme 11).¹³⁴ Carbon-chain



Reagents: i, $\text{PhSO}_2\text{CH}_2\text{MgX}$; ii, $\text{Bu}^t\text{OK-Bu}^t\text{OH}$, $o\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{Br}$, THF, 60°C ; iii, $\text{Al(Hg)-THF-H}_2\text{O}$, 0°C ; iv, 10% Pd/C, S, xylene, reflux; v, $\text{ClCOCH}_2\text{-CH}_2\text{CO}_2\text{Me-C}_5\text{H}_5\text{N-CH}_2\text{Cl}_2$, 0°C ; vi, $\text{CrO}_3\text{-C}_5\text{H}_5\text{N-H}_2\text{O}$; vii, heat.

Scheme 11

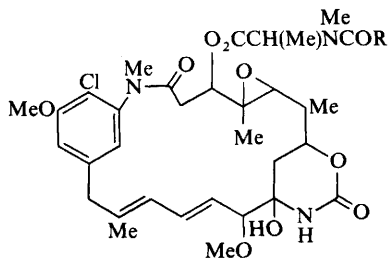
¹³³ G. V. Kramarenko and V. I. Popova, *Farm. Zhur. (Kiev)*, 1972, **27**, 40 (*Chem. Abs.*, 1973, **78**, 67 738a).

¹³⁴ M. A. Wuonola and R. B. Woodward, *J. Amer. Chem. Soc.*, 1973, **95**, 284.

extension of the imidazole (124) gave the activated β -keto-sulphone (125), which was condensed with *o*-nitrobenzyl bromide to give the phenylsulphonyl nitroketone (126). The key intermediate (127) was obtained by reduction of (126) but not without some contamination with cyclized reduction product (128). However, this latter was not a wasted by-product since it could be converted into the alkaloid isomacrorine (131). The remaining steps in the synthesis proceeded efficiently to give a product which was shown to be identical with natural dehydroisolongistrobine (129).

Maytenus buchananii and *M. ovatus*

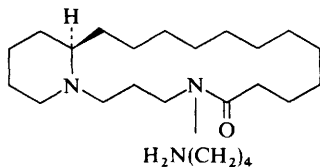
Three antileukaemic ansa macrolide-type compounds, maytansine (132; R = Me) (*M. ovatus*)¹³⁵ and maytanprine (132; R = CH₂Me) and maytanbutine (132; R = CHMe₂) (*M. buchananii*),¹³⁶ have been isolated. The structure of maytansine was established mainly by X-ray analysis while the structures of the other two alkaloids were determined by comparison of their spectral data with those of maytansine. Sesquiterpenoid alkaloids have been previously obtained from *M. ovatus* (see Vol. 3 of these Reports, p. 56).



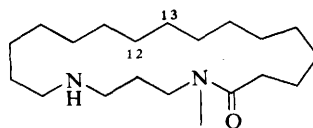
(132)

Oncinotis nitida and *O. inandensis* (Apocynaceae (Vol. 2, p. 282)

Reviews on spermine and spermidine alkaloids briefly summarize the investigations which led to the structural elucidation of oncinotine (133) and inanidenes A (134; 12-one) and B (134; 13-one).^{83a,137}



(133)



(134)

¹³⁵ S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1972, **94**, 1354.

¹³⁶ S. M. Kupchan, Y. Komoda, G. J. Thomas, and H. P. J. Hintz, *J.C.S. Chem. Comm.*, 1972, 1065.

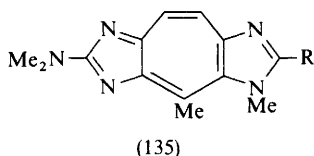
¹³⁷ M. Hesse and H. Schmid, *Izvest. Otdel. Khim. Nauki, Bulg. Akad. Nauk.*, 1972, **5**, 279 (*Chem. Abs.*, 1973, **78**, 43 814w).

