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# **The Alkaloids**

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A Specialist Periodical Report

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# The Alkaloids

Volume 5

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A Review of the Literature Published between  
July 1973 and June 1974

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## Foreword

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This fifth volume in the series of *Specialist Periodical Reports* on Alkaloids reviews the literature from July 1973 to June 1974. Since the whole field of alkaloid chemistry and biosynthesis has been covered, and since no additional, extended reviews are included, this volume will, it is hoped, give a clear indication of progress during the year under review, and the vigour and enthusiasm with which this fascinating subject is currently being studied. In common with previous years, the indole and benzyloquinoline groups dominate the scene with, of course, an ever increasing level of activity and sophistication in the realm of biosynthesis. The smaller groups of alkaloids, although not so intensively studied, continue, however, to provide examples of truly outstanding work; witness, for example, the ingenuity with which the immensely complicated diterpene alkaloids are being constructed.

Alkaloid chemistry is thus in a very healthy state, and it is on this optimistic note that we present this volume, the last with which I shall be involved as Senior Reporter. Volume 6 will be prepared under the direction of Professor M. F. Grundon. It remains for me to acknowledge, as always, the enthusiastic co-operation of my co-authors, but on this occasion I should also like to thank all those distinguished alkaloid chemists who have contributed to the first five volumes.

As this volume was being prepared for publication the sad news of the death of Sir Robert Robinson was announced. Sir Robert it was who introduced me, as an undergraduate, to alkaloid chemistry, and who later inspired me with enthusiasm for the subject as a postgraduate student and subsequently as post-doctoral Research Fellow. Numerous other organic chemists have shared the inestimable privilege of working with him, but such has been Sir Robert's contribution to the subject and his influence on its development that all organic chemists can be said to be his beneficiaries, and not simply those who have worked directly with him. Many eloquent tributes will, I hope, be paid to his achievements and to his memory, but a brief note of appreciation is particularly apt in a volume on alkaloid chemistry for he, more than any other single chemist, helped to raise the subject to the exciting discipline it is today by his own unique gifts, a combination of a rare chemical insight and originality, a complete mastery of organic chemistry, and quite remarkable intuitive powers.



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'Being very anxious to find by experiment some support for this still purely speculative view....'

'It was completely unforeseen and opens to physiology new horizons, distant, but sure'

L. Pasteur<sup>1</sup>

## 1 Introduction

As this is the fifth of these Reports the Reporter is prompted to look back over the past five years in an attempt to recall the important developments of the period. There has of course been a prodigious amount of experimental work and it can be said fairly accurately that the gross topography of the biosynthesis of almost all the plant bases is now known. In a general sense, and rising out of consideration of the detail of biosynthetic pathways, it is the tracing of the stereochemistry of the biological processes which has proved the most fascinating and stimulating both from an intellectual and from an experimental point of view. As a worthwhile consequence more effort is being expended in attempts to understand the enzymic processes involved in biosynthetic processes. In a different direction a recent development has been the harnessing of plants for the synthesis of unnatural alkaloids.<sup>2-6</sup> At its most sophisticated this can also provide information on enzyme function.

The major siege that was laid against the redoubtable problem of the biosynthesis of a large group of indole alkaloids, represented by ajmalicine (1), akuammicine (2), and catharanthine (3), had been raised by the beginning of the quinquennium with the discovery that the non-indolic C<sub>9</sub>-C<sub>10</sub> unit of each (indicated by heavy bonding) had a common terpenoid origin and that loganin (4)

<sup>1</sup> L. Pasteur, Lectures to the French Chemical Society (Paris, 1861); English translation made by the Alembic Club, Reprint No. 14, Edinburgh, 1897; *via Tetrahedron*, 1974, **30**, 1477.

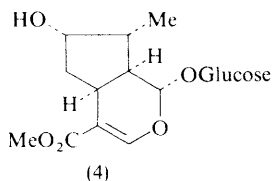
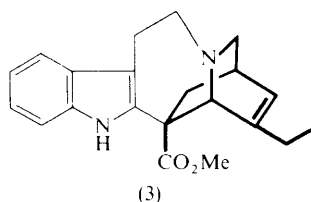
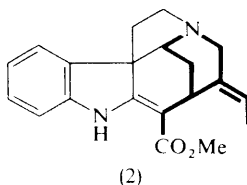
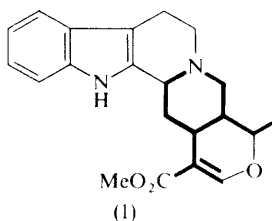
<sup>2</sup> M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, **93**, 7021; *ibid.*, 1970, **92**, 5528; E. Leete, G. B. Bodem, and M. F. Manuel, *Phytochemistry*, 1971, **10**, 2687.

<sup>3</sup> R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3, p. 32.

<sup>4</sup> G. W. Kirby, S. R. Massey, and P. Steinreich, *J.C.S. Perkin I*, 1972, 1642.

<sup>5</sup> R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4, p. 15.

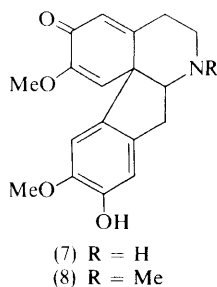
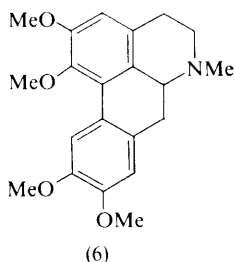
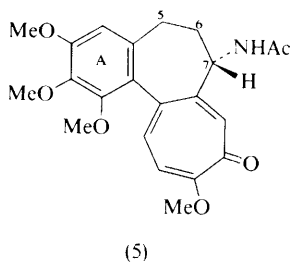
<sup>6</sup> H. Rosenberg and A. G. Paul, *J. Pharm. Sci.*, 1973, **62**, 403; R. B. Herbert, in ref. 5, p. 43.



is a key intermediate.<sup>7,8</sup> More information followed,<sup>9-11</sup> and related pathways to the *Cinchona* and *Ipecac* alkaloids were delineated.<sup>9</sup> Yet there remains fascinating detail to be uncovered.

The solution to the enigma of the biosynthesis of colchicine (5) is of longer standing. More details on the unexpected but simple pathway to this non-basic alkaloid have come with the publication of full papers.<sup>12</sup>

In the light of established pathways to aporphine alkaloids (see p. 15) study of the biosynthesis of glaucine (6) and related bases in *Dicentra eximia* might have been expected to yield orthodox results. On the contrary, however, a novel pathway was unearthed which implicates dienone intermediates of quite un-



<sup>7</sup> A. R. Battersby, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1, p. 31.

<sup>8</sup> A. I. Scott, *Accounts Chem. Res.*, 1970, 3, 151.

<sup>9</sup> J. Staunton, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1972, Vol. 2, p. 1.

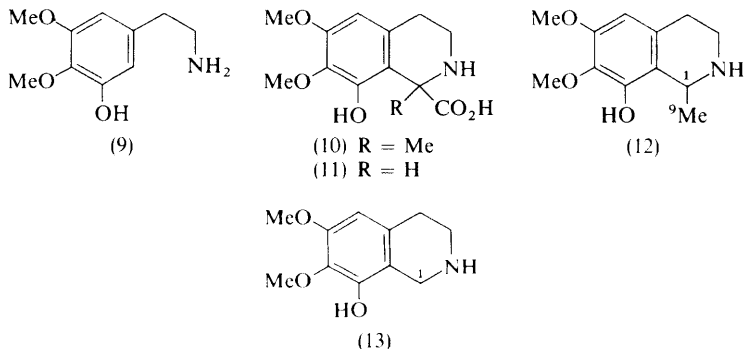
<sup>10</sup> R. B. Herbert, in ref. 3, p. 1.

<sup>11</sup> R. B. Herbert, in ref. 5, p. 30; see also this Report p. 25.

<sup>12</sup> (a) A. R. Battersby, R. B. Herbert, L. Pijewska, F. Santavý, and P. Sedmera, *J.C.S. Perkin I*, 1972, 1736; A. R. Battersby, T. A. Dobson, D. M. Foulkes, and R. B. Herbert, *ibid.*, p. 1730; (b) A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *ibid.*, p. 1741; R. B. Herbert, in ref. 5, p. 19.

expected structure: (7)/(8) for glaucine (6).<sup>13</sup> There is good evidence that the dienone (7) is also involved in the elaboration of the *Erythrina* alkaloids, along a pathway which has several remarkable features.<sup>14</sup>

Hidden in the old literature was the solution to the long-standing problem of the biosynthesis of the C<sub>2</sub> unit (C-1 and C-9) of anhalonidine (12) and the C<sub>1</sub> unit (C-1) of anhalamine (13). Only recently was the original suggestion for the biosynthesis of these cactus alkaloids<sup>15</sup> examined, with positive results.<sup>16</sup> Thus the two acids (10) and (11) were found to be precursors for (12) and (13) respectively. They apparently derive in turn from the phenethylamine (9) and pyruvic acid or



glyoxylic acid. Attention should be drawn at this point to the very detailed mapping of phenethylamine biosynthesis in cactus species.<sup>17</sup>

Much was already known of the gross features of Amaryllidaceae alkaloid biosynthesis five years ago and in the ensuing period it has been the revelation of the intricate stereochemistry of the processes involved which has proved most interesting. Newer aspects of this work are discussed in this Report (p. 19).

Structural relationships are not always what they seem: it has recently been demonstrated that the mesembrine alkaloids, superficially related to those of the Amaryllidaceae, arise by a quite different pathway, albeit from the same amino-acids (see p. 22).

Research on the biosynthesis of piperidine alkaloids has been consistently stimulating and interesting. There has been a most successful marriage of hypothesis and experiment which can be traced back over the past five years. As a result of the detailed and sophisticated studies elegant theory now stands on a firm experimental base. In particular, it is the fates of individual tritium and

<sup>13</sup> A. R. Battersby, J. L. McHugh, J. Staunton, and M. Todd, *Chem. Comm.*, 1971, 985; J. Staunton, in ref. 9, p. 12.

<sup>14</sup> D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc. (C)*, 1970, 1213; R. B. Herbert, in ref. 7, p. 22; see also this Report, p. 24.

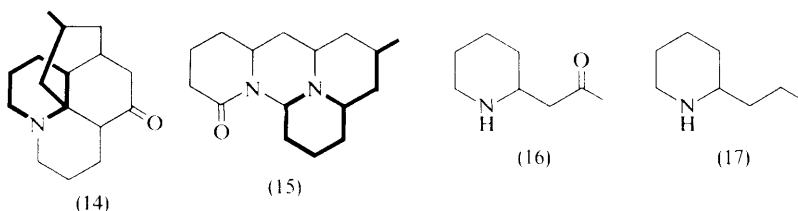
<sup>15</sup> G. Hahn, L. Bärwald, O. Schales, and H. Werner, *Annalen*, 1935, **520**, 107; G. Hahn and K. Stiehl, *Ber.*, 1936, **69**, 2627; G. Hahn and F. Rumpf, *Ber.*, 1938, **71**, 2141.

<sup>16</sup> G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Fayed, Y. N. Vaishnav, and H. M. Fales, *J. Amer. Chem. Soc.*, 1970, **92**, 6943; J. Staunton, in ref. 9, p. 10.

<sup>17</sup> J. Lundström, *Acta Pharm. Suecica*, 1971, **8**, 275, and refs. cited; R. B. Herbert, in ref. 7, p. 16; in ref. 3, p. 16.

carbon atoms in the conversion of lysine into these alkaloids which has allowed the development of the pathway as it now stands (see p. 5). Of significance here is the demonstration that L-lysine is the preferred progenitor of piperidine alkaloids whereas the D-isomer is converted into pipecolic acid in the same plant (see p. 7).

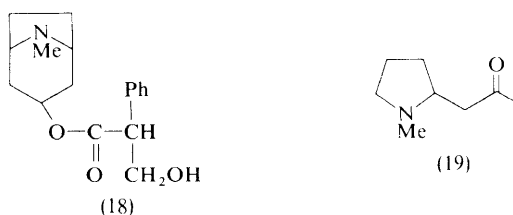
In this area the biosynthesis of the *Lycopodium* alkaloids, e.g. lycopodine (14) and cernuine (15), is of further interest. Lycopodine and cernuine were considered to be modified dimers of pelletierine (16) because two intact molecules of precursors like lysine and  $\Delta^1$ -piperidine were used for the construction of a single molecule of the alkaloids. Paradoxically, however, pelletierine (16) only gives rise



to one of two  $C_8N$  units (heavy bonding) of (14) and (15).<sup>18</sup> It is now clear that pelletierine is an obligatory intermediate in lycopodine biosynthesis and a satisfying explanation has been advanced to account for the paradox.<sup>19</sup>

Although structurally very similar to pelletierine (16) the hemlock alkaloid coniine (17) is notably of quite different origins, arising as it does from acetate in a fairly well understood pathway.<sup>20</sup>

The biosynthesis of alkaloids containing a pyrrolidine ring such as hyoscyamine (18) and hygrine (19) is similar to the biosynthesis of those with a piperidine



nucleus only in so far as the alkaloids arise from homologous amino-acids. The notable difference is that early N-methylation (of ornithine) is apparently an important reaction in the elaboration of pyrrolidine alkaloids,<sup>21</sup> whereas N-methylation occurs late in the formation of the piperidine bases.

<sup>18</sup> Y. K. Ho, R. N. Gupta, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1971, **49**, 3352; M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1970, **48**, 2911, 1893; R. B. Herbert, in ref. 3, p. 28.

<sup>19</sup> J.-C. Braekman, R. N. Gupta, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1972, **50**, 2591; R. B. Herbert, in ref. 5, p. 1.

<sup>20</sup> E. Leete and J. O. Olsen, *J. Amer. Chem. Soc.*, 1972, **94**, 5472; R. B. Herbert in ref. 5, p. 10.

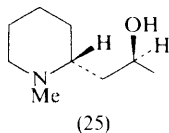
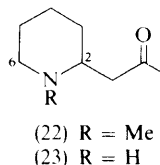
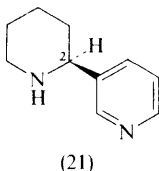
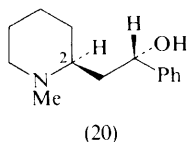
<sup>21</sup> J. Staunton, in ref. 9, p. 27, and refs. cited; R. B. Herbert, in ref. 7, p. 9, and refs. cited.

There has been a steady progress in the fitting together of the pieces that make up the pattern of furoquinoline and ergot alkaloid biosynthesis so that the pathways for each of these groups is now fairly clear. Both have been the subject of recent publication (see p. 35 and 27).

In the above, discussion has been curtailed on important topics which appear later in this Report, and the reader is referred to the appropriate sections for a fuller treatment.

## 2 Piperidine, Pyridine, and Pyrrolidine Alkaloids

**Piperidine Alkaloids.**—There is now a wealth of detail on the incorporation of lysine into the piperidine nucleus of alkaloids such as sedamine (20), anabesine (21), and *N*-methypelletierine (22).<sup>22</sup> Five of the carbon atoms of L-lysine (26) (C-2 to C-6) are incorporated into the piperidine ring of these bases in a manner which does not allow carbons 2 and 6 of lysine to become equivalent, *i.e.* no symmetrical intermediates are permissible. However, in the conversion of lysine into the piperidine rings of the related bases cernuine (15), lycopodine (14),<sup>18</sup> decodine,<sup>23</sup> and the lupine alkaloids<sup>24</sup> C-2 and C-6 do become equivalent and at least one symmetrical intermediate must therefore be involved. Such an intermediate could be cadaverine (27). Cadaverine is a specific precursor for anabesine (21)<sup>25</sup> and is also incorporated into pseudopelletierine (24) and *N*-methypelletierine (22).<sup>26</sup> This is paradoxical, for as stated above *N*-methypelletierine (22) and anabesine (21) are derived from lysine in unsymmetrical fashion.



One way in which the unsymmetrical incorporation of lysine could be explained was by invoking mono-*N*-methyl derivatives<sup>27</sup> as adduced analogously

<sup>22</sup> R. B. Herbert in ref. 3, p. 25, and refs. cited.

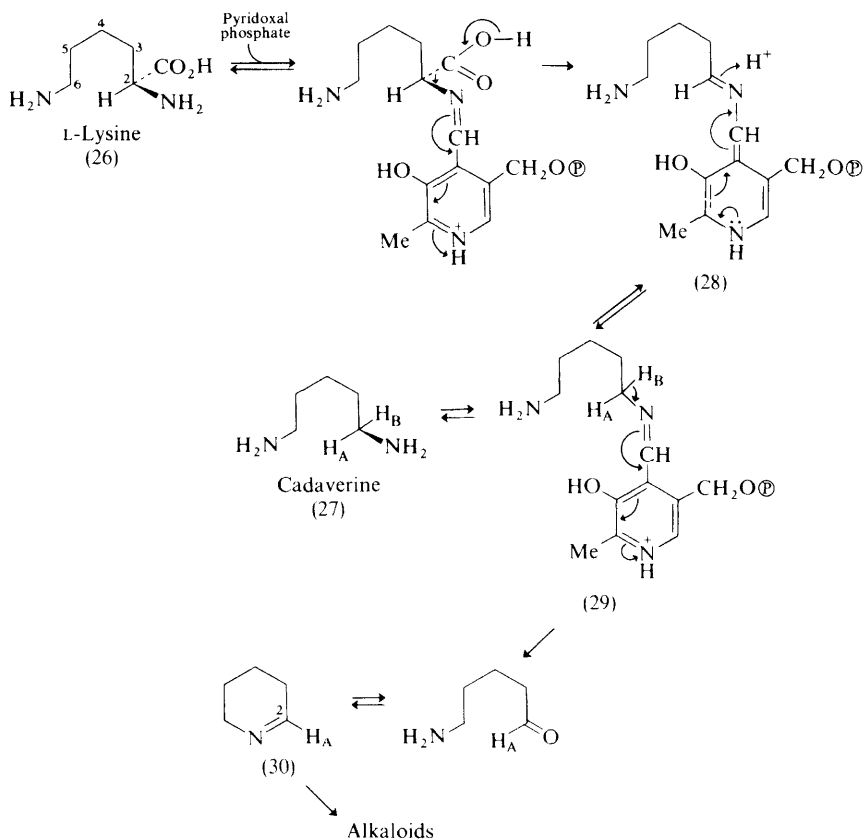
<sup>23</sup> S. H. Koo, R. N. Gupta, I. D. Spenser, and J. T. Wrobel, *Chem. Comm.*, 1970, 396; R. B. Herbert, in ref. 7, p. 6.

<sup>24</sup> H. R. Schütte, in 'Biosynthese der Alkaloide', ed. K. Mothes and H. R. Schütte, VEB Deutscher Verlag der Wissenschaften, Berlin, 1969, p. 324.

<sup>25</sup> E. Leete, *J. Amer. Chem. Soc.*, 1958, **80**, 4393.

<sup>26</sup> H. W. Liebisch, N. Marekov, and H. R. Schütte, *Z. Naturforsch.*, 1968, **23b**, 1116.

<sup>27</sup> R. N. Gupta and I. D. Spenser, *Phytochemistry*, 1970, **9**, 2329; R. B. Herbert, in ref. 3, p. 25.



Scheme 1

for the biosynthesis of the related pyrrolidine alkaloids.<sup>21</sup> Intermediates which follow lysine on this pathway are  $\epsilon$ -N-methyl-lysine and N-methylcadaverine. The former compound was shown<sup>28</sup> to be present in *Sedum acre*, a plant which also produces sedamine (20). Further, its formation from [6-<sup>3</sup>H]lysine and [Me-<sup>14</sup>C]methionine could also be demonstrated. But the <sup>14</sup>C:<sup>3</sup>H ratio of the derived  $\epsilon$ -N-methyl-lysine was quite different from that of the sedamine (20) isolated in the same experiment. Furthermore, attempts to demonstrate the formation of N-methylcadaverine in two *Sedum* species and *Nicotiana glauca* [a plant which produces anabesine (21)] were unsuccessful. More direct evidence comes from feeding DL-[2-<sup>14</sup>C,N-Me-<sup>3</sup>H]-N-methyl-lysine to *S. acre*.<sup>29</sup> The precursor was poorly converted into sedamine with alteration of the isotope ratio, which indicated non-intact incorporation. These results, as well as data on

<sup>28</sup> E. Leistner and I. D. Spenser, *J. Amer. Chem. Soc.*, 1973, **95**, 4715.

<sup>29</sup> P. Korzan and T. J. Gilbertson, *Phytochemistry*, 1974, **13**, 435.

the biosynthesis of anabesine,<sup>30,31</sup> require rejection of the 'N-methylation' hypothesis.

In further consideration of the biosynthesis of the piperidine alkaloids the question of the significance of the incorporation of cadaverine must be answered. Accordingly further research has been directed to this point and it has been shown<sup>28</sup> that cadaverine is a normal component of *S. acre*, that it is a specific precursor of sedamine (20), and that it is formed from lysine at the same time as sedamine. It follows then that any scheme for the biosynthesis of the piperidine alkaloids which does not accommodate cadaverine as a normal component is unrealistic.

An eminently reasonable hypothesis<sup>28</sup> which fits all the evidence is shown in Scheme 1; it was anticipated in last year's Report.<sup>31</sup> For those alkaloids derived from lysine without the intervention of a symmetrical intermediate, cadaverine formed by decarboxylation of lysine must remain enzyme-bound and therefore unsymmetrical. Exogenous cadaverine enters the pathway at this point by absorption on to the enzyme to give (29). In order to explain the incorporation of lysine into some alkaloids by way of a symmetrization step it is necessary only to postulate equilibration of bound with unbound cadaverine. The proposal that pyridoxal phosphate is involved in this pathway is more than mechanistically attractive, for L-lysinedecarboxylase (EC 4.1.1.18, L-lysine carboxy-lyase) and diamine oxidase [EC 1.4.3.6, diamine:oxygen oxidoreductase (deaminating)], the two enzymes whose participation in the conversion of lysine into  $\Delta^1$ -piperidine (30) is likely, both require pyridoxal phosphate as a co-factor.<sup>32</sup>

The validity of the above scheme was further explored<sup>28</sup> with cadaverine samples chirally labelled with tritium at C-1. (The samples were obtained by decarboxylation of L-lysine mediated by L-lysinedecarboxylase from *Bacillus cadaveris*. The absolute configuration of the two materials is unknown and they were accordingly named [1A-<sup>3</sup>H]- and [1B-<sup>3</sup>H]-cadaverine.) The labelling pattern of the derived *N*-methylpelletierine (22) was in accord with stereospecific oxidative deamination to  $\Delta^1$ -piperidine (30) and in agreement with the proposed model. Both cadaverine samples afforded *N*-methylpelletierine (22) with a label at C-6 but only [1A-<sup>3</sup>H]cadaverine labelled C-2. (The puzzling loss of 25% of the tritium from non-chirally labelled [1-<sup>14</sup>C,1-<sup>3</sup>H]cadaverine on incorporation into *N*-methylpelletierine<sup>26</sup> is now explained in terms of this model, the tritium loss being exactly as predicted. It seems that subsequent elaboration of *N*-methylpelletierine (22) to pseudopelletierine (24) is accompanied by preferential tritium retention at C-6 by a primary isotope effect.<sup>26,28</sup>)

In a notable piece of research it was shown that the L-isomer of lysine was much preferred for anabesine biosynthesis whereas the D-isomer was preferentially utilized for L-pipecolic acid biosynthesis in *N. glauca*.<sup>33</sup> In a more rigorous study this was confirmed for sedamine (20), *N*-methylpelletierine (22), *N*-methylallosedridine (25) (in two *Sedum* species), and anabesine (in *N. glauca*) and also for

<sup>30</sup> E. Leete and M. R. Chedekel, *Phytochemistry*, 1972, **11**, 2751.

<sup>31</sup> R. B. Herbert, in ref. 5, p. 4.

<sup>32</sup> M. Dixon and E. C. Webb, 'The Enzymes', 2nd Edn., Longmans, London, 1964, pp. 688, 762.

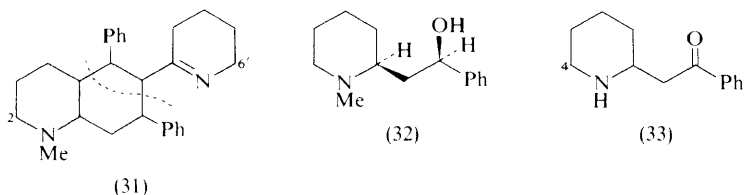
<sup>33</sup> T. J. Gilbertson, *Phytochemistry*, 1972, **11**, 1737; R. B. Herbert, in ref. 3, p. 25.

pipecolic acid in each of these plants.<sup>34\*</sup> Thus, in terms of the model, both decarboxylation and oxidative deamination are stereospecific.

This study with the chirally labelled cadaverines brings to light an apparent anomaly. Decarboxylation of L-[2-<sup>3</sup>H]lysine by the enzyme from *B. cadaveris* affords [1*B*-<sup>3</sup>H]cadaverine. When this material is converted into *N*-methyl-pelletierine (22) and *N*-methylallosedridine in *S. sarmentosum* the tritium destined for C-2 is lost. On the other hand conversion of lysine into the sedamine in *S. acre* results in the retention of tritium originally present at C-2.<sup>27</sup> The simplest explanation of this is that the protonation of (28) in the micro-organism and the plants proceeds with opposite stereochemistry.

A final point arises from the fact that the stereochemistry at C-2 is not the same in different piperidine bases. For example (–)-sedamine (20) is 2*S* whereas (–)-pelletierine [as (23)] is 2*R*. This indicates that addition of the side chain to Δ<sup>1</sup>-piperidine (30) can occur on both the *re* and *si* faces of the molecule, for later epimerization at C-2 seems to be excluded by tritium retention at this site.

**Lobinaline.**—Discussion of the biosynthesis of lobinaline (31) was omitted from earlier Reports and so is included here. Both lobinaline and 8-phenyl-lobelol-I (32) are constituents of *Lobelia inflata*. The structure of lobinaline may be broken visually along the dashed line in (31) into two units of the type seen in (32) and



sedamine (20).<sup>35</sup> Sedamine, it is known, is formed by the union of a C<sub>6</sub>-C<sub>2</sub> unit derived from phenylalanine and a cyclic C<sub>5</sub>N unit originating from lysine without intervention of symmetrical intermediates.<sup>27,28,36</sup>

In accord with the dimer hypothesis phenylalanine and lysine were found to be specific precursors for both 'halves' of lobinaline and label appeared at the expected sites with apparently equal distribution of activity between the 'halves' of lobinaline.<sup>35</sup> Further substantiation of the hypothesis came with the specific and efficient incorporation of [4-<sup>14</sup>C]-2-phenacylpiperidine [as (33)] with equal labelling of C-2 and C-6'.

<sup>34</sup> E. Leistner, R. N. Gupta, and I. D. Spenser, *J. Amer. Chem. Soc.*, 1973, **95**, 4040.

<sup>35</sup> R. N. Gupta and I. D. Spenser, *Canad. J. Chem.*, 1971, **49**, 384.

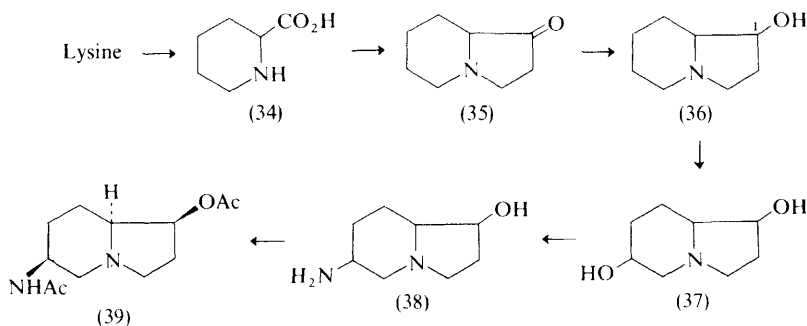
<sup>36</sup> R. N. Gupta and I. D. Spenser, *Canad. J. Chem.*, 1967, **45**, 1275.

\* The method described avoids the uncertainty associated with a simple comparison of incorporation efficiencies. Instead the comparison was conducted by use of an internal standard, simply achieved by employing mixed <sup>3</sup>H- and <sup>14</sup>C-labelled samples. (In this case the complementary sets L-[4,5-<sup>3</sup>H<sub>2</sub>]/DL-[6-<sup>14</sup>C]lysine and DL-[4,5-<sup>3</sup>H<sub>2</sub>]/D-[6-<sup>14</sup>C]lysine were used.) The method deserves wide applicability.



**Slaframine.**—Further details<sup>37</sup> are now available on the biosynthesis of slaframine (39), a toxin produced by the mould *Rhizoctonia leguminicola*. Both DL-[1-<sup>14</sup>C]- and DL-[6-<sup>14</sup>C]-lysine afforded labelled slaframine, indicating intact incorporation of all the carbons of the amino-acid. Addition of inactive pipecolic acid (34) to the cultures diluted the lysine label in the derived slaframine, and pipecolic acid was labelled by radioactive lysine. Further carboxyl- and ring-labelled pipecolic acids [as (34)] were both well incorporated into slaframine. A clear indication is thus obtained of the biosynthetic sequence: lysine → pipecolic acid (34) → slaframine (39); 2-hydroxymethylpiperidine is not a precursor. Attention is drawn to the discovery of a similar pathway to a metabolite of similar structure also produced by *R. leguminicola*.<sup>38</sup>

The incorporation of (36), (35), and (37) with increasing efficiency allowed further definition of the pathway to slaframine.<sup>37</sup> The results indicate that a tritium label at C-1 of (36) is retained on formation of (39), and so (36) must follow (35) on the pathway. Further support for this relationship comes from the discovery that a cell-free extract of *R. leguminicola* would catalyse the NADPH-dependent reduction of (35) to (36). This extract also catalysed the acetyl-CoA-dependent formation of slaframine (39) from (38). The pathway to slaframine so far deduced is illustrated in Scheme 2.



L-Pipecolic acid [as (34)] is derived from D-lysine in several higher plants,<sup>33,34,39</sup> rats,<sup>40</sup> and the bacterium *Pseudomonas putida*.<sup>41</sup> In contrast, recent evidence indicates that L-pipecolic acid arises from L-lysine in the mould *R. leguminicola*;<sup>42</sup> D-lysine, it appears, is converted into  $\epsilon$ -N-acetyl-lysine. Otherwise the evidence

<sup>37</sup> F. P. Guengerich, J. J. Snyder, and H. P. Broquist, *Biochemistry*, 1973, **12**, 4264.

<sup>38</sup> F. P. Guengerich, S. J. DiMari, and H. P. Broquist, *J. Amer. Chem. Soc.*, 1973, **95**, 2055; R. B. Herbert, in ref. 5, p. 12.

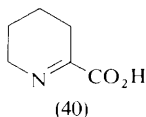
<sup>39</sup> R. H. Aldag and J. L. Young, *Planta*, 1970, **95**, 187.

<sup>40</sup> J. A. Grove, T. J. Gilbertson, R. H. Hammerstedt, and L. M. Henderson, *Biochim. Biophys. Acta*, 1969, **184**, 329; J. Grove and L. M. Henderson, *ibid.*, 1968, **165**, 113; P. Boulanger, R. Osteux, E. Secquet, and H. Charlier, *ibid.*, 1969, **184**, 338.

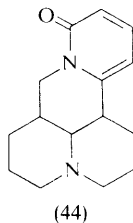
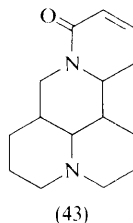
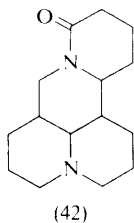
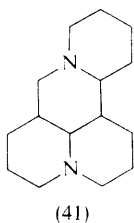
<sup>41</sup> Y.-F. Chang and E. Adams, *Biochem. Biophys. Res. Comm.*, 1971, **45**, 570; D. L. Miller and V. W. Rodwell, *J. Biol. Chem.*, 1971, **246**, 2758.

<sup>42</sup> F. P. Guengerich and H. P. Broquist, *Biochemistry*, 1973, **12**, 4270.

is that formation of pipecolic acid is *via*  $\Delta^1$ -piperidine-2-carboxylic acid (40) as expected.<sup>27</sup>



**Quinolizidine Alkaloids.**—Analysis of *Goebelia pachycarpa* shoots after administration of  $^{14}\text{C}$ -labelled matridine (41) and matrine (42) has indicated the sequence for alkaloid biosynthesis as: matridine, matrine, matrine *N*-oxide, sophocarpine (43), sophocarpine *N*-oxide, and sophoramine (44).<sup>43</sup>



Efficient and specific incorporations of various  $^{14}\text{C}$ -labelled matridines into matrine have been recorded.<sup>44</sup>

**Securinine.**—A unique tetracyclic structure is a feature of the alkaloids of the *Securinega* genus (family Euphorbiaceae). Study of the biosynthesis of the most commonly occurring base, securinine (47), has revealed an appropriately unusual genesis for rings C and D.

Incorporation of DL-[2- $^{14}\text{C}$ ]tyrosine<sup>45,46</sup> was to give specific labelling of C-1, whilst the results with L-[U- $^{14}\text{C}$ ]tyrosine<sup>46</sup> confirmed the utilization of this amino-acid as the source of a  $\text{C}_8$  unit for rings C and D. (Tyramine, dopa, and homogentisic acid were much less effective precursors<sup>46</sup> for securinine, and homogentisic acid label was randomized.) The results<sup>45,46</sup> with phenylalanine exclude it as a precursor and provide yet another example of the non-equivalence of phenylalanine and tyrosine in biosynthesis in higher plants.

The remaining carbons and the nitrogen of securinine (47) manifestly arise from lysine and accordingly satisfactory incorporations of this amino-acid and cadaverine were recorded.<sup>46</sup> Degradation of material derived from [1,5- $^{14}\text{C}_2$ ]-cadaverine established a specific incorporation with equal labelling of the expected positions, C-9 and C-13. Regrettably no degradation was carried out on the securinine generated from [2- $^{14}\text{C}$ ]lysine to see whether incorporation was in a

<sup>43</sup> A. A. Takanaev, *Khim. Rast. Veshchetv.*, 1972, 31 (*Chem. Abs.*, 1973, 79, 765).

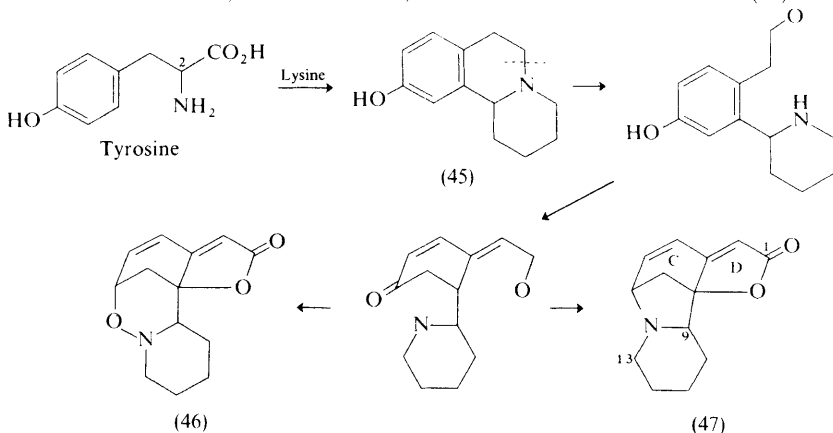
<sup>44</sup> B. A. Abdusalamov, A. A. Takanaev, Kh. A. Aslanov, and A. S. Sadykov, *Nauch. Trudy, Tashkent Univ.*, 1972, No. 419, p. 235 (*Chem. Abs.*, 1973, 79, 15 891).

<sup>45</sup> R. J. Parry, *Tetrahedron Letters*, 1974, 307.

<sup>46</sup> U. Sankawa, K. Yamasaki, and Y. Ebizuka, *Tetrahedron Letters*, 1974, 1867.

symmetrical or unsymmetrical manner (see discussion above). Curiously DL-lysine was reported as a much better precursor than L-lysine for securinine when one would have expected the reverse.<sup>33,34</sup> However, the authors<sup>46</sup> do not refer to this and there may be a simple explanation arising from the experimental method.

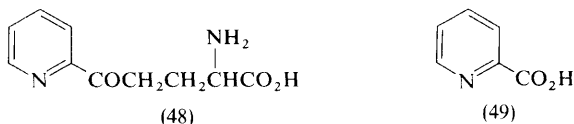
The above results allowed a plausible biosynthetic route to securinine, illustrated in Scheme 3, to be advanced;<sup>45</sup> C—N fission as illustrated in (45) has



Scheme 3

precedent in the biosynthesis of other alkaloids.<sup>47</sup> Also included in the Scheme is the base phyllantidine (46), which appears to retain the phenolic oxygen of tyrosine.

**Proferrosamine A.**—The *Pseudomonas roseus fluorescens* metabolite proferrosamine A (48) derives efficiently from picolinic acid (49).<sup>48</sup> A further result<sup>49</sup> is that L-[U-<sup>14</sup>C]lysine was also well incorporated and again the activity was confined to the picolinic acid moiety of (48).



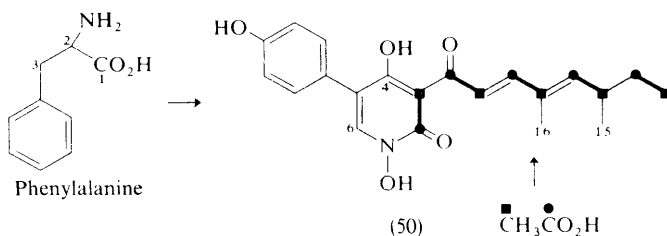
**Tenellin.**—The recent study on the structure and biosynthesis of tenellin (50) provides a good example of the use of <sup>13</sup>C labelling. Firstly, <sup>13</sup>C n.m.r. was used in conjunction with biosynthetic labelling of tenellin to provide valuable insight

<sup>47</sup> A. R. Battersby, R. J. Francis, E. A. Ruveda, and J. Staunton, *Chem. Comm.*, 1965, 89; A. R. Battersby and R. J. Parry, *Chem. Comm.*, 1971, 30; *ibid.*, p. 31.

<sup>48</sup> M. Pouteau-Thouvenot, J. Padikkala, M. Barbier, A. Helbling, and M. Viscontini, *Helv. Chim. Acta*, 1972, **55**, 2295; R. B. Herbert, in ref. 5, p. 9.

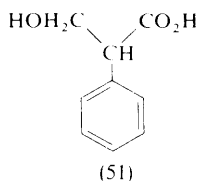
<sup>49</sup> M. Pouteau-Thouvenot, J. Padikkala, M. Barbier, and M. Viscontini, *Helv. Chim. Acta*, 1973, **56**, 1067.

into the structure of this metabolite of *Beauvaria* species.<sup>50</sup> Secondly, feeding experiments with putative precursors singly labelled with <sup>13</sup>C led to the conclusion<sup>51</sup> about the origins of the carbon skeleton shown in Scheme 4; C-15 and



**Scheme 4**

C-16 arise from methionine. Of note is the fact that C-1 of phenylalanine appears at C-4 of tenellin and C-2 at C-6. The implied rearrangement finds analogy in the biosynthesis of tropic acid (51)<sup>52</sup> from phenylalanine.



Incorporation of [1,2-<sup>13</sup>C]acetate gave tenellin with the expected satellite resonances due to <sup>13</sup>C-<sup>13</sup>C spin-spin coupling, from which the intact two-carbon acetate-derived units could be discerned (see Scheme 4). (For an even more powerful application of doubly labelled [<sup>13</sup>C]acetate to biosynthetic problems see ref. 53.)

**Tropane Alkaloids.**—Previous research had shown that the tiglic acid (55) moieties of the ester alkaloids of *Datura* species, e.g. (56), (57), and meteloidine (58), arise specifically from L-isoleucine (52).<sup>54</sup> This amino-acid is also a source for angelic acid (the geometric isomer of tiglic acid) in *Cynoglossum officinale*<sup>55</sup> and it is degraded in animal tissues to tiglic acid,<sup>56</sup> probably by way of 2-keto-3-

<sup>50</sup> A. G. McInnes, D. G. Smith, C.-K. Wat, L. C. Vining, and J. L. C. Wright, *J.C.S. Chem. Comm.*, 1974, 281.

<sup>51</sup> A. G. McInnes, D. G. Smith, J. A. Walter, L. C. Vining, and J. L. C. Wright, *J.C.S. Chem. Comm.*, 1974, 282.

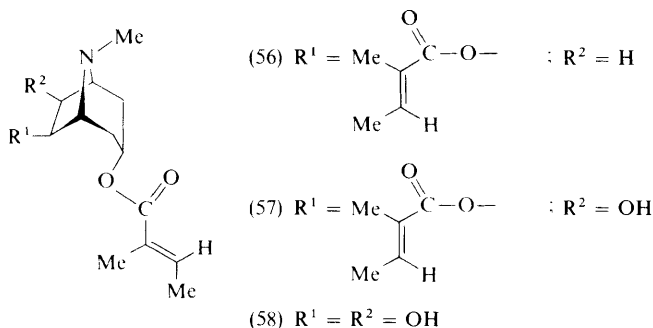
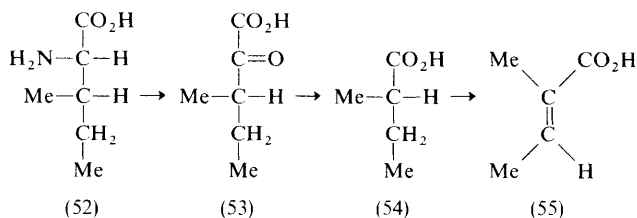
<sup>52</sup> H. W. Liebisch, in ref. 24, p. 183; R. B. Herbert, in ref. 5, p. 13.

<sup>53</sup> H. Seto, L. W. Cary, and M. Tanabe, *J.C.S. Chem. Comm.*, 1973, 867; H. Seto and M. Tanabe, *Tetrahedron Letters*, 1974, 651.

<sup>54</sup> J. G. Woolley, *Abhandl. Deut. Akad. Wiss. Berlin, Klasse Chem. Geol. Biol.*, 1966, No. 3, p. 531; E. Leete and J. B. Murrill, *Tetrahedron Letters*, 1967, 1233.

<sup>55</sup> D. H. G. Crout, *J. Chem. Soc. (C)*, 1967, 1233.

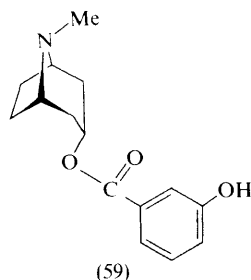
<sup>56</sup> W. G. Robinson, B. K. Bachhawat, and M. J. Coon, *J. Biol. Chem.*, 1956, **218**, 391; M. J. Coon, N. S. B. Abrahamsen, and G. S. Green, *J. Biol. Chem.*, 1952, **195**, 805; *ibid.*, **199**, 75.



methylvaleric acid (53) and 2-methylbutyric acid (54). Recent experiments with (*RS*)-[1- $^{14}\text{C}$ ]-2-methylbutyric acid [as (54)] establish this acid as a specific precursor for the tigloyl moieties of (56) and (57) in *D. innoxia*<sup>57</sup> and meteloidine (58) in *D. meteloides*.<sup>58</sup> It is thus a probable intermediate between L-isoleucine (52) and tiglic acid (55). Further, since the isoleucine is 3-*S* it is probable that the actual intermediate is the (*S*)-isomer of 2-methylbutyric acid.

2-Hydroxy-2-methylbutyric acid was not a precursor for the tigloyl moieties of (56) and (57), which indicates that introduction of the double bond is by dehydrogenation rather than dehydration. (A parallel feeding experiment was carried out with 2-methylbutyric acid in an attempt to ensure the reliability of this negative result.<sup>57</sup>)

Unusual in the structure (59) for cochlearine is the benzoic acid residue with a *meta*-hydroxy-group. In a preliminary study<sup>59</sup> shikimic acid and acetate were



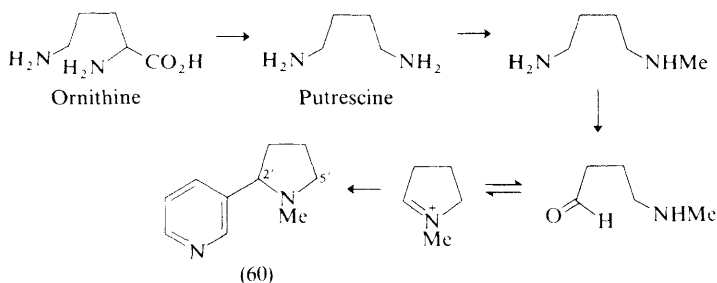
<sup>57</sup> K. Basey and J. G. Woolley, *Phytochemistry*, 1973, **12**, 2197.

<sup>58</sup> E. Leete, *Phytochemistry*, 1973, **12**, 2203.

<sup>59</sup> H.-W. Liebisch, H. Bernash, and H. R. Schütte, *Z. Chem.*, 1973, **10**, 372.

found to be only poor precursors for (59). Good incorporations of *m*-tyrosine, phenylalanine and, as expected, putrescine were, however, recorded. [3-<sup>14</sup>C,3'-<sup>3</sup>H]Phenylalanine was incorporated with 69% tritium retention. Whether this is due to a simple isotope effect or an 'NIH' type shift<sup>60</sup> is not yet clear.