Papaver somniferum

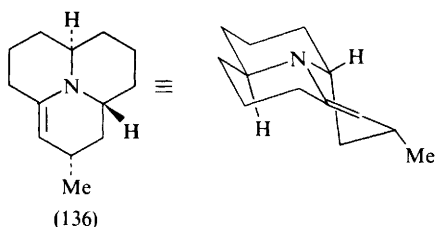
Choline has been isolated from the callus tissue of the opium poppy.¹³⁸

Parazoanthus axinellae (Zoantharia)

The interesting heteroaromatic base zoanthoxanthin (135; R = NH₂) has been isolated.¹³⁹ Spectral and chemical evidence was obtained; however, the structure was conclusively established by X-ray crystallographic analysis of the chloro-derivative (135; R = Cl), obtained by treatment of zoanthoxanthin with sodium nitrite in hydrochloric acid solution. The Zoanthidae are a group of marine animals related to sea anemones and corals which have not been well classified. Thus the distribution of these pigments may be of chemotaxonomic utility.

*Propylaea quatuordecimpunctata* (Coleoptera, Coccinellidae)

Spectral evidence suggested that propylein, the alkaloid isolated¹⁴⁰ from this beetle, is a dehydro-derivative of precoccinellin (108a), which had been previously obtained from *Coccinella septempunctata*. This was confirmed by hydrogenation of propylein to give precoccinellin (108a). Furthermore, propylein shows no u.v. absorption and one vinyl hydrogen multiplet at δ 4.78 in the n.m.r. spectrum. Of the three possible dehydroprecoccinellin structures which may now be written for propylein, model studies indicate that only (136) would not be expected to show enamine u.v. absorption owing to the lack of overlap of the π -electron system with the nitrogen lone pair. Thus structure (136) is suggested for propylein.

*Pseudomonas bromoutilis*

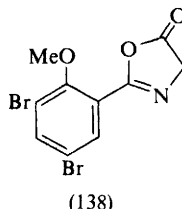
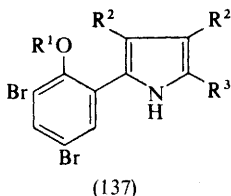
A short synthesis of the pyrrole derivative (137; R¹ = Me, R² = R³ = H), which had been previously converted into the marine antibiotic 3,3',4,5,5'-penta-

¹³⁸ T. Furuya, A. Ikuta, and K. Syono, *Phytochemistry*, 1972, **11**, 3041.

¹³⁹ L. Cariello, S. Crescenzi, G. Prota, F. Giordano, and L. Mazzarella, *J.C.S. Chem. Comm.*, 1973, 99.

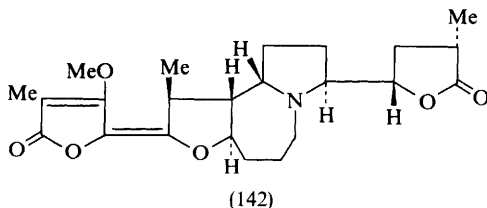
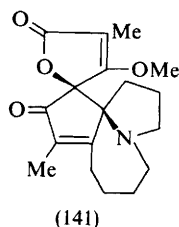
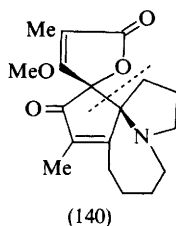
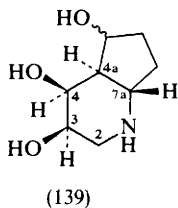
¹⁴⁰ B. Tursch, D. Daloze, and C. Hootele, *Chimia (Switz.)*, 1972, **26**, 74.

bromopseudilin (137; $R^1 = H$, $R^2 = R^3 = Br$), has been reported.¹⁴¹ A 1,3-dipolar cycloaddition reaction between the oxazolone (138) and diethyl acetylenedicarboxylate gave the diester (137; $R^1 = Me$, $R^2 = CO_2Me$, $R^3 = H$), which upon hydrolysis and decarboxylation provided the pyrrole (137; $R^1 = Me$, $R^2 = R^3 = H$).



Rhizoctonia leguminicola

The pyridine structure (139) has been assigned to an alkaloid isolated from this fungus on the basis of extensive spectral and chemical information.¹⁴² The stereochemical formulation of all chiral centres with the exception of C(5) could be assigned on the basis of the observed coupling constants ($J_{4a,7a} = 9$ Hz, $J_{2ax,3} = 7$ Hz, and $J_{3,4} = 4.5$ Hz) in the n.m.r. spectrum. Biosynthetic experiments indicate that compound (139) is produced by a pathway similar to that of slaframine, a parasympathomimetic indolizidine alkaloid also produced by *R. leguminicola*.