**Nicotine.**—A wealth of experimental work has led to confusion rather than clarity about the biosynthesis of the pyrrolidine ring of nicotine (60). Tracer<sup>61</sup> and enzymic<sup>62</sup> evidence seems to favour a pathway involving at least one symmetrical intermediate (putrescine), illustrated in Scheme 5, although others are possible.



**Scheme 5**

Conflicting evidence has been obtained as a result of experiments with <sup>14</sup>CO<sub>2</sub>. One set of data indicates formation of the pyrrolidine ring *via* at least one symmetrical intermediate<sup>63</sup> whereas the other is consistent with a route involving only unsymmetrical intermediates.<sup>64</sup> Some doubt<sup>65</sup> about the integrity of part of the degradation procedure used for determining the activity at C-5' has been resolved without affecting the tracer results.<sup>66</sup>

Recent research with <sup>14</sup>CO<sub>2</sub> has been directed towards resolving the conflict and a more rigorous approach has been employed.<sup>67</sup> The <sup>14</sup>CO<sub>2</sub> was administered under steady-state conditions<sup>68</sup> and this was coupled with a degradation which specifically included a new method for determining the radioactivity of C-2' of nicotine with complete integrity. In a series of experiments<sup>67</sup> in *Nicotiana glutinosa* different results were obtained. Some of the labelling patterns were

<sup>60</sup> G. Guroff, J. W. Daly, D. M. Jerina, B. Witkop, and S. Udenfriend, *Science*, 1967, **157**, 1524.

<sup>61</sup> D. Gross, in ref. 24, p. 234.

<sup>62</sup> S. Mizusaki, Y. Tanabe, M. Noguchi, and E. Tamaki, (a) *Phytochemistry*, 1972, **11**, 2757; (b) *Plant Cell Physiol.*, 1971, **12**, 633.

<sup>63</sup> H. R. Zielke, R. U. Byerrum, R. M. O'Neal, L. C. Burns, and R. E. Koeppe, *J. Biol. Chem.*, 1968, **243**, 4757.

<sup>64</sup> W. L. Alworth, A. A. Liebman, and H. Rapoport, *J. Amer. Chem. Soc.*, 1964, **86**, 3375; A. A. Liebman, F. Morsingh, and H. Rapoport, *ibid.*, 1965, **87**, 4399; A. A. Liebman, B. P. Mundy, and H. Rapoport, *ibid.*, 1967, **89**, 664.

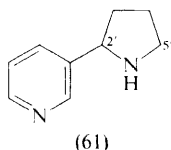
<sup>65</sup> E. Leete, *Chem. Comm.*, 1971, 1524; R. B. Herbert, in ref. 3, p. 32.

<sup>66</sup> A. A. Liebman, B. P. Mundy, and H. Rapoport, *J.C.S. Chem. Comm.*, 1972, 1022.

<sup>67</sup> M. L. Rueppel, B. P. Mundy, and H. Rapoport, *Phytochemistry*, 1974, **13**, 141.

<sup>68</sup> H. I. Parker, G. Blaschke, and H. Rapoport, *J. Amer. Chem. Soc.*, 1972, **94**, 1276.

symmetrical whereas others were unsymmetrical. This led to the suggestion that elaboration of nicotine in *Nicotiana* could proceed by two different pathways, one involving symmetrical intermediates and the other unsymmetrical intermediates. Support for this comes from the results<sup>69</sup> of an experiment where [2-<sup>14</sup>C]-ornithine was added to an excised root culture of *N. rustica*. The nornicotine (61) isolated was shown to have two-thirds of its activity located at C-2' with



one-third at C-5' by difference. This then is also explained in terms of the two pathways advanced above.

There is an alternative way of viewing the above results, however. It could be that the biosynthetic pathway to the pyrrolidine ring of nicotine is similar (in part) to the route to the piperidine alkaloids. Part of the model suggested<sup>28,31</sup> for the biosynthesis of the piperidine nucleus from lysine (see above) could be easily adapted to account for the <sup>14</sup>CO<sub>2</sub> and nornicotine results, that is variable/incomplete equilibration of bound putrescine (arising by enzyme-mediated decarboxylation of ornithine) with unbound material. L-Ornithine decarboxylase (EC 4.1.1.17, L-ornithine carboxy-lyase) occurs widely in higher plants<sup>70</sup> and like L-lysine decarboxylase requires pyridoxal phosphate as a co-factor.<sup>71</sup>

### 3 Isoquinoline Alkaloids

**Aporphine Alkaloids.**—Isothebaine (65) derives from orientaline (62) along a pathway which involves the dienone (63) and the dienol (64).<sup>72</sup> The biosynthesis of the aporphine alkaloids of *Dicentra eximia* is quite different<sup>13</sup> but dienone intermediates are also implicated. By comparison the biosynthesis of bulbocapnine (66) is simple, for the alkaloid arises directly from reticuline (67), in *Corydalis cava*, by *ortho-ortho* phenol oxidative coupling.<sup>73</sup>

Further experiments have been directed towards proving that reticuline is a natural constituent of *C. cava*.<sup>74</sup> Thus it could be diluted out with inactive material after feeding DL-[2-<sup>14</sup>C]dopa. Circumstantial evidence for its presence in the plant comes from the isolation of sinoacutine (68) from this plant: presumably

<sup>69</sup> S. Mizusaki, T. Kasaki, and E. Tamaki, *Agric. and Biol. Chem. (Japan)*, 1965, **29**, 714.

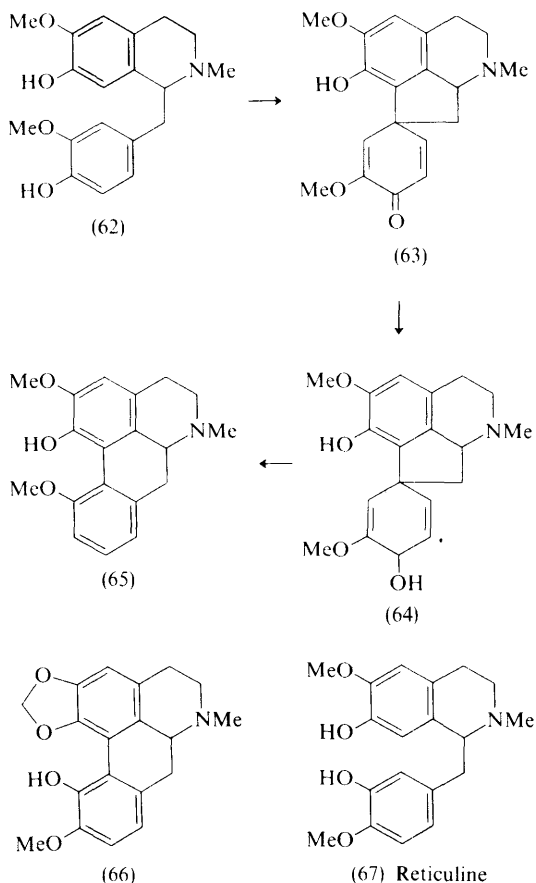
<sup>70</sup> K. Hasse, O. T. Ratych, and J. Salnikow, *Hoppe-Seyler's Z. physiol. Chem.*, 1967, **348**, 843; and unpublished work quoted in ref. 62b.

<sup>71</sup> M. Dixon and E. C. Webb, in ref. 32, p. 762.

<sup>72</sup> A. R. Battersby, R. T. Brown, J. H. Clements, and G. G. Iverach, *Chem. Comm.*, 1965, 230; A. R. Battersby and T. H. Brown, *ibid.*, 1966, 170; A. R. Battersby, T. J. Brocksom, and R. Ramage, *ibid.*, 1969, 464; R. B. Herbert, in ref. 7, p. 19.

<sup>73</sup> G. Blaschke, *Arch. Pharm.*, 1968, **301**, 432; G. Blaschke, *ibid.*, 1970, **303**, 358; R. B. Herbert in ref. 7, p. 21.

<sup>74</sup> G. Blaschke, G. Waldheim, M. von Schantz, and P. Peura, *Arch. Pharm.*, 1974, **307**, 122.



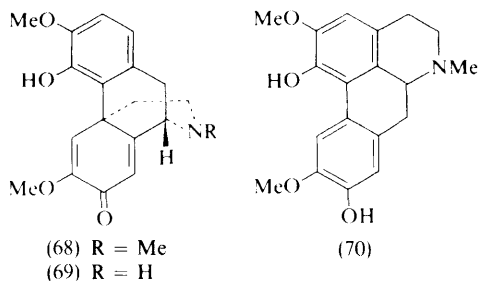
this dienone also arises by phenol oxidative coupling from reticuline (67). With the natural occurrence of reticuline (67) demonstrated in this plant the participation of (67) as an intermediate in bulbocapnine biosynthesis is most likely.

Reticuline (67) is also a precursor for isoboldine (70) (in *Papaver somniferum*).<sup>75</sup> Orientaline (62) has been isolated from *P. somniferum* for the first time, by adding inactive material as a carrier during isolation, after feeding ( $\pm$ )-[3-<sup>14</sup>C]nor-laudanosoline.<sup>76</sup> However, it was shown not to be a precursor for isoboldine (70) in this plant, thus indicating a unique biosynthetic pathway for isoboldine from reticuline.

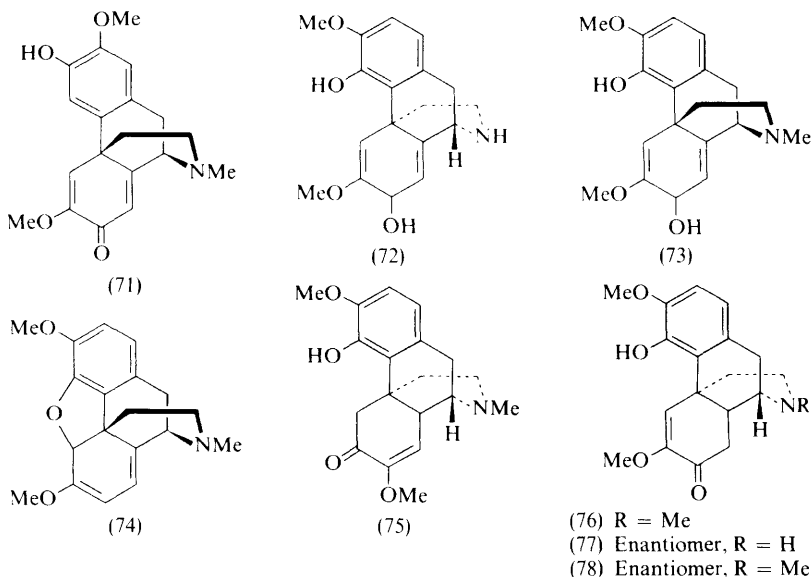
<sup>75</sup> E. Brochmann-Hanssen, C.-C. Fu, and L. Y. Misconi, *J. Pharm. Sci.*, 1971, **60**, 1880; R. B. Herbert, in ref. 3, p. 19.

<sup>76</sup> E. Brochmann-Hanssen, C. H. Chen, H.-C. Chiang, C.-C. Fu, and H. Nemoto, *J. Pharm. Sci.*, 1973, **62**, 1291.





**Alkaloids of *Croton* Species.**—The biosynthesis of flavinantine (71) from two molecules of phenylalanine by way of reticuline (67) in *Croton flavens* was reviewed when the results appeared in preliminary form.<sup>77</sup> Additional results which appear in the full paper<sup>78</sup> are: (a) sinoacutine (68) and norsinoacutine (69) are interconvertible; (b) the norsinoacutinols (72) could be converted by the plant into norsinoacutine (69) and sinoacutine (68), which stands in contrast to *P. somniferum* where dehydration of the related dienol, salutaridinol (73), occurs<sup>79</sup> to give thebaine (74); (c) administered sinomenine (75) is convertible into sinoacutine and norsinoacutine, and a better substrate was isosinomenine (76) [the conversion of sinoacutine (68) into sinomenine (75) in *Sinomenium acutum* has been demonstrated<sup>80</sup>]; and (d) not surprisingly, the dienones (77) and (78) were not



<sup>77</sup> K. L. Stuart, V. Teetz, and B. Franck, *Chem. Comm.*, 1969, 333; R. B. Herbert in ref. 7, p. 20.

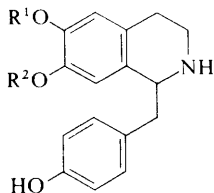
<sup>78</sup> K. L. Stuart and L. Graham, *Phytochemistry*, 1973, 12, 1967.

<sup>79</sup> H. R. Schütte, in ref. 24, p. 367.

<sup>80</sup> D. H. R. Barton, A. J. Kirby, and G. W. Kirby, *J. Chem. Soc. (C)*, 1968, 929.

incorporated into, respectively, norsinoacutine or flavinantine and sinoacutine or norsinoacutine. In conclusion it should be noted that almost all the incorporations reported were low, so the significance of the results may be questionable.

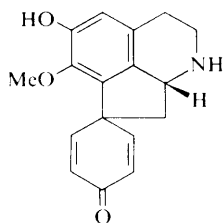
( $\pm$ )-Coclaurine (79) and ( $\pm$ )-norcoclaurine (80), but not isococlaurine (81), are precursors for crotonosine (82) in *Croton linearis*,<sup>81</sup> whilst 8,14-dehydronorsalutaridine (77) is labelled by radioactive coclaurine, norcoclaurine, and isococlaurine (81).<sup>82</sup> Crotonosine is also derivable from linearisine (83)<sup>83,84</sup>



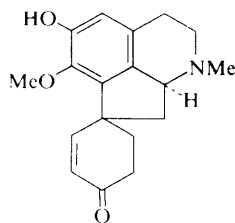
(79)  $R^1 = \text{Me}, R^2 = \text{H}$

(80)  $R^1 = R^2 = \text{H}$

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



(82)



(83)

and it seems that this conversion in female plants is about ten times more efficient than in male plants, although the age of the plants may also have been of some influence.<sup>84</sup>

**Homoaporphine Alkaloids.**—Full details of the research on the biosynthesis of the homoaporphine alkaloids of *Kreysigia multiflora* have been published.<sup>85</sup> In essence there is no information additional to that published in preliminary form<sup>86</sup> and reviewed.<sup>87</sup>

**Colchicine.**—It is clearly established that ring A and carbons 5, 6, and 7 of colchicine (5) arise from phenylalanine by way of cinnamic acid.<sup>88</sup> Beyond cinnamic acid the next known intermediate is a phenethylisoquinoline;<sup>12b</sup> it is not as yet known whether reduction of the double bond in cinnamic acid occurs before or after construction of the isoquinoline ring.

The conversion of phenylalanine into cinnamic acid is mediated by phenylalanine ammonia lyase (PAL) and the elimination reaction involves loss of the

<sup>81</sup> D. H. R. Barton, D. S. Bhakuni, G. M. Chapman, G. W. Kirby, L. J. Haynes, and K. L. Stuart, *J. Chem. Soc. (C)*, 1967, 1295.

<sup>82</sup> L. J. Haynes, G. E. M. Husbands, and K. L. Stuart, *J. Chem. Soc. (C)*, 1968, 951.

<sup>83</sup> K. L. Stuart and L. Graham, *Chem. Comm.*, 1971, 392; J. Staunton, in ref. 9, p. 15.

<sup>84</sup> K. L. Stuart and L. Graham, *Phytochemistry*, 1973, **12**, 1973.

<sup>85</sup> A. R. Battersby, P. Böhler, M. H. G. Munro, and R. Ramage, *J.C.S. Perkin I*, 1974, 1399.

<sup>86</sup> A. R. Battersby, P. Böhler, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1969, 1066.

<sup>87</sup> R. B. Herbert, in ref. 7, p. 22.

<sup>88</sup> 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; E. Leete and P. E. Nemeth, *J. Amer. Chem. Soc.*, 1960, **82**, 6055; E. Leete, *ibid.*, 1963, **85**, 3666.

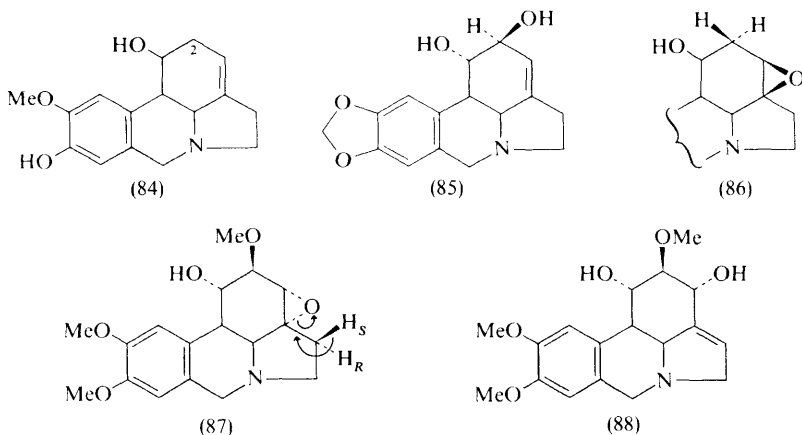
3-*pro-S* hydrogen.<sup>89,90</sup> Accordingly, incorporation of phenylalanine into colchicine might be expected to result in retention of the 3-*pro-R* hydrogen and results of experiments with the appropriate precursors in *Colchicum autumnale* have shown this to be true.<sup>89</sup>

This result obtained in a whole plant adds further weight to the conclusion reached about the stereochemistry of PAL action with an isolated enzyme and contrasts with the results obtained with Amaryllidaceae alkaloids where apparently subsequent modification of the cinnamic acid results in loss of all the tritium originally present at C-3 (see below).<sup>89</sup>

#### 4 Amaryllidaceae Alkaloids

Investigation continues on the stereochemical detail of the reactions by which the norbelladine skeleton is transformed into the rich structural variety of the Amaryllidaceae alkaloids.

The epoxide (86) has been tentatively invoked to explain the unusual hydroxylation with inversion of configuration at C-2 of norpluviine (84) which leads to lycorine (85) in daffodils.<sup>91,92</sup> (In *Clivia miniata* on the other hand hydroxylation occurs with 'normal' retention of configuration<sup>92,93</sup>). It was considered<sup>94</sup> that an analogous epoxide (87) could give narcissidine (88) in the manner shown by loss



of the *pro-S* hydrogen from C-4; a suitable substrate for epoxidation is galanthine (89).

<sup>89</sup> R. H. Wightman, J. Staunton, A. R. Battersby, and K. R. Hanson, *J.C.S. Perkin I*, 1972, 2355.

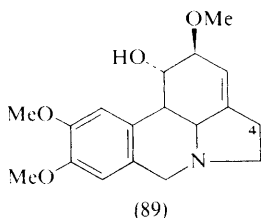
<sup>90</sup> R. Ife and E. Haslam, *J. Chem. Soc. (C)*, 1971, 2818.

<sup>91</sup> I. T. Bruce and G. W. Kirby, *Chem. Comm.*, 1968, 207; *Chimia (Switz.)*, 1968, **22**, 314.

<sup>92</sup> R. B. Herbert, in ref. 5, p. 24.

<sup>93</sup> C. Fuganti and M. Mazza, *J.C.S. Chem. Comm.*, 1972, 936.

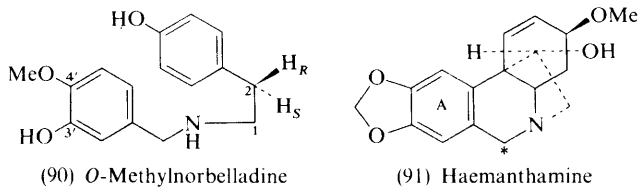
<sup>94</sup> C. Fuganti, D. Ghiringhelli, and P. Grasselli, *J.C.S. Chem. Comm.*, 1974, 350.



[1- $^{14}\text{C}$ ,2- $^3\text{H}$ ]-*O*-Methylnorbelladine [as (90)] when fed to *Sempre Avanti* daffodils afforded galanthine (89) (98% tritium retention) and narcissidine (88) (46% tritium retention).<sup>94</sup> Loss of hydrogen from C-4 of the tetracyclic precursor [as (89)] for narcissidine is therefore stereospecific (a non-stereospecific reaction would lead to a high tritium retention as a result of a primary isotope effect). That the hydrogen atom lost was the 2-*pro-S* hydrogen of (90) [equivalent to the 4-*pro-R* hydrogen of (87)] followed from the results with two *O*-methylnorbelladine samples stereospecifically labelled with tritium at C-2: incorporation of the (2*R*)-isomer was with almost complete retention of tritium, whereas the (2*S*)-isomer gave narcissidine almost devoid of tritium. The stereochemistry observed, it was concluded, was evidence against intermediates of the type (87).

An efficient conversion of galanthine (89) into narcissidine (88) did at least establish this compound as a late precursor for narcissidine.<sup>94</sup>

Radioactive haemanthamine (91) was also isolated in the above experiments and the results obtained provide further confirmation that the conversion of



*O*-methylnorbelladine (90) into haemanthamine (91) involves loss of the *pro-R* hydrogen from C-2,<sup>95-97</sup> *i.e.* loss in the opposite sense to that found for narcissidine. Of course the formation of haemanthamine (91) involves entry of a hydroxy-group at this site and so the reaction appears to be quite different from that which involves this centre in narcissidine biosynthesis.

Hydroxylation at saturated carbon is commonly effected by a mixed-function oxidase in conjunction with molecular oxygen. Oxygen is inserted into the C—H bond and the stereochemical result is retention of configuration.<sup>98</sup> The results for

<sup>95</sup> A. R. Battersby, J. Kelsey, and J. Staunton, *Chem. Comm.*, 1971, 183; G. W. Kirby and J. Michael, *ibid.*, pp. 187, 415.

<sup>96</sup> J. Staunton, in ref. 9, p. 20.

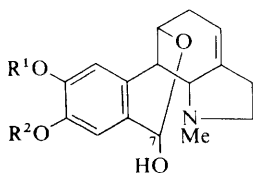
<sup>97</sup> A. R. Battersby, J. E. Kelsey, J. Staunton, and K. E. Suckling, *J.C.S. Perkin I*, 1973, 1609.

<sup>98</sup> G. A. Hamilton, *Adv. Enzymol.*, 1969, 32, 55; O. Hayaishi, *Ann. Rev. Biochem.*, 1969, 38, 21.

haemanthamine are in accord with such a mechanism and the range of examples of this type of reaction is thus extended into the alkaloid field. Research by one group on this topic has now been published in full.<sup>97</sup> In essence no new information has appeared, so the reader is referred to the earlier review for a full discussion.<sup>96</sup> [It is incidentally most useful to have the experimental details of the preparation of (2*R*)- and (2*S*)-tritiotyramines.]

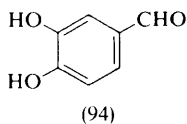
In common with other Amaryllidaceae alkaloids the C<sub>6</sub>-C<sub>1</sub> unit of haemanthamine (91), i.e. ring A plus C\*, arises from phenylalanine *via* cinnamic acid.<sup>99</sup> The presence has been demonstrated of the necessary enzyme, phenylalanine ammonia lyase, in Amaryllidaceae plants<sup>100</sup> and the elimination of ammonia mediated by enzyme isolated from potatoes occurs in an antiperiplanar manner to give *trans*-cinnamic acid, with loss of the 3-*pro-S* hydrogen.<sup>89,90</sup> It might be expected then that phenylalanine would be incorporated into Amaryllidaceae alkaloids with retention of the 3-*pro-R* hydrogen. Feeding experiments in 'King Alfred' daffodils, however, showed that tritium originally present at C-3 of phenylalanine, whatever the configuration, was lost in the formation of haemanthamine (91) and oduline (92).<sup>89</sup> Clearly fragmentation of the cinnamic acid involves oxidation of C-3 to the ketone or acid level.

The *in vivo* transformation of protocatechualdehyde (94) into lycorenine (93), which proceeds *via* *O*-methylnorbelladine (90) and norpluviine (84), involves first a reduction of the aldehyde carbonyl and then, in the generation of lycorenine (93), oxidation of this same carbon atom. It has been shown that hydrogen addition and removal is stereospecific and takes place on the *re*-face of the molecules concerned. The hydrogen initially introduced is the one later removed.<sup>101</sup>

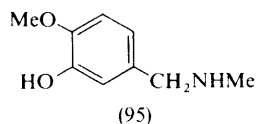


(92) R<sup>1</sup>, R<sup>2</sup> = CH<sub>2</sub>

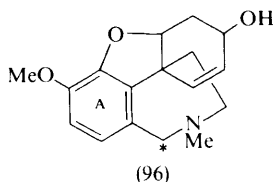
(93) R<sup>1</sup> = R<sup>2</sup> = Me



(94)



(95)



(96)

It has been observed that 3-hydroxy-4-methoxy-*N*-methylbenzylamine (95) is built into the C<sub>6</sub>-C<sub>1</sub> unit (ring A plus C\*) of haemanthamine (91) and

<sup>99</sup> H. R. Schütte, in ref. 24, p. 420.

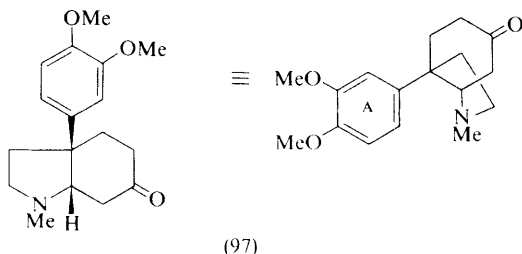
<sup>100</sup> R. J. Suhadolnik, A. G. Fischer, and J. Zulalian, *Biochem. Biophys. Res. Comm.*, 1963, 11, 208.

<sup>101</sup> C. Fuganti and M. Mazza, *Chem. Comm.*, 1971, 1196; C. Fuganti and M. Mazza, *J.C.S. Perkin I*, 1973, 954; R. B. Herbert, in ref. 3, p. 23; in ref. 5, p. 23.

galanthamine (96) with loss of the *N*-methyl group.<sup>102</sup> A reasonable explanation of this was that (95) was converted by an amino-oxidase into 3-hydroxy-4-methoxybenzaldehyde which was then incorporated as a C<sub>6</sub>-C<sub>1</sub> unit *via* *O*-methyl-norbelladine (90).<sup>102</sup> Benzylamine samples labelled stereospecifically and randomly with tritium on the benzylic methylene were fed to 'King Alfred' daffodils.<sup>103</sup> The derived haemanthamine (91), galanthamine (96) and oduline (92), each showed nearly the same high tritium retention (80–85%). Hydrogen loss from the benzylic carbon of (95) is thus governed by a primary isotope effect and is non stereospecific. Further, the tritium retention values observed for oduline suggest that the sequence of reactions which results in the observed substitution pattern at C-7 of this base is similar to that deduced for lycorenine (93).

### 5 Mesembrine Alkaloids

The mesembrine alkaloids, *e.g.* mesembrine (97), bear a strong structural resemblance to the Amaryllidaceae alkaloids of the crinine type, *e.g.* haemanthamine (91), but careful investigation<sup>104,105</sup> has shown that the only aspect of biosynthesis common to these two groups is their origin from the same amino-acids, phenylalanine and tyrosine.<sup>104</sup>



Full details have been published<sup>105</sup> of part of the research on the biosynthesis of the mesembrine alkaloids of *Sceletium strictum* (Aizoaceae). Some of the work has appeared in a preliminary communication<sup>106</sup> and has been reviewed.<sup>107</sup>

Key intermediates in the biosynthesis of the crinine alkaloids are norbelladiene and 4'-*O*-methylnorbelladine (90).<sup>99</sup> It became clear, however, as the result of experiments with doubly labelled precursors that neither these compounds nor 3'-*O*-methyl-, *N*-methyl-, or 3'-*ON*-dimethyl-norbelladine were directly involved in mesembrine biosynthesis; the moderate levels of incorporation observed were found to be the result of prior fragmentation of the precursors. In an ultimate test

<sup>102</sup> D. H. R. Barton, G. W. Kirby, J. B. Taylor, and G. M. Thomas, *J. Chem. Soc.*, 1963, 4545.

<sup>103</sup> C. Fuganti, D. Ghiringhelli, and P. Grasselli, *Tetrahedron Letters*, 1974, 2261.

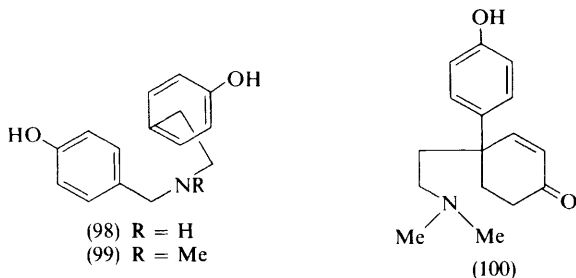
<sup>104</sup> P. W. Jeffs, W. C. Archie, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, 1971, 93, 3752; R. B. Herbert, in ref. 3, p. 23.

<sup>105</sup> P. W. Jeffs, H. F. Campbell, D. S. Farrier, G. Ganguli, N. H. Martin, and G. Molina, *Phytochemistry*, 1974, 13, 933.

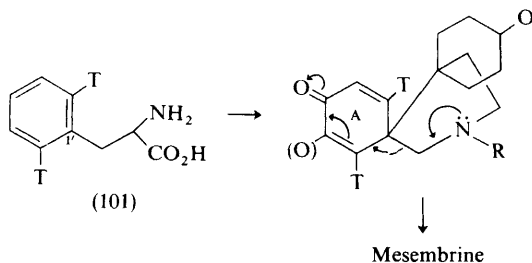
<sup>106</sup> P. W. Jeffs, H. F. Campbell, D. S. Farrier, and G. Molina, *Chem. Comm.*, 1971, 228.

<sup>107</sup> J. Staunton, in ref. 9, p. 18.

of the role of precursors of the norbelladine type, (98) and (99) were tested, for it was felt that entry of a third hydroxy-group might have occurred at a late stage of biosynthesis. This idea arose from consideration of the structure (100) assigned<sup>108</sup> to joubertiamine, an alkaloid isolated from *S. joubertii*. Again the results were negative.



Phenylalanine is incorporated into the aromatic ring of mesembrine (97) with complete loss of its side-chain whilst tyrosine serves as the source of the carbon atoms of the octahydroindole portion of the molecule.<sup>104</sup> A most important result came from the feeding of [ $1\text{'-}^{14}\text{C}$ ,  $2\text{'},6\text{'-}^3\text{H}_2$ ]phenylalanine [as (101)]. It was found<sup>105</sup> that both tritium atoms were retained without rearrangement. This definitely excluded the crinine pathway (which requires loss of one tritium atom) and further indicated that bond formation between the unit derived from phenylalanine and that arising from tyrosine must occur at the carbon corresponding to C-1' of phenylalanine. This leads logically to a ring A spirodienone which, in order to retain both tritiums, must undergo aromatization by a process of the type illustrated in Scheme 6. A notable analogy exists in the biosynthesis of *Erythrina* alkaloids, namely the conversion of (103) into (104).<sup>109</sup>



**Scheme 6**

The authors make two final comments. One is that in retrospect perhaps the differences in the biosynthesis of crinine and mesembrine alkaloids are not entirely unexpected in view of the widely different phylogenetic origins of the

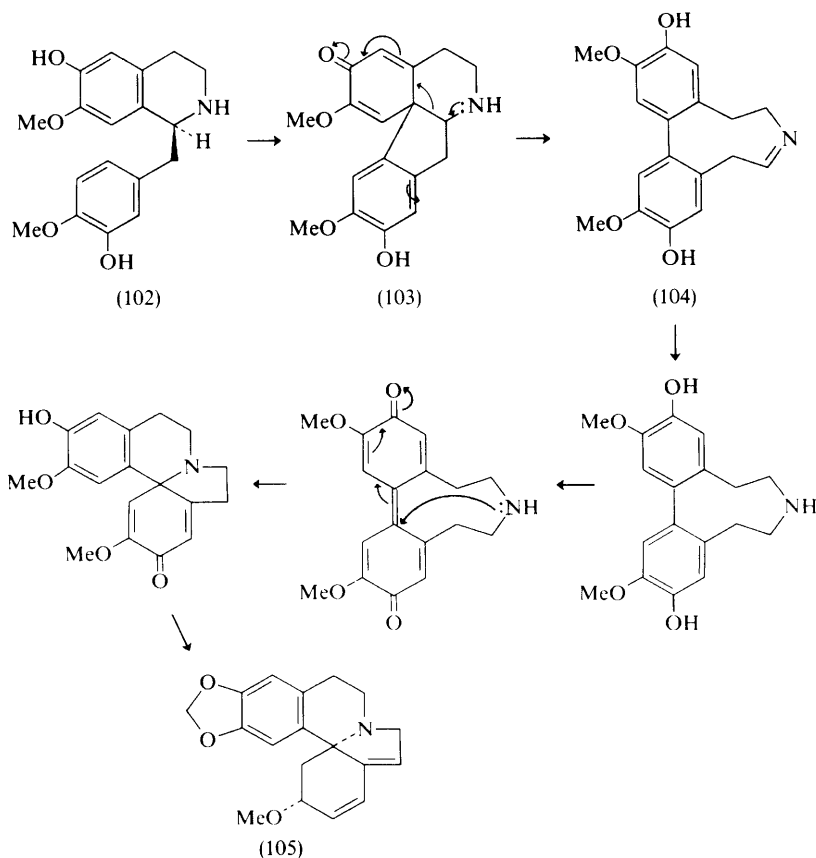
<sup>108</sup> R. R. Arndt and P. E. J. Kruger, *Tetrahedron Letters*, 1970, 3237.

<sup>109</sup> D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc. (C)*, 1970, 1213; R. B. Herbert, in ref. 7, p. 22.

Amaryllidaceae and Aizoceae families. Second, without use of doubly labelled precursors erroneous conclusions on mesembrine alkaloid biosynthesis would have been reached.

### 6 *Erythrina* Alkaloids

There is sound evidence<sup>109</sup> that the biosynthesis of *Erythrina* alkaloids, e.g. erythraline (105), proceeds by the novel pathway shown in Scheme 7. New evidence<sup>110</sup> of a negative kind supports the previously established role of (*S*)-norprotosinomenine (102) as an intermediate in the biosynthesis of these alkaloids.



**Scheme 7**

The detection of *N*-nororientaline and orientaline (62) in a number of *Erythrina* species suggested that they might be involved in the elaboration of *Erythrina* alkaloids. In the event neither tritiated (+)-*N*-nororientaline nor tritiated

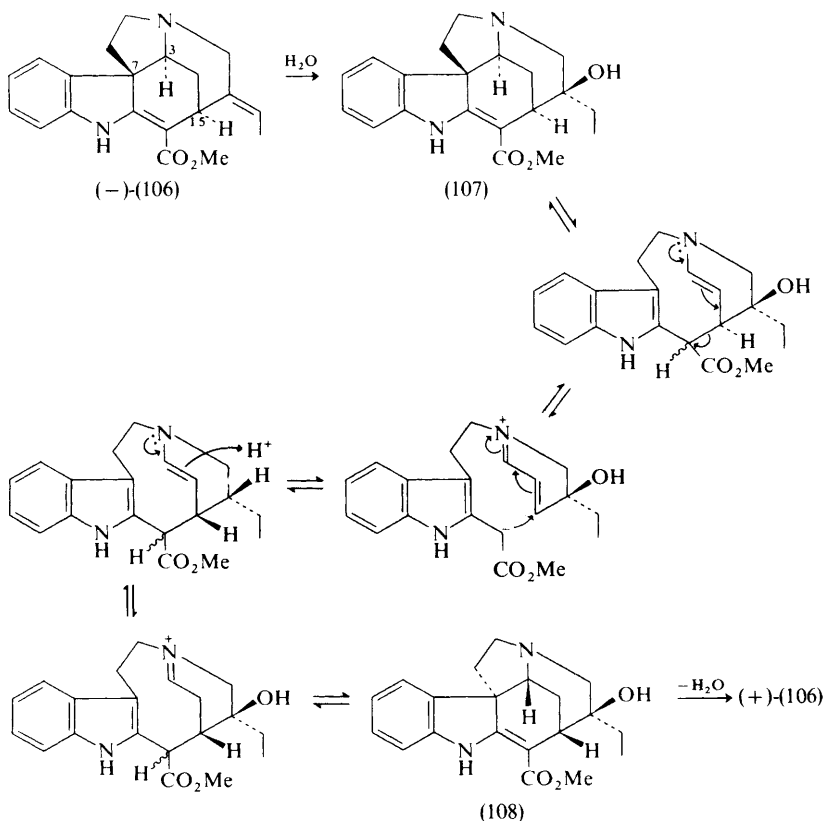
<sup>110</sup> D. H. R. Barton, C. J. Potter, and D. A. Widdowson, *J.C.S. Perkin I*, 1974, 346.



( $\pm$ )-*N*-nor-reticuline was significantly incorporated into erythraline (105) or the erythroidines under conditions when *N*-norprotosinomenine (102) was. [( $-$ )-*N*-Nororientaline was not tested as a precursor.] Evidence is thus provided for *N*-norprotosinomenine being an exclusive precursor for the erythrinan system.

## 7 Alkaloids Derived from Tryptophan

**Terpenoid Indole Alkaloids.**—Enormous strides have been made in understanding the biosynthesis of this large group of alkaloids<sup>7-11,111</sup> and yet much detail remains to be uncovered. One particular problem concerns the natural occurrence of enantiomeric forms of akuammicine (106) and the diastereoisomers ( $-$ )-lochneridine (107) and ( $+$ )-20-epilochneridine (108).

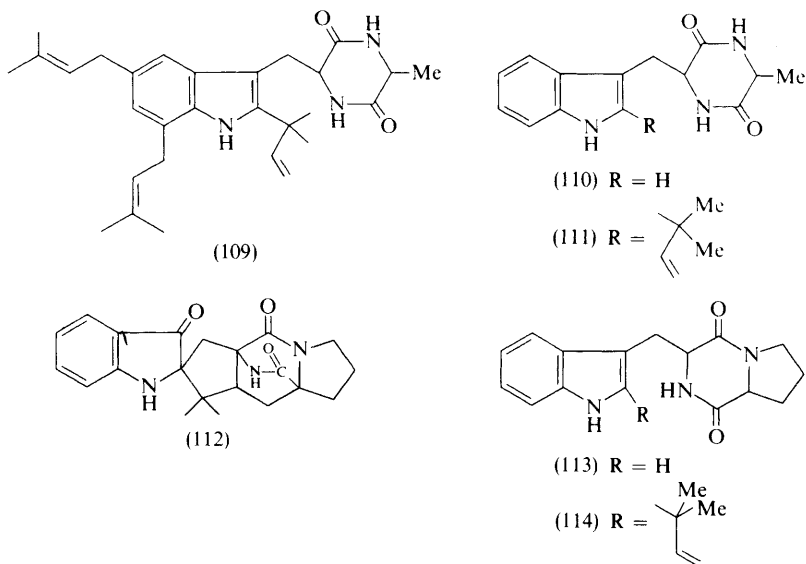


Scheme 8

<sup>111</sup> A. I. Scott, in 'Alkaloids', ed. K. Wiesner, (M.T.P. International Review of Science), Organic Chemistry Series One, Vol. 9, Butterworths, London, 1973, p. 105; A. I. Scott, *Recent Adv. Phytochem.*, 1973, **6**, 117.

An ingenious solution to this problem has been suggested which involves inversion at C-3, C-7, and C-15 *via* dihydropyridine intermediates (Scheme 8) and is similar to that proposed to account for the biosynthesis of antipodal pentacyclic *Aspidosperma* alkaloids.<sup>8</sup> The feasibility of such a mechanism chemically has been demonstrated with the thermal transformation of (107; 20 $\alpha$ -H) into (108; 20 $\alpha$ -H).

**Brevianamide.**—Echinulin (109) is elaborated in *Aspergillus amstelodami* along a pathway which includes (110) and (111).<sup>112</sup> The structurally related metabolite, brevianamide A (112), isolated from *Penicillium brevicompactum*, appears to be derived in a similar way.<sup>113</sup> Radioactive mevalonate, proline, and tryptophan gave labelled brevianamide A. Incorporation of *cyclo*-L-[methylene-<sup>14</sup>C]-tryptophyl-L-[5-<sup>3</sup>H]proline [as (113)] without change in isotope ratio indicated that this precursor was utilized intact for brevianamide A production. As further evidence of its role in brevianamide A biosynthesis (113) has been isolated from *P. brevicompactum* cultures.<sup>114</sup> By analogy with echinulin biosynthesis, (114) could lie between (113) and brevianamide A (112). Its isolation<sup>115</sup> (from *A. ustus*) provides support for this suggestion.



**Cyclopiazonic Acid.**—Cyclopiazonic acid (115) is formed in *Penicillium cyclopium* from mevalonate, tryptophan, and an acetate-derived C<sub>4</sub> unit [heavy bonding

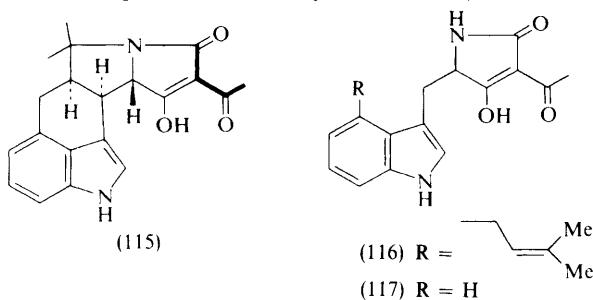
<sup>112</sup> G. P. Slater, J. C. MacDonald, and R. Nakashima, *Biochemistry*, 1970, **9**, 2886; C. M. Allen, jun., *J. Amer. Chem. Soc.*, 1973, **95**, 2386; R. B. Herbert in ref. 5, p. 29.

<sup>113</sup> J. Baldas, A. J. Birch, and R. A. Russell, *J.C.S. Perkin I*, 1974, 50.

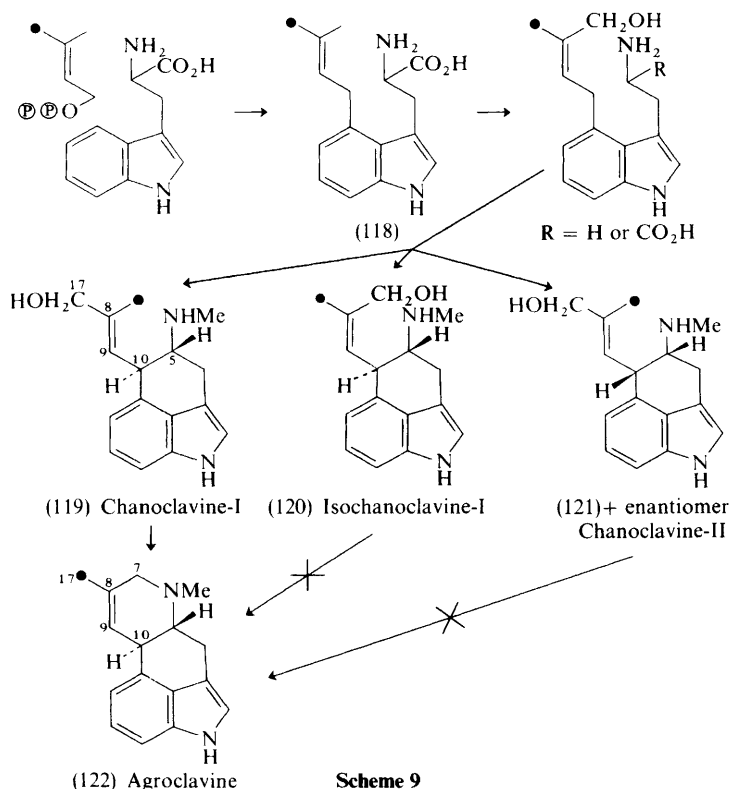
<sup>114</sup> A. J. Birch and R. A. Russell, *Tetrahedron*, 1972, **28**, 2999.

<sup>115</sup> P. S. Steyn, *Tetrahedron*, 1973, **29**, 107.

in (115)]<sup>116</sup> via (116).<sup>117</sup> It is likely that (117), isolated from a cell-free extract of *P. cyclopium*, is also implicated in the biosynthesis of (115).<sup>118</sup>



**Ergot Alkaloids.**—The elaboration of the tetracyclic ergoline skeleton, as represented by agroclavine (122), is more complex than cursory examination



**Scheme 9**

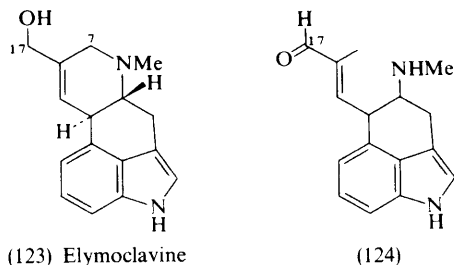
<sup>116</sup> C. W. Holzapfel and D. C. Wilkins, *Phytochemistry*, 1971, **10**, 351.

<sup>117</sup> J. C. Schabert, International Symposium on the Control of the Human Environment, Abstract, p. 62, Johannesburg, 1969; quoted in ref. 118.

<sup>118</sup> R. M. McGrath, P. S. Steyn, and N. P. Ferreira, *J.C.S. Chem. Comm.*, 1973, 812.

would suggest. Thus two *cis-trans* isomerizations take place at the allyl double bond, one occurring in the sequence of steps leading to chanoclavine-I (119) and the other in the subsequent transformation into agroclavine (see Scheme 9).<sup>119</sup> It is an attractive hypothesis that the two ring-closure reactions are associated in some way with double-bond isomerization. An attempt, however, to establish such a link in the formation of ring C failed to produce the expected results.<sup>120</sup>

In the conversion of chanoclavine-I (119) into elymoclavine (123) one of the C-17 hydrogens is lost. (The other appears at C-7 of elymoclavine as expected.)<sup>121,122</sup> This suggested that the aldehyde (124) might be an intermediate. This was strongly supported by the efficient incorporation of (124) into elymoclavine; tritium label from C-17 in the precursor appeared at C-7 of the product



and little was lost in the process. Further, two deuterium atoms at C-3' of a mevalonate sample fed to *Claviceps* (C-3' of mevalonate is the source of C-17 of chanoclavine-I) were retained in the derived chanoclavine-I [as (119)] and only one of these appeared in the elymoclavine isolated. The deuterium label in the latter was located at C-7 and was mostly equatorial. This proves that the changes in oxidation level which occur at this centre are the result of normal physiological processes.

The properties of an enzyme system isolated from ergot which catalyses the transformation of chanoclavine-I (119) to agroclavine (122) have been investigated.<sup>123</sup> The enzyme system was found to convert chanoclavine-I and chanoclavine-I-aldehyde (124), but not isochanoclavine-I (120) into agroclavine (122). Further evidence is thus provided for the normal elaboration of ergot alkaloids as being chanoclavine-I (119) → the aldehyde (124) → agroclavine (122).

In considering the transformation of chanoclavine-I (119) into agroclavine (122) and the attendant *cis-trans* isomerization of the allyl double bond,

<sup>119</sup> E. Ramstad, *Lloydia*, 1968, **31**, 327; H. G. Floss, in 'Biochemie und Physiologie der Alkaloide', Fourth International Symposium, 1969, ed. K. Mothes, Akademie-Verlag, Berlin, p. 395; R. Thomas and R. A. Bassett, *Progr. Phytochem.*, 1972, **3**, 47.

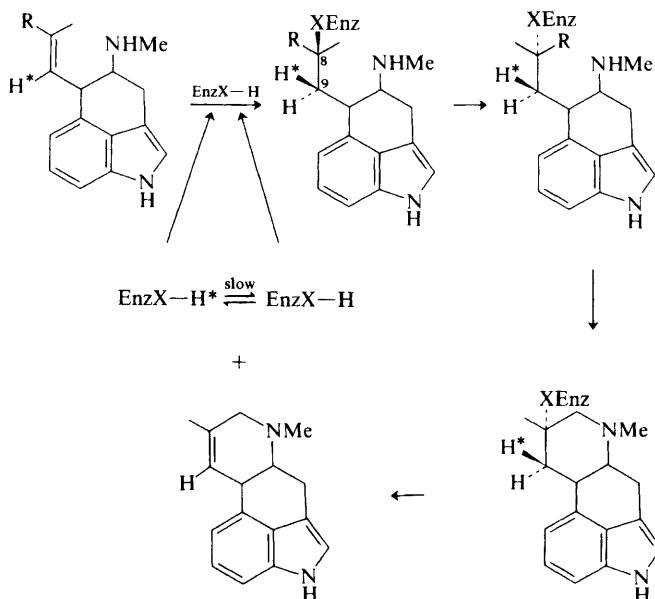
<sup>120</sup> (a) C. I. Abou-Chaar, H. F. Guenther, M. F. Manuel, J. E. Robbers, and H. G. Floss, *Lloydia*, 1972, **35**, 272; R. B. Herbert, in ref. 5, p. 32; see also (b) M. Seiler, W. Acklin, and D. Arigoni, *Chem. Comm.*, 1970, 1394; *Chimia (Switz.)*, 1970, **24**, 449.

<sup>121</sup> B. Naidoo, J. M. Cassady, G. E. Blair, and H. G. Floss, *Chem. Comm.*, 1970, 471; R. B. Herbert, in ref. 7, p. 27.

<sup>122</sup> H. G. Floss, M. Tcheng-Lin, C. Chang, B. Naidoo, G. E. Blair, C. I. Abou-Chaar, and J. M. Cassady, *J. Amer. Chem. Soc.*, 1974, **96**, 1898.

<sup>123</sup> D. Erge, W. Maier, and D. Gröger, *Biochem. Physiol. Pflanzen*, 1973, **164**, 234.

knowledge of the fates of two hydrogen atoms is important, *i.e.* those at C-9 and C-10. In this regard it has been shown that the C-10 hydrogen is completely retained.<sup>124,125</sup> On the other hand only incomplete retention (*ca.* 70%) of the C-9 hydrogen was observed.<sup>125</sup> The findings were accommodated in a route which envisaged an enzyme-mediated intermolecular hydrogen transfer as illustrated in Scheme 10.<sup>122,125</sup> After addition of some X—H group across the



Scheme 10

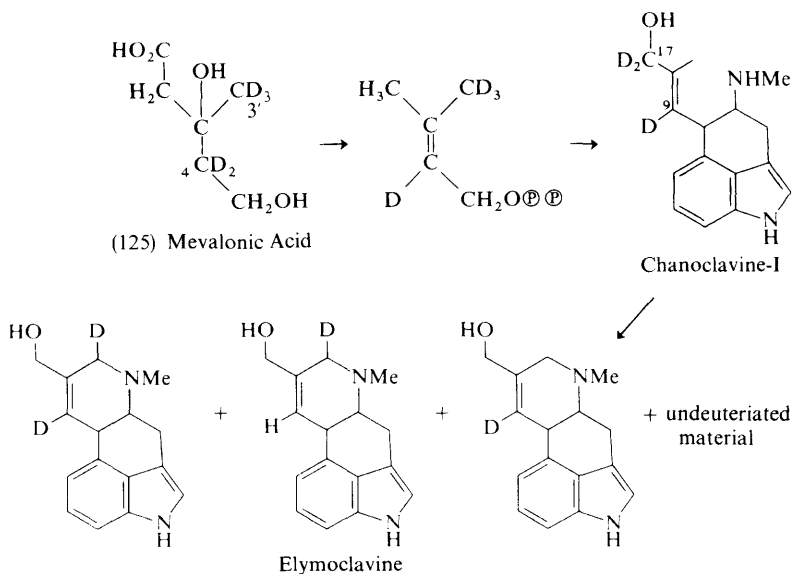
double bond, rotation around the 8,9-bond allows transfer of the original hydrogen at C-9 to the enzyme in the subsequent elimination step. Assuming slow exchange of this hydrogen on the enzyme most of it would be transferred to another molecule of chanoclavine-I in the next cycle. This hypothesis was examined in a study<sup>122,126</sup> notable not least for well thought-out use of stable isotopes.

In the first instance the incorporation of the pentadeuteriomevalonic acid (125) was examined. This material afforded trideuteriochanoclavine-I (see Scheme 11) as a mixture with undeuteriated material. Unexceptional conversion of this mixture into elymoclavine (123) should give dideuterioelymoclavine

<sup>124</sup> S. Agurell, *Acta Pharm. Suecica*, 1966, 3, 71.

<sup>125</sup> H. G. Floss, U. Hornemann, N. Schilling, K. Kelley, D. Gröger, and D. Erge, *J. Amer. Chem. Soc.*, 1968, 90, 6500.

<sup>126</sup> H. G. Floss, *Lloydia*, 1972, 35, 399.



Scheme 11

[intermediacy of (124) requires loss of one deuterium atom], but if an intermolecular hydrogen transfer of the type outlined in Scheme 10 was in operation, a deuterium atom removed from C-9 would be introduced either into a molecule with a C-9 deuterium, in which case there would be no net charge, or into an unlabelled molecule, which would result in the formation of two  $[^2\text{H}_1]$ -molecules from one  $[^2\text{H}_2]$ - and one  $[^2\text{H}_0]$ -species of (124). This operation will thus result in an increase in  $[^2\text{H}_1]$ -species at the expense of  $[^2\text{H}_2]$ - and  $[^2\text{H}_0]$ -molecules, and the extent of this redistribution will depend on the  $[^2\text{H}_3]:[^2\text{H}_0]$  ratio of the chanoclavine-I.

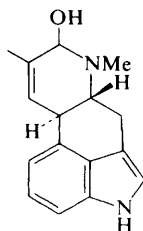
Following the elegance of this argument it was pleasing to see that the incorporation of the pentadeuterio mevalonic acid (125) into elymoclavine and peniclavine was in accord with the hydrogen-transfer hypothesis, although the results were complicated by the hydrogen loss from C-17 discussed above. (Chronologically, the argument was developed without taking this into account. For simplicity here loss of hydrogen from C-17 has been discussed first.)

Additional support was obtained by studying the incorporation of a 1:1 mixture of  $[2\text{-}^{13}\text{C}]$ - and  $[4\text{-}^2\text{H}_2]$ -mevalonic acid into chanoclavine-I and elymoclavine. Mass spectral analysis showed that none of the chanoclavine-I molecules contained deuterium and  $^{13}\text{C}$ . On the other hand the elymoclavine and peniclavine were made up of molecules containing both  $^{13}\text{C}$  and deuterium.

In each of the above experiments calculation of the distribution of the label in the elymoclavine expected from the intermolecular exchange was achieved by including a radioactive label in the mevalonic acid fed, which allowed measurement of the dilution of labelled precursor by unlabelled material. The observed

values were close to the calculated. It should also be noted that label from C-9 was shown not to be transferred to other sites in elymoclavine.

The results make it clear that the simple hydrogen-transfer mechanism which appears in Scheme 10 is correct in essence but needs modification in order to account for the probable intermediacy of the aldehyde (124). This then is the substrate on which hydrogen transfer occurs. Attendant *cis-trans* isomerization leads to the carbinolamine (126) which would be the first of the tetracyclic bases.

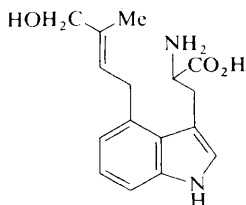


(126)

In the final model suggested<sup>122</sup> the aldehyde group was masked in order to allow for what would otherwise be an 'anti-Michael' addition to the double bond of an  $\alpha\beta$ -unsaturated aldehyde.

Finally if the steps which lie between chanoclavine-I and proton removal are reversible and if proton abstraction is rate-limiting, the tritium enrichment of unreacted chanoclavine-I, which was observed in the above experiments, is also explained. (Loss of tritium is slower than loss of hydrogen as the result of a primary isotope effect.) So we now have a most satisfying rationale for the steps involved in the formation of the tetracyclic ergot alkaloids from chanoclavine-I.

4-Dimethylallyltryptophan (118) is the first intermediate after tryptophan on the pathway to the clavine alkaloids.<sup>119,127</sup> Support for hydroxylation of one of the methyl groups as the next step was gained by the incorporation of (127)



(127)

into elymoclavine<sup>128</sup> (but not agroclavine).<sup>129</sup> Additional support for this suggestion has come from the isolation from *Claviceps purpurea* of a compound identified as (127) or its double-bond isomer.<sup>130</sup>

<sup>127</sup> S. Agurell and J.-E. Lindgren, *Tetrahedron Letters*, 1968, 5127; J. E. Robbers and H. G. Floss, *Arch. Biochem. Biophys.*, 1968, **126**, 967.

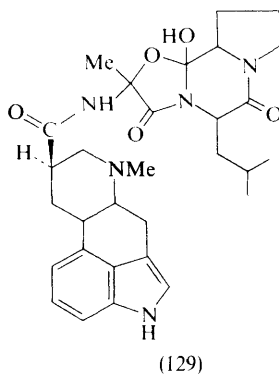
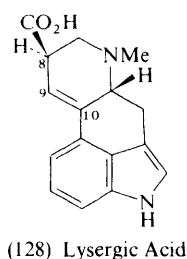
<sup>128</sup> H. Plieninger, C. Wagner, and H. Immel, *Annalen*, 1971, **743**, 95; J. Staunton, in ref. 9, p. 8.

<sup>129</sup> H. Plieninger, quoted in ref. 130.

<sup>130</sup> J. A. Anderson and M. S. Saini, *Tetrahedron Letters*, 1974, 2107.

Biosynthesis of the ergot bases involves an *N*-methylation step and it has been shown that the *N*-methyl group arises intact from methionine.<sup>131</sup> It is as yet unknown, however, at which stage the methylation occurs but since *N*-methyltryptophan and *N*-methyltryptamine<sup>132</sup> are not intermediates, the reaction must occur at a stage between (118) and chanoclavine-I (119). The failure of radioactive *N*-demethylchanoclavine-I (or *N*-demethylchanoclavine-II) to label elymoclavine (123) in *Claviceps* cultures indicates that *N*-methylation occurs before formation of the chanoclavine skeleton.<sup>133</sup>

Lysergic acid (128) is an intermediate in the biological elaboration of peptidic ergot alkaloids.<sup>119</sup> The role of the  $\Delta^{8,9}$ -isomer is less clear and the steps involving migration of the double bond are but poorly understood. Dihydroclavine alkaloids, in which ring D is saturated, are considered to be formed by reduction of the corresponding clavine bases.



It was thus of interest to establish the point at which saturation occurred in the biosynthesis of the peptidic alkaloid (129). It is known that mevalonic acid is built into the clavine alkaloids, *e.g.* agroclavine (122), with retention of the 5-*pro-R* hydrogen at C-10.<sup>120b</sup> Retention or loss of tritium from C-5 mevalonic acid on formation of (129) would show whether  $\Delta^{9,10}$ -intermediates were involved in the biosynthesis of (129). The results obtained<sup>134</sup> with *Sphacelia sorghi* were that tritium was retained and so  $\Delta^{9,10}$ -intermediates are excluded.

Chanoclavine-I (119), festuclavine (130), dihydroelymoclavine (131), and dihydrolysergic acid (132) were found to be present in *S. sorghi*.<sup>134</sup> The dihydrobases (130), (131), and (132) were shown to be similarly efficient precursors of (129), which suggested the biosynthetic sequence (130)  $\rightarrow$  (131)  $\rightarrow$  (132)  $\rightarrow$  (129). This is in contrast to normal ergot alkaloid biosynthesis where successive oxidation of the C-8 methyl group occurs on  $\Delta^{8,9}$ -substrates.

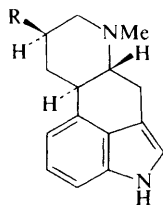
<sup>131</sup> R. M. Baxter, S. I. Kandel, A. Okany, and R. G. Pyke, *Canad. J. Chem.*, 1964, **42**, 2936.

<sup>132</sup> H. G. Floss and D. Gröger, *Z. Naturforsch.*, 1964, **19b**, 393; *ibid.*, 1963, **18b**, 519.

<sup>133</sup> J. M. Cassady, C. I. Abou-Chaar, and H. G. Floss, *Lloydia*, 1973, **36**, 390.

<sup>134</sup> K. D. Barrow, P. G. Mantle, and F. R. Quigley, *Tetrahedron Letters*, 1974, 1557.



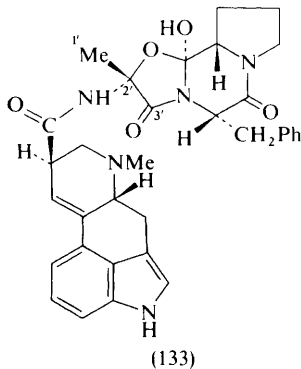


- (130) R = Me  
 (131) R = CH<sub>2</sub>OH  
 (132) R = CO<sub>2</sub>H

In these experiments feeding of radioactive festuclavine (130) led to considerable accumulation of activity in dihydroelymoclavine (131) and this suggested<sup>134</sup> that festuclavine may be a precursor for dihydroelymoclavine in *C. gigantea*, where it has been found that elymoclavine is but poorly utilized.<sup>135</sup>

Agroclavine (122) was found to be a poor precursor of (129) and its role in the biosynthesis of (129) was thus unclear.

The biosynthesis of ergotamine (133) has been subjected to rigorous scrutiny and the origins of the skeleton have been clearly defined.<sup>136</sup> Thus specific incorporations into the lysergyl moiety of (133) were observed of tryptophan,



mevalonic acid, formate, and the methyl group of methionine, whilst phenylalanine and proline were specific precursors for the side-chain fragment.

Previous studies<sup>137-140</sup> on the incorporation of alanine into the hydroxy-amino-acid fragment of ergot alkaloids have tended to give inconclusive results

<sup>135</sup> S. Agurell and E. Ramstad, *Acta Pharm. Suecica*, 1965, **2**, 231; *Arch. Biochem. Biophys.*, 1962, **98**, 457; S. Agurell, unpublished work, quoted in ref. 124.

<sup>136</sup> R. A. Bassett, E. B. Chain, and K. Corbett, *Biochem. J.*, 1973, **134**, 1.

<sup>137</sup> J. Majer, J. Kybal, and I. Komerosova, *Folia Microbiol. (Prague)*, 1967, **12**, 489; U. Nelson and S. Agurell, *Acta Chem. Scand.*, 1969, **23**, 3393.

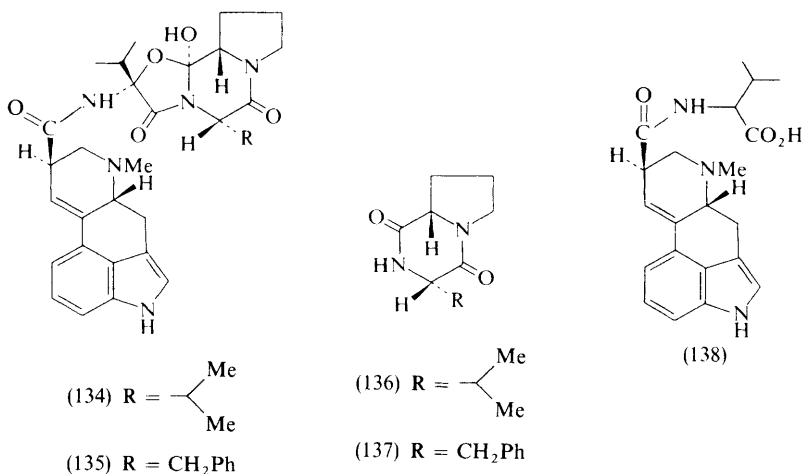
<sup>138</sup> D. Gröger, D. Erge, and H. G. Floss, *Z. Naturforsch.*, 1968, **23b**, 177; N. Castagnoli, jun., K. Corbett, E. B. Chain, and R. Thomas, *Biochem. J.*, 1970, **117**, 451.

<sup>139</sup> H. G. Floss, G. P. Basmadjian, M. Cheng, C. Spalla, and A. Minghetti, *Lloydia*, 1971, **34**, 442.

<sup>140</sup> R. B. Herbert in ref. 7, p. 29; in ref. 3, p. 7.

because of considerable randomization of label. A shorter incubation period and addition of radioactive alanine at a later stage of fermentation resulted in less randomization of activity and it is now clear from the results obtained<sup>136</sup> that alanine is an intact precursor for C-1', C-2', and C-3' of ergotamine (133). Contradictory evidence<sup>137,139-141</sup> exists for the participation of L-alaninol in the biosynthesis of the hydroxy-amino-acid fragment of ergot bases, so the manner in which alanine is utilized is still obscure.

The L-phenylalanine-L-proline lactam (137), which has been found to be present in *C. purpurea* cultures,<sup>142</sup> serves as a precursor for ergotamine (133).<sup>143</sup> This result mirrors the derivation of ergocryptine/ergocryptinine (134) from the L-leucyl-L-proline lactam (136).<sup>144</sup> A pointer for ergotamine (133) biosynthesis is the clear implication of D-lysergyl-L-valine (138) in the biosynthesis of (134).<sup>144</sup> However, lysergylalanine has been found to be a non-intact precursor of ergotamine.<sup>139</sup>



Hypothetical bond formation between D-lysergyl-L-valine (138) and the lactam (136) gives (139) which, on subsequent hydroxylation, leads to (134). A similar hypothetical intermediate for the biosynthesis of the related alkaloid ergocristine (135) is (140). Support for this and the general hypothesis for the formation of these peptidic alkaloids comes from the isolation of the C-11' epimer of (140) from *C. purpurea* cultures;<sup>145</sup> this compound branches, it is suggested, from the pathway to ergocristine by irreversible epimerization at C-11'.

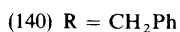
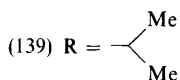
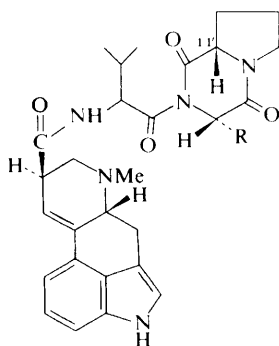
<sup>141</sup> A. Minghetti and F. Arcamone, *Experientia*, 1969, **25**, 926.

<sup>142</sup> M. Abe, M. Fukuhara, S. Ohmoto, M. Hori, and T. Tabuchi, *Agric. and Biol. Chem. (Japan)*, 1971, **35**, A6.

<sup>143</sup> M. Abe, T. Ohashi, S. Ohmoto, and T. Tabuchi, *Agric. and Biol. Chem. (Japan)*, 1971, **35**, A1.

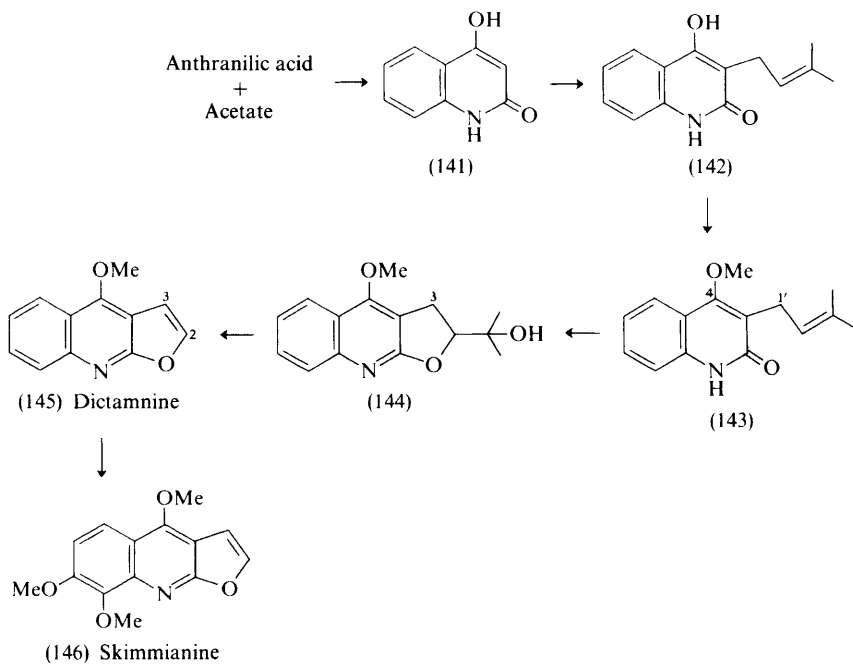
<sup>144</sup> T. Ohashi, H. Takahashi, and M. Abe, *Nippon Nogei Kagaku Kaishi*, 1972, **46**, 535; R. B. Herbert in ref. 5, p. 33.

<sup>145</sup> P. Stütz, R. Brunner, and P. A. Stadler, *Experientia*, 1973, **29**, 936.



### 8 Miscellaneous Bases of Aromatic Origin

**Furoquinoline Alkaloids.**—The biosynthetic route to the furoquinoline alkaloids, *e.g.* dictamnine (145) and skimmianine (146), which has been traced (see Scheme

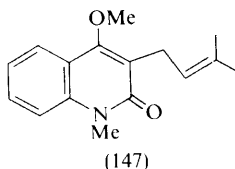


**Scheme 12**

12) follows from an extensive study.<sup>146,147</sup> Further work has allowed greater definition of the pathway.<sup>148,149</sup>

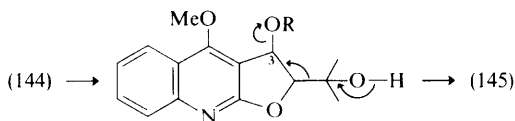
[3-<sup>14</sup>C,2,3-<sup>3</sup>H<sub>2</sub>]Dictamnine [as (145)] was efficiently incorporated into skimmianine (146) without change in isotope ratio. This corroborates the conclusion<sup>147</sup> that dictamnine is an intermediate in skimmianine biosynthesis and that, as in the formation of the furanocoumarins,<sup>150</sup> aromatic hydroxylation occurs after formation of the furan ring.

The prenylquinoline derivatives (142), (143), and (147) and 4-hydroxy- and 4-methoxy-2-quinolone are good precursors for dictamnine. Incorporation of



(147) must involve an N-demethylation reaction, and the results raised the question of whether perhaps the O-methyl group at C-4 of (143) was also enzymically labile. The incorporation of [1'-<sup>14</sup>C,O-methyl-<sup>3</sup>H]-4-methoxy-3-prenylquinolone [as (143)] without change in isotope ratio excluded this possibility.<sup>148</sup>

Platydesmine (144) is an efficient precursor of dictamnine (145) and the mechanism of the interesting reaction involved has been studied.<sup>148</sup> Retention of approximately half the tritium label in skimmianine (146) derived from [1'-<sup>14</sup>C,1'-<sup>3</sup>H]-4-methoxy-3-prenylquinolone [as (143)] provides support for a mechanism in which stereospecific allylic hydroxylation occurs at C-3 of (144) followed by loss of the isopropyl group as shown (Scheme 13). The results are



**Scheme 13**

also consistent with initiation of the fragmentation reaction on platydesmine (144) by hydride abstraction from C-3.

<sup>146</sup> M. Matsuo and Y. Kasida, *Chem. and Pharm. Bull. (Japan)*, 1966, **14**, 1108; I. Monković, I. D. Spenser, and A. O. Plunkett, *Canad. J. Chem.*, 1967, **45**, 1935; M. Cobet and M. Luckner, *European J. Biochem.*, 1968, **4**, 76; M. Cobet and M. Luckner, *Phytochemistry*, 1971, **10**, 1031; J. F. Collins and M. F. Grundon, *Chem. Comm.*, 1969, 621; M. F. Grundon and K. J. James, *Chem. Comm.*, 1911, 1311; A. O. Colonna and E. G. Gros, *Phytochemistry*, 1971, **10**, 1515; R. B. Herbert, in ref. 7, p. 12; in ref. 3, p. 34; J. Staunton, in ref. 9, p. 28.

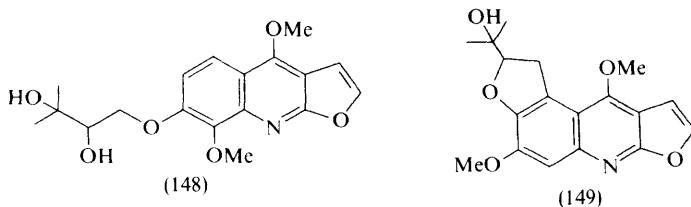
<sup>147</sup> J. F. Collins, W. J. Donnelly, M. F. Grundon, D. M. Harrison, C. G. Spyropoulos, *J.C.S. Chem. Comm.*, 1972, 1029; R. B. Herbert in ref. 5, p. 43.

<sup>148</sup> M. F. Grundon, D. M. Harrison, and C. G. Spyropoulos, *J.C.S. Chem. Comm.*, 1974, 51.

<sup>149</sup> D. Boulanger, B. K. Bailey, and W. Steck, *Phytochemistry*, 1973, **12**, 2399.

<sup>150</sup> D. J. Austin and S. A. Brown, *Phytochemistry*, 1973, **12**, 1657.

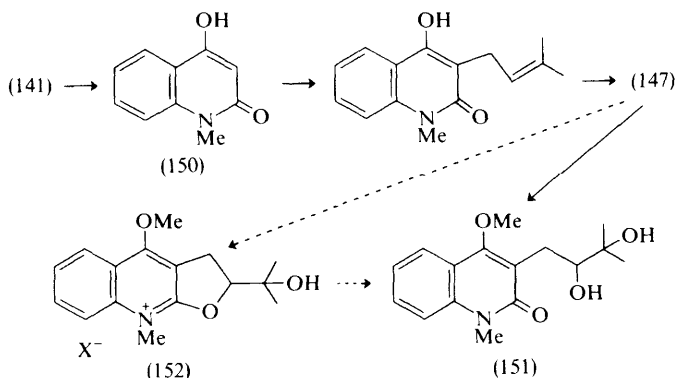
Evoxine (148) and choisyine (149) isolated in the above double-labelling experiments were found to have isotope ratios similar to those of skimmianine. Accordingly aromatic hydroxylation again appears to occur at a late stage.



Supporting evidence for the biosynthetic pathway to the furoquinoline alkaloids gleaned in whole plants comes from an investigation using cell suspension cultures of *Ruta graveolens*, which produced furoquinoline bases and edulinine (151).<sup>149</sup>

Production of both dictamnine (145) and edulinine (151) was stimulated by added 4-hydroxy-2-quinolone (141), a known precursor of furoquinoline alkaloids in intact plants. Subsequent feeding experiments indicated that this precursor (141) was at a branch point for biosynthesis of the two alkaloid types with competitive methylation, which yields (150), causing diversion from furoquinoline to edulinine biosynthesis, a conclusion which may be extendable to whole plants.

The results obtained for edulinine (151) allowed delineation of the pathway shown in Scheme 14. A platydesminium salt (152) is also a possible intermediate but the question of its involvement was left open.



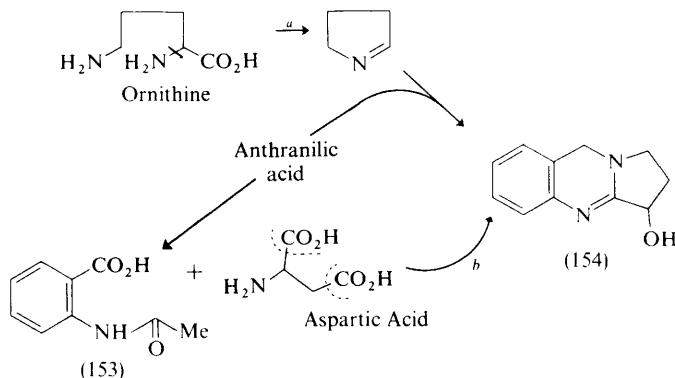
### Scheme 14

**Peganine.**—The biosynthesis of peganine (154) has been the subject of investigation in two plants. The pathway so far supported in *Peganum harmala*<sup>151–153</sup> is

<sup>151</sup> D. R. Liljegren, *Phytochemistry*, 1968, 7, 1299.

<sup>152</sup> D. R. Liljegren, *Phytochemistry*, 1971, **10**, 2661.

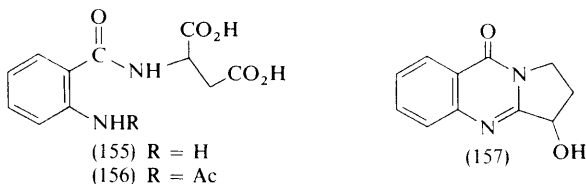
<sup>153</sup> R. B. Herbert, in ref. 3, p. 35.



Scheme 15

illustrated as path *a* of Scheme 15. In *Adhatoda vasica*, on the other hand, a different pathway (Scheme 15; path *b*) has been deduced.<sup>153,154</sup> Only anthranilic acid is common to both paths.<sup>155</sup>

In the latter pathway anthranilic acid and aspartic acid are used to construct peganine. In accord with this it has been shown recently that anthranoylaspartic acid (155) is a fairly specific precursor for peganine (154) in *A. vasica*.<sup>156</sup> *N*-Acetyl-anthranilic acid (153) is built into peganine intact, so perhaps the most important precursor for peganine may be (156).



Negative results were obtained on feeding labelled *N*-oxalylanthranilic acid and, in agreement with earlier work,<sup>152</sup> a precursor-product relationship between vasicinone (157) and peganine (154) could not be established.

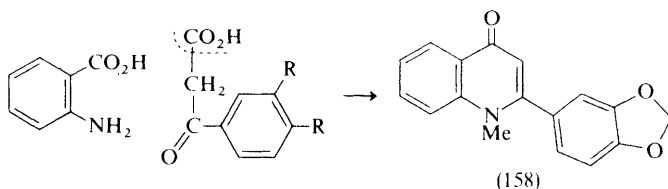
**Graveoline.**—Graveoline (158), the major alkaloid of *Ruta angustifolia*, shares with the furoquinoline alkaloids and peganine a common origin in anthranilic acid. [*carboxyl*-<sup>14</sup>C,*U*-<sup>3</sup>H,<sup>15</sup>N]Anthranilic acid was incorporated intact; some loss of activity from the carboxy-group of the anthranilic acid is probably attributable to cycling of the precursor through a pathway involving a tryptophan.<sup>157</sup>

<sup>154</sup> D. Gröger, S. Johne, and K. Mothes, *Abhandl. Deut. Akad. Wiss. Berlin Klasse Chem. Geol. Biol.*, 1966, 581; S. Johne and D. Gröger, *Z. Pflanzenphysiol.*, 1969, **61**, 353.

<sup>155</sup> D. Gröger and K. Mothes, *Arch. Pharm.*, 1960, **293**, 1049; D. Gröger, S. Johne, and K. Mothes, *Experientia*, 1965, **21**, 13; S. Johne, D. Gröger, and G. Richter, *Arch. Pharm.*, 1968, **301**, 721.

<sup>156</sup> S. Johne, K. Waiblinger, and D. Gröger, *Pharmazie*, 1973, **28**, 403.

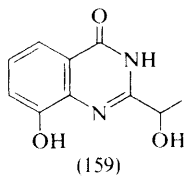
<sup>157</sup> M. Blaschke-Cobet and M. Luckner, *Phytochemistry*, 1973, **12**, 2393.



Experiments with tritium and  $^{14}\text{C}$ -labelled phenylalanine samples established that this amino-acid was incorporated intact as a  $\text{C}_8$  unit (with loss of C-1). Support for a pathway proceeding *via* cinnamic acid and hydroxylated derivatives and benzoylactic acid derivatives was provided in further experiments with cinnamic acid, ferulic acid/isoferulic acid, and the (easily hydrolysed) ethyl esters of benzoylactic acid and piperonylactic acid. As far as they go the results suggest that a mixed pathway is in operation with introduction of hydroxy- and methylenedioxy-groups on more than one intermediate.

Retention of 50% of the tritium in graveoline (158) derived from [ $3\text{-}^{14}\text{C}, 4'\text{-}^3\text{H}$ ]-phenylalanine indicated that the entry of the two hydroxy-groups was normal, *i.e.* hydroxylation at C-4' with 'NIH' shift<sup>60</sup> of tritium to C-3'/5' followed by hydroxylation at C-3' with consequent loss of half the tritium.

**Chrysogine.**—Production of chrysogine (159), a metabolite of *Penicillium chrysogenum*, has been found to be stimulated by added anthranilic acid, a likely precursor, but lactic acid, a possible source of the remaining three carbons, caused a decrease in the yield.<sup>158</sup>



**Benzodiazepine Bases.**—It has been shown that the carbon skeleton and the nitrogen atoms of cyclophenin (162) and cyclophenol (163) are derived from anthranilic acid, phenylalanine, and methionine.<sup>159</sup> The epoxide and aromatic oxygen atoms arise from molecular oxygen,<sup>160</sup> and cyclophenin (162) is a precursor of cyclophenol (163).<sup>161</sup> The phenylalanine moiety of cyclophenin suffers aromatic hydroxylation with a partial 'NIH' shift.<sup>160</sup> The enzyme cyclophenase converts cyclophenin and cyclophenol into other metabolites of *P. cyclopium*, viridicatin (164) and viridicatol (165), respectively.<sup>162</sup>

<sup>158</sup> H. Hikino, S. Nabetani, T. Takemoto, *Yakugaku Zasshi*, 1973, **93**, 619.

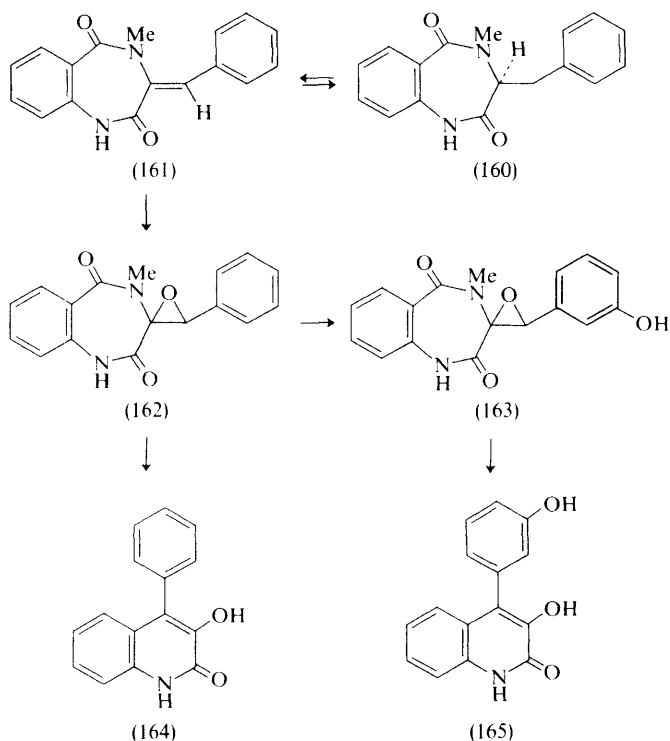
<sup>159</sup> L. Nover and M. Luckner, *European J. Biochem.*, 1969, **10**, 268; R. B. Herbert, in ref. 7, p. 15.

<sup>160</sup> L. Nover and M. Luckner, *F.E.B.S. Letters*, 1969, **3**, 292.

<sup>161</sup> L. Nover and M. Luckner, in ref. 119, p. 535.

<sup>162</sup> M. Luckner, *European J. Biochem.*, 1967, **2**, 74; M. Luckner, K. Winter, and J. Reisch, *ibid.*, 1969, **7**, 380; M. Luckner and L. Nover, in ref. 119, p. 525.

Feeding experiments with various possible intermediates have shown<sup>163</sup> that the two *N*-methyl cyclic peptides cyclopeptine (160) and its dehydro-derivative (161) are precursors for cyclopenin and cyclopenol. Further, (160) and (161) could be isolated from the culture and were themselves labelled by radioactive phenylalanine and anthranilic acid. In addition, cyclopeptine (160) was found to be reversibly transformed into dehydrocyclopeptine (161). Negative results with compounds likely to be implicated earlier on the pathway suggested that the formation of cyclopeptine (160) from the precursor amino-acids took place with enzyme-bound intermediates. The pathway established so far is summarized in Scheme 16.



Scheme 16

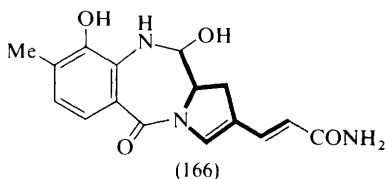
**Anthramycin.**—The aromatic ring of tyrosine suffers minor modification on incorporation into securinine (see above) whilst utilization in betalain biosynthesis results in ring cleavage between C-3' and C-4' after hydroxylation to dopa (see below). Similar degradation of tyrosine occurs in the biosynthesis of anthramycin (166), an antibiotic produced by *Streptomyces refuineus*. var *thermotolerans*.<sup>164</sup>

<sup>163</sup> J. Framm, L. Nover, A. El Azzouny, H. Richter, K. Winter, S. Werner, and M. Luckner, *European J. Biochem.*, 1973, 37, 78.

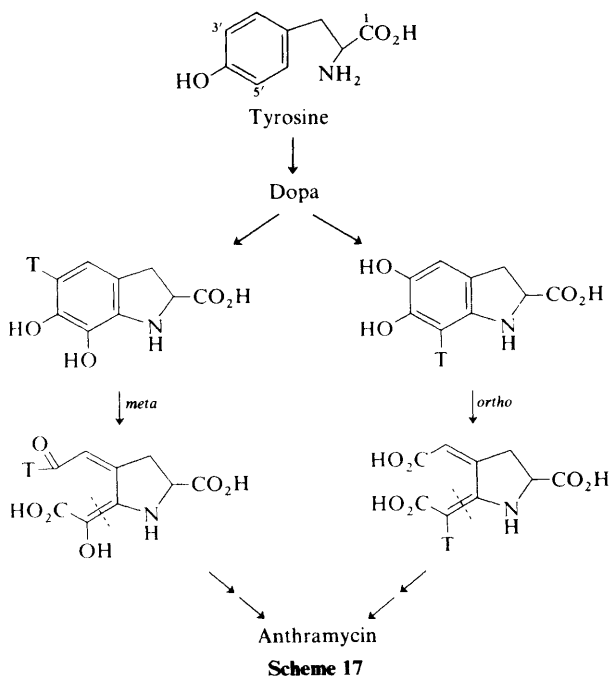
<sup>164</sup> L. H. Hurley and M. Zmijewski, *J.C.S. Chem. Comm.*, 1974, 337.



Both L-[U- $^{14}\text{C}$ ]tyrosine and L-[1- $^{14}\text{C}$ ]dopa were efficiently incorporated into anthramycin and the activity from the tyrosine feed was found to be confined to the portion of the molecule shown with heavy bonding in (166). Half the tritium was lost from [1- $^{14}\text{C}$ ,3',5'- $^3\text{H}_2$ ]tyrosine on conversion into anthramycin.



This is in accord with a mechanism involving hydroxylation of tyrosine to give dopa (with expected loss of half the tritium), 'meta' cleavage (which is formally similar to the mechanism of cleavage in betalain biosynthesis), and finally loss of two ring carbons (see Scheme 17, where the alternative 'ortho' cleavage is also

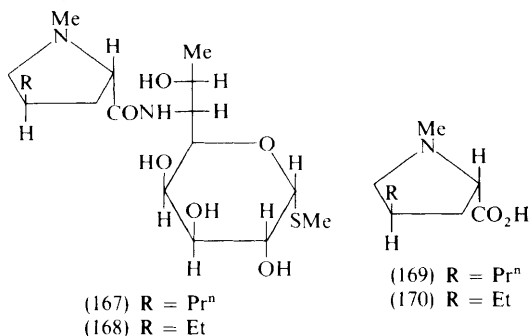


illustrated. This pathway should result in loss of all the tritium present in the precursor. Both of these paths are based on proposals for lincomycin biosynthesis.<sup>165</sup> A 64% tritium retention on incorporation of [U- $^{14}\text{C}$ ,3',5'- $^3\text{H}_2$ ]tyrosine

<sup>165</sup> D. F. Witz, E. J. Hessler, and T. L. Miller, *Biochemistry*, 1971, **10**, 1128.

was consistent with the transfer of seven of the nine carbon atoms of tyrosine to anthramycin and in accord with the adduced pathway.

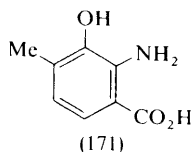
Structures analogous to the tyrosine-derived portion of anthramycin are to be seen in the propyl- and ethyl-proline moieties of lincomycin (167) and (168), which are produced by another *Streptomyces* species. These substituted proline residues had been shown<sup>165</sup> earlier to arise from tyrosine too: C-1 of tyrosine was incorporated efficiently and specifically into the carboxy-groups of (169) and (170), and a <sup>15</sup>N study showed that the nitrogen atom of the proline ring came from



tyrosine also. Some evidence was obtained that seven of the nine carbon atoms of tyrosine were used for the generation of (169) and (170). Methionine was found to be the source of the *N*-methyl and *C*-methyl groups of (169) and (170) but not of the methylene carbons in either case. This indicated that (170) was not a precursor of (169) but that they were similarly derived from intermediates differing by one carbon atom.

Label from methionine was roughly equally split between the two halves of anthramycin<sup>164</sup> [normal and heavy bonding in (166)]. A mixed [<sup>3</sup>H,<sup>14</sup>C]-labelled sample was shown to give the aromatic *C*-methyl of anthramycin without tritium loss whilst incorporation into the acrylamide-proline moiety was with complete loss of tritium. The inference from this was that methionine gives the carbonyl carbon of this moiety.