Stemona japonica (Stemonaceae)

Two racemic alkaloids, stemonamine (140) and isostemonamine (141), have been isolated.¹⁴³ The structure of stemonamine (140) was established by *X*-ray crystallographic analysis. Since isostemonamine shows spectral data very similar

¹⁴¹ J. W. ApSimon, D. G. Durham, and A. H. Rees, *Chem. and Ind.*, 1973, 275.

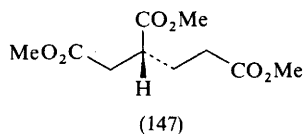
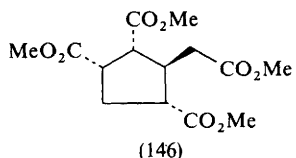
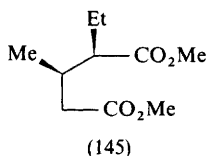
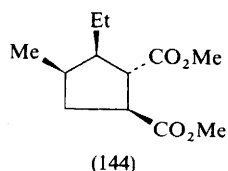
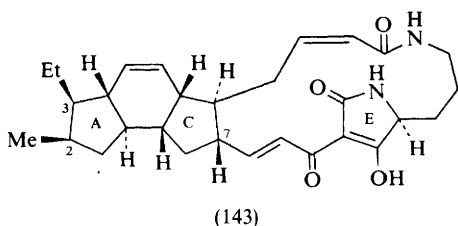
¹⁴² F. P. Guengerich, S. J. DiMari, and H. P. Broquist, *J. Amer. Chem. Soc.*, 1973, **95**, 2055.

to those of stemonamine, the spiro stereoisomeric structure (141) is proposed for isostemonamine. Since both alkaloids are found in the racemic form, their biogenesis and possible chemical interconvertibility may involve the intermediacy of an optically inactive molecule resulting from a β -amino-ketone-type fragmentation [cf. dotted line in (140)].

Prostemonine, an alkaloid also isolated from *S. japonica*, has been shown to possess structure and absolute stereochemistry (142) on the basis of an X-ray crystallographic analysis of its methanol solvate and comparison with stemonine, a related alkaloid of known absolute configuration.¹⁴⁴

Streptomyces phaeochromogenes var. *ikaruganensis*. (Vol. 3, p. 43)

The absolute stereochemistry of the antibiotic ikarugamycin has now been established and is shown in structure (143).¹⁴⁵ First, the stereochemistry of ring A was established by synthesis of four possible racemic cyclopentane-1,2-dicarboxylic esters, one of which (144) corresponded with that obtained by oxidation of ikarugamycin. The absolute configuration of C(2) and C(3) was determined by the synthesis of (–)-dimethyl erythro-2-ethyl-3-methylglutarate (145), another oxidation product of the antibiotic. Ring C relative stereochemistry was deduced from the stereospecific synthesis of the cyclopentanetetra-carboxylate derivative (146), which was also available from oxidative degradation of ikarugamycin. Finally, (+)-trimethylbutane-1,2,4-tricarboxylate (147) had been obtained from degradation of hexahydroikarugamycin. Since the absolute configuration of (147) was known, this information established the absolute configuration at C(7) of ikarugamycin. Since the absolute configuration in ring E had been previously determined from the isolation of L-ornithine, the absolute stereochemistry of ikarugamycin is given by (143). The biogenesis of the antibiotic from two C₁₂-polyacetate units and L-ornithine was proposed.¹⁴⁵



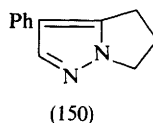
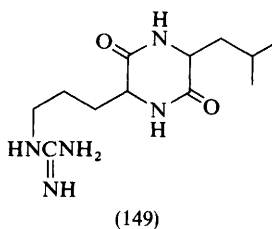
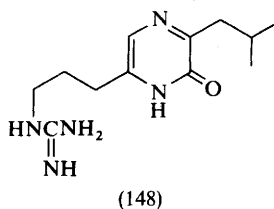
¹⁴³ H. Iizuka, H. Irie, N. Masaki, K. Osaki, and S. Uyeo, *J.C.S. Chem. Comm.*, 1973, 125.

¹⁴⁴ H. Irie, K. Ohno, K. Osaki, T. Taga, and S. Uyeo, *Chem. and Pharm. Bull. (Japan)*, 1973, 21, 451.