The remaining atoms in anthramycin (166) can be identified with 4-methyl-3-hydroxyanthranilic acid (171), an intermediate in the biosynthesis of actinomycins from tryptophan.<sup>166</sup> In accord, [7a-<sup>14</sup>C]tryptophan was well incorporated into anthramycin.<sup>164</sup>



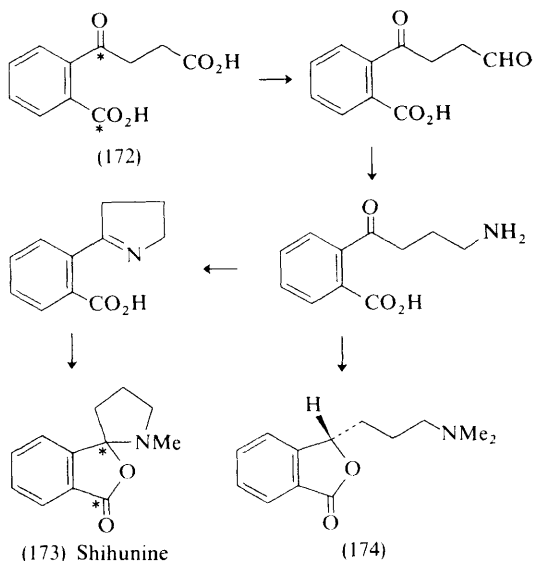
**Shihunine.**—The diacid (172) is an important intermediate in the biosynthesis of several 1,4-naphthoquinones, *viz.* lawsone, juglone, and the bacterial mena-

<sup>166</sup> L. Salzmann, H. Weissbach, and E. Katz, *Arch. Biochem. Biophys.*, 1969, **130**, 536.

quinones.<sup>167,168</sup> The interesting hypothesis that this compound could also serve as a precursor of the orchid alkaloids shihunine (173) and pierardine (174) has been examined.<sup>169</sup>

The diacid (172) (<sup>14</sup>C-labelling indicated by \*) was fed to the orchid *Dendrobium pierardii* and a very efficient incorporation into shihunine was recorded. A very much lower incorporation (a factor of 10<sup>-3</sup>) was found for pierardine (174) and this may indicate that this alkaloid was not being synthesized at the time of the experiment.

Degradation of the radioactive shihunine (173) showed that the label was equally distributed between the carbons marked \*. Thus (172) is established as a direct precursor of shihunine (173); the suggested pathway<sup>169</sup> is illustrated in Scheme 18.



Scheme 18

The naturally occurring naphthoquinones such as lawsone and juglone are products of the shikimic acid pathway to aromatic amino-acids but the path which leads to these naphthoquinones branches from the main pathway before the formation of aromatic compounds,<sup>170</sup> probably no later than chorismic acid.<sup>167</sup> It will be most interesting to see whether the biosynthesis of shihunine also follows this route: all the other bases of plant origin which arise from products of the shikimic acid pathway derive from *aromatic* precursors.

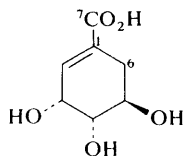
<sup>167</sup> P. Dansette and R. Azerad, *Biochem. Biophys. Res. Comm.*, 1970, **40**, 1090.

<sup>168</sup> I. M. Campbell, D. J. Robins, M. Kelsey, and R. Bentley, *Biochemistry*, 1971, **10**, 3069.

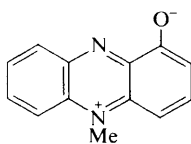
<sup>169</sup> E. Leete and G. B. Bodem, *J.C.S. Chem. Comm.*, 1973, 522.

<sup>170</sup> M. H. Zenk and E. Leistner, *Lloydia*, 1968, **31**, 275.

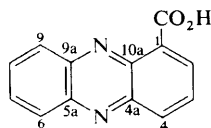
**Phenazines.**—DL-[1,6- $^{14}\text{C}_2$ ]Shikimic acid [as (175)] is a specific precursor for pyocyanin (176) and phenazine-1-carboxylic acid (177) in *Pseudomonas* species.<sup>171</sup> The activity was found to be approximately equally divided between the two groups of atoms C-1, C-4, C-6, and C-9 and C-4a, C-5a, C-9a, and C-10a [see (177)]. Additional, more definitive, results were subsequently obtained<sup>172</sup> with D-[6- $^{14}\text{C}$ ] shikimic acid: activity in the derived phenazine-1-carboxylic acid was confined to C-4a, C-5a, C-9a, and C-10a.



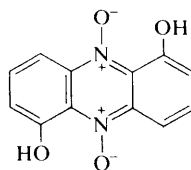
(175) Shikimic acid



(176)

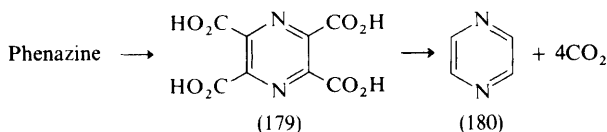


(177)



(178)

Administration of the same precursor to *Brevibacterium iodinum* gave radio-active iodinin (178). This material was subjected to the usual degradation (Scheme 19). In accord with the labelling pattern observed in phenazine-1-carboxylic acid (177), 100% of the activity appeared in the pyrazine (180) but strangely 12% also appeared in the carbon dioxide.



Scheme 19

Another group<sup>173</sup> found different results for the incorporation of D-[6- $^{14}\text{C}$ ]shikimic acid into iodinin (178), but further study<sup>174</sup> of iodinin derived from D-[1- $^{14}\text{C}$ ]shikimic acid revealed that the degradative procedure used by both groups<sup>171-173</sup> was faulty. Copper chromite decarboxylation of pyrazinetetracarboxylic acid (179) gives a satisfactory sample of pyrazine (180) but the carbon dioxide obtained appears to derive to some extent from the ring as well as from the

<sup>171</sup> U. Hollstein and L. G. Marshall, *J. Org. Chem.*, 1972, **37**, 3510; R. B. Herbert, in ref. 5, p. 46.

<sup>172</sup> U. Hollstein and D. A. McCamey, *J. Org. Chem.*, 1973, **38**, 3415.

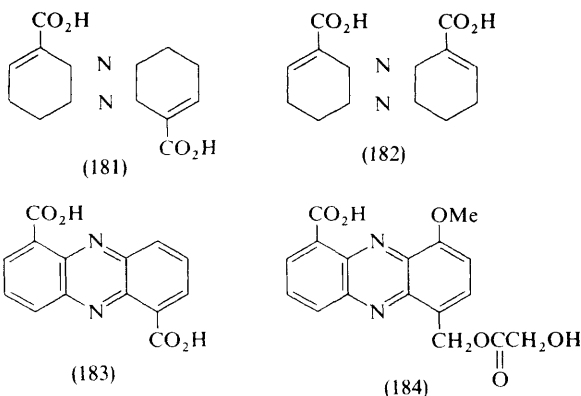
<sup>173</sup> R. B. Herbert, F. G. Holliman, and P. N. Ibberson, *Tetrahedron Letters*, 1974, 151.

<sup>174</sup> R. B. Herbert, F. G. Holliman, and J. B. Sheridan, *Tetrahedron Letters*, 1974, 4201.

carboxy-groups. This leads to values greater than zero for material derived from [6- $^{14}\text{C}$ ]shikimic acid. No such difficulty arises if copper-quinoline is used for the decarboxylation.

The results obtained for iodinin (178) with D-[6- $^{14}\text{C}$ ]-,<sup>172,174</sup> D-[1- $^{14}\text{C}$ ]-,<sup>174</sup> and D-[1,6,7- $^{14}\text{C}_3$ ]shikimic<sup>174</sup> acids and for phenazine-1-carboxylic acid (177) with D-[6- $^{14}\text{C}$ ]-<sup>172</sup> and DL-[1,6- $^{14}\text{C}_2$ ]shikimic<sup>171</sup> acids are now in agreement with each other and argue strongly that earlier results<sup>175</sup> are incorrect.

The above results do not allow one to decide whether one or two molecules of shikimic acid are involved in the biosynthesis of the phenazine nucleus but there is other evidence<sup>176</sup> that the number of molecules involved is two. If this is accepted there are two ways in which the shikimic acid units can be arranged, (181) and (182); (181) is preferred, for such an arrangement of  $\text{C}_7$  units is to be seen in phenazine-1,6-dicarboxylic acid (183)<sup>177</sup> and in the griseolutesins, e.g. griseolutein A (184).<sup>178</sup>



6-Hydroxyphenazine-1-carboxylic acid was shown<sup>173</sup> to be present in cultures producing iodinin (178) (by dilution after feeding [6- $^{14}\text{C}$ ]shikimic acid). This strengthens its assigned position as an intermediate in iodinin biosynthesis.

**Ephedrine.**—Feeding experiments with phenylalanine and cinnamic acid, supported by positive results with benzaldehyde and benzoic acid, indicate a biosynthetic pathway to ephedrine (185) which involves a  $\text{C}_6\text{—C}_1$  unit derived from phenylalanine. These results, which have been published in preliminary form<sup>179</sup> and reviewed,<sup>180</sup> are now available in a full paper.<sup>181</sup> Attention was drawn to the low incorporation of phenylalanine and cinnamic acid relative to

<sup>175</sup> M. Podojil and N. N. Gerber, *Biochemistry*, 1970, 9, 4616.

<sup>176</sup> W. M. Ingledew and J. J. R. Campbell, *Canad. J. Microbiol.*, 1969, 15, 535.

<sup>177</sup> N. N. Gerber, *J. Heterocyclic Chem.*, 1969, 6, 297.

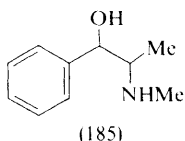
<sup>178</sup> S. Nakamura, E. L. Wang, M. Murase, K. Maeda, and H. Umezawa, *J. Antibiotics (A)*, 1959, 12, 55.

<sup>179</sup> K. Yamasaki, U. Sankawa, and S. Shibata, *Tetrahedron Letters*, 1969, 4099.

<sup>180</sup> R. B. Herbert, in ref. 7, p. 18.

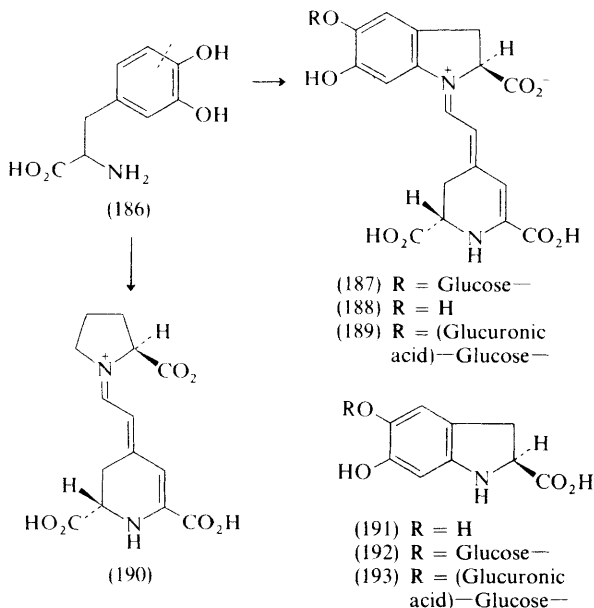
<sup>181</sup> K. Yamasaki, T. Tamaki, S. Uzawa, U. Sankawa, and S. Shibata, *Phytochemistry*, 1973, 12, 2877.

benzoic acid, suggesting that the benzoic acid might arise in part directly from shikimic acid (175). Such a possibility has been suggested for C<sub>6</sub>-C<sub>1</sub>-derived benzofuran derivatives of fungal origin.<sup>182</sup>



Methionine serves as the source of the *N*-methyl group of ephedrine (185) but the origin of the remaining C<sub>2</sub>N unit is not clear. On the one hand results with C<sub>2</sub> and C<sub>3</sub> amino-acids were not definitive. On the other, relatively high incorporations were recorded of [6-<sup>14</sup>C]glucose and [*U*-<sup>14</sup>C]aspartate into the C<sub>2</sub>N unit, indicating that aspartate or a close relative might be implicated, but the good incorporation of formate into this unit made a firm conclusion difficult.

**Betalains.**—Betacyanins, *e.g.* betanin (187), are red-violet pigments found in plants of the Centrospermae order. Radioactive dopa [as (186)] has been found to label the dihydroindole portion of betanin to a minor extent.<sup>183</sup> Most of the label appears in the dihydropyridine moiety. This moiety, in betanin (187)<sup>184</sup>



<sup>182</sup> J. D. Bu'Lock, B. Kaye, and A. T. Hudson, *Phytochemistry*, 1971, **10**, 1037.

<sup>183</sup> H. E. Miller, H. Rösler, A. Wohlpert, H. Wyler, M. E. Wilcox, H. Frohofer, T. J. Mabry, and A. S. Dreiding, *Helv. Chim. Acta*, 1968, **51**, 1470.

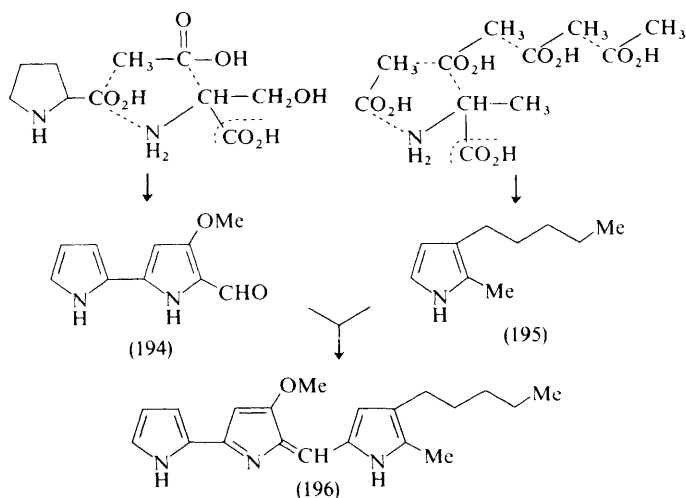
<sup>184</sup> N. Fischer and A. S. Dreiding, *Helv. Chim. Acta*, 1972, **55**, 649; R. B. Herbert, in ref. 3, p. 8.

and the yellow pigment indicaxanthin (190),<sup>185</sup> has been shown to arise from extradiol cleavage of the aromatic ring of dopa, followed by cyclization to the heterocyclic system. The reported conversion of betanidin (188) into betanin (187) indicates that glycosylation is a late step.<sup>186</sup>

*Celosia plumosa* was selected for further study<sup>187</sup> of betalain biosynthesis as yellow varieties of this species showed, on administration of appropriate substrates, an ability to synthesize the red pigment amaranthin (189) normally produced by other varieties of the same species. The experimental work was thus simplified because in some cases it was not necessary to employ radioactive precursors: the consequence of feeding a particular substrate could be correlated with the appearance of red pigment.

The results were that whereas conversion of betanidin (188) into betanin (187) was efficient subsequent conversion into amaranthin (189) was not. On the other hand (*S*)-*cyclo*-dopa (191) and (*S*)-*cyclo*-dopa-5-*O*- $\beta$ -D-glucoside (192) were efficiently converted into amaranthin (189). The major pathway which these results indicate then is *cyclo*-dopa (191)  $\rightarrow$  (192)  $\rightarrow$  (193)  $\rightarrow$  amaranthin (189).

**Prodigiosin.**—The final step in the formation of prodigiosin (196) involves condensation of (194) with (195).<sup>188</sup> The origin of the tri-pyrrolic skeleton of this microbial metabolite has been defined<sup>189</sup> recently mainly by use of <sup>13</sup>C-labelled



Scheme 20

<sup>185</sup> G. Impellizzeri and M. Piattelli, *Phytochemistry*, 1972, **11**, 2499; R. B. Herbert, in ref. 5, p. 38.

<sup>186</sup> S. Sciuto, G. Oriente, and M. Piattelli, *Phytochemistry*, 1972, **11**, 2259.

<sup>187</sup> S. Sciuto, G. Oriente, M. Piattelli, G. Impellizzeri, and V. Amico, *Phytochemistry*, 1974, **13**, 947.

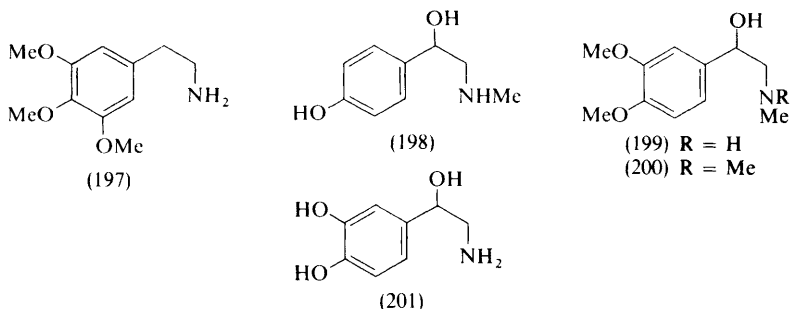
<sup>188</sup> H. H. Wasserman, J. E. McKeon, and U. V. Santer, *Biochem. Biophys. Res. Comm.*, 1960, **3**, 146.

<sup>189</sup> R. J. Cushley, D. R. Anderson, S. R. Lipsky, R. J. Sykes, and H. H. Wasserman, *J. Amer. Chem. Soc.*, 1971, **93**, 6284; H. H. Wasserman, R. J. Sykes, P. Peverada, C. K. Shaw, R. J. Cushley, and S. R. Lipsky, *J. Amer. Chem. Soc.*, 1973, **95**, 6874.

precursors. The results indicate a pathway without precedent among other naturally occurring pyrroles (see Scheme 20). The pattern revealed was of particular clarity and, in addition to allowing deduction of the primary routes to prodigiosin, secondary pathways could also be discerned.

**Phenethylamines.**—The biosynthesis of phenethylamines, *e.g.* mescaline (197), in cactus plants has been the subject of an exhaustive study. The pathways to these bases<sup>17</sup> and the related isoquinolines, *e.g.* anhalonidine (12),<sup>16</sup> is now well understood.

The  $\beta$ -hydroxyphenethylamine synephrine (198) appears to arise in *Citrus* from tyrosine *via* tyramine and *N*-methyltyramine.<sup>190</sup> Normacromerine (199) and macromerine (200) are found in the cactus *Coryphantha macromeris* var. *runyonii*.<sup>191</sup> Their genesis has also been studied.<sup>192</sup> Specific incorporations of DL-[3-<sup>14</sup>C]tyrosine, [1-<sup>14</sup>C]tyramine, DL-[2-<sup>14</sup>C]dopa, and [1-<sup>14</sup>C]dopamine into normacromerine established a pattern of biosynthesis similar to that of the other cactus alkaloids and again a C<sub>6</sub>–C<sub>2</sub> unit is implicated. [This contrasts with the biosynthesis of the superficially similar base ephedrine (185), discussed above.]



Norepinephrine (201) was a reasonably efficient precursor for normacromerine which indicates that  $\beta$ -hydroxylation can be an early step, whilst the occurrence of synephrine (198) in *C. macromeris*<sup>191</sup> indicates that *N*-methylation can likewise occur early.

Very low incorporations of the above precursors into macromerine (200) suggested that *N*-methylation of normacromerine is slow.

**Dolichotheline.**—Dolichotheline (202) is an unusual imidazole alkaloid produced by the cactus *Dolichothele sphaerica* along a pathway which involves condensation of histamine with isovaleric acid.<sup>193</sup> Administration of isocaproic acid and 4(5)-aminomethylimidazole led to the production of the unnatural alkaloids (203) and (204), respectively.<sup>194</sup>

<sup>190</sup> T. A. Wheaton and I. Stewart, *Phytochemistry*, 1969, **8**, 85.

<sup>191</sup> W. J. Keller, J. L. McLaughlin, and L. R. Brady, *J. Pharm. Sci.*, 1973, **62**, 408.

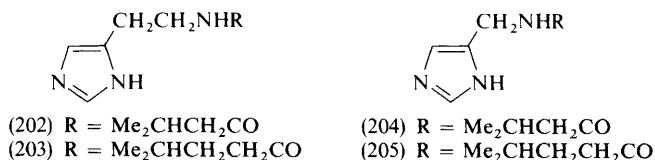
<sup>192</sup> W. J. Keller, L. A. Spitznagle, L. R. Brady, and J. L. McLaughlin, *Lloydia*, 1973, **36**, 397.

<sup>193</sup> H. Rosenberg and A. G. Paul, *Lloydia*, 1971, **34**, 372; R. B. Herbert in ref. 3, p. 17.

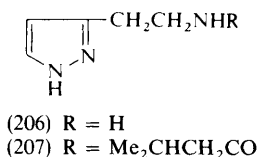
<sup>194</sup> H. Rosenberg and A. G. Paul, *J. Pharm. Sci.*, 1973, **62**, 403; R. B. Herbert, in ref. 5, p. 42.



In an extension of this work isocaproic acid and 4(5)-aminomethylimidazole were fed together to this plant.<sup>195</sup> Not only was the expected unnatural alkaloid (205) produced but interestingly the efficiency of the conversion into unnatural



alkaloid was improved ten-fold (14% conversion) compared with when the substrates were fed separately. It seems then as if both substrates must be in sufficient concentration to trigger or promote appropriate enzyme action. In a similar experiment isovaleric acid and the pyrazole isomer (206) of histamine afforded the unnatural base (207).



In another variation on this theme cinnamic acid was found to act as a suitable substrate for alkaloid production in this cactus.<sup>196</sup> *N*-Cinnamoylhistamine, which is found naturally in species of the Australian Leguminosae,<sup>197</sup> was produced in 0.22% yield.

These results show further the versatility of enzymes involved in the biosynthesis of secondary metabolites and suggest that it may be possible to make use of plants for the synthesis of perhaps otherwise inaccessible compounds of pharmaceutical interest.

## 9 Miscellaneous Bases of Aliphatic Origin

**Tenuazonic Acid.**—Tenuazonic acid (208) is generated in the fungus *Alternaria tenuis* from L-isoleucine and acetate.<sup>198</sup> Recent experiments<sup>199</sup> show that butyric acid is a specific precursor; it is presumably implicated *via* acetoacetic acid. The likely mode of linking of acetoacetate and L-isoleucine was indicated by the isolation of (211) from the cultures.

In experiments analogous to those discussed for dolichotheline above, *A. tenuis* was found to be able to substitute added L-valine and L-leucine for L-isoleucine and elaborate the tenuazonic acid analogues (209) and (210) respectively.<sup>200</sup>

<sup>195</sup> H. Rosenberg, S. J. Stohs, and A. G. Paul, *Phytochemistry*, 1974, 13, 823.

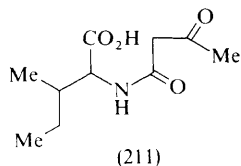
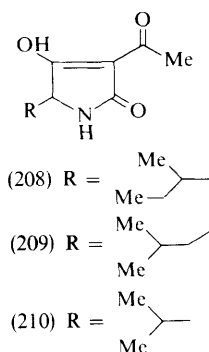
<sup>196</sup> H. Rosenberg and S. J. Stohs, *Lloydia*, 1974, 37, 313.

<sup>197</sup> J. S. Fitzgerald, *Austral. J. Chem.*, 1964, 17, 375.

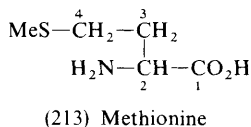
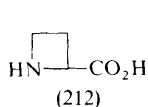
<sup>198</sup> C. E. Stickings and R. J. Townsend, *Biochem. J.*, 1961, 78, 412.

<sup>199</sup> S. Gatenbeck and J. Sierankiewicz, *Acta Chem. Scand.*, 1973, 27, 1825.

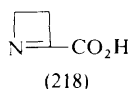
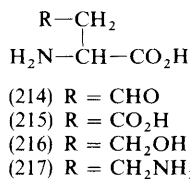
<sup>200</sup> S. Gatenbeck and J. Sierankiewicz, *Antimicrob. Agents Chemother.*, 1973, 3, 308.



**Azetidine-2-carboxylic Acid.**—Early investigations of the biosynthesis of this unusual heterocyclic acid (212) were without significant issue.<sup>201</sup> Later work established that methionine (213)<sup>202–204</sup> and *S*-adenosylmethionine<sup>204</sup> were similarly effective precursors and it seemed highly probable that the carbon chain of methionine was utilized intact.<sup>203</sup> An attractive mechanism for ring closure of methionine was envisaged<sup>202</sup> which involved intramolecular displacement of thiomethyladenosine by the  $\alpha$ -amino-group of *S*-adenosylmethionine, but experimental support was lacking.



A specific incorporation of [1-<sup>14</sup>C,4-<sup>3</sup>H]methionine [as (213)] into azetidine-2-carboxylic acid (212) without change in isotope ratio showed that the oxidation level at C-4 was unaffected in the biotransformation of (213) into (212), thus excluding as intermediates aspartic- $\beta$ -semialdehyde (214) and aspartic acid (215).<sup>204</sup> Conflicting evidence on the relative levels of incorporation of homoserine (216) and methionine has been obtained<sup>204,205</sup> (but the differences are quite small). However, when a relatively large amount of inactive homoserine was fed together



<sup>201</sup> P. Linko, *Acta Chem. Scand.*, 1958, **12**, 101; L. Fowden and M. Bryant *Biochem. J.*, 1959, **71**, 210.

<sup>202</sup> E. Leete, *J. Amer. Chem. Soc.*, 1964, **86**, 3162.

<sup>203</sup> E. F.-W. Su and B. Levenberg, *Acta Chem. Scand.*, 1967, **21**, 493.

<sup>204</sup> E. Leete, G. E. Davis, C. R. Hutchinson, K. W. Woo, and M. R. Chedekel, *Phytochemistry*, 1974, **13**, 427.

<sup>205</sup> M.-L. Sung and L. Fowden, *Phytochemistry*, 1971, **10**, 1523.

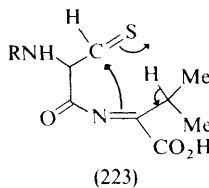
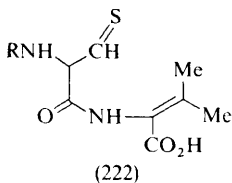
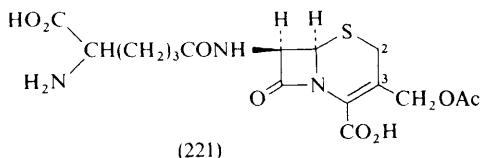
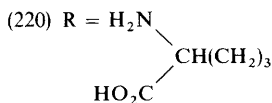
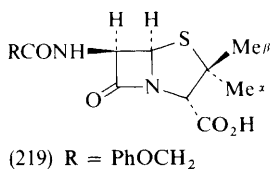
with labelled methionine incorporation of the latter decreased.<sup>204</sup> It seems likely therefore that homoserine (216) is a biosynthetic intermediate.

More significantly [ $1\text{-}^{14}\text{C}, 2\text{-}^3\text{H}$ ]methionine [as (213)] was incorporated with almost complete tritium loss and so methionine (213) and *S*-adenosylmethionine cannot be the ultimate precursors for (212).<sup>204</sup> Further, 2,4-diaminobutyric acid (217) has been found to be a better precursor of (212) than methionine.<sup>205</sup>

Loss of tritium originally present at C-2 of methionine can be accounted for if 4-amino-2-ketobutyric acid is an intermediate derivable from 2,4-diaminobutyric acid. Ring closure of the amino-ketone would give azetine-2-carboxylic acid (218) which in turn would generate azetidine-2-carboxylic acid (212) on reduction.<sup>204</sup>

**$\beta$ -Lactam Antibiotics.**—The ring systems of penicillin [as (219)] and cephalosporin C (221) have been shown to have their genesis from *L*-valine and *L*-cysteine,<sup>206</sup> and it is known as a result of complementary studies with valine stereospecifically labelled with  $^{13}\text{C}$  on the methyl groups that it is the 3-*pro-R* methyl group which gives C-2 of cephalosporin C (221)<sup>207,208</sup> and the  $\beta$ -methyl group of penicillin [as (219)].<sup>208,209</sup> However, the way in which the ring-closure reactions occur is still a mystery.

An important intermediate in the biosynthesis of penicillin, it has been suggested,<sup>206</sup> could be (222), derived from *L*-cysteinyl-*L*-valine or possibly *L*- $\alpha$ -aminoadipoyl-*L*-cysteinyl-*L*-valine. An alternative is (223), which could ring-close



<sup>206</sup> P. A. Lemke and D. R. Brannon, in 'Cephalosporins and Penicillins', ed. E. H. Flynn, Academic Press, New York, 1972, p. 370.

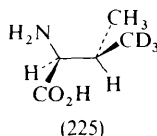
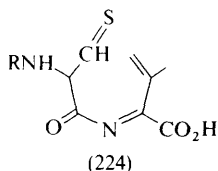
<sup>207</sup> N. Neuss, C. H. Nash, J. E. Baldwin, P. A. Lemke, and J. B. Grutzner, *J. Amer. Chem. Soc.*, 1973, **95**, 3797; R. B. Herbert, in ref. 5, p. 40.

<sup>208</sup> H. Kluender, C. H. Bradley, C. J. Sih, P. Fawcett, and E. P. Abraham, *J. Amer. Chem. Soc.*, 1973, **95**, 6149.

<sup>209</sup> P. A. Lemke, C. H. Nash, and S. W. Pieper, *J. Gen. Microbiol.*, in the press; quoted in ref. 207.

by a variant of the 'ene' reaction.<sup>210</sup> In addition the compound (224) has been suggested as a suitable substrate for cyclization in cephalosporin biosynthesis.<sup>206</sup> Its possible intermediacy in the biosynthesis of cephalosporin and penicillin has been examined with deuteriovaline derivatives.

[Me<sub>2</sub>-<sup>2</sup>H<sub>6</sub>]Valine gave penicillin N (220)<sup>211</sup> and penicillin V (219)<sup>212</sup> with complete retention of deuterium, and thus intermediates of the type (224) are excluded from penicillin biosynthesis. In support (2*S*,3*S*)-[4,4,4-<sup>2</sup>H<sub>3</sub>]valine (225) and (2*S*,3*R*)-[4,4,4-<sup>2</sup>H<sub>3</sub>]valine each afforded exclusively trideuteriated penicillin N (220).<sup>211</sup>



Experiments<sup>211</sup> on cephalosporin C biosynthesis using these precursors were less conclusive as mass spectrometric analysis seemed to be complicated by deuterium scrambling in the spectrometer. It appeared that although two deuterium atoms were located on the exocyclic methylene group in cephalosporin C derived from (225), perhaps one (rather than two) was located at C-2 in material arising from the C-3 epimer. N.m.r. spectroscopy, however, indicated within the limits of measurement that two deuterium atoms were present at C-2. Further, no deuterium was incorporated into cephalosporin C produced microbially in deuterium oxide. It is thus probable that incorporation of the C-3 epimer of (225) is with retention of two deuterium atoms and it follows that formation of the Δ<sup>3</sup>-cepham nucleus does not proceed *via* a Δ<sup>2</sup>-cepham intermediate. On the other hand the results are in accord with intermediacy of compounds like (224).

Study of a mutant of *Cephalosporium* species has led to the conclusion that acetylation is the terminal biosynthetic step and that deacetylcephalosporin is an intermediate.<sup>213</sup>

**Mitomycins, Geldanamycin, Rifamycin S, and Streptovaricin D.**—Continuing experiments<sup>214,215</sup> on the biosynthesis of the mitomycins, *e.g.* mitomycin B (226), with labelled glucosamine samples have firmly established that glucosamine serves intact as the origin for C-1, C-2, C-3, C-9, C-9a, and C-10 and the nitrogen atom of the aziridine ring.

<sup>210</sup> J. E. Baldwin, S. B. Haber, and J. Kitchin, *J.C.S. Chem. Comm.*, 1973, 790; see also J. Cheney, C. J. Moores, J. A. Raleigh, A. I. Scott, and D. W. Young, *ibid.*, 1974, 47.

<sup>211</sup> H. Kluender, F.-C. Huang, A. Fritzberg, H. Schnoes, C. J. Sih, P. Fawcett, and E. P. Abraham, *J. Amer. Chem. Soc.*, 1974, 96, 4054.

<sup>212</sup> D. J. Aberhart, J.Y.-R. Chu, N. Neuss, C. H. Nash, J. Occolowitz, L. L. Huckstep, and N. De La Higuera, *J.C.S. Chem. Comm.*, 1974, 564.

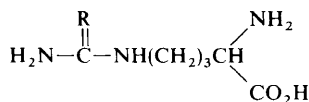
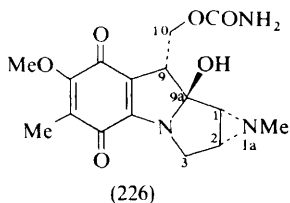
<sup>213</sup> Y. Fujisawa, H. Shirafuji, M. Kida, and K. Nara, *Nature New Biol.*, 1973, 246, 154.

<sup>214</sup> U. Hornemann and J. C. Cloyd, *Chem. Comm.*, 1971, 301; U. Hornemann and M. J. Aikman, *J.C.S. Chem. Comm.*, 1973, 88; R. B. Herbert in ref. 5, p. 40.

<sup>215</sup> U. Hornemann, J. P. Kehrer, C. S. Nunez, and R. L. Ranieri, *J. Amer. Chem. Soc.*, 1974, 96, 320.

D-[1- $^{13}\text{C}$ ,1- $^{14}\text{C}$ , $^{15}\text{N}$ ]Glucosamine gave mitomycin B the mass spectrum of which showed a fragment ion (which arises from C-1, C-2, C-3, and N-1a and the attached methyl group) corresponding to  $\text{C}_3^{13}\text{CH}_8^{15}\text{N}$  with low-intensity ions corresponding to  $\text{C}_3^{13}\text{CH}_8\text{N}$  and  $\text{C}_2^{13}\text{C}_2\text{H}_8\text{N}$ ; an intact incorporation of the precursor was indicated. It follows that the conversion of D-glucosamine into mitomycin B (226), which necessarily requires an inversion at C-1, does not involve loss of nitrogen from C-1.

Degradation of mitomycin C derived from D-[6- $^{14}\text{C}$ ]glucosamine showed that the label was predominantly at C-10.

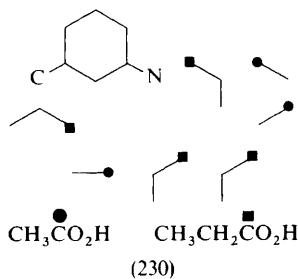
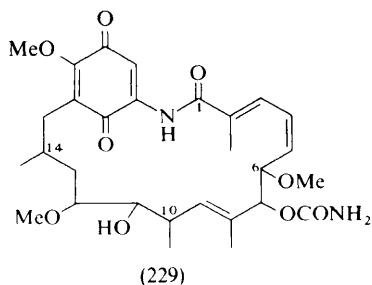


(227) R = O

(228) R = NH

Competition feeding experiments between L-[ureido- $^{14}\text{C}$ ]citrulline [as (227)] and L-[guanidino- $^{14}\text{C}$ ]arginine [as (228)] showed that although both were similarly taken up into the mycelium, L-citrulline was more readily incorporated into the mitomycins; the incorporation was shown to be specifically into the carbamoyl group. The origin of the remaining  $\text{C}_7$  unit including the other nitrogen is not yet clear although it appears to derive from carbohydrate metabolism. A similar unit can be discerned in other antibiotics such as the biologically important ansamycins, e.g. geldanamycin (229), and a similar origin for these  $\text{C}_7\text{N}$  units has been suggested.<sup>215</sup>

The biosynthesis of geldanamycin (229) has been studied mainly by use of  $^{13}\text{C}$  labelling. The results,<sup>216</sup> summarized in (230), indicated a continuous



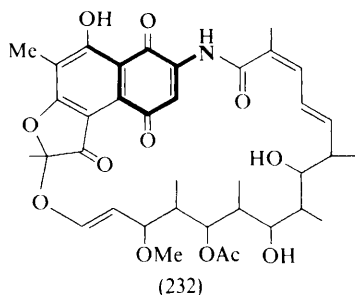
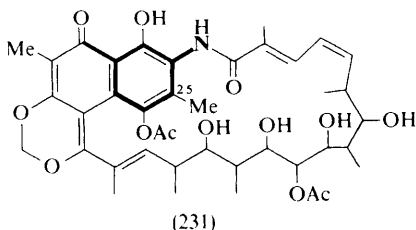
sequence of acetate and propionate from C-14 through C-1. The  $\text{C}_7\text{N}$  benzoquinone unit was not labelled by either propionate or methionine.

The related antibiotics streptovaricin D (231) and rifamycin S (232) are derived along similar mixed acetate-propionate pathways, deduced as above by use of

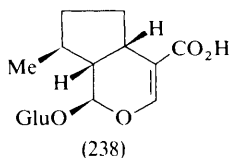
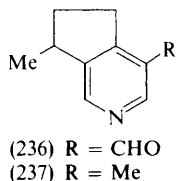
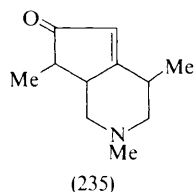
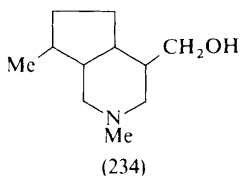
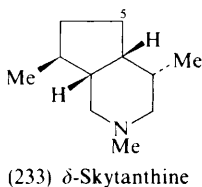
<sup>216</sup> R. D. Johnson, A. Haber, and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1974, **96**, 3316.

$^{13}\text{C}$ -labelled precursors.<sup>217,218</sup> The C-25 methyl group of streptovaricin D (231) was shown to derive from methionine.<sup>219</sup>

A similar  $\text{C}_7\text{N}$  unit [heavy bonding in (231) and (232)] of unknown origin is again apparent in both antibiotics. Neither the usual precursors of aromatic rings, such as shikimate or acetate, served as precursors for this unit in rifamycin S (232)<sup>218</sup> nor was label from propionate incorporated into the  $\text{C}_7\text{N}$  unit of streptovaricin D (231).<sup>217</sup>



**Monoterpenoid Alkaloids.**—In accord with previous studies on the biosynthesis of the monoterpenoid alkaloids<sup>220</sup> it has been found<sup>221</sup> that mevalonate is incorporated into  $\delta$ -skytanthine (233), tecostanine (234), tecomanine (235), and boschniakine (236) in *Tecoma stans*.



Similarly low incorporations of DL-actinidine (237) and loganin (4) suggested their exclusion as intermediates. On the other hand good conversions were

<sup>217</sup> B. Milavetz, K. Kakinuma, K. L. Rinehart, jun., T. P. Rolls and W. J. Haak, *J. Amer. Chem. Soc.*, 1973, **95**, 5793.

<sup>218</sup> R. J. White, E. Martinelli, G. G. Gallo, G. Lancini, and P. J. Beynon, *Nature*, 1973, **243**, 273; E. Martinelli, R. J. White, G. G. Gallo, and P. J. Beynon, *Tetrahedron Letters*, 1974, 1367.

<sup>219</sup> B. I. Milavetz, unpublished work; quoted in ref. 216.

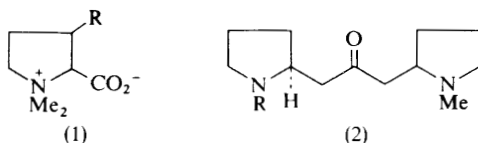
<sup>220</sup> H. R. Schütte, in ref. 24, p. 601.

<sup>221</sup> D. Gross, W. Berg, and H. R. Schütte, *Biochem. Physiol. Pflanzen*, 1972, **163**, 576.

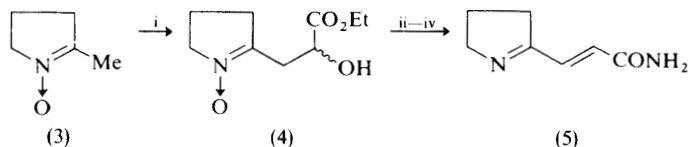
found of *N*-demethylskytanthine and  $\delta$ -skytanthine (233) into the piperidine bases  $\Delta^5$ -dehydroskytanthine, tecostanine (234), and tecomanine (235), and with the former precursor,  $\delta$ -skytanthine (233), suggesting them to be biosynthetic intermediates, derived perhaps from deoxyloganic acid (238). Methionine was found to provide the methyl groups of the N-methylated alkaloids.

## 1 Pyrrolidine Alkaloids

The leaves of 33 species of the family Capparidaceae have been shown to contain L-stachydrine (1; R = H) and L-3-hydroxystachydrine (1; R = OH).<sup>1</sup> ( $\pm$ )-Stachydrine has also been found in *Courbonia glauca*<sup>2</sup> and *Desmodium triflorum*.<sup>3</sup> Further investigation of *Dendrobium chrysanthum* has yielded *N*-cis- and *N*-trans-cinnamoylnorcuscohygrine (2; R = *cis*-COCH=CHPh) and (2; R = *trans*-COCH=CHPh).<sup>4</sup> The structures were determined by spectral methods and confirmed by synthesis of the racemate of the *trans*-isomer.



The synthesis of desdanine (5), isolated from *Streptomyces* culture, has been accomplished (Scheme 1).<sup>5</sup> Treatment of the pyrrolidine *N*-oxide (3) with the hemiacetal of glyoxylic acid ethyl ester provided (4) which upon successive ammonolysis, electrolytic reduction, and dehydration gave desdanine (5). The



Reagents: i, (RO)<sub>2</sub>CHCO<sub>2</sub>Et, PhH, 80°C; ii, conc. NH<sub>4</sub>OH; iii, electrolysis, CF<sub>3</sub>CO<sub>2</sub>H, MeOH; iv, CF<sub>3</sub>CO<sub>2</sub>H

Scheme 1

<sup>1</sup> P. Dealaveau, B. Koudogbo, and J. L. Pousset, *Phytochemistry*, 1973, **12**, 2893.

<sup>2</sup> D. A. Taylor and A. J. Henry, *Phytochemistry*, 1973, **12**, 1178.

<sup>3</sup> S. Ghosal, R. S. Srivastava, S. K. Bhattacharya, and P. K. Debnath, *Planta Med.*, 1973, **23**, 321.

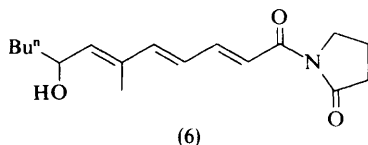
<sup>4</sup> U. Ekevag, M. Elander, L. Gawell, K. Leander, and B. Luning, *Acta Chem. Scand.*, 1973, **27**, 1982.

<sup>5</sup> W. Martin and W. Duerckheimer, *Tetrahedron Letters*, 1973, 1459.



pyrrole derivative corresponding to (5), synthesized by a different route, showed no antibacterial activity.

A number of new analogues of variotin (6), the antifungal antibiotic produced by *Paecilomyces varioti*, have been synthesized.<sup>6</sup> The key step, a mild N-acylation of *N*-trimethylsilyl-2-pyrrolidone, was generalized for Me<sub>3</sub>Si derivatives of six- and seven-membered ring lactams.<sup>7</sup>



## 2 Piperidine Alkaloids

The distribution and chemotaxonomic significance of piperidine alkaloids in the Leguminosae have been reviewed.<sup>8</sup> A number of Leguminosae species of Spanish and Portuguese origin have been shown to contain alkaloids.<sup>9</sup> The piperidine alkaloids isolated from *Lythrum* plants are the subject of a review which is not readily available.<sup>10</sup> The alkaloidal components of a number of fire-ant venoms (*Solenopsis* species) have been investigated in order to determine their potential taxonomic utility.<sup>11</sup> In general, all venoms were found to contain 2-methylpiperidines substituted at the 6-position with C<sub>11</sub>, C<sub>13</sub>, and C<sub>15</sub> carbon chains. However, in some cases (*Solenopsis* sp. from Brazil; *S. geminata* and *S. richteri* from the United States), trace amounts of alkaloids tentatively identified as *cis*- and *trans*-2-methyl-6-*n*-nonylpiperidine were found. *S. richteri* ants also appear to produce *cis*- and *trans*-C<sub>7</sub> alkaloids but these have not been elucidated.

Details concerning the isolation and structural elucidation of oncinotine (7), neo-oncinotine (8), and iso-oncinotine (9), isolated from *Oncinotis nitida*, are now available.<sup>12</sup> Although (7) and (8) constitute an inseparable mixture, separation can be achieved by treatment with Bu<sup>t</sup>OK, under which conditions (8) is converted into (9), and (7), the major alkaloid, is obtained in pure form. The structures of these macrocyclic spermidine alkaloids rest on extensive spectral evidence and Hofmann degradation. Their absolute configurations were determined by c.d. and o.r.d. correlation with (*R*)-*N*-methylconiine. The *N*-acylpiperidines (10) and (11) have been isolated from *Achillea millefolium* and the thiophen amides (12) and (13) have been obtained from *Otanthus maritimus* (both of the family Anthemi-

<sup>6</sup> M. Sakakibara and M. Matsui, *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 1131.

<sup>7</sup> M. Sakakibara and M. Matsui, *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 1139.

<sup>8</sup> J. A. Mears and T. J. Mabry, in 'Chemotaxonomy of the Leguminosae', ed. J. B. Harborne, D. Boulter, and B. L. Turner, Academic Press, London, 1971, p. 73.

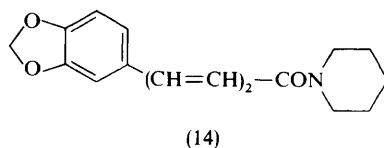
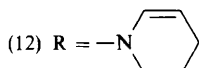
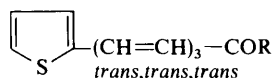
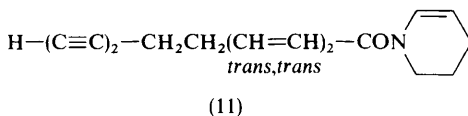
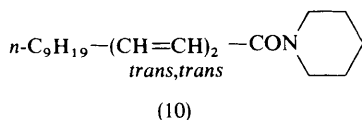
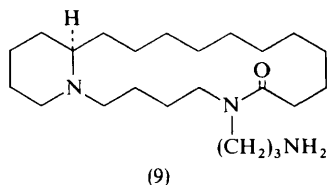
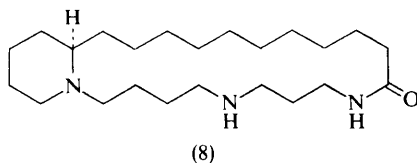
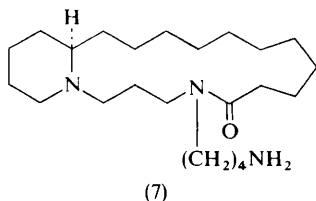
<sup>9</sup> G. Faugergas, E. Valdes-Bermejo, and R. Paris, *Plant. Med. Phytother*, 1973, **7**, 68 (*Chem. Abs.*, 1973, **79**, 63 549n).

<sup>10</sup> E. Fujita, *Farumashia*, 1973, **9**, 599 (*Chem. Abs.*, 1974, **80**, 80 040c).

<sup>11</sup> J. G. MacConnell, R. N. Williams, J. M. Brand, and M. S. Blum, *Ann. Entomol. Soc. Amer.*, 1974, **67**, 134.

<sup>12</sup> A. Guggisberg, M. M. Badawi, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1974, **57**, 414.

deae).<sup>13</sup> *Piper nigrum*<sup>14</sup> and *P. aurantiacum*<sup>15</sup> of Indian origin have been shown to contain piperine (14). The related bases, piperettine and sylvatine, have also been isolated from the last species.<sup>15</sup>



Structural elucidation work on a number of *Lythrum* alkaloids has been summarized in Vol. 4 of these Reports. Two new members of this class are lythrumine (15; R = H) and monoacetyl-lythrumine (15; R = Ac) isolated from *L. lanceolatum*.<sup>16</sup> The structure and absolute configuration of lythrumine was determined by X-ray analysis of its hydrobromide. The co-occurrence of a lythranine-type [piperidine variant of (15), cf. Vol. 4] and decinine (16) (previously isolated from other *Lythraceae* species) with lythrumine and monoacetyl-lythrumine in *L. lanceolatum* points to a common biogenetic origin for these alkaloids.

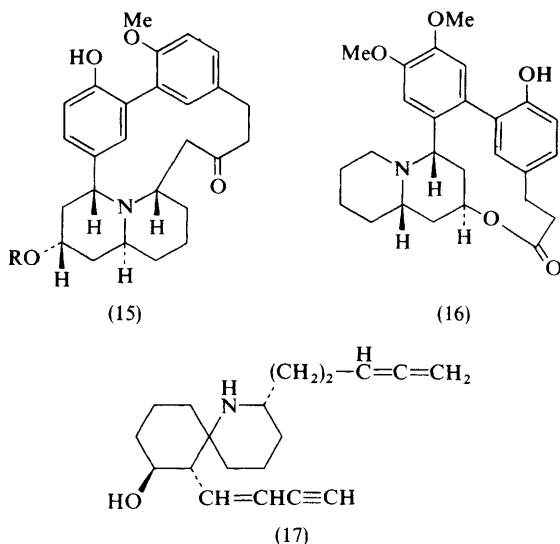
<sup>13</sup> F. Bohlmann, C. Zdero, and A. Suwita, *Chem. Ber.*, 1974, **107**, 1038.

<sup>14</sup> H. K. Desai, D. H. Gawad, T. R. Govindachari, B. S. Joshi, V. N. Kamat, J. D. Modi, P. C. Parthasarathy, J. Radhakrishnan, and M. N. Shanbhag, *Indian J. Chem.*, 1973, **11**, 840.

<sup>15</sup> J. M. Rao, K. Subrahmanyam, and K. V. J. Rao, *Current Sci.*, 1974, **43**, 76 (*Chem. Abs.*, 1974, **80**, 105 903b).

<sup>16</sup> H. Wright, J. Clardy, and J. P. Ferris, *J. Amer. Chem. Soc.*, 1973, **95**, 6467.

Details of the X-ray crystallographic determination of the structure of dihydro-isohistronicotoxin (17), a unique spiro-piperidine alkaloid from the Colombian frog *Dendrobates histrionicus*, have appeared.<sup>17</sup>



A synthesis of ( $\pm$ )-oncinotine (7) has been achieved.<sup>18</sup> The key step was the formation of the macrocyclic lactam by treatment of the appropriate amino-acid chloride precursor with triethylamine under high-dilution conditions.

Two syntheses of ( $\pm$ )-decaline (22a) have been described in preliminary communications (Scheme 2).<sup>19,20</sup> In one of these,<sup>19</sup> isopelletierine (18), prepared by a new method,<sup>21</sup> was condensed with 6-bromoisovanillin (19) under basic conditions to give the quinolizidine (20) which upon methylation and stereo-selective reduction using Henbest's catalyst gave mainly the axial alcohol (21) in high yield. Acetylation followed by Ullmann condensation with methyl 4-hydroxyhydrocinnamate provided the diphenyl ether (22) which upon hydrolysis and lactonization gave ( $\pm$ )-decaline (22a). The alternative synthesis<sup>20</sup> of this alkaloid is similar although the order of steps is different. This approach has also been used<sup>22</sup> to prepare the related *Lythrum* alkaloid, vertaline, which is epimeric with decaline (22a) at C-10.

<sup>17</sup> I. L. Karle, *J. Amer. Chem. Soc.*, 1973, **95**, 4036.

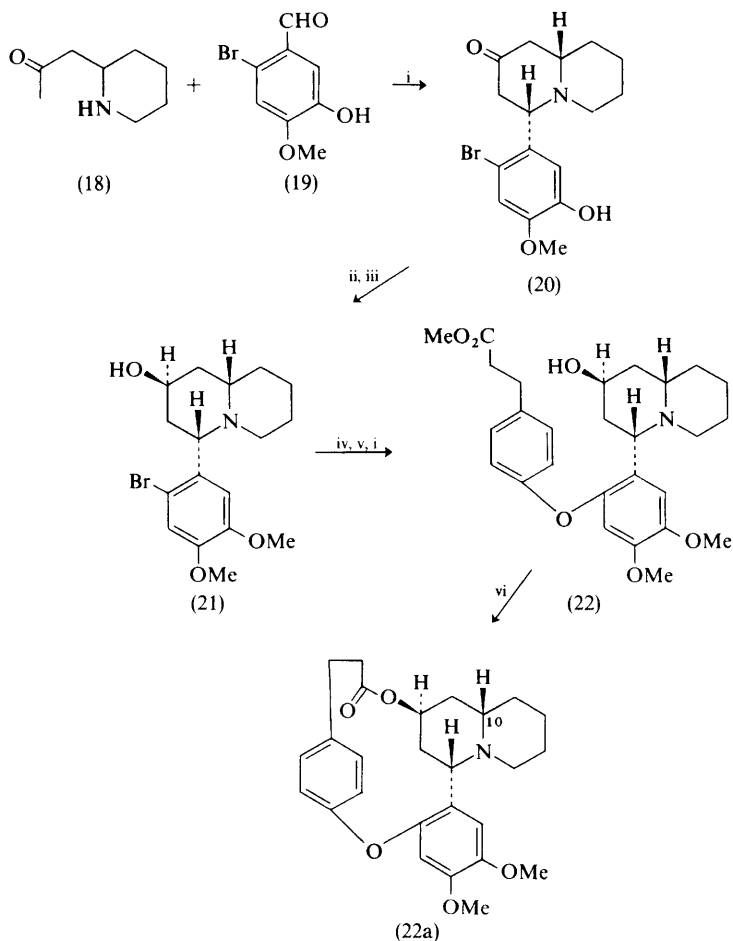
<sup>18</sup> F. Schneider, K. Bernauer, A. Guggisberg, P. Van den Broek, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1974, **57**, 434.

<sup>19</sup> M. Hanaoka, N. Ogawa, and Y. Arata, *Tetrahedron Letters*, 1973, 2355.

<sup>20</sup> J. T. Wrobel and W. M. Golebiewski, *Tetrahedron Letters*, 1973, 4293.

<sup>21</sup> M. Hanaoka, N. Ogawa, and Y. Arata, *Yakugaku Zasshi*, 1974, **94**, 531 (*Chem. Abs.*, 1974, **81**, 13 670r).

<sup>22</sup> M. Hanaoka, N. Ogawa, and Y. Arata, *Chem. and Pharm. Bull. (Japan)*, 1974, **22**, 973.



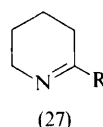
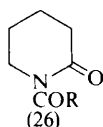
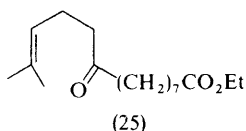
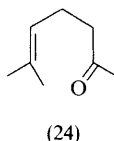
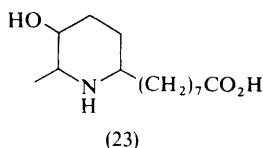
Reagents: i, NaOH; ii, MeI; iii,  $\text{IrCl}_4$ , HCl,  $\text{P}(\text{OMe})_3$ ; iv,  $\text{Ac}_2\text{O}$ ,  $\text{C}_5\text{H}_5\text{N}$ ; v,  $p\text{-HOC}_6\text{H}_4\text{-CH}_2\text{CH}_2\text{CO}_2\text{Me}$ , CuO,  $\text{C}_5\text{H}_5\text{N}$ ; vi, TsOH,  $\text{C}_6\text{H}_6$

**Scheme 2**

A new route to ( $\pm$ )-carpamic acid (23) has been devised.<sup>23</sup> The key synthon (24), prepared by a general route,<sup>24</sup> was converted into the keto-ester (25) by a number of unexceptional steps. Ozonolysis followed by treatment with nitroethane and reductive cyclization yielded ( $\pm$ )-carpamic acid (23) together with ( $\pm$ )-3-iso-carpamic acid.

<sup>23</sup> E. Brown and A. Bourgouin, *Chem. Letters*, 1974, 109.

<sup>24</sup> E. Brown, E. Guilmet, and J. Touet, *Tetrahedron*, 1973, **29**, 2589.



Details regarding the thermal *N*-acyl-lactam rearrangement (26)  $\rightarrow$  (27) have appeared.<sup>25</sup> A hydrazinium mesitylenesulphonate of arecoline has been prepared.<sup>26</sup>

The oscillopolarography of lobeline hydrochloride has been studied.<sup>27</sup> Some arecaine quaternary salts have been shown to exhibit muscarine-like activity.<sup>28</sup>

### 3 Pyridine Alkaloids

Applications of <sup>13</sup>C n.m.r. spectroscopy to structural elucidation of *Nicotiana* alkaloids have been reviewed.<sup>29</sup>

The chemistry and pharmacology of anabasine, nicotine, and nornicotine isolated from *Nicotiana* species native to the Canary Islands have been summarized.<sup>30</sup> Trigonelline has been isolated from *Desmodium triflorum*.<sup>3</sup>

An interesting paper<sup>31</sup> describes the tolerance of the larvae of the tobacco hawk moth to a variety of alkaloid-rich plants including *Nicotiana*.

The diastereomeric nicotine 1-*N*-oxides and 1,1'-dioxides have been characterized by n.m.r.<sup>32</sup> The diastereomeric pair, (28a) and (28b), are metabolites of nicotine.<sup>32a</sup> The racemization of anabasine derivatives has been studied.<sup>33</sup>

<sup>25</sup> B. P. Mundy, K. B. Lipkowitz, M. Lee, and B. R. Larsen, *J. Org. Chem.*, 1974, **39**, 1963.

<sup>26</sup> Y. Tamura, J. Minamikawa, Y. Kita, J. H. Kim, and M. Ikeda, *Tetrahedron*, 1973, **29**, 1063.

<sup>27</sup> I. F. Shcherbak, N. F. Tsareva, and Z. G. Shcherbak, *Fiz.-Khim. Probl. Sovrem. Biol. Med., Mater. Konf.*, 1970, 190 (*Chem. Abs.*, 1974, **80**, 6990w).

<sup>28</sup> E. Mutschler and K. Hultzsche, *Arzneim.-Forsch.*, 1973, **23**, 732 (*Chem. Abs.*, 1973, **79**, 53 147r).

<sup>29</sup> E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Accounts Chem. Res.*, 1974, **7**, 46.

<sup>30</sup> A. Gonzalez Gonzalez and F. Diaz Rodriguez, *Farm. Nueva*, 1973, **38**, 459, 467, 471 (*Chem. Abs.*, 1973, **79**, 134 304s).

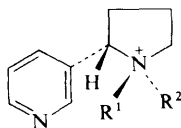
<sup>31</sup> E. Nowacki and G. R. Waller, *Flora*, 1973, **162**, 108.

<sup>32</sup> A. H. Beckett, P. Jenner, and J. W. Gorrod, *Xenobiotica*, 1973, **3**, 557.

<sup>32a</sup> P. Jenner and J. W. Gorrod, *Res. Commun. Chem. Pathol. Pharmacol.*, 1973, **6**, 829;

A. H. Beckett and A. H. Sheikh, *J. Pharm. Pharmacol.*, 1973, **25** (Suppl.), 171P.

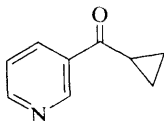
<sup>33</sup> A. A. Abdvakhobov, N. Z. Nazurullaeva, Kh. A. Aslanov, and A. S. Sadykov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 1325 (*Chem. Abs.*, 1973, **79**, 105 452h).



(28a) a;  $R^1 = \text{Me}$ ,  $R^2 = \text{O}^-$   
 b;  $R^1 = \text{O}^-$ ;  $R^2 = \text{Me}$

Reactions of anabasine with sodium,<sup>34</sup> with methyl methacrylate,<sup>35</sup> and with phosphorus acid derivatives<sup>36</sup> have been investigated. Dehydrogenation of anabasine may be effected with *N*-aminopyridinium salts.<sup>37</sup> A number of nitronicotine derivatives have been prepared.<sup>38</sup>

An interesting synthesis of  $(\pm)$ -[2'-<sup>14</sup>C]nicotine using the cyclopropyl-imine synthon (for other applications, see Vol. 2, p. 133 and Vol. 3, p. 211) has been reported.<sup>39</sup> Thus treatment of 3-[<sup>14</sup>C]-cyanopyridine with cyclopropyl-lithium gave, after hydrolysis, the ketone (29) which, when refluxed in *N*-methylformamide, produced  $(\pm)$ -[2'-<sup>14</sup>C]nicotine.



(29)

T.l.c. characteristics of nicotine on alumina sintered glass plates have been reported.<sup>40</sup> Extraction of nicotine alkaloids using water vapour distillation<sup>41</sup> and fatty acids<sup>42</sup> has been studied.

A large number of continuing studies are concerned with chemical changes occurring during various stages of tobacco leaf growth and processing. The following selection may be of some interest to the chemist: a culture technique which reduced the content of alkaloids in tobacco;<sup>42a</sup> the inhibition of potato

<sup>34</sup> A. A. Ziyaev, O. S. Otroshchenko, A. S. Sadykov, G. A. Tolkacheva, and T. A. Khodzhaeva, *Nauch. Tr., Tashkent, Univ.*, 1972, 200 (*Chem. Abs.*, 1973, **79**, 31 804a); A. A. Ziyaev, O. S. Otroshchenko, A. S. Sadykov, V. I. Akhmedzhanova, and G. A. Tolkacheva, *Khim. geterotsikl. Soedinenii*, 1973, 1076 (*Chem. Abs.*, 1973, **79**, 136 949e).

<sup>35</sup> A. A. Ziyaev, O. S. Otroshchenko, A. S. Sadykov, and T. A. Khodzhaeva, *Nauch. Tr., Tashkent. Univ.*, 1972, 207 (*Chem. Abs.*, 1973, **79**, 79 013u).

<sup>36</sup> E. P. Kukhta and Yu. N. Forostyan, *Izvest. Vyssh. Ucheb. Zaved., Khim. i khim. Tekhnol.*, 1973, **16**, 1066 (*Chem. Abs.*, 1973, **79**, 105 046d).

<sup>37</sup> S. V. Zalyalieva, Yu. V. Kurbatov, O. S. Otroshchenko, A. S. Sadykov, and R. Azzamova, *Khim. geterotsikl. Soedinenii*, 1973, 816 (*Chem. Abs.*, 1973, **79**, 92 449k).

<sup>38</sup> Ya. L. Gol'dfarb, V. G. Klimenko, and F. M. Stoyanovich, *Khim. geterotsikl. Soedinenii*, 1973, 1062; (*Chem. Abs.*, 1973, **79**, 136 957f).

<sup>39</sup> R. A. Comes, M. T. Core, M. D. Edmonds, W. B. Edwards, and R. W. Jenkins, jun., *J. Labelled Compounds*, 1973, **9**, 253.

<sup>40</sup> T. Okumura and T. Kadono, *J. Chromatography*, 1973, **86**, 57.

<sup>41</sup> E. Nurimov and M. Ya. Lovkova, *Priklad Biokhim. Mikrobiol.*, 1973, **9**, 789 (*Chem. Abs.*, 1974, **80**, 30 635e).

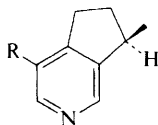
<sup>42</sup> L. Jusiak, *Acta Polon. Pharm.*, 1973, **30**, 49.

<sup>42a</sup> J. Deletang, *Compt. rend.* 1973, **277**, D, 1997.

virus replication by treatment of leaves with nicotine;<sup>43</sup> and lack of alkaloid content variation upon drying as evidenced by chromatography.<sup>44</sup> Finally, it appears that alkaloids from cigarette smoke are present mainly as salts and thus do not contribute greatly to the taste and aroma of smoke!<sup>45</sup>

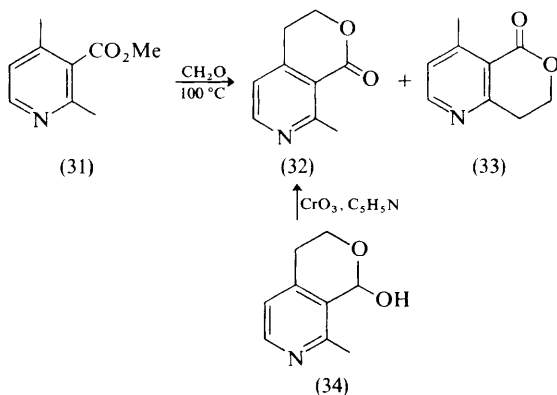
#### 4 Monoterpenoid Alkaloids

Plantagonine (30a), indicaine (30b), and indicamine have been obtained from *Plantago psyllium* as well as other *Plantago* species.<sup>46</sup> Both (+)-indicaine and (+)-boschniakine were believed to possess gross structure (30a) and to differ



(30) a; R = CO<sub>2</sub>Me  
b; R = CHO

only in stereochemistry.<sup>47</sup> It has now been shown<sup>48</sup> that these two alkaloids are identical and are both represented by structure (30a). The original suspected difference was due to the unfortunate formation of a diethylacetal during picrate derivatization of one of the alkaloids in ethanol solution.



Scheme 3

<sup>43</sup> M. Kamienska-Zyla, *Zesz. Probl. Postepow Nauk Roln.*, 1972, 13 (*Chem. Abs.*, 1973, **79**, 49 494j).

<sup>44</sup> T. Constantinescu, *Ind. Aliment. (Bucharest)*, 1973, **24**, 255 (*Chem. Abs.*, 1973, **79**, 113 330g).

<sup>45</sup> T. Constantinescu, *Lucr. Cercet., Inst. Cercet. Proiect. Aliment.*, 1972, **10**, 257 (*Chem. Abs.*, 1974, **80**, 130 644a).

<sup>46</sup> M. S. Karawya, S. I. Balbaa, and M. S. Afifi, *U.A.R. J. Pharm. Sci.*, 1971, **12**, 53 (*Chem. Abs.*, 1972, **77**, 13 729e) S. I. Balbaa, M. S. Karawya, and M. S. Afifi, *ibid.*, 1971, **12**, 35 (*Chem. Abs.*, 1972, **77**, 156 311c).

<sup>47</sup> D. Gross, *Fortschr. Chem. org. Naturstoffe*, 1971, **28**, 109.

<sup>48</sup> D. Gross, W. Berg, and H. R. Schuette, *Z. Chem.*, 1973, **13**, 296.

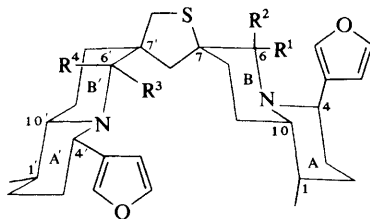
The oxidation product (32) of gentiatibetine (34), an alkaloid elaborated by numerous *Gentiana* species, has been synthesized (Scheme 3).<sup>49</sup> Hantzsch reaction of crotonaldehyde with  $\beta$ -aminocrotonate provided the pyridine (31) which upon treatment with formaldehyde gave the desired product (32) together with the isomeric lactone (33).

Gentianine has been shown to possess some sedative action.<sup>50</sup>

## 5 Sesquiterpenoid Alkaloids

**Nuphar Alkaloids.**—A preliminary screening of *Nuphar variegatum* and *Nymphaea tuberosa* from the Minnesota lakes region (U.S.A.) has produced alkaloid-positive reactions.<sup>51</sup>

Chemical<sup>52</sup> and spectral<sup>52,53</sup> investigations have led to the assignment of the structure and relative configuration of thiobinupharidine (35a). The configuration at C-1(C-1'), C-4(C-4'), and C-10(C-10') was shown to be the same as that in the monomeric alkaloid, deoxynupharidine (36), as follows: (i) Bohlmann i.r. absorptions of (35a) and (36) are very similar indicating that both quinolizidine rings of the dimeric alkaloid are *trans*-fused; (ii) n.m.r. absorption at  $\tau$  6.9—7.3 (two overlapping quartets,  $J = 1.5, 10$  Hz) in (35a) may be ascribed to C-4 and C-4' axial protons on the basis of comparison with the C-4 absorption in (36); and (iii) the 8 Hz upfield shift for the C-1(C-1')-methyl absorption in (35a) upon changing from  $\text{CDCl}_3$  to benzene is consistent with equatorial methyl configuration by analogy with previous observations in the monomeric alkaloid series.



- (35a) a;  $R^1 = R^2 = R^3 = R^4 = \text{H}$   
 b;  $R^1 = R^3 = \text{H}; R^2 = R^4 = \text{D}$   
 c;  $R^1, R^2 = R^3, R^4 = \text{H, OH}$   
 d;  $R^1, R^2 = \text{H, OEt}; R^3 = R^4 = \text{H}$   
 e;  $R^1, R^2 = R^3, R^4 = \text{H, OEt}$

Next, the stereochemistry of the thiomethylene attachment to the A'B' quinolizidine ring in (35a) was established. The epimeric model quinolizidines (37a) and (37b) showed n.m.r. absorptions for the  $\text{CH}_2\text{S}$  protons at  $\tau$  7.2 and  $\tau$  7.6,

<sup>49</sup> F. Rulko and K. Witkiewicz, *Roczniki Chem.*, 1973, **47**, 1871 (*Chem. Abs.*, 1974, **80**, 83 347u).

<sup>50</sup> B. L. Danilevskii, N. Tulyaganov, and F. Sadritdinov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 136 (*Chem. Abs.*, 1974, **80**, 103 861n).

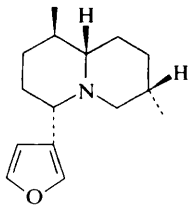
<sup>51</sup> K. L. Su, E. J. Staba, and Y. Abul-Hajj, *Lloydia*, 1973, **36**, 72.

<sup>52</sup> R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Amer. Chem. Soc.*, 1973, **95**, 6342.

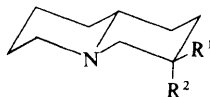
<sup>53</sup> J. T. Wrobel, B. Bobeszko, T. I. Martin, D. B. MacLean, N. Krishnamachari, and C. Calvo, *Canad. J. Chem.*, 1973, **51**, 2810.



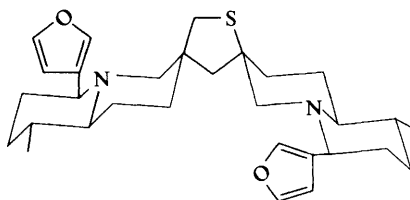
respectively, while the corresponding absorptions in neothiobinupharidine (38) and thiobinupharidine (35a) appeared at  $\tau$  7.3 and  $\tau$  7.68, respectively. Since *X*-ray studies have established that the  $\text{CH}_2\text{S}$  group is axially oriented in (38); the n.m.r. information allows the conclusion that this function is equatorially disposed with respect to the A'B' quinolizidine ring in (35a).



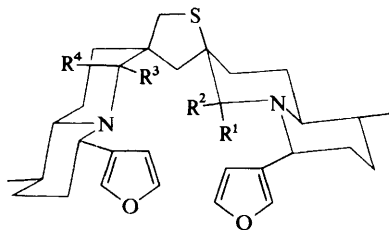
(36)



(37) a;  $\text{R}^1 = \text{Me}$ ;  $\text{R}^2 = \text{CH}_2\text{SMe}$   
 b;  $\text{R}^1 = \text{CH}_2\text{SMe}$ ;  $\text{R}^2 = \text{Me}$



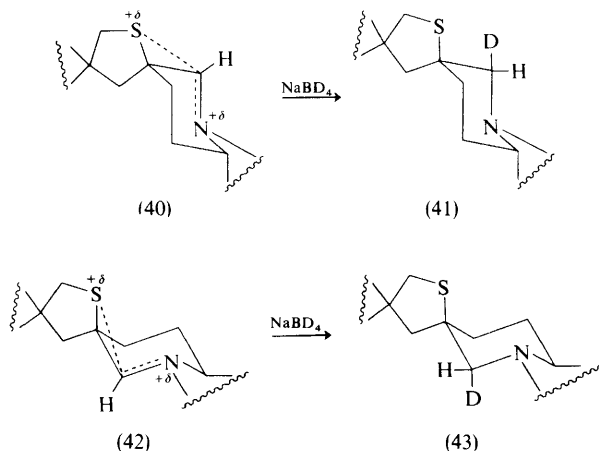
(38)



(39) a;  $\text{R}^1 = \text{R}^4 = \text{D}$ ;  $\text{R}^2 = \text{R}^3 = \text{H}$   
 b;  $\text{R}^1, \text{R}^2 = \text{R}^3, \text{R}^4 = \text{H}, \text{OH}$   
 c;  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$

The stereochemistry of the sulphur linkage to the AB quinolizidine ring of thiobinupharidine was deduced from the n.m.r. spectra of thio[6,6'- $^2\text{H}_2$ ]binupharidine (35b) and thio[6,6'- $^2\text{H}_2$ ]nuphlutine-B (39a) obtained by sodium borodeuteride reduction of 6,6'-dihydroxythiobinupharidine (35c) and 6,6'-dihydroxythionuphlutine-B (39b) respectively (see Vol. 2 of these Reports). It was shown by parallel spectral and chemical studies that the relative stereochemistry at C-1(C-1'), C-4(C-4'), C-10(C-10'), and the  $\text{CH}_2\text{S}$  group in thionuphlutine-B (39c) and thiobinupharidine (35a) are identical. Therefore, the

identical stereochemical result (axial deuterium introduction) must be provided by the C-6' hemiaminal centres in (35c) and (39b). Consequently, the sulphur attachment to the AB quinolizidine ring must provide the difference in stereochemical results [equatorial and axial deuterium introduction for (35c) and (39b), respectively]. This difference may be interpreted in terms of the episulphonium ion intermediates (40) and (42) which produce (41) and (43), respectively (Scheme 4). The sum of the above information leads to (35a) and (39b) as the relative stereochemical formulations for the alkaloids thiobinupharidine and 6,6'-dihydroxythionuphlutine-B, respectively.



Scheme 4

Consistent with the sulphur-immonium interaction proposal, *e.g.* (40), was the appearance of u.v. absorption in the 290–300 nm region for compounds (35c) and (39b). Since (35c) and (39b) have been chemically correlated with thiobinupharidine (35a) and thionuphlutine-B (39c), respectively, the assignment of absolute stereochemistry to (35a) and (39c) could be made on the basis of appropriate c.d. effect studies.<sup>54</sup> The absolute configuration of thiobinupharidine as depicted in (35a) has been confirmed by an X-ray crystallographic study.<sup>53</sup>

Two new alkaloids, ethoxythiobinupharidine (35d) and diethoxythiobinupharidine (35e), have been isolated recently from *Nuphar luteum*.<sup>55</sup> Another alkaloid, thionupharodioline, which has been assigned structure (35c), is presumably identical with 6,6'-dihydroxythiobinupharidine.

A number of the dimeric *Nuphar* alkaloids have been shown to exhibit antibacterial activity.<sup>56</sup>

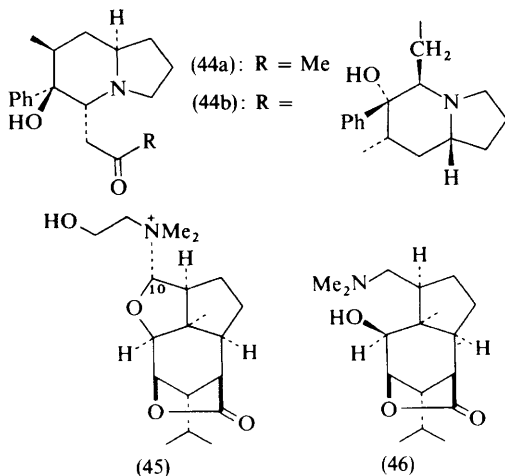
<sup>54</sup> C. F. Wong and R. T. LaLonde, *J. Org. Chem.*, 1973, **38**, 3225.

<sup>55</sup> J. T. Wrobel, M. Gielynska, A. Iwanow, and W. Starzec, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1973, **21**, 551 (*Chem. Abs.*, 1973, **79**, 137 334n).

<sup>56</sup> W. P. Cullen, R. T. LaLonde, C. J. Wang, and C. F. Wong, *J. Pharm. Sci.*, 1973, **62**, 826.

**Dendrobium Alkaloids.**—Recent structural elucidation work on *Dendrobium* alkaloids by the Lünig group has been summarized.<sup>57</sup> New alkaloids crepidamine (44a) and dendrocrepine (44b) related to crepidine (see Vol. 3 of these Reports) have been obtained from *D. crepidatum*.<sup>58</sup> The structure of dendrocrepine (44b) has been established by X-ray crystallographic analysis of its hydrobromide.<sup>59</sup>

Dendrowardine (45) from *D. wardianum* has been converted into the known dihydronobilonine (46) thus establishing its structure and stereochemistry at all centres except C-10.<sup>60</sup> This assignment could be made on the basis of the n.m.r. spectrum which showed a doublet at  $\tau$  4.97 ( $J = 4.5$  Hz) for the C-10 hydrogen.



Details concerning the total synthesis of ( $\pm$ )-dendrobine by Inubushi and co-workers (see Vol. 4 of these Reports) are now available.<sup>61</sup>

**Celastrus and Euonymus Alkaloids.**—Two alkaloids bearing close structural similarity to the *Maytenus* bases (see Vol. 3 of these Reports) have been isolated from *Celastrus paniculatus*.<sup>62</sup> The part structures (47a) and (47b) have been advanced for celapanine and celapanigine, respectively, on the basis of comparison of n.m.r. spectra with those of the *Maytenus* alkaloids whose structures have been determined by X-ray crystallographic analysis. The corresponding sesquiterpenoid of (47) has also been isolated from *C. paniculatus*.

<sup>57</sup> M. Elander, *Chem. Comm., Univ. Stockholm*, 1973, No. 6, 28pp. (*Chem. Abs.* 1973, **79**, 53 642y); K. Leander, *Chem. Comm., Univ. Stockholm*, 1973, No. 10, 31pp. (*Chem. Abs.*, 1973, **79**, 53 644a).

<sup>58</sup> M. Elander, K. Leander, J. Rosenblom, and E. Ruusa, *Acta Chem. Scand.*, 1973, **27**, 1907.

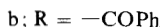
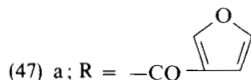
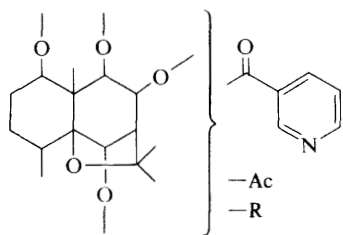
<sup>59</sup> A. M. Pilotti and A. C. Wiehager, *Acta Cryst.*, 1973, **B29**, 1563.

<sup>60</sup> L. Blomqvist, S. Brandange, L. Gawell, K. Leander, and B. Lünig, *Acta Chem. Scand.*, 1973, **27**, 1439.

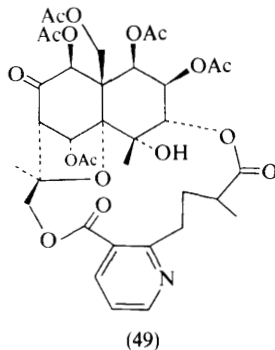
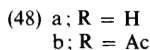
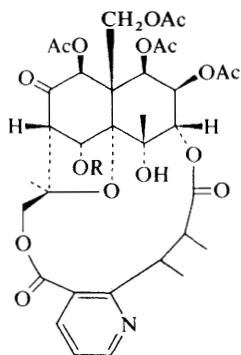
<sup>61</sup> Y. Inubushi, T. Kikuchi, T. Ibuka, K. Tanaka, I. Saji, and K. Tokane, *Chem. and Pharm. Bull. (Japan)*, 1974, **22**, 349.

<sup>62</sup> H. Wagner, E. Heckel, and J. Sonnenbichler, *Tetrahedron Letters*, 1974, 213.

Details regarding the determination of the complete structure and stereochemistry of evonine (48a) and neoevonine (48b) isolated from *Euonymus sieboldiana* by Yamada and co-workers (see Vols. 3 and 4 of these Reports)



have become available.<sup>63</sup> A second paper by the same group describes some fascinating chemistry of these two alkaloids and their derivatives which contributed less significantly to the structural elucidation problem.<sup>64</sup>



Closer examination of the extract from *E. europaea* led to the isolation of a minor alkaloid, evonimine (isoevonine) (49)<sup>65,66</sup> which had also been previously obtained from *E. sieboldiana* (see Vol. 4 of these Reports). Details regarding the structural elucidation of evonimine are now provided.<sup>66</sup>

<sup>63</sup> Y. Shizuri, H. Wada, K. Sugiura, K. Yamada, and Y. Hirata, *Tetrahedron*, 1973, **29**, 1773.

<sup>64</sup> Y. Shizuri, H. Wada, K. Yamada, and Y. Hirata, *Tetrahedron*, 1973, **29**, 1795.

<sup>65</sup> L. Dubravkova, J. Tomko, and L. Dolejs, *Phytochemistry*, 1973, **12**, 944.

<sup>66</sup> L. Dubravkova, L. Dolejs, and J. Tomko, *Coll. Czech. Chem. Comm.*, 1973, **38**, 2132.

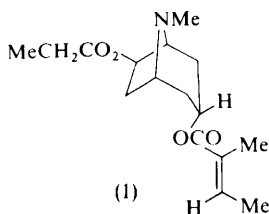
## 3

## Tropane Alkaloids

BY J. E. SAXTON

The results of investigations into the constituent alkaloids of three *Datura* species, namely *D. pruinosa* Greenm., indigenous to Mexico,<sup>1</sup> *D. discolor* Bernh. (S.E. California and Mexico),<sup>2</sup> and *D. metel* var. *fastuosa*, grown in Bangladesh,<sup>3</sup> are recorded in Table 1. The alkaloids identified, either by isolation or by comparative chromatography with authentic specimens, are those familiar to this genus, and no new alkaloids appear to have been isolated. A somewhat similar alkaloid content has been found in two representatives of a Western Australian genus, *Anthocercis littorea* Labill. and *A. viscosa* R. Br.<sup>4</sup> Cannon *et al.*<sup>6</sup> had earlier isolated (–)-hyoscyamine from *A. viscosa* and littorine, meteloidine and traces of hyoscyamine (partly racemized) from *A. littorea*, but the remaining alkaloids had not previously been detected in these species. Extracts of *Physalis alkekengi* L. var. *franchetti* roots and rhizomes have been reported to have expectorant, anti-tussive, and oxytocic properties;<sup>7</sup> previous extractions<sup>7,8</sup> have established the presence of alkaloids, one of which<sup>7</sup> has been identified as 3 $\alpha$ -tigloyloxytropane. It has now been confirmed<sup>5</sup> that this is the major alkaloid; tigloidine, tropine, pseudotropine, cuscohygrine, and three unidentified alkaloids were also obtained.

In a re-investigation of the constituents of *Datura innoxia* Miller roots a new alkaloid, 6 $\beta$ -propanoyloxy-3 $\alpha$ -tigloyloxytropane (1), has been isolated.<sup>9</sup> Its



<sup>1</sup> W. C. Evans and P. G. Treagust, *Phytochemistry*, 1973, **12**, 2077.

<sup>2</sup> W. C. Evans and A. O. Somanabandhu, *Phytochemistry*, 1974, **13**, 304.

<sup>3</sup> K. Anwar and A. Ghani, *Bangladesh Pharm. J.*, 1973, **2**, 25 (*Chem. Abs.*, 1974, **80**, 57 429).

<sup>4</sup> W. C. Evans and P. G. Treagust, *Phytochemistry*, 1973, **12**, 2505.

<sup>5</sup> K. Basey and J. G. Woolley, *Phytochemistry*, 1973, **12**, 2557.

<sup>6</sup> J. R. Cannon, K. R. Joshi, G. V. Meehan, and J. R. Williams, *Austral. J. Chem.*, 1969, **22**, 221.

<sup>7</sup> H. Yamaguchi and K. Nishimoto, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 217.

<sup>8</sup> R. Haraoka, T. Takano, and S. Horibe, *Yakugaku Kenkyu*, 1958, **30**, 58 (*Chem. Abs.*, 1959, **53**, 20 699).

<sup>9</sup> P. J. Beresford and J. G. Woolley, *Phytochemistry*, 1974, **13**, 1249.

**Table 1** *Constituent alkaloids of three Datura species, two Anthocercis species and a Physalis species*

Alkaloid	Datura pruinosa <sup>1</sup>		D. discolor <sup>2</sup>		D. metel var. fastuosa <sup>3</sup> Roots
	Aerial parts	Roots	Aerial parts	Roots	
Total alkaloids, % dry wt.	0.16	0.46	0.17	0.31	
Atropine	+	+		+	} (+)
Hyoscyamine			+		
Noratropine					} (+)
Norhyoscyamine		+			
Apoatropine	+				
Noratropine	+				
Hyoscyne	+	+	+	+	+
Apohyoscyne	(+)		+		(+)
Norhyoscyne	+		+	+	(+)
Littorine	(+)	(+)		+	
Meteloidine	+	+	+	+	(+)
Tigloidine	(+)	+			(+)
3 $\alpha$ -Tigloyloxytropine	+	+			(+)
3 $\alpha$ ,6 $\beta$ -Ditigloyloxytropine		+		+	+
6 $\beta$ -Tigloyloxytropine-3 $\alpha$ -ol					
3 $\alpha$ ,6 $\beta$ -Ditigloyloxytropine-7 $\beta$ -ol		+		+	(+)
Tropane-3 $\alpha$ ,6 $\beta$ -diol					
3 $\alpha$ -Acetoxytropane					(+)
Tropine	(+)	(+)	(+)	(+)	(+)
Pseudotropine	(+)	(+)	(+)	(+)	(+)
Cuscohygrine		+		+	(+)
Unidentified alkaloid(s)			(+)	(+)	

<sup>a</sup> Principal alkaloid. ( ) Alkaloid identified by chromatographic behaviour only.

structure was elucidated by mass and n.m.r. spectroscopy and confirmed by two syntheses, from (–)3 $\alpha$ ,6 $\beta$ -ditigloyloxytropine via (–)6 $\beta$ -hydroxy-3 $\alpha$ -tigloyloxytropine, and from (±)-6 $\beta$ -hydroxytropine-3-one via (±)-6 $\beta$ -propanoyloxytropine-3-one and (±)-6 $\beta$ -propanoyloxytropine-3 $\alpha$ -ol; the latter synthesis necessarily affords racemic alkaloid. The occurrence of hetero di-esters of dihydroxytropine in the Solanaceae is uncommon, although two other examples are known. The occurrence of a propanoic acid ester in this family, however, appears to be unique. The only other propanoic acid ester hitherto encountered in the tropane group, 3 $\alpha$ -propanoyloxytropine, was isolated from *Bruguiera sexangula* and *B. exaristata* (fam. Rhizophoraceae).<sup>10</sup>

Hyoscyne *N*-oxide has been shown to be a constituent of the roots, leaves, and stems of *Datura stramonium* and *Hyoscyamus niger*, and the *N*-oxides of hyoscyamine have been isolated from the seeds, roots, leaves, and stems of *Atropa belladonna*.<sup>11</sup> Control experiments established that the *N*-oxides were not formed during the isolation procedure. Four *Hyoscyamus* species have also

<sup>10</sup> J. W. Loder and G. B. Russell, *Austral. J. Chem.*, 1969, **22**, 1271.

<sup>11</sup> J. D. Phillipson and S. S. Handa, *J. Pharm. Pharmacol.*, 1973, **25**, Suppl., 116P.

Table 1 (cont.)

Anthrocercis littorea <sup>4</sup>			A. viscosa <sup>4</sup>		Physalis alkekengi <sup>5</sup>
<i>Aerial parts</i>	<i>Roots</i>	<i>Flowers</i>	<i>Aerial parts</i>	<i>Roots</i>	<i>Roots and rhizomes</i>
0.16	0.10	0.15	0.11	0.12	0.084–0.104
} +	+ <sup>a</sup>	(+) <sup>a</sup>	+	+ <sup>a</sup>	
} +	+	(+)	+	(+)	
+	+		(+)	(+)	
+	+	(+)	(+)	(+)	
+	+				
+	+	(+)	(+)	(+)	
+	+	(+)	(+)	(+)	
+	+			(+)	+
+	(+)		(+)	(+)	+ <sup>a</sup>
+					
	+			(+)	
			(+)		
+	+		(+)	(+)	+
(+)	+		(+)	(+)	+
	+			(+)	+
+	+			+	+

been re-investigated.<sup>12</sup> Many known alkaloids already found in these species were isolated (see Table 2), together with littorine, tigloidine, cuscohygrine, pseudotropine, hygrine, apohyoscyne, norhyoscyne, and 3 $\alpha$ -tigloyloxytropene, which had not previously been recorded from these particular sources.

Irradiation ( $\gamma$ , <sup>60</sup>Co) of the seeds of *Hyoscyamus niger* has been reported to result in an increase in the hyoscyamine content of the leaves in the plants subsequently grown.<sup>13</sup> A 50% increase in hyoscyamine content was observed following a 2 krad dose of irradiation.

The variation of alkaloid content (scopolamine and hyoscyamine) during the day in *Scopolia tangutica* has been studied.<sup>14</sup> Apparently the alkaloid content reaches maxima at noon and 8 p.m. and minima at midnight and 4 p.m. Two other investigations have been concerned with the dynamics of alkaloid production during the various vegetative phases of the plants. Thus it was reported that

<sup>12</sup> A. Ghani, W. C. Evans, and V. A. Woolley, *Bangladesh Pharm. J.*, 1972, 1, 12 (*Chem. Abs.*, 1973, 79, 75 871).

<sup>13</sup> S. Malik, M. Akram, S. Ur-Rehman, and N. A. Malik, *Pakistan J. Sci. Ind. Res.*, 1972, 15, 384.

<sup>14</sup> N. I. Ryabova, *Rast. Resur.*, 1973, 9, 548 (*Chem. Abs.*, 1974, 80, 105 856).

Table 2<sup>12</sup>

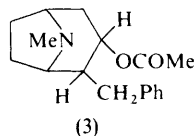
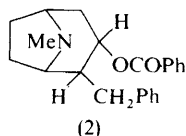
Alkaloid	<i>H. albus</i> L. roots	<i>H. aureus</i> L. roots	<i>H. niger</i> L. roots	<i>H. pusillus</i> L. roots
Apohyscine	(+)		(+)	
Apoatropine	(+)			
Tigloidine	(+)			
Hyoscine	+	+	(+)	
Norhyoscine			(+)	
3 $\alpha$ -Tigloyloxytropane	(+)			(+)
Littorine	+			(+) <sup>a</sup>
Atropine	+			
Hyoscyamine		+	(+)	(+)
Cuscohygrine	+	+ <sup>a</sup>	(+)	(+)
Tropine/ $\psi$ -tropine	(+)			
'Hygrine-like base'		+		

<sup>a</sup> Principal alkaloid. ( ) Alkaloid identified by chromatographic behaviour only.

in *S. sinensis* and *S. tangutica* the alkaloid composition remains constant, but that the scopolamine content is greater at the onset of flowering than at the fruit-bearing stage.<sup>15</sup> The optimum time for harvesting the plants for scopolamine is thus during flowering. In a similar study of *Datura innoxia* it has been shown that the maximum content of scopolamine occurs at the flowering and fruit-ripening stages.<sup>16</sup> In an independent investigation, the alkaloids (atropine and scopolamine) of the various organs of *S. sinensis* have been separated by paper chromatography and assayed colorimetrically.<sup>17</sup>

*Physochlaina alaica* E. Korot, which has apparently not been investigated previously, contains hyoscyamine, scopolamine, and 6-hydroxyhyoscyamine.<sup>18</sup> The major alkaloid, which represented 60–70% of the total alkaloids in the various parts of plants collected from May to August, was hyoscyamine; other alkaloids were generally present to the extent of 2–10% except in seeds collected in August, in which the scopolamine content reached 20%.