¹⁴⁵ S. Ito and Y. Hirata, *Tetrahedron Letters*, 1972, 2557.

Streptomyces spp.

Arglecin, a metabolite produced by several *Streptomyces* species, has been shown to possess the revised structure (148) on the basis of spectroscopic and chemical evidence.¹⁴⁶ The structural revision was initially based on the similarity of the u.v. spectra of arglecin and flavacol (106; R = H) and related products (see *Aspergillus ochraceus*). Confirmation of structure (148) for arglecin was obtained by independent synthesis of the cyclic dipeptide (149) obtained by successive bromination and zinc-acetic acid reduction of arglecin.

*Withania somnifera* (Solanaceae) (Vol. 1, p. 460)

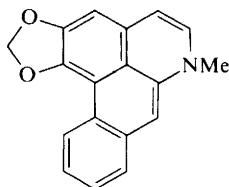
The previously discussed biogenetic-type synthesis of the unique pyrazole alkaloid withasomnine (150) has been reported in detail.¹⁴⁷

¹⁴⁶ K. Tatsuta, T. Tsuchiya, S. Umezawa, H. Naganawa, and H. Umezawa, *J. Antibiot.*, 1972, **25**, 674.

¹⁴⁷ T. Onaka, *Itsuu Kenkyusho Nempo*, 1971, **75** (*Chem. Abs.*, 1972, **77**, 48 328e).

Addendum to Chapter 9

A new amorphous aporphine believed to be didehydroaporphine [\equiv didehydro-roemerine] has been isolated in small amount from *Papaver urbanianum* Fedde (Papaveraceae), $\lambda_{\text{max}}^{\text{EtOH}}$ 208, 217, 252, 260, 328, and 385 nm (log ϵ 4.24, 4.19, 4.37, 4.41, 3.83, and 3.20).



Didehydroaporphine

Complete details of the synthesis of (\pm)-apomorphine, (\pm)-apocodeine, (\pm)-*N*-*n*-propylnorapomorphine, and (\pm)-*N*-*n*-propylnorapocodeine by the Reissert-Pschorr approach have been given. (–)-Apocodeine [\equiv (–)-10-methoxy-11-hydroxyaporphine] was also prepared by selective monomethylation of (–)-apomorphine with diazomethane. Pharmacological evaluation suggested that (–)-apomorphine and (\pm)-apomorphine and their corresponding *N*-*n*-propyl homologues were qualitatively similar in their emetic and CNS effects, but that the racemates were approximately half as potent in their emetic effects in dogs as their respective laevo-isomers.² This result concurs with those obtained by Saari, King, and Lotti (see ref. 179, p. 252).

(\pm)-9,10-Dihydroxyaporphine, (+)-, (–)-, and (\pm)-1,2-dihydroxyaporphine and (+)-1,2,9,10-tetrahydroxyaporphine have also been prepared and evaluated. The relevant observation was thus made that emetic and CNS activities reside principally in those aporphines that are substituted with phenolic hydroxy-groups at C-10 and C-11. Shifting the hydroxy-groups to C-9,10, or -1,2 markedly reduced pharmacological potency.³

Another significant observation is that diesters of (–)-apomorphine showed prolonged CNS activity and lower toxicity than the parent base.⁴

¹ V. Preininger and V. Tošnarová, *Planta Medica*, 1973, **23**, 233.

² J. L. Neumeyer, B. R. Neustadt, K. H. Oh, K. K. Weinhardt, C. B. Boyce, F. J. Rosenberg, and D. G. Teiger, *J. Medicin. Chem.*, 1973, **16**, 1223.

³ J. L. Neumeyer, M. McCarthy, S. P. Battista, F. J. Rosenberg, and D. G. Teiger, *J. Medicin. Chem.*, 1973, **16**, 1228.

⁴ D. Seidelmann, R. Schmiechen, R. Horowski, W. Kehr, D. Palenschat, and G. Paschelke, G.P. 2 154 162 (*Chem. Abs.*, 1973, **79**, 18930u).

Errata

Volume 3, 1973

Page 115, line 14. The structure of xanthoxoline should have read '(48; $R^1 = OH$, $R^2 = R^3 = OMe$, $R^4 = H$, *N*-demethyl)'

Page 183. The bottom line of type was inadvertently omitted. This would have read '... previously.⁶ Comparison of the reported physical and spectroscopic data with ...'

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