A second member of the family Proteaceae has yielded alkaloids belonging to the tropane group. This is *Knightia deplanchei* Vieill. ex Brongn. et Gris. (from New Caledonia), whose leaves contain several alkaloids, among which are a new group of 2-benzyltropane derivatives Alkaloids A–D (2–5).<sup>19</sup> These



<sup>15</sup> S. A. Minina and E. A. Marchenko, *Rast. Resur.*, 1973, **9**, 203 (*Chem. Abs.*, 1973, **79**, 15907).

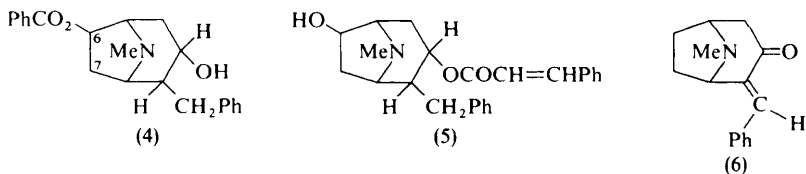
<sup>16</sup> W. Czabajska, B. Jernas, J. Lutowski, and M. Turowska, *Herba Pol.*, 1973, **19**, 223 (*Chem. Abs.*, 1974, **80**, 130 509).

<sup>17</sup> M. Szymanska, *Pol. J. Pharmacol. Pharm.*, 1973, **25**, 201 (*Chem. Abs.*, 1973, **79**, 102 854).

<sup>18</sup> R. T. Mirzamatov, V. M. Malikov, K. L. Lutfullin, O. Khakimov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, **9**, 566.

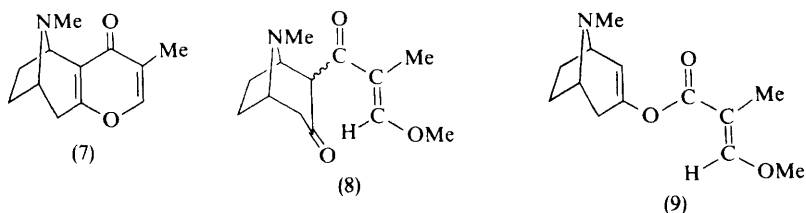
<sup>19</sup> C. Kan-Fan and M. Lounasmaa, *Acta Chem. Scand.*, 1973, **27**, 1039.





structures were deduced almost entirely from a study of their mass and n.m.r. spectra, and no stereochemical conclusions were reached; however, it was noted that Alkaloids A and B afford the same alcohol on hydrolysis, whereas C and D give rise to different alcohols. At this stage the isomeric structures for Alkaloids C and D in which the benzoyloxy- and hydroxy-groups, respectively, are situated at position 7 instead of position 6 are equally consistent with the available evidence. The gross structures for Alkaloids A and B have recently been confirmed by synthesis.<sup>20</sup> ( $\pm$ )-*trans*-2-Benzylidenetropinone (6), obtained by condensation of tropinone with benzaldehyde under carefully controlled conditions, was hydrogenated to a mixture of 2-benzyltropinones which, without separation, were reduced ( $\text{LiAlH}_4$ ) to the corresponding ( $\pm$ )-2-benzyltropan-3-ols. One of these alcohols, tentatively regarded as the  $2\beta,3\alpha$ -isomer, proved to be identical with the alcohol obtained by hydrolysis of Alkaloids A and B. Esterification with benzoyl or acetyl chloride to give Alkaloids A and B completed the structure elucidation, and also confirmed the original proposal<sup>19</sup> that these alkaloids occur as racemates. No details are given concerning the stereochemical arguments, and further work is necessary before the assignment can be regarded as established.

Bellendine (7), the pyranotropane alkaloid of *Bellendena montana*, and the first alkaloid to be isolated from the Proteaceae, is accompanied in the plant by



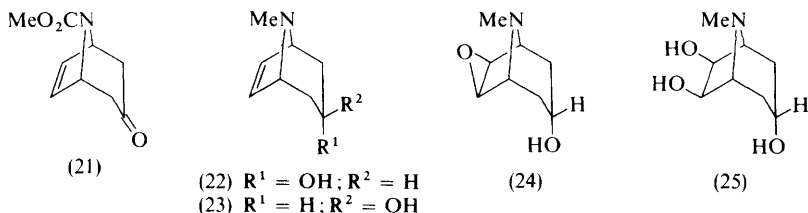
other alkaloids, one of which is a methylbellendine.<sup>21</sup> The structure (7) for bellendine itself has now been confirmed by synthesis.<sup>22</sup> Acylation of tropinone by means of 3-methoxy-2-methylacryloyl chloride-sodium hydride gave the diketone (8), which on brief treatment with aqueous mineral acid afforded ( $\pm$ )-bellendine (7) in low overall yield. This low yield is mainly accounted for by the formation of a considerable amount of the enol ester (9) of tropinone in the first stage of the synthesis.

<sup>20</sup> M. Lounasmaa and C.-J. Johansson, *Tetrahedron Letters*, 1974, 2509.

<sup>21</sup> I. R. C. Bick, private communication to authors of ref. 19, quoted in ref. 19.

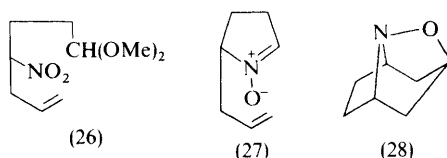
<sup>22</sup> I. R. C. Bick, J. B. Bremner, and J. W. Gillard, *Tetrahedron Letters*, 1973, 5099.



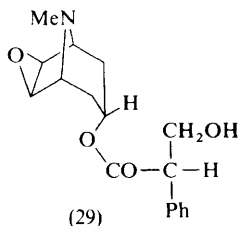


A potentially more important use of the adducts (16) and (17) consists in the removal of the bromine atoms without hydrogenation of the double bond by means of Zn-Cu in methanol to give the unsaturated ketone (21). Reduction of (21) by means of  $Bu^i_2AlH$  then affords the alcohols (22) and (23) (in proportion 93:7), the former of which is a vital intermediate for the synthesis of alkaloids such as scopolamine (24) and telodine (25).

Another comparatively new synthetic method, the nitron-induced oxidative cyclization, has been applied to a novel synthesis of pseudotropine.<sup>25</sup> Michael addition of 4-nitrobut-1-ene to acrolein in methanol containing sodium methoxide gave the nitro-acetal (26), which was converted into the nitron olefin (27) by treatment with zinc in aqueous ammonium chloride. When heated in toluene the nitron olefin (27) cyclized with concomitant stereospecific oxidation of C-3 to give the isoxazolidine (28), which with methyl iodide followed by  $LiAlH_4$  gave pseudotropine (20).



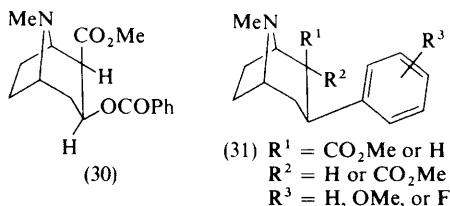
The quaternization of (–)-scopolamine (29) is often difficult with all but the simplest alkyl halides; this has been ascribed to the simultaneous formation of the quaternary salt and the related tertiary base hydrohalide. The quaternization has now been found to occur smoothly in the presence of ethylene oxide which presumably acts as base and removes hydrogen halide from the tertiary base hydrohalide.<sup>26</sup>



<sup>25</sup> J. J. Tufariello and E. J. Trybulski, *J.C.S. Chem. Comm.*, 1973, 720.

<sup>26</sup> A. Donetti and E. Bellora, *Tetrahedron Letters*, 1973, 3573.

In further attempts to obtain useful drugs related to cocaine (30) with modified pharmacological activity, a series of tropane esters (31) has been synthesized<sup>27</sup> in which the aromatic ring is attached directly to position 3. In most of the compounds synthesized a 5–60-fold increase in some biological parameters was observed, but a 10-fold reduction in local anaesthetic activity and a four-fold lowering of intravenous toxicity were also noted.



In an introduction to the  $^{13}\text{C}$  n.m.r. spectroscopy of alkaloids, Wenkert *et al.*<sup>28</sup> have discussed and interpreted the spectra of a number of tropane derivatives and simple alkaloids.

Further recent contributions to the analytical chemistry of the tropane alkaloids include the selective determination by g.l.c. of atropine/hyoscyamine and scopolamine in admixture with other amines (*e.g.* phenylpropanolamine and chlorpheniramine) often used in drug mixtures,<sup>29</sup> the separation and identification of tropane alkaloids by g.l.c. of their trimethylsilyl ethers,<sup>30</sup> and the separation of alkaloid mixtures by high-speed, high-pressure liquid chromatography.<sup>31</sup>

Details have been published<sup>32</sup> of Ingold's work on the nitroxide radical, nortropan-*N*-oxyl.

<sup>27</sup> R. L. Clarke, S. J. Daum, A. J. Gambino, M. D. Aceto, J. Pearl, M. Levitt, W. R. Cumiskey, and E. F. Bogado, *J. Medicin. Chem.*, 1973, **16**, 1260.

<sup>28</sup> E. Wenkert, J. S. Bindra, C. J. Chang, D. W. Cochran, and F. M. Schell, *Accounts Chem. Res.*, 1974, **7**, 46.

<sup>29</sup> R. S. Santoro, P. P. Progner, E. A. Ambush, and D. E. Guttman, *J. Pharm. Sci.*, 1973, **62**, 1346.

<sup>30</sup> H. W. Liebisch, H. Bernasch, and H. R. Schütte, *Z. Chem.*, 1973, **13**, 469.

<sup>31</sup> M. H. Stutz and S. Sass, *Analyt. Chem.*, 1973, **45**, 2134.

<sup>32</sup> G. D. Mendenhall and K. U. Ingold, *J. Amer. Chem. Soc.*, 1973, **95**, 6390, 6395.

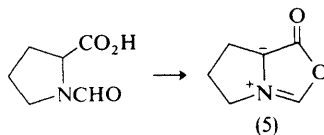
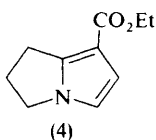
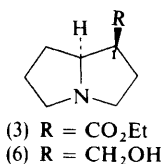
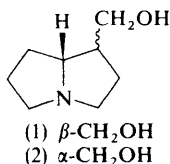
# 4

## The Pyrrolizidine Alkaloids

BY J. E. SAXTON

### 1 The Necine Bases and Simple Alkaloids

In an earlier study<sup>1</sup> the acetate of the sample necine base laburnine (1) was isolated from *Vanda cristata* Lindl. In further investigations on the same genus and the related *Vandopsis* genus<sup>2</sup> both laburnine and its diastereoisomer lindelofidine (2), together with their acetates, have been shown to be present in *Vandopsis lissochiloides* Pfitz. and *Vandopsis gigantea* Pfitz. The same two acetates occur in *Vanda helvola* Bl. and laburnine acetate occurs in *Vanda hindsii* Lindl. The behaviour of a constituent of *Vanda luzonica* Loher indicates that it is either laburnine acetate or its enantiomer.



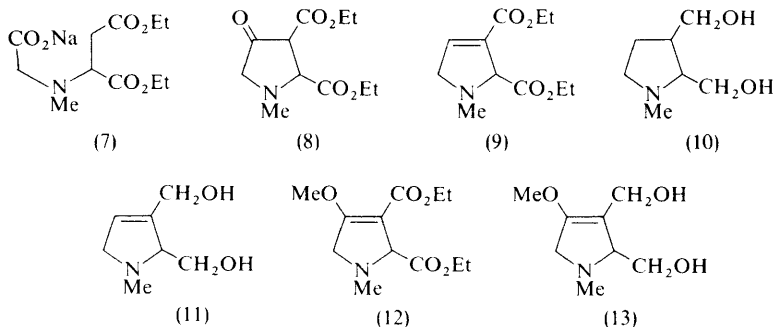
An interesting two-step procedure has been reported<sup>3</sup> which allows the stereo-specific synthesis of the racemate (3) in 80% overall yield. *N*-Formyl-L-proline, prepared from L-proline and acetic-formic anhydride, is treated with ethyl propiolate in acetic anhydride to give the ester (4), the cycloaddition presumably proceeding *via* the dipolar intermediate (5). Hydrogenation of (4) in the presence of palladized charcoal affords the stereochemically pure ethyl ( $\pm$ )-isoretronecanolate (3), which on reduction provides ( $\pm$ )-isoretronecanol (6). Since the ester (3) can be efficiently epimerized at C-1 this synthesis also affords a convenient route to the pseudoheliotridine series.

<sup>1</sup> B. Lindström and B. Luning, *Acta Chem. Scand.*, 1969, **23**, 3352.

<sup>2</sup> S. Brandänge and I. Granelli, *Acta Chem. Scand.*, 1973, **27**, 1096.

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

Mattocks has given details<sup>4</sup> of the syntheses of several pyrroline derivatives (synthanecines) which may be regarded as the monocyclic analogues of the bicyclic necine bases contained in the toxic pyrrolizidine alkaloids. Addition of sodium sarcosinate to diethyl fumarate gave the adduct (7), which on esterification and Dieckmann cyclization afforded the key intermediate ester (8). Reduction ( $\text{NaBH}_4$ ) of (8) followed by dehydration ( $\text{TsCl}$ -pyridine) and further reduction (e.g.  $\text{LiAlH}_4$ ) gave the pyrrolidine diol (10) (synthanecine B) *via* the pyrroline diester (9). Alternatively, reduction of (9) by means of di-isobutyl aluminium hydride gave the pyrroline diol (11) (synthanecine A). Similar reduction of the enol ether (12), prepared by diazomethane methylation of the ketone (8), gave synthanecine C (13).



Several of the synthanecine derivatives, and in particular the carbamates of synthanecine A (11), were shown to be metabolically dehydrogenated to pyrrole derivatives by rat liver *in vivo* and to cause toxic effects in animals very similar to, if not identical with, those produced by the toxic pyrrolizidine alkaloids. The synthetic pyrrole relatives of the synthanecines, like the pyrrolic analogues of the toxic alkaloids, were also capable of cross-linking DNA *in vitro*, and of causing cytotoxic effects in rats.<sup>4</sup>

In recent years several species of butterflies and moths have been shown to contain simple dihydropyrrolizine derivatives. For example, male butterflies of the family Nymphalidae, subfamily Danainae, possess a pair of extrusible hair-pencils which are used to disseminate pheromonal substances during courtship. Meinwald *et al.*<sup>5</sup> earlier isolated the dihydropyrrolizine derivative (14) from the hair-pencil secretions of *Lycorea ceres ceres* (Cramer), *Danaus gilippus berenice* (Cramer), and *D. gilippus strigosus*, and it has been shown<sup>6,7</sup> to be essential for the mating process in the Queen butterfly (*D. gilippus berenice*). More recently, Culvenor and his collaborators<sup>8</sup> have investigated the hair-pencil secretions of six species of Danainae found in Northern Australia, and have isolated the ketone

<sup>4</sup> A. R. Mattocks, *J.C.S. Perkin I*, 1974, 707.

<sup>5</sup> J. M. Meinwald and Y. C. Meinwald, *J. Amer. Chem. Soc.*, 1966, **88**, 1305; J. M. Meinwald, Y. C. Meinwald, and P. H. Mazzocchi, *Science*, 1969, **164**, 1174.

<sup>6</sup> T. E. Pliske and T. Eisner, *Science*, 1969, **164**, 1170.

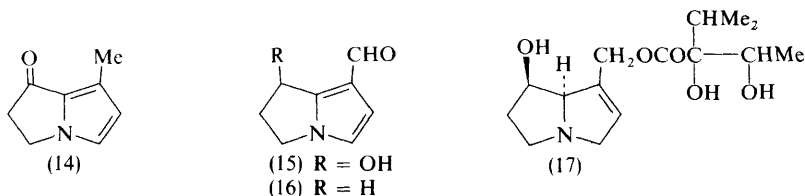
<sup>7</sup> D. Schneider and U. Seibl, *Science*, 1969, **164**, 1173.

<sup>8</sup> J. A. Edgar, C. C. J. Culvenor, and L. W. Smith, *Experientia*, 1971, **27**, 761.

**Table 1** The occurrence of dihydropyrrolizines in butterfly species, subfamily *Danainae*

	Compound		
	(14)	(15)	(16)
<i>Danaus hamatus hamatus</i> (Macle.)	+	+	—
<i>D. affinis affinis</i> (Fab.)	+	—	+
<i>D. plexippus plexippus</i> (L.)	—	—	—
<i>Euploea tulliolus tulliolus</i> (Fab.)	—	+	—
<i>E. sylvester sylvester</i> (Fab.)	trace?	+	—
<i>E. core corinna</i> (Macle.)	—	—	—

(14) and the related aldehydes (15) and (16). The pattern of occurrence of these three compounds in these species (see Table 1) indicates that it may well be of importance in maintaining the integrity of the individual *Danainae* species.



Presumably these dihydropyrrolizine compounds are derived from precursors, e.g. pyrrolizidine alkaloids, found in the butterflies' food plants. This is supported by the observation that adult male butterflies are strongly attracted to, and sometimes feed on, dead or withering plants containing pyrrolizidine alkaloids. With one species, *Danaus chrysippus petilea* (Stoll), Culvenor and his collaborators<sup>9</sup> have shown that when dihydropyrrolizine-deficient laboratory-reared specimens are given access to *Heliotropium amplexicaule* Vahl, they soon acquire the ketone (14) which is normally found in the hair-pencils of this species. Even more convincing is the isolation and identification of lycopsamine (17) from the hair-pencil extracts of two Australian danaid species, *Danaus hamatus hamatus* (Macleay) and *Euploea tulliolus tulliolus* (Fabricius), captured in the field in Queensland.<sup>10</sup> It is notable that this alkaloid is typical of those occurring in the plants to which the male butterflies show specific attraction; its complexity and the fact that the branched-chain acid component is unique in nature to these plant alkaloids, leaves no doubt that this hair-pencil constituent is of plant origin.

The occurrence of pyrrolizidine derivatives in the Lepidoptera is not confined to butterflies, but has also been observed in the tiger moth,<sup>11</sup> where their function may be similar to that established in one species of butterfly. Male tiger moths (fam. Arctiidae) possess scent organs in the form of inflatable coremata which have a pheromone-distributing function. Some of these species are known to use plants containing pyrrolizidine alkaloids, e.g. *Heliotropium europaeum* and *Echium*

<sup>9</sup> J. A. Edgar, C. C. J. Culvenor, and G. S. Robinson, *J. Austral. Ent. Soc.*, 1973, **12**, 144.

<sup>10</sup> J. A. Edgar and C. C. J. Culvenor, *Nature*, 1974, **248**, 614.

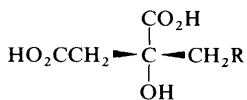
<sup>11</sup> C. C. J. Culvenor and J. A. Edgar, *Experientia*, 1972, **28**, 627.

*lycopsis*, as larval host plants. Two such Australian moths, *Utetheisia pulchelloides* (Hamps.) and *U. lotrix* (Cram.) have been investigated.<sup>11</sup> The coremata and associated genitalia of the former species contained 1-formyl-7-hydroxy-6,7-dihydro-5*H*-pyrrolizine (15); in contrast, the remainder of the carcasses contained no detectable amounts of (15), but instead contained heliotrine, heleurine, and supinine. Lasiocarpine and europine, the other known alkaloids of *H. europaeum*, could not be detected; there thus appears to be some selectivity in the storage of alkaloids in the bodies of the moths, since the samples investigated were collected from a field of *H. europaeum*. The coremata of moths collected from a field of *E. lycopsis* also yielded (15), but the bodies of the moths contained alkaloids different from those collected from the field of *H. europaeum*. The coremata and genitalia of male *U. lotrix* collected on *Crotalaria mucronata* contained both the aldehyde (15) and its deoxy derivative (16).

## 2 The Ester Alkaloids

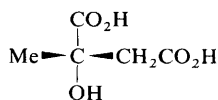
The aerial parts of *Senecio vernalis* Waldst. et Kit. contain three alkaloids, but none has been identified so far.<sup>12</sup> *Crotalaria assamica* Benth. contains an alkaloid which may be monocrotaline;<sup>13</sup> it appears not to have been positively identified, the investigation having been concerned mainly with the alkaloid's pharmacological activity. It was reported to inhibit the growth of transplanted tumours in white mice, but it is also hepatotoxic to dogs and mice. The variation of alkaloid content (platyphylline, seneciphylline, and sarracine) with altitude in Caucasian plantations of *Senecio platyphylloides* and *S. rhombifolius* has been studied;<sup>14</sup> the highest alkaloid content was found in plants grown at an altitude of 2000—2500 m.

(-)-2-Isobutylmalic acid (18) and (-)-2-benzylmalic acid (19), the constituent acids of cornucervine and phalaenopsine La, respectively, have now been shown<sup>15</sup> to have the *R*-configuration. This was established by a partial asymmetric synthesis of the enantiomers of these acids and comparison of the c.d. spectra of their molybdate complexes with that of the molybdate complex of (+)-citramalic acid (20) of known *S*-configuration.



(18) R = CHMe<sub>2</sub>

(19) R = Ph



(20)

<sup>12</sup> F. Rulko and K. Witkiewicz, *Roczniki Chem.*, 1973, **47**, 71 (*Chem. Abs.*, 1973, **79**, 2767).

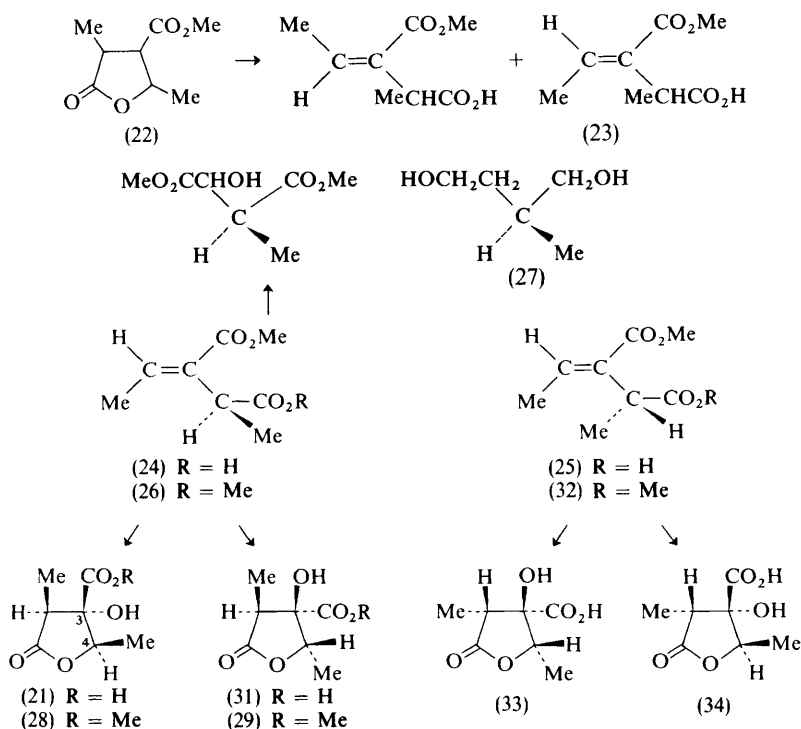
<sup>13</sup> Tumour Research Group, *Chung-Hua I Hsueh Tsa Chih*, 1973, 472 (*Chem. Abs.*, 1974, **80**, 66 666).

<sup>14</sup> G. K. Kuznetsova, V. S. Khazanov, D. M. Shishov, L. N. Zaiko, A. Kh. Nakaidze, M. N. Geier, and V. I. Mukhina, *Rast. Resur.*, 1974, **10**, 82 (*Chem. Abs.*, 1974, **80**, 143 052).

<sup>15</sup> S. Brandänge, S. Josephson, and S. Vallén, *Acta Chem. Scand.*, 1973, **27**, 3668.

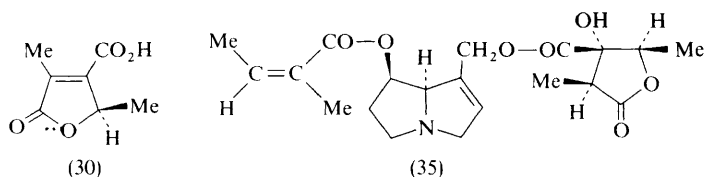


The stereochemistry and absolute configuration of latifolic acid (21), the acid component of latifoline, has also been established.<sup>16</sup> Treatment of a mixture of diastereoisomeric ( $\pm$ )-2,4-dimethyl-3-methoxycarbonylbutyrolactones (22) in dry ether with sodium hydride gave a mixture of unsaturated ester-acids, from which the pure racemic geometrical isomer (23) was isolated. Resolution by means of brucine gave the pure enantiomers (24) and (25), the absolute configurations of which were established by conversion of the methyl ester (26) into *S*-( $-$ )-2-methylbutane-1,4-diol (27) of known absolute configuration. *cis*-Hydroxylation of (26) gave the butyrolactones (28) and (29), the relative configurations of which at C-3 and C-4 were readily deduced by spectral comparison with racemic material synthesized earlier.<sup>17</sup> Hydrolysis of (28) with dilute hydrochloric acid gave the corresponding acid (21), which was identified as latifolic acid, together with an  $\alpha\beta$ -unsaturated acid (30). Similar treatment of (29) afforded the acid (31), and the series was completed by analogous syntheses of the acids (33) and (34) from the unsaturated ester (32). Comparison of these lactone acids securely established the absolute configuration of latifolic acid (21) as 2*S*,3*S*,4*R*, and that of latifoline as (35).



<sup>16</sup> T. Matsumoto, T. Okabe, and K. Fukui, *Chem. Letters*, 1973, 773.

<sup>17</sup> T. Matsumoto, T. Okabe, and K. Fukui, *Chem. Letters*, 1972, 29.



In another stereochemical investigation, Matsumoto *et al.*<sup>18</sup> have revised the configurations of fulvinic and crispatic acids, the acid constituents of fulvine and crispatine, respectively. Since these isomeric acids are both optically inactive forms of 3-hydroxy-2,3,4-trimethylglutaric acid, it was earlier assumed that they are the two *meso* forms,<sup>19</sup> a conclusion that was accepted by later workers<sup>20</sup> who tentatively proposed the *R-meso* structure (36) for fulvinic acid and the *S-meso* configuration for crispatic acid on the basis of a partial asymmetric synthesis of fulvinic and crispatic acids, and the diastereoisomeric racemic acid. A new asymmetric synthesis of these acids has resulted in a reversal of the earlier proposal, so that fulvinic acid is now known to have the *S-meso* configuration (37) and crispatic acid the *R-meso* configuration (36). The Reformatsky reaction of 3-phenylbutan-2-one with methyl  $\alpha$ -bromopropionate gave a mixture of the three diastereoisomeric esters (38)–(40) (the fourth possible stereoisomer was not detected in the product). Conversion of (38)–(40) into the alcohols (41) and (42) was achieved by standard methods, the esters (39) and (40) giving rise to the same alcohol (42). The same alcohols were obtained by a direct Grignard reaction of 3-phenylbutan-2-one with isopropylmagnesium bromide or with isopropyl bromide–lithium, the isomer (42) predominating. By Cram's rule the predominant product should have the configuration (42), and therefore the configuration (41) follows for the minor product, and so do the configurations of the esters (38)–(40). Ozonolysis of these esters, followed by conversion into the corresponding dibasic acids, afforded fulvinic acid (37) from the ester (40), and crispatic acid (36) from the ester (38). The ester (39) gave on similar treatment an acid which, as expected, proved to be a racemate.<sup>18</sup> This configuration for fulvinic acid presumably allows two structures (43a) and (43b) to be written for fulvine itself. Of these, the former structure (43a) has been established by the X-ray crystal structure determination by Sussman and Wodak.<sup>21</sup>

Synthetic work by another Japanese group has resulted in the synthesis of  $\alpha$ - and  $\beta$ -retusanecic acids,<sup>22</sup> and retusaminic acid.<sup>23</sup> The retusanecic acids are obtained by the alkaline hydrolysis of retusine (44), and have been shown to be epimeric 4-hydroxy-2,3,4-trimethylglutaric acid lactones. Since in acidic solution the equilibrium favours the  $\beta$ -acid, it is formulated as (45), in which the C-2 methyl group is *trans* with respect to the C-3 methyl group;  $\alpha$ -retusanecic acid is

<sup>18</sup> T. Matsumoto, K. Fukui, and J. D. Edwards, *Chem. Letters*, 1973, 283.

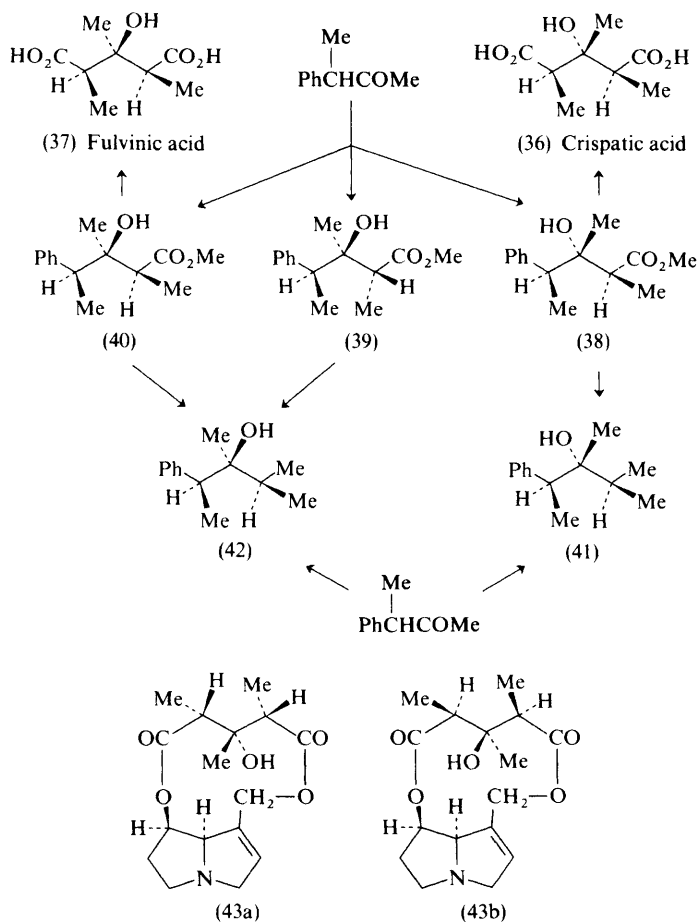
<sup>19</sup> C. C. J. Culvenor and L. W. Smith, *Austral. J. Chem.*, 1963, **16**, 239.

<sup>20</sup> J. D. Edwards and T. Matsumoto, unpublished work, quoted by F. L. Warren in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1970, Vol. XII, p. 282.

<sup>21</sup> J. L. Sussman and S. J. Wodak, *Acta Cryst.*, 1973, **B29**, 2918.

<sup>22</sup> S. Kiyooka and T. Hase, *Bull. Chem. Soc. Japan*, 1973, **46**, 3609.

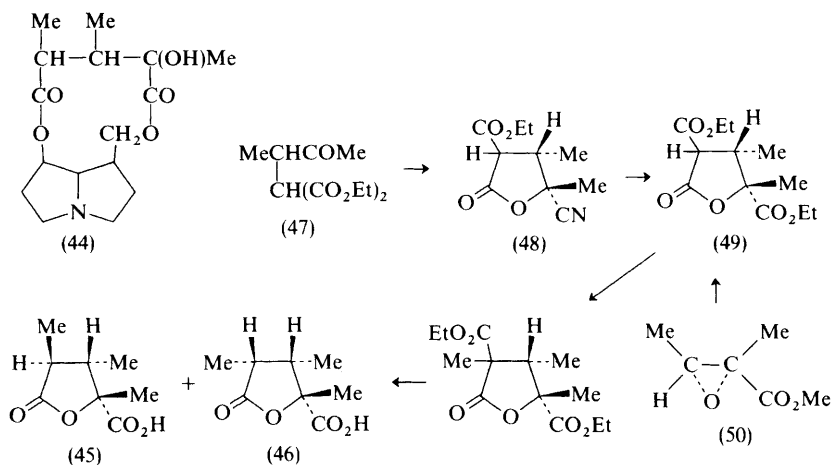
<sup>23</sup> S. Kiyooka, T. Hase, and J. D. Edwards, *Chem. Letters*, 1973, 963.



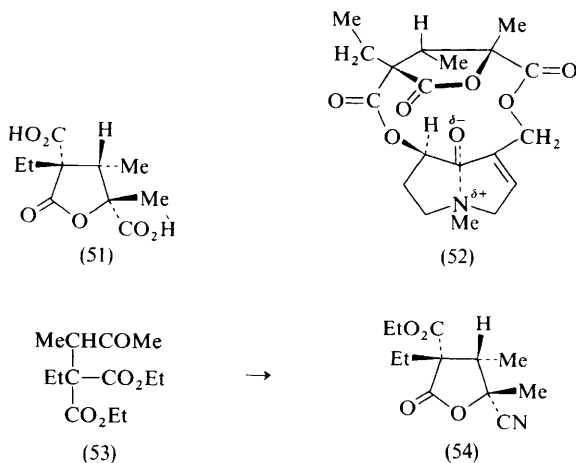
then (46), but the configuration of the C-4 methyl group was unknown before the present work. Addition of hydrogen cyanide to the keto-ester (47) gave the cyanolactone (48), which on ethanolysis gave the lactone diester (49). The *trans* disposition of the two methyl groups in (48) and (49) was predicted from the expected steric course of the cyanide addition to (47), but was securely established by an independent synthesis of (49) by the nucleophilic attack of sodium diethyl malonate on tiglic acid epoxide (50). Methylation of (49), followed by acid hydrolysis and decarboxylation, afforded a mixture of  $\alpha$ - and  $\beta$ -retusanecic acids, in which the latter (45) predominated.<sup>22</sup>

The synthesis<sup>23</sup> of retusaminic acid (51), the hydrolysis product of retusamine (52),<sup>24</sup> followed similar lines. Ethylation of the keto-ester (47) *via* its ethylene

<sup>24</sup> C. C. J. Culvenor and L. W. Smith, *Austral. J. Chem.*, 1957, **10**, 464; J. A. Wunderlich, *Chem. and Ind.*, 1962, 2089.



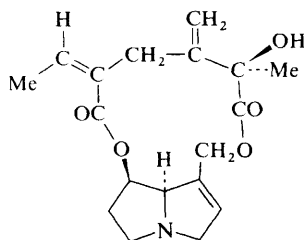
ketal afforded the keto-ester (53) which, on addition of cyanide, gave the cyano-lactone (54). Ethanolic hydrolysis followed by hydrolysis then gave ( $\pm$ )-retusaminic acid (51), which was resolved *via* its salt with cinchonidine.<sup>23</sup>



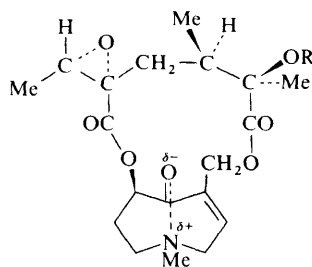
A Czech group has investigated the constituents of *Senecio fluviatilis* Wallr., collected in September when the flowers and leaves in most of the plants had withered.<sup>25</sup> The dried material contained 0.12% crude alkaloids, and 0.026% of alkaloids as *N*-oxides. The free alkaloids proved to be othosenine (55), seneciphylline (56), and florosenine (57); the last base had only been previously

<sup>25</sup> A. Klásek, B. Šula, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1973, **38**, 2658.

obtained from *Cacalia floridana*.<sup>26</sup> Reduction of the *N*-oxides yielded seneciphylline, othosenine, and others which were not identified.



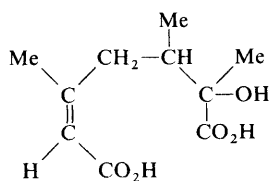
(56) Seneciphylline



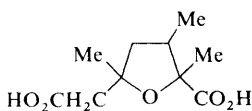
(55) R = H Othosenine

(57) R = Ac Florosene

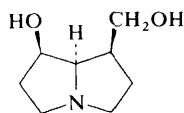
A new alkaloid, nemorensine, has been isolated from Bulgarian *Senecio nemorensis* L. var. *subdecurrens* Griseb., and the Czech plants *S. nemorensis* L. ssp. *Jacquinianus* (Rchb.) Durand and *S. nemorensis* L. ssp. *fuchsii* var. *nova* (Zlatnik).<sup>27</sup> The Bulgarian *Senecio* also furnished a dicarboxylic acid,  $C_{10}H_{16}O_5$ , whose structure was determined by analysis of its n.m.r. spectrum to be (58). Nemorensine has the molecular formula  $C_{18}H_{27}NO_5$ , and is a macrocyclic diester alkaloid which on hydrolysis affords platynecine (59) or a diastereoisomer (not positively identified) and a dicarboxylic acid also of uncertain structure; the latter is tentatively regarded as the tetrahydrofuran derivative (60), an obvious relative of the acid (58). On this basis nemorensine is formulated as (61), but the amount of alkaloid available was insufficient to allow a secure structure determination.<sup>27</sup>



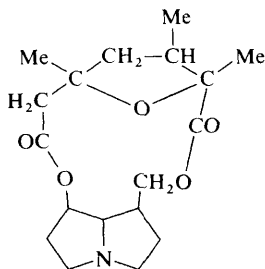
(58)



(60)



(59)



(61)

<sup>26</sup> M. P. Cava, K. V. Rao, J. A. Weisbach, R. F. Raffauf, and B. Douglas, *J. Org. Chem.*, 1968, **33**, 3570.

<sup>27</sup> A. Klásek, P. Sedmera, A. Boeva, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1973, **38**, 2504.

### 3 Pharmacological Aspects

The pharmacology of monocrotaline,<sup>28</sup> integerrimine, and renardine<sup>29</sup> has been reviewed.

It is of interest that guinea-pigs, unlike many laboratory and domestic animals, are not poisoned by pyrrolizidine alkaloids, and monocrotaline, for example, produces no clinical or pathological changes in them.<sup>30</sup> It appears that although the ability to convert monocrotaline into its *N*-oxide is the same as in rats, the level of dehydrogenation activity is much lower in guinea-pigs, and consequently pyrrolic analogues are not formed. In fact, monocrotaline pyrrole is toxic to guinea-pigs, and produces hepatic necrosis as in rats. These results suggest that the *N*-oxides of pyrrolizidine alkaloids are not the precursors of the toxic pyrrolic metabolites, at least in guinea-pigs, and are therefore not toxic *per se*. The *N*-oxides and the pyrroles are therefore formed by separate enzymic pathways.<sup>30</sup>

<sup>28</sup> A. R. Mattocks, *Pharmacol. Future Man, Proc. 5th Int. Congr. Pharmacol.* 1972, **2**, 114 (Pub. 1973) (*Chem. Abs.*, 1974, **80**, 494).

<sup>29</sup> A. G. Gonzalez and F. D. Rodriguez, *Farm. Nueva*, 1973, **38**, 459, 467, 471 (*Chem. Abs.*, 1973, **79**, 134 304).

<sup>30</sup> C. F. Chesney and J. R. Allen, *Toxicol. Appl. Pharmacol.*, 1973, **26**, 385.

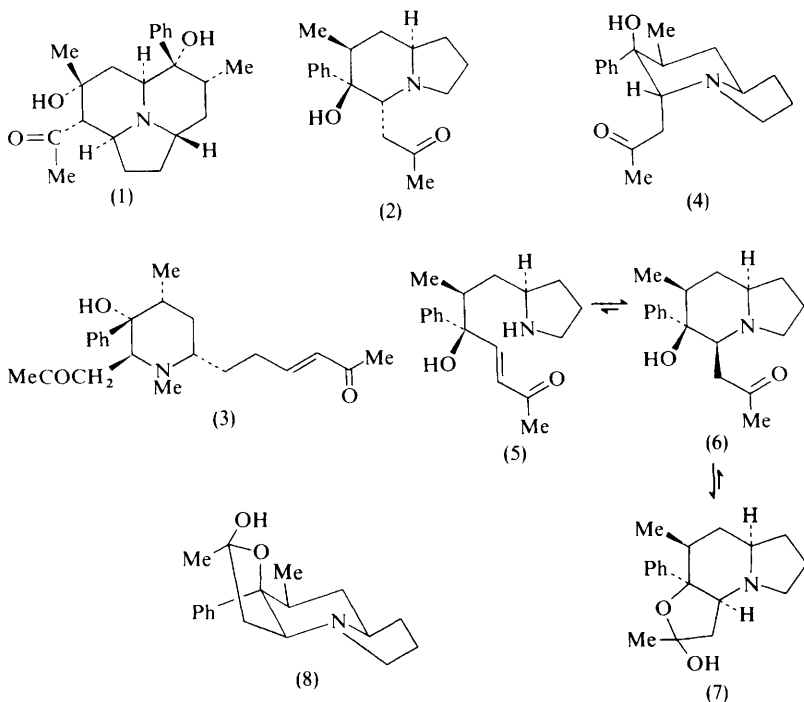
# 5

## Indolizidine Alkaloids

BY J. E. SAXTON

### 1 Indolizidine Alkaloids of *Dendrobium* Species

Two comparatively simple indolizidine derivatives accompany crepidine (1)<sup>1</sup> in *Dendrobium crepidatum* Lindl.<sup>2</sup> Crepidamine (2),  $C_{18}H_{25}NO_2$ , an optically inactive base, exhibits an n.m.r. spectrum similar to that of the tertiary base (3) obtained by the reaction of crepidine methiodide with base, apart from the

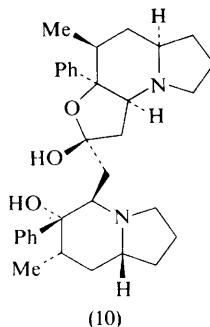
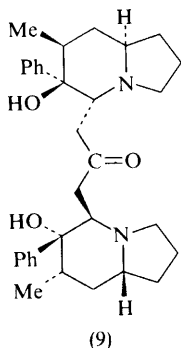


<sup>1</sup> P. Kirkegaard, A. M. Pilotti, and K. Leander, *Acta Chem. Scand.*, 1970, **24**, 3757; A. M. Pilotti, *Acta Cryst.*, 1971, **B27**, 887.

<sup>2</sup> M. Elander, K. Leander, J. Rosenblom, and E. Ruusa, *Acta Chem. Scand.*, 1973, **27**, 1907.

absence of an *N*-methyl group and an  $\alpha\beta$ -unsaturated ketone system. Since crepidamine is a tertiary base containing no olefinic double bonds it is formulated as the indolizidine derivative (2). The i.r. spectrum, which exhibits weak Bohlmann bands and indicates the presence of intramolecular hydrogen bonding, is interpreted in terms of the conformation (4). As a Mannich base crepidamine can be isomerized, presumably *via* the isomeric monocyclic unsaturated ketone (5), by boiling in ethanol or by chromatography on neutral alumina. The product, isocrepidamine, however, is not the simple stereoisomer (6) since its i.r. spectrum exhibits no carbonyl absorption. It is therefore regarded as the hemiketal (7) having the conformation (8).

A similar situation obtains with dendrocrepine,<sup>2</sup> a racemic alkaloid for which the structure (9) has been established by X-ray analysis.<sup>3</sup> Isomerization of dendrocrepine in ethanol or on alumina chromatography affords isodendrocrepine (10), which, like isocrepidamine, is formulated as a hemiketal. Both isocrepidamine and isodendrocrepine were earlier reported to be present in the plant, but since they were not isolated from fresh acidic extracts of the plant, they are now regarded as artifacts, formed during the isolation procedure.<sup>2</sup>



## 2 Slaframine

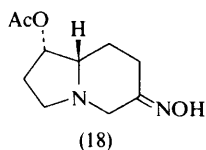
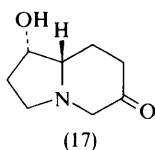
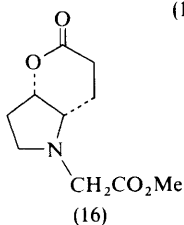
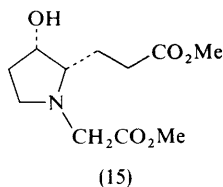
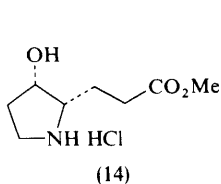
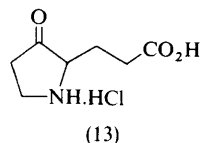
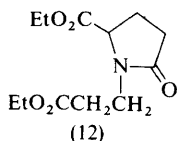
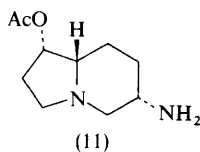
A second synthesis has been described<sup>4</sup> of slaframine (11), the amine which causes excessive salivation in livestock foraging on red clover infected with *Rhizoctonia leguminicola*. Condensation of L-(+)-glutamic acid with acrylonitrile, followed by esterification, gave ethyl *N*-( $\beta$ -ethoxycarbonyl-ethyl)-5-oxopyrrolidine-2-carboxylate (12), which on Dieckmann cyclization, hydrolysis, and decarboxylation afforded the racemic 3-oxopyrrolidine acid (13). Platinum-catalysed hydrogenation of the hydrochloride of (13) in methanol solution gave the alcohol-ester (14), which with methyl bromoacetate produced a mixture of the expected diester (15) and the lactone (16). Dieckmann cyclization of this mixture, followed by hydrolysis and decarboxylation, furnished the indolizidine hydroxyketone (17), isolated as the hydrochloride. Acetylation and oxime formation gave a mixture

<sup>3</sup> A. M. Pilotti and A. C. Wiehager, *Acta Cryst.*, 1973, **B29**, 1563.

<sup>4</sup> W. J. Gensler and M. W. Hu, *J. Org. Chem.*, 1973, **38**, 3848.



of *syn*- and *anti*-oximes (18), which were hydrogenated to ( $\pm$ )-slaframine (11). In this synthesis the second and third asymmetric centres are introduced during platinum-catalysed hydrogenation stages. If it is assumed that addition of hydrogen occurs at the less hindered side of the substrate in both reductions the relative configuration postulated in (11) is to be expected. This is in accordance with the stereochemistry previously deduced for slaframine, and is consistent with the n.m.r. data for the oximes (18) and *N*-acetylslaframine.<sup>4</sup>

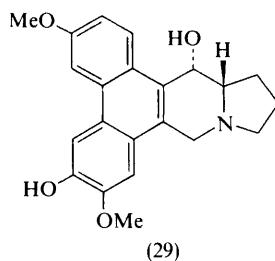
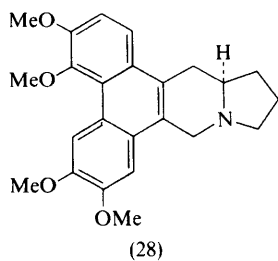
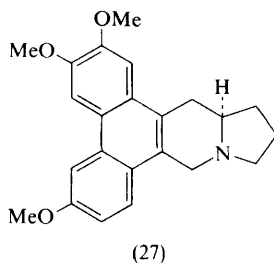
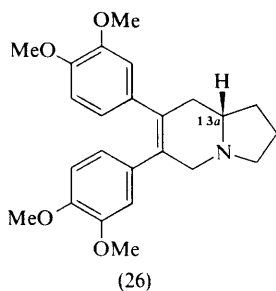
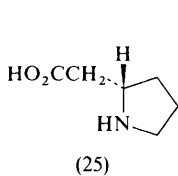
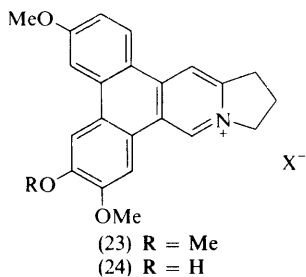
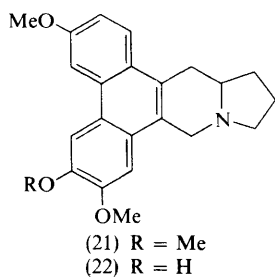
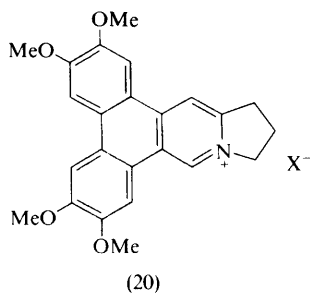
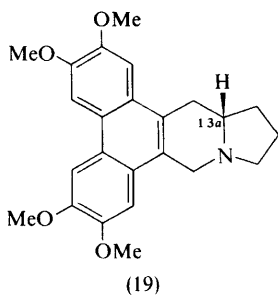


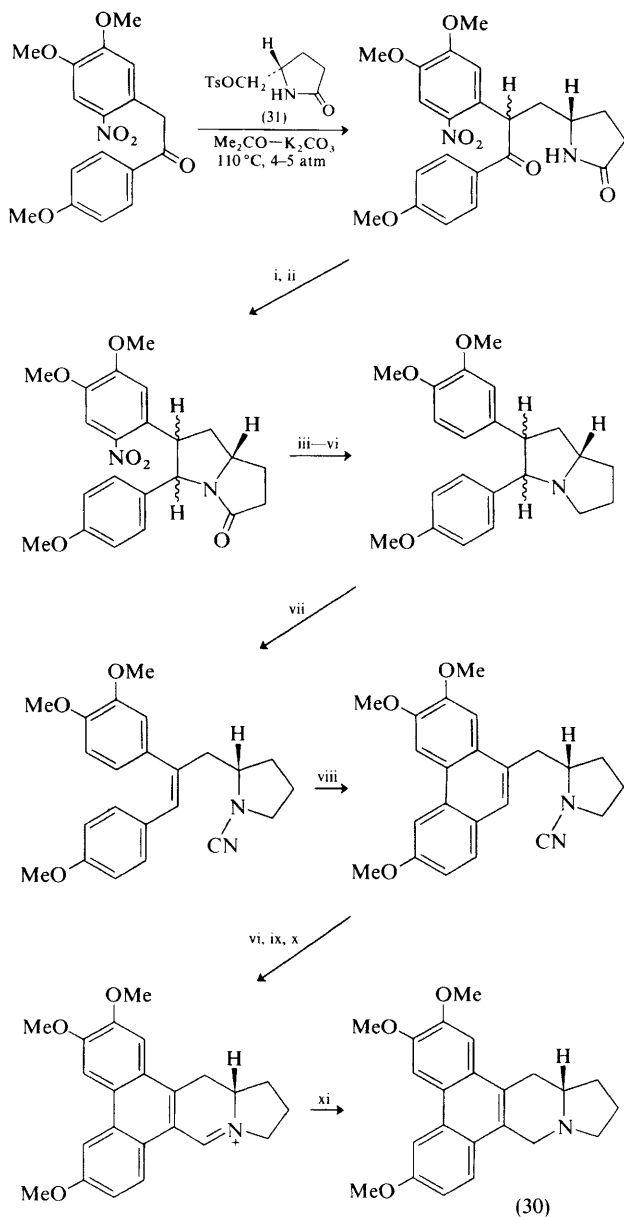
### 3 Alkaloids of *Tylophora* species

During the isolation of minor tertiary bases from *Tylophora asthmatica* Wight et Arn. the presence of water-soluble, quaternary bases was observed.<sup>5</sup> These were converted *via* the reineckates into their perchlorates, repeated recrystallizations of which eventually afforded a yellow salt,  $C_{24}H_{24}NO_8Cl$ , which on catalytic reduction gave ( $\pm$ )-tylophorine (19). The new alkaloid is thus a dehydrotylophorine of structure (20). Catalytic reduction of the crude perchlorate obtained from the mother liquors of the crystallization yielded more ( $\pm$ )-tylophorine contaminated with ( $\pm$ )-deoxytylophorinine (21) and ( $\pm$ )-deoxytylophorinidine (22). Presumably, therefore, the corresponding dehydroderivatives (23) and (24) were also contained in the water-soluble quaternary base fraction, although they were present in very small amount only, and could not be obtained pure. The known instability of phenanthroindolizidine alkaloids to light and air, and the preparation of the crystalline quaternary chloride

<sup>5</sup> T. R. Govindachari, N. Viswanathan, J. Radhakrishnan, R. Charubala, N. Nityanandra Rao, and B. R. Pai, *Indian J. Chem.*, 1973, **11**, 1215.

corresponding to (20) on exposure of a chloroform solution of tylophorine to light and air suggests that these dehydro-derivatives of the alkaloids are artifacts.<sup>5</sup>





Scheme

Reagents: i,  $\text{NaBH}_4-\text{H}_2\text{O}-\text{EtOH}$ ; ii,  $\text{HCl}-\text{AcOH}$ ; iii,  $\text{H}_2$ , Raney Ni; iv,  $\text{NaNO}_2$ ,  $\text{HCl}$ ; v, 30%  $\text{H}_3\text{PO}_2$ ; vi,  $\text{LiAlH}_4-\text{THF}$ ; vii,  $\text{BrCN}-\text{C}_6\text{H}_5$ ; viii,  $h\nu-\text{O}_2-\text{C}_6\text{H}_{12}$ ; ix, 98%  $\text{HCO}_2\text{H}$ ,  $180^\circ\text{C}$ ; x,  $\text{POCl}_3-\text{C}_6\text{H}_5\text{Me}$ ; xi,  $\text{NaBH}_4-\text{MeOH}$

The absolute configuration of tylophorine (19) has now been rigorously established<sup>6</sup> by exhaustive ozonolysis, which afforded *S*-pyrrolidine-2-acetic acid (25). This confirms that the photo-oxidative cyclization<sup>7</sup> of L-septicine (26), for which the *S*-configuration at position 13a had previously been established,<sup>8</sup> occurs with retention of configuration. Comparison<sup>6</sup> of the o.r.d. curves of tylophorine, antofine (27), and (+)-isotylocrebrine (28), indicates that this last alkaloid, like antofine, has the *R*-configuration at C-13a.

The structure of tylophorinidine (29) has been confirmed by *X*-ray analysis of its diacetate methiodide.<sup>9</sup> The absolute configuration (29) also confirms the *trans*-diaxial disposition of the C-13a and C-14 substituents, postulated earlier by Govindachari *et al.*<sup>10</sup>

Faber and Wiegrebe have reported a stereospecific synthesis of the enantiomer (30) of antofine, by the route shown in the Scheme.<sup>11</sup> Racemization was avoided by using the prolinol derivative (31) as the source of the asymmetric centre, and by cyclizing the formylpyrrolidine derivative at the penultimate stage of the synthesis. The optical purity of the final product was *ca.* 50%; this accords with the optical purity of the starting 5-oxoprolinol, which was estimated to be 51% when prepared by the route adopted.

<sup>6</sup> T. R. Govindachari, T. G. Rajagopalan, and N. Viswanathan, *J.C.S. Perkin I*, 1974, 1161.

<sup>7</sup> J. H. Russel, *Naturwiss.*, 1963, **50**, 443.

<sup>8</sup> J. H. Russel and H. Hunziker, *Tetrahedron Letters*, 1969, 4035.

<sup>9</sup> V. K. Wadhawan, S. K. Sikka, and N. B. Mulchandani, *Tetrahedron Letters*, 1973, 5091.

<sup>10</sup> T. R. Govindachari, N. Viswanathan, J. Radhakrishnan, B. R. Pai, S. Natarajan, and P. S. Subramaniam, *Tetrahedron*, 1973, **29**, 891.

<sup>11</sup> L. Faber and W. Wiegrebe, *Helv. Chim. Acta*, 1973, **56**, 2882.

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

**Occurrence, and Isolation of New Alkaloids.**—The bark of a thorny Spanish broom indigenous to the Canary Islands has been shown<sup>1</sup> to contain (+)-sparteine, retamine, anagyrine, and sophochryrine. Traces of sophoridine, *N*-methylcytisine, cytisine, and sophoramine were also detected. This plant is variously described in the literature as *Retama rhodorhizoides*,<sup>1,2a</sup> *R. monosperma* ssp. *rhodorhizoides*,<sup>2b</sup> and *Ulex vulgaris rhodorhizoides*,<sup>1</sup> but these are probably synonyms for *Genista rhodorhizoides* Webb et Berth.,<sup>2a</sup> a conclusion which is emphasized by the identity in alkaloid content.<sup>1,2a,2b</sup>

The qualitative and quantitative patterns of alkaloid content in the various organs of *Lupinus termis* Forsk., one of three *Lupinus* species indigenous to Egypt, have been studied.<sup>3</sup> The maximum alkaloid content was observed in the seeds of very ripe fruits thirteen weeks after flowering; at the same time the alkaloid content of the roots was at its minimum. Thin-layer chromatography provided evidence for the presence of nine alkaloids, of which the major one was identified as ( $\pm$ )-lupanine. A second alkaloid was reported to show the same chromatographic behaviour as 13-hydroxylupanine, but was not positively identified. This work confirms an earlier report<sup>4</sup> of the presence of these two alkaloids in Lebanese specimens of *L. termis*.

The flowers and leaves of *Genista hungarica* Kern. contain four alkaloids, three of which have been identified as anagyrine (major alkaloid), *N*-methylcytisine, and lupanine.<sup>5</sup> This plant is probably identical with *G. tinctoria* which, in an independent investigation, has been reported<sup>6</sup> to contain rhombifoline, *N*-methylcytisine, anagyrine, and cytisine. An older paper, previously overlooked,

<sup>1</sup> A. M. Mendez, A. G. Gonzalez, and F. D. Rodriguez, *Rec. Fac. Farm. Univ. Los Andes*, 1971, **8**, 77 (*Chem. Abs.*, 1974, **80**, 68 370).

<sup>2</sup> (a) A. G. Gonzalez, A. H. Toste, and B. R. Hernandez, *Anales de Quim.*, 1959, **55B**, 607 (*Chem. Abs.*, 1960, **54**, 8874); (b) F. D. Rodriguez, A. G. Gonzalez, and A. M. Mendez, *ibid.*, 1966, **62B**, 853 (*Chem. Abs.*, 1967, **66**, 73 215).

<sup>3</sup> S. M. Khafagy, S. El-Masry, M. R. I. Saleh, and S. W. A. Dabbas, *Pharmazie*, 1974, **29**, 65.

<sup>4</sup> C. I. Abou-Chaar, *Econ. Bot.*, 1967, **21**, 367.

<sup>5</sup> T. Adzet and J. L. Masso, *Trav. Soc. Pharm. Montpellier*, 1973, **33**, 349 (*Chem. Abs.*, 1974, **80**, 130 496).

<sup>6</sup> A. Gulubov and A. Venkov, *Nauch. Tr. Plovdivski Univ., Mat. Fiz. Khim. Biol.*, 1973, **11**, 87 (*Chem. Abs.*, 1974, **80**, 143 028).

is concerned with the alkaloid content of *Genista pumila* (Deg. et Rev.) Vierh. ssp. *pumila*,<sup>7</sup> from the moorland areas of the Guadalajara province of Spain. The four bases extracted from the plant were shown to be sparteine, anagryne, lupanine, and cytisine.

A survey has been contributed<sup>8</sup> of the alkaloid content of 16 species of Spanish and Portuguese Leguminosae belonging to the *Cytisus*, *Genista*, *Echinospartium*, *Stauracanthus*, and *Adenocarpus* genera; 13 quinolizidine or dipiperidine bases were identified, and their distribution in the various organs of the plants determined.

The cytisine content of *Thermopsis lanceolata*<sup>9</sup> and *T. dolichocarpa*<sup>10</sup> has been studied by an ion-exchange method. *Thermopsis chinensis* Benth. ( $\equiv$  *T. fabacea* DC.) has previously also been shown to contain cytisine. Recently a total of five alkaloids has been isolated from the roots; cytisine is present, together with *N*-methylcytisine, anagryne, lupanine, and *N*-formylcytisine.<sup>11</sup> This last constituent has also been tentatively identified in the aerial parts of *Euchresta japonica* Benth.<sup>11</sup>

The alkaloid content of *Petteria ramentacea* (Sieber) Presl. has been examined at various stages of development.<sup>12</sup> The seeds contain cytisine and *N*-methylcytisine, but very soon after germination cytisine is absent. After 15 days a trace of anagryne appears and is present in significant amounts after 60 days. Lupanine occurs in older plants (*ca.* 1.5 years), although the first traces appear at 90 days. After 30 days cytisine reappears and the amount present in the plant gradually increases. The overall result is that cytisine is the major alkaloid in the seeds, *N*-methylcytisine is the only alkaloid present in very young seedlings, and anagryne is the major alkaloid in older plants (*ca.* 1.5 years); lupanine appears never to be very abundant. However, all four alkaloids are present in these older plants, together with two unidentified alkaloids.<sup>12</sup>

In the *Sophora* genus, specimens of *S. tomentosa* collected in April in the Bonin Islands (Japan) contain in their aerial parts *N*-acetylcytisine, baptifoline, anagryne, matrine *N*-oxide (oxymatrine), matrine, *N*-methylcytisine, and cytisine.<sup>11,13</sup> The first four of these alkaloids had not previously been observed in this species; Cambie<sup>14</sup> had noted the presence of the last three bases only, together with one unidentified base. The alkaloid content of the seeds of *S. denudata* Bory (the small tamarind), a shrub found at 1600–2500 m on the island of Réunion, appears to be somewhat similar;<sup>15</sup> cytisine and matrine *N*-oxide,

<sup>7</sup> A. Orjales and I. Ribas, *Anales de Quim.*, 1969, **65**, 619.

<sup>8</sup> G. Faugeras, E. Valdes-Bermejo, and R. Paris, *Plant. Med. Phytother.*, 1973, **7**, 68 (*Chem. Abs.*, 1973, **79**, 63 549).

<sup>9</sup> B. Babaev and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1973, **9**, 440 (*Chem. Abs.*, 1973, **79**, 89 532).

<sup>10</sup> B. Babaev, T. T. Shakirov, U. G. Sidiyakin, and S. A. Khamidkhodzhaev, *Khim. prirod. Soedinenii*, 1973, **9**, 444 (*Chem. Abs.*, 1973, **79**, 102 797).

<sup>11</sup> S. Ohmiya, H. Otomasu, I. Murakoshi, and J. Haginiwa, *Phytochemistry*, 1974, **13**, 643.

<sup>12</sup> D. Kustrak and E. Steinegger, *Pharm. Acta Helv.*, 1969, **44**, 310; 1973, **48**, 517.

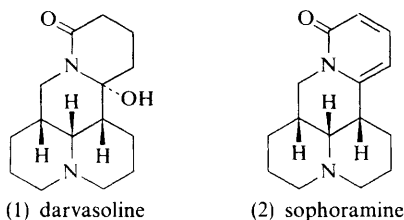
<sup>13</sup> S. Ohmiya, H. Otomasu, I. Murakoshi, and J. Haginiwa, *Phytochemistry*, 1974, **13**, 1016.

<sup>14</sup> R. C. Cambie, *N.Z.J. Sci.*, 1961, **4**, 13.

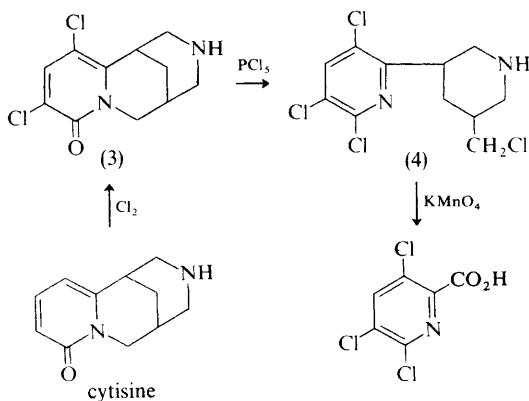
<sup>15</sup> G. Faugeras, R. Paris, and M. Peltier, *Ann. pharm. franç.*, 1973, **31**, 561.

the major alkaloids, occur in conjunction with *N*-methylcytisine, anagryne,  $\alpha$ -matrine, and baptifoline.

The only new alkaloid reported during the year in this group appears to be darvasoline (1), from *Leontice darwasica* Regel;<sup>16</sup> its structure follows from its reduction ( $\text{LiAlH}_4$ ) to matridine and its dehydration-dehydrogenation to sophoramine (2).



**Chemical, Spectroscopic, and Synthetic Studies.**—The chemical and spectroscopic properties of alkaloids containing a pyridine ring have been summarized.<sup>17</sup> The product of chlorination of cytisine has been shown to be 3,5-dichlorocytisine (3); reaction with phosphorus pentachloride affords the ring-opened tetrachloro-compound (4), which on oxidation gives rise to 2,3,5-trichloropyridine-6-carboxylic acid. The course of bromination of cytisine is exactly analogous.<sup>17</sup>



Details have been given<sup>18</sup> of the partial asymmetric syntheses of  $\beta$ -hydroxyesters by the Reformatsky reaction in the presence of (–)-sparteine, reported in brief earlier.<sup>19</sup> The optical purity of the products was occasionally very high, particularly when the carbonyl component was benzaldehyde, and reached  $95 \pm 3\%$  in the reaction between benzaldehyde, zinc, sparteine, and ethyl bromo-

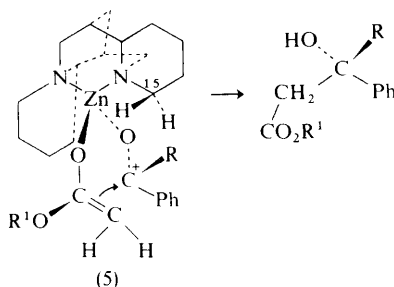
<sup>16</sup> A. Zunnunzhanov, S. Iskandarov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, **10**, 115 (*Chem. Abs.*, 1974, **80**, 121 169).

<sup>17</sup> A. Orjales, I. Ribas, and A. Varela, *Anales de Quim.*, 1972, **68**, 1419.

<sup>18</sup> M. Guetté, J. Capillon, and J. P. Guetté, *Tetrahedron*, 1973, **29**, 3659.

<sup>19</sup> M. Guetté, J. P. Guetté, and J. Capillon, *Tetrahedron Letters*, 1971, 2863.

acetate in acetone solution. The mechanism of the reaction has been discussed, and in order to account for the formation of products having the *S*-configuration an intermediate complex (5) is proposed in which the zinc enolate derived from the bromo-ester is co-ordinated with sparteine and the carbonyl component. With benzaldehyde as the carbonyl component the preferred six-membered transition state is that which places the bulky aryl group away from the C-15 methylene group, thus leading to a product having the *S*-configuration.



Asymmetric induction in the presence of various alkaloids, including sparteine, has also been observed in electrolytic reductions;<sup>20</sup> the optical yields, however, were generally low. For example, in the reduction of acetophenone on a mercury pool cathode in the presence of sparteine the optical yield of 1-phenylethanol was only 1.4% (chemical yield 26%).

Two recent communications have discussed in some detail the mass spectra of quinolizidine alkaloids.<sup>21,22</sup> The mass spectrum of allomatridine (6) contains peaks at *m/e* 98 and 137 owing to the ions (7) and (8); these are in the main (*ca.* 78%) formed by the obvious rupture of the molecule at the 7,11 and 5,17 bonds, as confirmed by the spectrum of [14,14-<sup>2</sup>H<sub>2</sub>]allomatridine (9) prepared by the deuteration of allomatrine (10) and subsequent reduction. Surprisingly, perhaps, the analogous ion at *m/e* 98 in the spectra of matridine (11) and isosophoridane (12) appears not to be derived in analogous fashion mainly from ring D since in the mass spectra of [14,14-<sup>2</sup>H<sub>2</sub>]matrine (13) and [14,14-<sup>2</sup>H<sub>2</sub>]isosophoridane (14) the ion at *m/e* 98 is much more abundant than the newly-appeared ion at *m/e* 100. This supports the similar conclusion reached earlier by other workers<sup>23</sup> following an analysis of the mass spectrum of [15,15-<sup>2</sup>H<sub>2</sub>]matridine. There is, however, insufficient evidence at present to formulate a precise formation mechanism, but it must involve the rupture of at least three carbon-carbon bonds if it is derived from rings A or B. The ion at *m/e* 84 (15) is derived principally from ring D in allomatridine and isosophoridane, but its genesis in the spectrum of matridine is mass spectra of [14,14-<sup>2</sup>H<sub>2</sub>]matrine (13) and [14,14-<sup>2</sup>H<sub>2</sub>]isosophoridane (14) the

<sup>20</sup> E. Kariv, H. A. Terni, and E. Gileadi, *J. Electrochem. Soc.*, 1973, **120**, 639.

<sup>21</sup> N. S. Wulfson, Z. S. Ziyavidinova, and V. G. Zaikin, *Org. Mass Spectrometry*, 1973, **7**, 1313.

<sup>22</sup> N. S. Wulfson, Z. S. Ziyavidinova, and V. G. Zaikin, *Khim. geterotsikl. Soedinenii*, 1974, 251 (*Chem. Abs.*, 1974, **81**, 13 678).

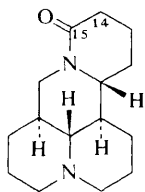
<sup>23</sup> S. Iskandarov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, 106.



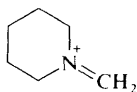
less specific. These differences presumably reflect the differences in stereochemistry between the three molecules; this is also shown, for example, by the fact that by far the strongest molecular ion is given, as expected, by the most stable, all-*trans* isomer, allomatridine.

(6) R = H, allomatridine

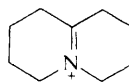
(9) R = D, [14,14-<sup>2</sup>H<sub>2</sub>]-allomatridine



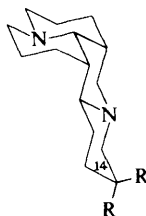
(10) allomatridine



(7) *m/e* 98

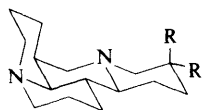


(8) *m/e* 137



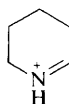
(11) R = H, matridine

(13) R = D, [14,14-<sup>2</sup>H<sub>2</sub>]matridine



(12) R = H, isosphoridane

(14) R = D, [14,14-<sup>2</sup>H<sub>2</sub>]-isosphoridane



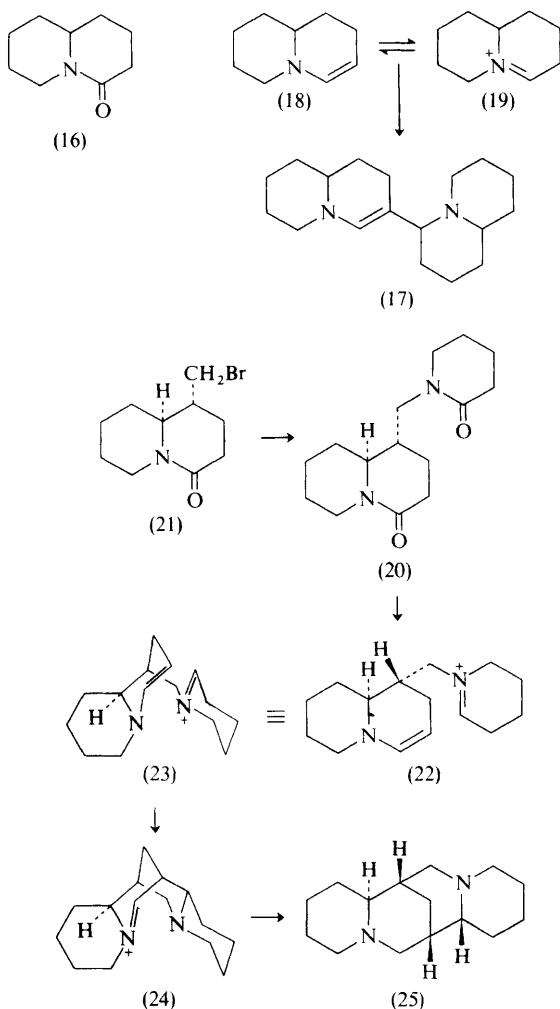
(15) *m/e* 84

Synthetic work in this area includes a new, stereospecific synthesis of sparteine<sup>24</sup> and a synthesis of isosphoramine.<sup>25</sup> The reduction of quinolizidone (16) by means of lithium aluminium hydride affords, as noted previously,<sup>26</sup> a dimeric product (17), presumably *via* condensation of the initially formed enamine (18) with the corresponding immonium cation (19). With di-isobutyl aluminium hydride the yield of (17) can be increased to 85%.<sup>24</sup> Analogous reduction of the dilactam (20), prepared by base-catalysed condensation of the bromo-lactam (21) with  $\alpha$ -piperidone, gave an intermediate (22), in which the enamine and immonium ion units are present within the same molecule. Intramolecular cyclization of (22), *via* a transition state derived from the conformation (23), spontaneously gave the

<sup>24</sup> F. Bohlmann, H. J. Müller, and D. Schumann, *Chem. Ber.*, 1973, **106**, 3026.

<sup>25</sup> E. Wenkert, B. Chauncy, K. G. Dave, A. R. Jeffcoat, F. M. Schell, and H. P. Schenk, *J. Amer. Chem. Soc.*, 1973, **95**, 8427.

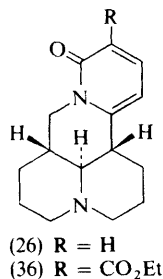
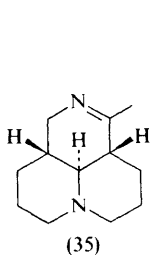
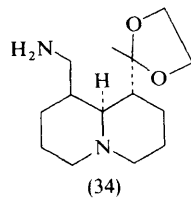
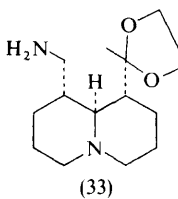
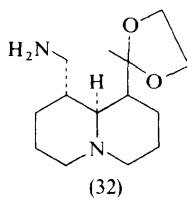
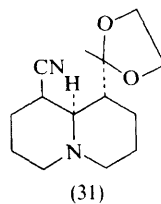
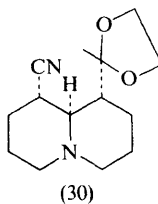
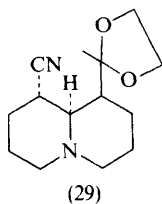
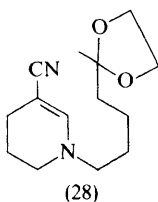
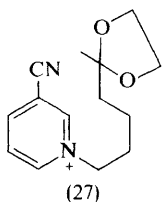
<sup>26</sup> Y. Arata, H. Kato, and T. Shioda, *J. Pharm. Soc. Japan*, 1968, **88**, 614 (*Chem. Abs.*, 1968, **69**, 96 426).



tetracyclic immonium ion (24), which on reduction ( $\text{NaBH}_4$ ) afforded ( $\pm$ )-sparteine (25).

The synthesis of isosphoramine (26) employs as crucial stages the partial hydrogenation of *N*-alkyl salts of  $\beta$ -acyl (or cyano) pyridines, and acid-catalysed cyclization of the resulting 1-alkyl-3-acyl (or cyano)-2-piperidineines. Alkylation of nicotinonitrile with 6-bromohexan-2-one ethylene ketal afforded the salt (27), which on palladium-catalysed hydrogenation yielded the piperidine (28). Anhydrous acid-catalysed ( $\text{TsOH}$ ) cyclization of (28) gave the three quinolizidine stereoisomers (29)—(31), which were separated and analysed by n.m.r. spectroscopy and equilibration studies in acid ( $\text{TsOH}-\text{C}_6\text{H}_6$ ) and alkaline ( $\text{KOBu}^t-\text{Bu}^t\text{OH}$ )

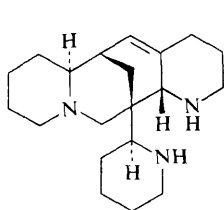
solution. Reduction ( $\text{LiAlH}_4$ ) of the separate isomers gave the corresponding primary amines (32)—(34), which were characterized as their crystalline acetyl derivatives. Acid hydrolysis of either diamine (32) or diamine (33) gave the *same* tricyclic imine (35) whose *trans*-quinolizidine structure was established by  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectroscopy. The final ring was added to (35) by base-catalysed condensation with diethyl ethoxymethylenemalonate followed by treatment with acid, which gave the pyridone ester (36). Finally, hydrolysis and decarboxylation gave ( $\pm$ )-isosphoramine (26).<sup>25</sup>



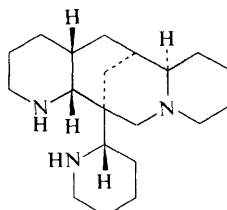
## 2 The *Ormosia* Alkaloids

The apparent anomaly, mentioned in last year's Report, concerning ormocastrine and podopetaline, for which the same structure (37) had been deduced, has now

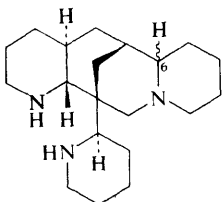
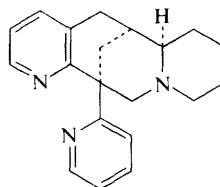
been simply explained.<sup>27</sup> The original specimen of ormosastrine, for which m.p. 263 °C was reported, was not a free base but was in fact a hydrochloride salt, which has now been shown to be identical with podopetaline hydrochloride. Addition of alkali liberates the base, m.p. 78–80 °C (*cf.* podopetaline, m.p. 77.5–79 °C). It has also been established that the alkaloid claimed to be 18-epiormosanine was 18-epiormosanine hydrochloride. Re-examination of the other two bases isolated in the same investigation<sup>28</sup> from *Ormosia semicastrata* has confirmed that they are ormosanine and piptanthine.



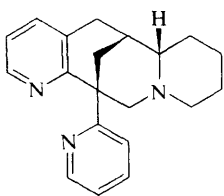
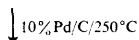
(37) podopetaline



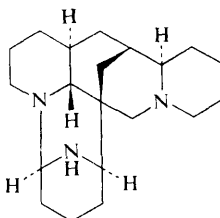
(38) (-)-templettine

(41) (-)-ormosanine,  $\alpha$ -H at C-6  
(43) (+)-piptanthine,  $\beta$ -H at C-6

(39) (-)-dehydropiptanthine



(40) (+)-dehydropiptanthine



(42) (-)-panamine

An interesting mixture of alkaloids of the quinolizidine group has been obtained from the leaves of *Templetonia retusa* (Vent.) R.Br.<sup>29</sup> In addition to (-)-cytisine, (-)-anagryne, (+)-lupanine, and a trace of ( $\pm$ )-piptanthine, a new alkaloid,

<sup>27</sup> S. McLean and R. Misra, *Canad. J. Chem.*, 1974, **52**, 1907.

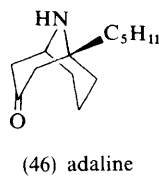
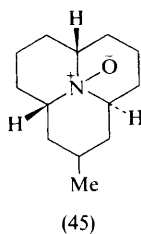
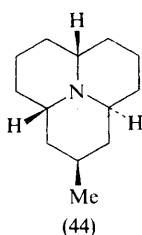
<sup>28</sup> S. McLean, M. L. Roy, H. J. Liu, and D. T. Chu, *Canad. J. Chem.*, 1972, **50**, 1639; S. McLean, P. K. Lau, S. K. Cheng, and D. G. Murray, *ibid.*, 1971, **49**, 1976.

<sup>29</sup> J. R. Cannon, J. R. Williams, J. F. Blount, and A. Brossi, *Tetrahedron Letters*, 1974, 1683.

(-)-templetine,  $C_{20}H_{35}N_3$ , m.p. 120.5–122 °C,  $[\alpha]_D - 52^\circ$ , was isolated. Since templetine failed to undergo catalytic hydrogenation it seemed likely that it belonged to the  $C_{20}$  group of *Ormosia* alkaloids, and this suspicion was confirmed when it was shown to give (-)-dihydropiptanthine on vigorous dehydrogenation. Its complete structure and absolute configuration (38) were established by *X*-ray crystal structure analysis. (-)-Dehydropiptanthine is thus (39), (+)-dehydropiptanthine is (40), and (-)-ormosanine is (41). (-)-Panamine, which can be reduced ( $NaBH_4$ ) to (-)-ormosanine [(-)-piptamine] is consequently (42), and (+)-piptanthine, the more stable C-6 epimer of (-)-ormosanine, is (43).

### 3 Alkaloids of the Coccinellidae

In previous work the isolation of hippodamine and convergeine from the American ladybird, *Hippodamia convergens*, was reported.<sup>30</sup> The structure proposed for hippodamine was (44), the configuration at C-2 being undetermined; convergeine was regarded as a 3a- or 6a-hydroxyhippodamine. A recent definitive *X*-ray crystal structure analysis of convergeine hydrochloride has shown convergeine to be the *N*-oxide (45); hippodamine is thus the tertiary base (44). The relationship between the two bases is confirmed by the preparation of convergeine by the monoperphthalic acid oxidation of hippodamine.<sup>31</sup> The earlier report<sup>30</sup> that convergeine exhibits carbonyl absorption characteristic of a carbonyl group in transannular interaction with a secondary amino-group is thus demonstrably incorrect, and the absorption is now attributed to an *N*-oxide hydrate function. In fact convergeine, unlike coccinellin, has only been obtained in the hydrated form. Another apparent anomaly in the light of the established structure and stereochemistry is the reported optical inactivity of convergeine, which led to the assumption that both hippodamine and convergeine are racemates. However, a re-examination of the rotations of convergeine hydrochloride in various solvents and at various concentrations shows that convergeine does show optical activity, but that the rotation values are very small, and strongly dependent on the solvent.



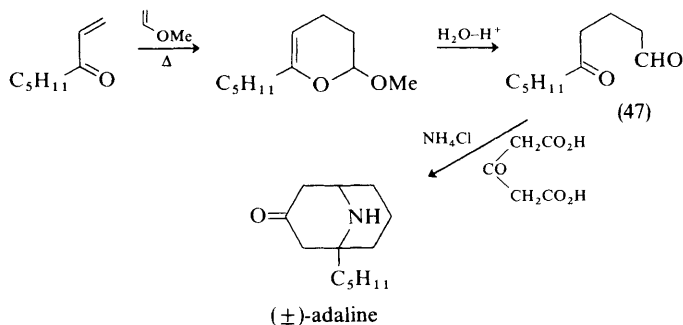
The *X*-ray determination<sup>32</sup> of the structure of adaline, the closely related defensive alkaloid of the ladybird *Adalia bipunctata*, defines its structure, but not

<sup>30</sup> B. Tursch, D. Daloze, J. M. Pasteels, A. Cravador, J. C. Braekman, C. Hootele, and D. Zimmermann, *Bull. Soc. chim. belges*, 1972, **81**, 649.

<sup>31</sup> B. Tursch, D. Daloze, J. C. Braekman, C. Hootele, A. Cravador, D. Losman, and R. Karlsson, *Tetrahedron Letters*, 1974, 409.

<sup>32</sup> B. Tursch, J. C. Braekman, D. Daloze, C. Hootele, D. Losman, and R. Karlsson, *Tetrahedron Letters*, 1973, 201.

necessarily its absolute configuration, as (46), in which the piperidine ring is a slightly flattened chair. Consideration of this conformation, together with the o.r.d. spectrum of adaline, demands that (46) be also the absolute configuration, a conclusion that is confirmed by a more refined *X*-ray crystal structure analysis.<sup>33</sup> The neat, direct synthesis of ( $\pm$ )-adaline is a simple adaptation of the Robinson tropinone synthesis using the keto-aldehyde (47), prepared as shown, acetone dicarboxylic acid, and ammonium chloride.<sup>34</sup>



The function of alkaloids in 30 species of ladybirds has been discussed.<sup>35</sup> The presence of alkaloids is shown to be related to the existence of aposematic colour and not to their carnivorous or phytophagous nature. Alkaloids constitute an effective defence against predators, *e.g.* ants, *Myrmica rubra*, and quails, *Coturnix coturnix*.

<sup>33</sup> R. Karlsson and D. Losman, unpublished work, reported in ref. 34.

<sup>34</sup> B. Tursch, C. Chome, J. C. Braekman, and D. Daloze, *Bull. Soc. chim. belges*, 1973, **82**, 699.

<sup>35</sup> J. M. Pasteels, C. Deroe, B. Tursch, J. C. Braekman, D. Daloze, and C. Hootele, *J. Insect Physiol.*, 1973, **19**, 1771.

# Quinoline, Quinazoline, Acridone, and Related Alkaloids

BY V. A. SNIIECKUS

## 1 Quinoline Alkaloids

Results of recent alkaloid isolation studies are summarized in the Table. In general, structural elucidation is based on spectral data and confirmed by synthesis. In one of the reports<sup>3</sup> concerned with the characterization of isomaculosidine (1), isolated from *Dictamnus albus*, details on the structural elucidation of the biogenetically significant alkaloid, preskimmianine (see Vol. 4 of these Reports) are also given. Another biogenetically interesting alkaloid, acutine (2), has been isolated from *Haplophyllum acutifolium*.<sup>4</sup> Some of the investigations of *Ruta graveolens* and *R. chalepensis* were carried out on plant material obtained from Cape Verde Islands and from the Canary Isles.<sup>11</sup> The structure proof of rutilinium salt (6) isolated from *R. graveolens* rests on spectral evidence and on its conversion into the known ribalinidine (8).<sup>12</sup> The known base, rutilinidine, was obtained from the nonpolar fractions of *R. graveolens*. Rutilinium salt (6) has also been isolated from *Balfourodendron riedelianum*.<sup>12</sup>

<sup>1</sup> A. Shueb, R. S. Kapil, and S. P. Popli, *Phytochemistry*, 1973, **12**, 2071.

<sup>2</sup> M. Gellert, I. Novak, K. Szendrei, J. Reisch, and E. Minker, *Herba Hung.*, 1971, **10**, 123 (*Chem. Abs.*, 1973, **79**, 2768m).

<sup>3</sup> R. Storer and D. W. Young, *Tetrahedron*, 1973, **29**, 1217.

<sup>4</sup> D. M. Razzakova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 206 (*Chem. Abs.*, 1973, **79**, 32 147a).

<sup>5</sup> I. A. Bessonova and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, 52 (*Chem. Abs.*, 1974, **80**, 121 152m).

<sup>6</sup> E. F. Nesmelova and G. P. Sidiyakin, *Khim. prirod. Soedinenii*, 1973, 548 (*Chem. Abs.*, 1974, **80**, 105 845j).

<sup>7</sup> V. I. Akhmedzhanova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, 109 (*Chem. Abs.*, 1974, **80**, 121 153n).

<sup>8</sup> I. Fouraste, J. Gleye, and E. Stanislas, *Plant. Med. Phytotherap.*, 1973, **7**, 216 (*Chem. Abs.*, 1974, **80**, 143 009x).

<sup>8a</sup> B. Kh. Zharekeev, Kh. N. Khashimov, and M. V. Telezhenetskaya, *Khim. prirod. Soedinenii*, 1974, 264 (*Chem. Abs.*, 1974, **80**, 13681v).

<sup>9</sup> K. Szendrei, I. Novak, M. Petz, J. Reisch, H. E. Bailey, and V. L. Bailey, *Lloydia*, 1973, **36**, 333.

<sup>10</sup> J. Reisch, Y. W. Mirhom, J. Korosi, K. Szendrei, and I. Novak, *Phytochemistry*, 1973, **12**, 2552.

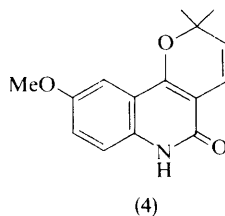
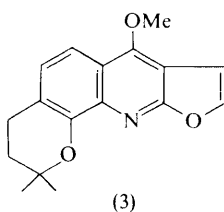
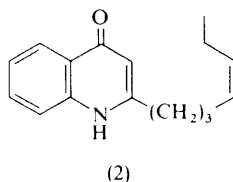
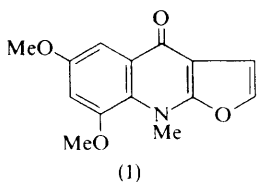
<sup>11</sup> A. Gonzalez Gonzalez, H. Lopez Dorta, M. Melian Rodriguez, and F. Rodriguez Luis, *Anales de Quim.*, 1974, **70**, 60 (*Chem. Abs.*, 1974, **80**, 130 487b).

<sup>12</sup> K. Szendrei, J. Reisch, I. Novak, L. Simon, Zs. Rozsa, E. Minker, and M. Koltai, *Herba Hung.*, 1971, **10**, 131 (*Chem. Abs.*, 1973, **79**, 15853k).

**Table** Isolation of quinoline and furoquinoline alkaloids

Species	Alkaloid <sup>a</sup> (structure)	Ref.
<i>Aegle marmelos</i>	Skimmianine	1
<i>Dictamnus albus</i>	Isodictamnine	2
	Isomaculosidine (1)	2, 3
<i>Haplophyllum acutifolium</i>	Acutine (2)	4
<i>H. foliosum</i>	Foliminine (3)	5
<i>H. latifolium</i>	Haploperine	6
	Skimmianine	6
<i>H. perforatum</i>	Haplamine (4)	7
<i>Monnieria triflora</i>	Arborinine	8
	Dictamnine	8
	Skimmianine	8
<i>Peganum harmala</i>	2-Methylquinoline	8a
	Quinoline	8a
<i>Ptelea trifoliata</i> subsp.	Balfouridine	9
<i>pallida</i> var. <i>confinis</i>	Hydroxylunine	9
<i>P. trifoliata</i>	<i>O</i> -Methylptelefolonium salt (5)	10
<i>Ruta chalepensis</i>	Kokusaginine	11
	Skimmianine	11
<i>R. graveolens</i>	Kokusaginine	11
	<i>N</i> -Methylplatydesmine	12
	<i>N</i> -Methylribalinium salt	12
	Rutalinium salt (6)	12
	Graveoline $\equiv$ Rutamine	11
<i>Spathelia sorbifolia</i>	<i>N</i> -Methyl-4,7,8-trimethoxy-2-quinolinone (7; $R^1 = \text{Me}$ , $R^2 = \text{H}$ , $R^3 = \text{OMe}$ )	13
<i>Xanthoxylon tsihaniposa</i>	Skimmianine	14

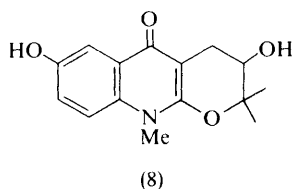
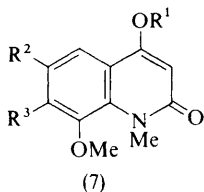
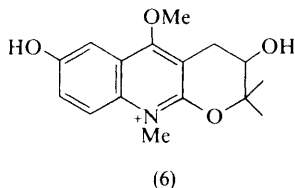
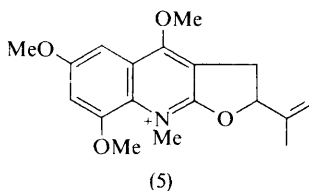
(a) Alkaloids for which structures are not given are known compounds, most of which may be found in previous volumes of these Reports.



<sup>13</sup> R. Storer, D. W. Young, D. R. Taylor, and J. M. Warner, *Tetrahedron*, 1973, **29**, 1721.

<sup>14</sup> N. Weber, *Chem. Ber.*, 1973, **106**, 3769.





Cell suspension cultures of *R. graveolens* grown in the presence of 4-hydroxy-2-quinolone show increased amounts of quinoline and furoquinoline alkaloid production.<sup>15,16</sup> For example, the concentration of dictamnine increased as long as 4-hydroxy-2-quinolone was present in the culture medium; as soon as the quinolone was depleted, rapid transformation of dictamnine into 8-methoxydictamnine was observed.<sup>15</sup>

Extensive n.m.r. studies of foliosidine,<sup>17</sup> haplophyllidine,<sup>18</sup> and a number of model compounds<sup>19</sup> have been carried out.

The readily available chiral epoxide (9), previously shown (see Vol. 4 of these Reports) to have the *S*-configuration, has been used to effect an asymmetric synthesis of (–)-*S*-lunacridine (11) (Scheme 1).<sup>20</sup> Thus, borohydride-catalysed diborane reduction of the epoxide (9; R = OMe) provided the expected alcohol (10) resulting from anti-Markovnikov ring-opening in agreement with literature precedent. The *S*-configuration is assigned to (10) on the basis of the accepted mechanism of the reductive ring-opening which proceeds with retention of configuration. Selective 2-demethylation of (10) by treatment with hydrogen chloride followed by reaction with diazomethane gave the trimethoxyquinoline (11) which clearly must possess the *S*-configuration. This compound was shown to be enantiomeric with the natural product, (+)-lunacridine (12), which must therefore be assigned the *R*-configuration. This study, together with known chemical interrelationships, allowed the assignment of absolute stereochemistry of other *Lunasia* alkaloids. Application of mixed hydride reduction (AlCl<sub>3</sub>–

<sup>15</sup> W. Steck, O. L. Gamborg, and B. K. Bailey, *Lloydia*, 1973, **36**, 93.

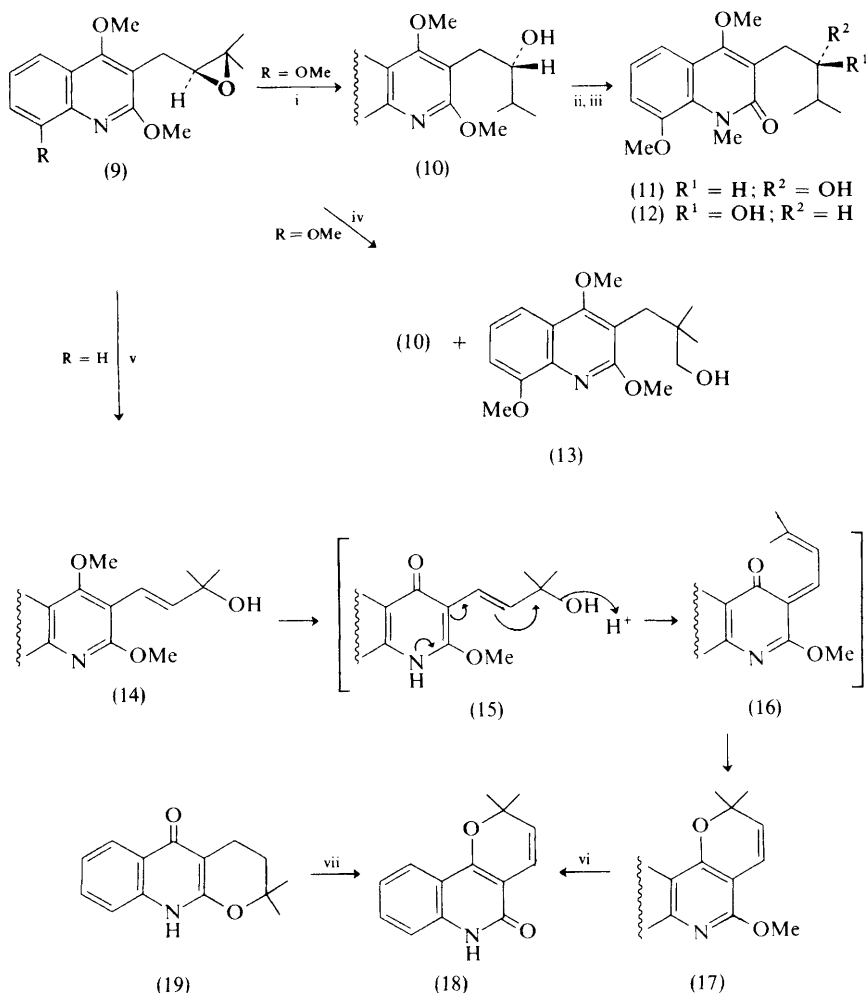
<sup>16</sup> D. Boulanger, B. K. Bailey, and W. Steck, *Phytochemistry*, 1973, **12**, 2399.

<sup>17</sup> M. R. Yagudaev and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 439 (*Chem. Abs.*, 1973, **79**, 92 447h).

<sup>18</sup> K. L. Seitanidi, M. R. Yagudaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 507 (*Chem. Abs.*, 1974, **80**, 60054g).

<sup>19</sup> M. R. Yagudaev and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, 55 (*Chem. Abs.*, 1974, **80**, 121 161p).

<sup>20</sup> R. M. Bowman, G. A. Gray, and M. F. Grundon, *J.C.S. Perkin I*, 1973, 1051.



Scheme 1

$\text{LiAlH}_4$ ) to epoxide (9;  $R = \text{OMe}$ ) gave a lower yield of the secondary alcohol (10) and the rearranged primary alcohol (13).

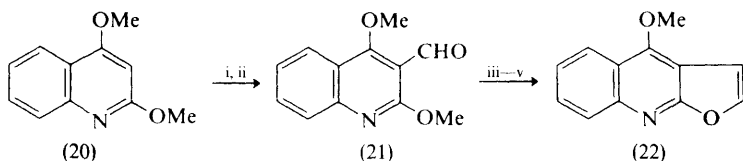
A study of the base-catalysed reaction of the epoxide (9;  $R = \text{H}$ ) led to a facile new synthesis of flindersine (18) (Scheme 1).<sup>21</sup> Thus, treatment of (9;  $R = \text{H}$ ) with potassium hydroxide afforded, after neutralization, a high yield of the py-

<sup>21</sup> R. M. Bowman, M. F. Grundon, and K. J. James, *J.C.S. Perkin I*, 1973, 1055.

ranoquinoline (17). An n.m.r. study of this reaction led to the isolation and detection of the intermediates (14) and (15), respectively. The final step, (15)  $\rightarrow$  (17), may proceed *via* the quinone methide (16) by an electrocyclic mechanism. Treatment of (17) with hydrobromic acid gave the alkaloid flindersine (18) whose biogenesis was also discussed in this paper.<sup>21</sup> Flindersine has been recently obtained by a dehydrogenative rearrangement reaction of khaplofoline (19).<sup>22</sup>

Conventional syntheses of robustine and haplophine have been reported.<sup>23</sup> Various furoquinoline derivatives have been prepared from 3-vinyl-2-quinolone derivatives which in turn were available from the reaction of *o*-aminoacetophenone with 3-butenoyl chloride in the presence of pyridine.<sup>24,25</sup>

An interesting synthesis of dictamnine (22) is initiated by lithiation of the quinoline (20) (Scheme 2) which is followed by formylation to give (21). Wittig reaction followed by two acid-catalysed steps gives dictamnine (22).<sup>26</sup> The related alkaloids, pteleine and evolitrine, were similarly synthesized.

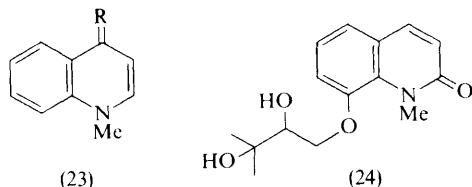


Reagents: i, lithiation; ii,  $\text{PhN(Me)CHO}$ ; iii,  $\text{Ph}_3\text{PCH}_2\text{OMe Cl}^+$ ,  $\text{KOtBu}^+$ ; iv, 20 %  $\text{HCl}$ ; v, PPA

**Scheme 2**

The synthesis of halfordamine (7;  $\text{R}^1 = \text{R}^3 = \text{H}$ ,  $\text{R}^2 = \text{OMe}$ ), isolated from *Halfordia kendack*, has been accomplished.<sup>27</sup>

Isolation of alkaloids from *Haplophyllum perforatum* by cation exchange chromatography has been reported.<sup>28</sup>



<sup>22</sup> L. Maat, A. W. Buijen Van Weelderen, and H. C. Beyerman, *Rec. Trav. chim.*, 1973, **92**, 1399.

<sup>23</sup> V. N. Ramachandran, B. R. Pai, N. Somasundaram, and C. S. Swaminathan, *Indian J. Chem.*, 1973, **11**, 1088.

<sup>24</sup> P. Shanmugam, P. Lakshminarayana, and R. Palaniappan, *Monatsh.*, 1973, **104**, 633.

<sup>25</sup> P. Shanmugam and R. Palaniappan, *Z. Naturforsch.*, 1973, **28b**, 196.

<sup>26</sup> N. S. Narasimhan and R. S. Mali, *Tetrahedron Letters*, 1973, 843.

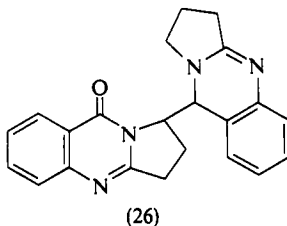
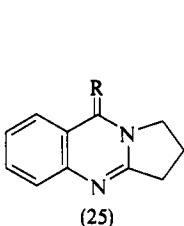
<sup>27</sup> R. Storer and D. W. Young, *Tetrahedron*, 1973, **29**, 1215.

<sup>28</sup> B. Babaev, P. Abdullaev, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1973, 445 (*Chem. Abs.*, 1973, **79**, 102 798q).

A large number of reports concerning the pharmacology of echinopsine (23; R = O), echinopsidine (23; R = NH), and their derivatives have appeared.<sup>29</sup> Antimicrobial,<sup>30</sup> antidiuretic,<sup>31</sup> and hypothermic<sup>32</sup> effects of some *Haplophyllum* alkaloids have been studied. Synergistic effects of skimmianine, haplofoline, robustine, and foliosidine with certain hypnotic and narcotic drugs has been noted.<sup>33,34</sup> Foliosidine (24) has been shown to prevent cardiac arrhythmia in cats<sup>35</sup> while haplophyllidine has been reported to eliminate atropine-induced psychosis.<sup>36</sup> The effects of long-term administration of skimmianine have been studied.<sup>37</sup>

## 2 Quinazoline Alkaloids

*Peganum harmala* has yielded deoxypeganidine (25; R = H, CH<sub>2</sub>COMe) whose structure rests on spectral data and oxidation to vasicinone (25; R = O).<sup>38</sup> The same species has also yielded dipegine (26), the first dimeric quinazoline alkaloid.<sup>8a</sup> An additional base, isopeganidine, was isolated and described as a 'racemic diastereomer of peganidine'.<sup>8a</sup> It is possible that both peganidine and dipegine are artefacts formed in the isolation procedure.

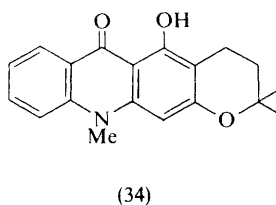
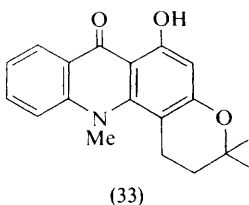
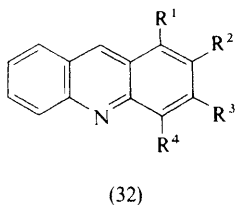
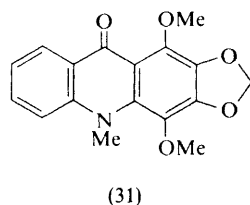
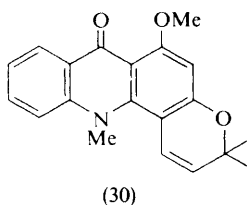
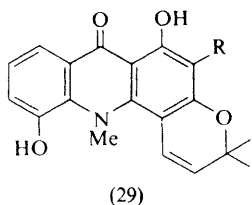
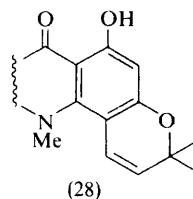
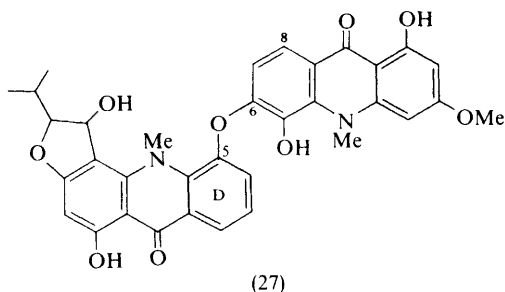


- <sup>29</sup> P. Vainauskas and V. P. Kramarenko, *Farm. Zhur. (Kiev)*, 1973, **28**, 82 (*Chem. Abs.*, 1974, **80**, 10 213n); O. Angelova and B. Avramova, *Trudy Nauchnoizsled. Khim.-Farm. Inst.*, 1972, **8**, 291 (*Chem. Abs.*, 1973, **79**, 38 523s); D. Stefanova, N. Tyutyulkova, and L. Daleva, *ibid.*, 1972, **7**, 271 (*Chem. Abs.*, 1973, **79**, 27 216t); L. Daleva, St. Vankov, I. Mikhailova, and G. Nakova, *ibid.*, 1972, **8**, 227 (*Chem. Abs.*, 1973, **79**, 38 521q); I. Ilarionov and S. Zarkova, *ibid.*, 1972, **7**, 259 (*Chem. Abs.*, 1973, **79**, 27 215s).
- <sup>30</sup> I. Isamukhamedov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 185 (*Chem. Abs.*, 1974, **80**, 116 598g).
- <sup>31</sup> N. P. Polievtev, N. I. Evdokimova, and M. B. Sultanov, *Doklady Akad. Nauk Uzb. S.S.R.*, 1970, **27**, 31 (*Chem. Abs.*, 1974, **80**, 10 504h).
- <sup>32</sup> N. P. Polievtev, N. I. Evdokimova, and M. B. Sultanov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 41 (*Chem. Abs.*, 1974, **80**, 103 867u).
- <sup>33</sup> N. I. Evdokimova, N. P. Polievtev, and M. B. Sultanov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 47 (*Chem. Abs.*, 1974, **80**, 103 868v).
- <sup>34</sup> S. F. Fakhruddinov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 64 (*Chem. Abs.*, 1974, **80**, 103 863q).
- <sup>35</sup> N. P. Polievtev and M. M. Azimov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 58 (*Chem. Abs.*, 1974, **80**, 103 870q).
- <sup>36</sup> B. L. Danilevskii, N. Tulyaganov, and F. Sadritdinov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 136 (*Chem. Abs.*, 1974, **80**, 103 861n).
- <sup>37</sup> N. I. Evdokimova and Kh. M. Malikov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 55 (*Chem. Abs.*, 1974, **80**, 103 869w).
- <sup>38</sup> B. Kh. Zharekeev, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 279 (*Chem. Abs.*, 1973, **79**, 32 158e).

The distribution of quinazoline alkaloids in various parts of *Linaria genistifolia* and *L. vulgaris* has been studied.<sup>39</sup>

### 3 Acridone Alkaloids

Atalanine (27) and ataline (28), isolated from *Atalantia ceylanica*, represent the first examples of dimeric acridone alkaloids.<sup>40</sup> Their structures rest on accurate mass measurement as well as other spectral data using monomeric alkaloids for comparison purposes. The assignment of the ether bridge C-5' to C-6 is tentative and based on (a) biogenetic considerations (all acridones have C-5 hydroxyl functions) and (b) n.m.r. data which eliminate a C-8 to ring D O-linkage. Two additional new alkaloids, (29; R = H) and (29; R = CH<sub>2</sub>CH=CM<sub>2</sub>), have also been isolated from *A. ceylanica*.<sup>41</sup>



<sup>39</sup> K. G. Lupu, *Rast. Resur.*, 1973, **9**, 206 (*Chem. Abs.*, 1973, **79**, 15 906e).

<sup>40</sup> A. W. Fraser and J. R. Lewis, *J.C.S. Chem. Comm.*, 1973, 615.

<sup>41</sup> A. W. Fraser and J. R. Lewis, *J.C.S. Perkin I*, 1973, 1173.

Acronycine (30) and melicopidine (31) have been isolated from *Bauerella baueri*.<sup>42</sup> Dubamine (32;  $R^1 = R^4 = H$ ,  $R^2 + R^3 = OCH_2O$ ) has been obtained from *Haplophyllum latifolium*<sup>6</sup> and arborinine (32;  $R^1 = OH$ ,  $R^2 = R^3 = OMe$ ,  $R^4 = H$ ) has been extracted from *Monnieria triflora*.<sup>8</sup>

Condensation of 2,2-dimethyl-5,7-chromandiol with anthranilic acid provides a low yield of nordihydroacronycine (33), the major product being the linear tetracyclic isomer (34).<sup>43</sup>

The effect of acronycine (30) on the growth of cultured cells<sup>44</sup> and of nucleoside uptake and incorporation into nucleic acids by the cells<sup>45</sup> has been studied. It was found that, although acronycine does not inhibit nucleic acid synthesis, it does inhibit the accumulation of extracellular uridine and thymidine nucleotides in the precursor pool. Oral administration of dubamine to mice shows no apparent toxic effects.<sup>34</sup>

*Addendum.* A comprehensive review on the occurrence of alkaloids in the Rutaceae family has appeared.<sup>46</sup> The broad spectrum of alkaloid types, including quinolines, furoquinolines, and acridones, may be appreciated from the list of species given in this review.

<sup>42</sup> M. Bert, M. Koch, and M. Plat, *Phytochemistry*, 1974, 13, 301.

<sup>43</sup> F. N. Lahey and R. V. Stick, *Austral. J. Chem.*, 1973, 26, 2311.

<sup>44</sup> P. Tan and N. Auersperg, *Cancer Res.*, 1973, 33, 2320.

<sup>45</sup> B. P. Dunn, P. W. Gout, and C. T. Beer, *Cancer Res.*, 1973, 33, 2310.

<sup>46</sup> I. Mester, *Fitoterapia*, 1973, 44, 123.

### 1 General

The past year has provided a large number of comprehensive reviews, most of which have devoted at least one or more chapters to the isoquinoline class of alkaloids. An authoritative team has reviewed the bisphenethylisoquinoline, homoaporphine, homomorphinan, homoproaporphine, and homoerythrina alkaloids.<sup>1</sup> Highlights from the alkaloid literature published during 1971 have been summarized.<sup>2</sup> A review concerning asymmetric alkaloid synthesis from  $\alpha$ -amino-acids is not readily available.<sup>3</sup> The synthesis and reactions of isoquinolines are a subject of review in one volume of a new review series.<sup>4</sup> Another volume of this series, devoted to alkaloids, contains chapters on the spiro-benzylisoquinoline<sup>5</sup> and benzyl- and homobenzyl-isoquinoline<sup>6</sup> alkaloids in the initial volume. The appearance of this volume begs a comparison with the well established Manske treatise: both offer contributions which are critically and authoritatively written; the major difference appears to be that Manske contains comprehensive accounts, whereas the MTP series has self-contained articles of limited scope also suitable for the reading of the non-specialist. Finally, of timely interest is a review on the application of the enamide photocyclization reaction to the synthesis of crinan, benzo[c]phenanthridine, aporphine, protoberberine, and yohimbine alkaloids.<sup>7</sup>

A number of publications deal with large-scale alkaloid screening studies.<sup>8-10</sup> Other reviews concerned with alkaloids of the Leguminosae,<sup>11,12</sup> chemistry of

<sup>1</sup> T. Kametani and M. Koizumi, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1973, Vol. 14, p. 265.

<sup>2</sup> H. F. Hodson, *Ann. Reports (B)*, 1972, **69**, 487.

<sup>3</sup> S. Yamada, *Kagaku To Seibutso*, 1973, **11**, 70 (*Chem. Abs.*, 1973, **79**, 66 752j).

<sup>4</sup> W. L. F. Armarego, in 'Heterocyclic Compounds', ed. K. Schofield (MTP International Review of Science), Organic Chemistry, Series One, Vol. 4, Butterworths, London, 1973, p. 137.

<sup>5</sup> S. McLean and J. Whelan, in 'Alkaloids', ed. K. Wiesner (MTP International Review of Science), Organic Chemistry, Series One, Vol. 9, Butterworths, London, 1973, p. 161.

<sup>6</sup> T. Kametani and K. Fukumoto, ref. 5, p. 181.

<sup>7</sup> I. Ninomiya, *Heterocycles*, 1974, **2**, 105.

<sup>8</sup> T. G. Hartley, E. A. Dunstone, J. S. Fitzgerald, S. R. Johns, and J. A. Lamberton, *Lloydia*, 1973, **36**, 217.

<sup>9</sup> S. J. Smolenski, H. Silinis, and N. R. Farnsworth, *Lloydia*, 1973, **36**, 359.

<sup>10</sup> S. J. Smolenski, H. Silinis, and N. R. Farnsworth, *Lloydia*, 1974, **37**, 30.

<sup>11</sup> J. A. Mears and T. J. Mabry, in 'Chemotaxonomy of the Leguminosae', ed. J. B. Harborne, D. Boulter, and B. L. Turner, Academic Press, London, 1971, p. 73.

<sup>12</sup> B. L. Turner, ref. 11, p. 549.

the peyote alkaloids,<sup>13</sup> the search for hallucinogenic cacti,<sup>14</sup> and the hallucinogenic and stimulant plants of the Incas<sup>15</sup> are of general interest.

An expert review on the utility of the dehydrogenation reaction for the structural elucidation of alkaloids has appeared.<sup>16</sup> A review on the periodate oxidation reaction deals with a few examples of isoquinoline alkaloid oxidations.<sup>17</sup>

The continuing importance of mass spectrometric investigations in structural elucidation of alkaloids is evidenced by recent publications concerning biochemical applications,<sup>18</sup> the study of stilbene-type methines of benzyloisoquinoline alkaloids,<sup>19</sup> the McLafferty rearrangement as exemplified by alkaloids,<sup>20</sup> and an investigation of the mass spectral Hofmann elimination.<sup>21</sup>

The colour and sensitivity of the potassium hexaiodoplatinate reagent for the detection of alkaloids has been discussed.<sup>22</sup>

The partial ether cleavage of methoxy- and methylenedioxy-substituted isoquinoline alkaloids has been reviewed in a new journal.<sup>23</sup> Additional reviews concerning the use of Reissert compounds in the total synthesis of isoquinoline alkaloids and related compounds,<sup>24</sup> electro-oxidation and isoquinoline alkaloid biosynthesis,<sup>25</sup> and the synthesis of isoquinoline alkaloids by a systematic design<sup>26</sup> have appeared in early issues of the same journal. The chemotaxonomy of alkaloids, together with distribution within plants, biosynthesis, structural classification, and physiological activity, has been treated in a monograph.<sup>27</sup>

## 2 $\beta$ -Phenethylamines

Full accounts on the products obtained from the irradiation of the *N*-chloroacetyl- $\beta$ -phenethylamine derivatives (1; R = H, Me, or CH<sub>2</sub>Ph) have appeared (Scheme 1).<sup>28,29</sup> The structures of (2; R = Me) and of the *NN'*-diacetate of (3; R = H) were established by *X*-ray crystallographic analysis.<sup>28</sup> The effect of solvents on the nature and yield of the photoproducts of (1; R = H) was studied: in aqueous solution at both acidic and alkaline, as well as neutral, pH, compound

<sup>13</sup> G. J. Kapadia and M. B. E. Fayez, *Lloydia*, 1973, **36**, 9.

<sup>14</sup> J. G. Bruhn, *Planta Med.*, 1973, **24**, 315.

<sup>15</sup> J. G. R. Elferink, *Planta Med.*, 1974, **25**, 289.

<sup>16</sup> Z. Valenta, 'Elucidation of Organic Structures by Physical and Chemical Methods', ed. K. W. Bentley and G. W. Kirby, Vol. IV, Part II, Wiley, New York, 1973, p. 1.

<sup>17</sup> A. J. Fatiadi, *Synthesis*, 1974, 229.

<sup>18</sup> S. D. Sastry, in 'Biochemical Application of Mass Spectrometry', ed. G. R. Waller, Wiley-Interscience, New York, 1972, p. 655.

<sup>19</sup> L. Dolejs and J. Slavik, *Org. Mass Spectrometry*, 1973, **7**, 775.

<sup>20</sup> D. G. I. Kingston, J. T. Bursey, and M. M. Bursey, *Chem. Rev.*, 1974, **74**, 215.

<sup>21</sup> P. J. Smith, *Canad. J. Chem.*, 1974, **52**, 365.

<sup>22</sup> F. Sita, V. Chmelova, and K. Chmel, *Cesk. Farm.*, 1973, **22**, 234.

<sup>23</sup> S. Teitel and A. Brossi, *Heterocycles*, 1973, **1**, 73.

<sup>24</sup> F. D. Popp, *Heterocycles*, 1973, **1**, 165.

<sup>25</sup> J. M. Bobbit, *Heterocycles*, 1973, **1**, 181.

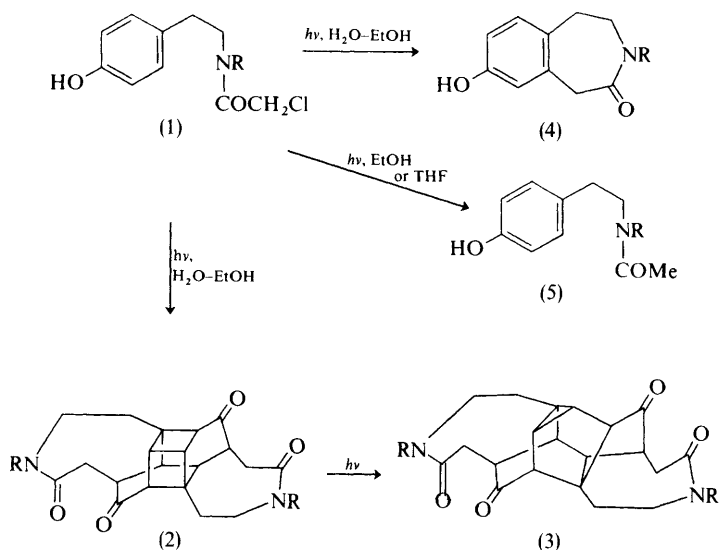
<sup>26</sup> T. Kametani and K. Fukumoto, *Heterocycles*, 1973, **1**, 129.

<sup>27</sup> D. W. Hughes and K. Genest, in 'Phytochemistry', ed. L. P. Miller, Van Nostrand, New York, 1973, Vol. 2, p. 118.

<sup>28</sup> T. Iwakuma, H. Nakai, O. Yonemitsu, and B. Witkop, *J. Amer. Chem. Soc.*, 1974, **96**, 2564.

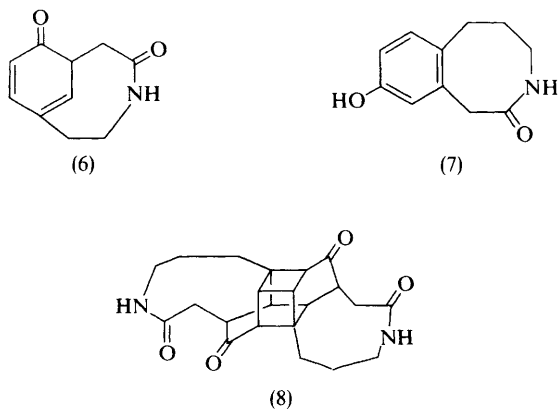
<sup>29</sup> T. Iwakuma, K. Hirao, and O. Yonemitsu, *J. Amer. Chem. Soc.*, 1974, **96**, 2570.



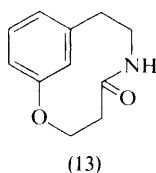
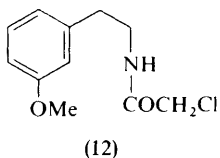
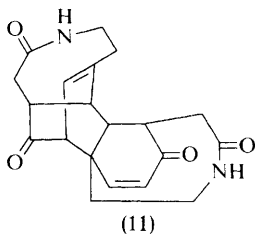
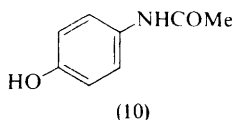
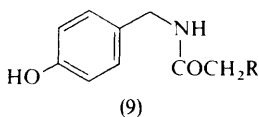


Scheme 1

(4; R = H) and the dimers (2; R = H) and (3; R = H) were formed; on the other hand, in hydrogen-donating solvents, especially in THF, the reduction product,  $N$ -acetyl- $\beta$ -phenethylamine (5; R = H), was the sole product isolated. A plausible mechanism for the formation of (2; R = H) and (3; R = H), involving the intermediacy of the cyclohexa-2,4-dienone (6), which then undergoes a series of  $[4_\pi + 2_\pi]$ ,  $[2_\pi + 2_\pi]$ , and  $[\sigma 2_a + \sigma 2_a]$  cycloadditions to give the observed products, was proposed.<sup>28</sup> The homologous  $N$ -chloroacetyl- $p$ -hydroxyphenylpropylamine gave the expected benzazocinone (7) and the cage dimer (8). In contrast, the



photolysis of *N*-chloroacetyl-*p*-hydroxybenzylamine (9; R = Cl) gave no dimer; instead a single product, *N*-acetyl-*p*-hydroxybenzylamine (9; R = H) was isolated. In alkaline solution, *p*-hydroxyacetanilide (10) and (9; R = H) were obtained. A mechanistic rationale for the formation of (10) was formulated.<sup>28</sup> The dimerization of (6) to (11), its further photochemical conversion into (2; R = H), and the novel acid-catalysed reversion (2; R = H)  $\rightarrow$  (11) were studied in detail.<sup>29</sup> The photolysis of *N*-chloroacetyl-*m*-methoxyphenethylamine (12) in aqueous solution has been previously shown to give mainly benzazepine derivatives (*cf.* Vol. 2 of these Reports). It has now been found that irradiation in organic solvents favours the formation of the ten-membered-ring lactam (13).<sup>30</sup> The mechanism of this reaction was investigated in detail.

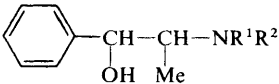


The  $^1L_b$  Cotton effect of ephedrine, pseudoephedrine, and some homologous and cyclic derivatives has been investigated (Table 1).<sup>31</sup> In the model compounds, norephedrine and norpseudoephedrine, the amplitude of the Cotton effect decreases as the amount of N-protonation increases. Using Sneath's sector rules for the benzene chromophore, a conformational interpretation was given; the *erythro*- and *cis*-diastereomers showed a preferred conformation in which the oxygen atom was very close to the plane of the phenyl groups whereas the *threo*- and *trans*-diastereomers exhibited a preferred arrangement in which the oxygen took up a position in a plane perpendicular to that of the phenyl group.

<sup>30</sup> Y. Okuno and O. Yonemitsu, *Tetrahedron Letters*, 1974, 1169.

<sup>31</sup> B. Testa, *Pharm. Acta Helv.*, 1973, **48**, 389.

**Table 1**

		
R <sup>1</sup>	R <sup>2</sup>	
H	H	(1 <i>R</i> ,2 <i>S</i> )-(–)-Norephedrine (1 <i>S</i> ,2 <i>S</i> )-(+)-Norpseudoephedrine
H	Me	(1 <i>R</i> ,2 <i>S</i> )-(–)-Ephedrine (1 <i>S</i> ,2 <i>S</i> )-(+)-Pseudoephedrine
Me	Me	(1 <i>R</i> ,2 <i>S</i> )-(–)- <i>N</i> -Methylephedrine (1 <i>S</i> ,2 <i>S</i> )-(+)- <i>N</i> -Methylpseudoephedrine
H	Et	(1 <i>R</i> ,2 <i>S</i> )-(–)- <i>N</i> -Ethylnorephedrine (1 <i>S</i> ,2 <i>S</i> )-(+)- <i>N</i> -Ethylnorpseudoephedrine
Et	Et	(1 <i>S</i> ,2 <i>S</i> )-(+)- <i>N</i> -Diethylnorpseudoephedrine (1 <i>R</i> ,2 <i>S</i> )-(–)- <i>N</i> -Diethylnorephedrine

The 2,4,5-trimethylpyrrole-3-carboxylic acid ester of ephedrine has been synthesized by a mixed-anhydride procedure mild enough to leave intact the acid-labile pyrrolecarboxylic acid as well as the alkaloid moiety.<sup>32</sup>

Results of isolation and structural elucidation work on  $\beta$ -phenethylamine alkaloids are recorded in Table 2. The investigation of *Aegle marmelos*, a medicinal plant of India, revealed the presence of the amide alkaloid tembamide.<sup>33</sup>

**Table 2** Isolation of  $\beta$ -phenethylamine alkaloids

Species	Alkaloid	Ref.
<i>Aegle marmelos</i>	Tembamide ( <i>N</i> -Benzoyl-4-methoxy- $\beta$ -hydroxy-phenethylamide)	33
<i>Alhagi pseudalhagi</i>	3,4-Dihydroxy- $\beta$ -phenethylammonium hydroxide	36
	Hordeanine	36
	<i>N</i> -Methyl- $\beta$ -phenethylamine	36
	<i>N</i> -Methylmescaline	36
	$\beta$ -Phenethylamine	36
<i>Ariocarpus agavoides</i>	<i>NN</i> -Dimethyl-4-hydroxy-3-methoxyphenethylamine	34
	Hordeanine	34
	<i>N</i> -Methyl-3,4-dimethoxyphenethylamine	34
<i>Catha edulis</i>	D-Norpseudoephedrine	37
<i>Coryphantha calipensis</i>	(–)- <i>NN</i> -Dimethyl-3,4-dimethoxy- $\beta$ -methoxy-phenethylamine [(–)- $\beta$ - <i>O</i> -methylmacromerine]	35
	(–)- <i>N</i> -Methyl-3,4-dimethoxy- $\beta$ -methoxy-phenethylamine	35
	<i>N</i> -Methyl-3,4-dimethoxyphenethylamine	35
	(–)- $\beta$ - <i>O</i> -Methylnormacromerine	35
	(–)-Normacromerine	35

<sup>32</sup> J. A. Waters, C. R. Creveling, and B. Witkop, *J. Medicin. Chem.*, 1974, 17, 488.

<sup>33</sup> A. Shueb, R. S. Kapil, and S. P. Popli, *Phytochemistry*, 1973, 12, 2071.

<sup>34</sup> J. G. Bruhn and C. Bruhn, *Econ. Bot.*, 1973, 27, 241.

<sup>35</sup> J. G. Bruhn and S. Agurell, *J. Pharm. Sci.*, 1974, 63, 574.

<sup>36</sup> S. Ghosal and R. S. Srivastava, *J. Pharm. Sci.*, 1973, 62, 1555.

<sup>37</sup> G. Ruecker, H. Kroeger, M. Schikarshi, and S. Qedan, *Planta Med.*, 1973, 24, 61.

Table 2—continued

Species	Alkaloid	Ref.
<i>Desmodium triflorum</i>	3,4-Dihydroxyphenethyltrimethylammonium hydroxide	38
	Hordeanine	38
	$\beta$ -Phenethylamine	38
	Tyramine	38
<i>Dolichothele sphaerica</i>	$\beta$ -O-Ethylsynephrine,HCl (artefact)	39
	N-Methylphenethylamine,HCl	39
	$\beta$ -O-Methylsynephrine,HCl	39
	N-Methyltyramine,HCl	39
	Synephrine,HCl	39
<i>D. surculosa</i>	Hordeanine,HCl	40
	N-Methylphenethylamine,HCl	40
	N-Methyltyramine,HCl	40
	Synephrine,HCl	40
<i>Mammillaria elongata</i>	Hordeanine,HCl	41
	N-Methyltyramine	41
	$\beta$ -O-Methylsynephrine	41
	Synephrine,HCl	41
	Tyramine	41
<i>M. heyderi</i>	N-Methyl-3,4-dimethoxyphenethylamine	34
<i>Obregonia denegrii</i>	Hordeanine	34
	N-Methyltyramine	34
	Tyramine	34
<i>Pelecyphora aselliformis</i>	Anhalidine	34
	NN-Dimethyl-3-hydroxy-4,5-dimethoxyphenethylamine	34
	Hordeanine	34
	Pellotine	34
<i>P. pseudopectinata</i>	Hordeanine	34
<i>Solisia pectinata</i>	Hordeanine	34
	N-Methyltyramine	34
<i>Trichocereus pachanoi</i>	Mescaline,HCl	42
	3-Methoxytyramine,HCl	42
<i>Turbinicarpus</i>	Hordeanine	34
<i>pseudomacrochele</i>		
<i>Vicia narbonensis</i>	L-Dopa	43
<i>V. faba minor</i>	L-Dopa	43

An alkaloidal and ethnobotanical survey of Mexican peyote cacti and related species which for various reasons were considered or suggested to be psychoactive covered the following species: *Ariocarpus agavoides*, *Mammillaria heyderi*, *Obregonia denegrii*, *Pelecyphora aselliformis*, *P. pseudopectinata*, *Solisia pectinata*, and *Turbinicarpus pseudomacrochele*.<sup>34</sup> All of these except *Mammillaria heyderi* contain hordeanine. These 'peyote' cacti appear not to have any aboriginal use as hallucinogens or medicinal plants. Furthermore, there is no justification in

<sup>38</sup> S. Ghosal, R. S. Srivastava, S. K. Bhattacharya, and P. K. Debnath, *Planta Med.*, 1973, **23**, 321.

<sup>39</sup> J. J. Dingerdissen and J. L. McLaughlin, *J. Pharm. Sci.*, 1973, **62**, 1663.

<sup>40</sup> J. J. Dingerdissen and J. L. McLaughlin, *Lloydia*, 1973, **36**, 419.

<sup>41</sup> L. G. West and J. L. McLaughlin, *Lloydia*, 1973, **36**, 346.

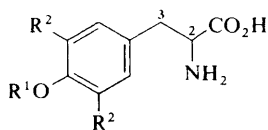
<sup>42</sup> D. M. Crosby and J. L. McLaughlin, *Lloydia*, 1973, **36**, 416.

<sup>43</sup> R. Longo, A. Castellani, P. Sberze, and M. Tibolla, *Phytochemistry*, 1974, **13**, 167.

calling these cacti 'peyote' on the basis of alkaloid content. A possible exception is *Pelecypora aselliformis*, which closely resembles *Lophophora williamsii*. Two new alkaloids, *N*-methyl-3,4-dimethoxy- $\beta$ -methoxyphenethylamine and *NN*-dimethyl-3,4-dimethoxy- $\beta$ -methoxyphenethylamine, have been isolated from *Coryphantha calipensis*.<sup>35</sup> From the roots of *Desmodium triflorum*, four  $\beta$ -phenethylamines were obtained together with other alkaloids.<sup>38</sup> The total alkaloid extract of *D. triflorum* produced a number of significant pharmacological actions, e.g. antispasmodic, sympathomimetic, CNS-stimulant, and curarimimetic.<sup>38</sup> Hordenine has been found for the first time in a *Dolichothele* species.<sup>40</sup> From chromatographic screening of *D. longimamma*, *D. uberiformis*, *D. melaleuca*, *D. baumii*, and *D. surculosa*, it was concluded that the genus *Dolichothele* is rich in alkaloids.<sup>40</sup> *D. sphaerica* yielded four  $\beta$ -phenethylamine alkaloids.<sup>39</sup> The occurrence of a 3,4,5-trioxygenated  $\beta$ -phenethylamine (*N*-methylephedrine) has been demonstrated outside the family Cactaceae.<sup>36</sup> No differences were found between the chemical compositions of the fresh and dried plants of *Catha edulis* from three different regions and all were shown to contain D-norpseudoephedrine.<sup>37</sup> Five recognized sympathomimetic alkaloids were found in *Mammillaria elongata* in such small quantities that any potential the plant might have for becoming a source for drug abuse can be discounted.<sup>41</sup> The cactus *Trichocereus pachanoi* yielded mescaline hydrochloride and 3-methoxytyramine hydrochloride.<sup>42</sup> A survey of L-dopa distribution in *Vicia narbonensis* and *V. faba minor* has been carried out.<sup>43</sup>

A report concerning a synthesis of mescaline sulphate is not readily available.<sup>44</sup> The synthesis of some substituted  $\beta$ -phenethylamines of the general type 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>NREt [R = H, 4-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>CO, 4-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>CH<sub>2</sub>CO, 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CO, 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH=CHCO, 4-MeOC<sub>6</sub>H<sub>4</sub>CH(Ph)CH<sub>2</sub>CO, 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH(Ph)CH<sub>2</sub>CO] and their lithium aluminium hydride reduction products has been described.<sup>45</sup>

As evidenced above, the interest in peyote has shown no abatement over the past year. The 56 identified constituents of this resourceful cactus have been tabulated.<sup>13</sup> The amino-acid analogue of mescaline, 3,4,5-trimethoxyphenethylalanine (14; R<sup>1</sup> = Me, R<sup>2</sup> = OMe) has been prepared in three steps and in good yield from hydantoin and 3,4,5-trimethoxybenzaldehyde.<sup>46</sup> G.c.-m.s. examination



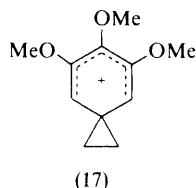
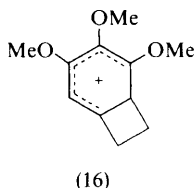
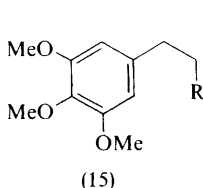
(14)

<sup>44</sup> M. Oho, M. Shimamine, and K. Takahashi, *Eisei Shikenjo Kokoku*, 1973, **91**, 33 (*Chem. Abs.*, 1974, **80**, 108 718f).

<sup>45</sup> L. Sh. Pirdzhanov, A. A. Agekyan, and E. A. Markaryan, *Armenian. khim. Zhur.*, 1973, **26**, 751 (*Chem. Abs.*, 1974, **80**, 83 355v).

<sup>46</sup> M. L. Sethi, G. S. Rao, and G. J. Kapadia, *J. Pharm. Sci.*, 1973, **62**, 1802.

of the amino-acid fraction from peyote gave no evidence for the presence of (14;  $R^1 = \text{Me}$ ,  $R^2 = \text{OMe}$ ). The oxidation of tyrosine (14;  $R^1 = R^2 = \text{H}$ ), a precursor of morphine, by the enzyme polyphenolase from *Papaver somniferum* may be of some interest.<sup>47</sup> A series of  $\alpha$ -methyldopamine derivatives have been synthesized and pharmacologically evaluated.<sup>48</sup> Stable carbonium ions (16) and/or (17) from  $\beta$ -arylalkyl derivatives (15;  $R = \text{OH}$ ) related to mescaline (15;  $R = \text{NH}_2$ ) were produced in  $\text{SbF}_5\cdot\text{SO}_2$ . These may be reasonable intermediates



in the *in vivo* reactions of mescaline derivatives.<sup>49</sup> Effective *NN*-dimethylation of  $\beta$ -phenethylamine derivatives may be achieved by using a mixture of formaldehyde and formic acid in DMF solution.<sup>50</sup>

6-Hydroxydopamine has been shown to prolong the duration of hexobarbital sleep in rats.<sup>51</sup> A molecular orbital-biological activity study of 2,4,5-trihydroxy- $\beta$ -phenethylamines has appeared.<sup>52</sup> The role of L-dopa and its metabolites in the treatment of Parkinson's disease has been discussed, with emphasis on the formation of the alkaloid metabolites salsolinol and tetrahydropapaveroline.<sup>53</sup>

An ephedrine, HCl assay using a magnesium oxide extraction method has been developed.<sup>54</sup> The determination of the purity of L-dopa and its products by g.l.c. on a methyl silicone column has given good results.<sup>55</sup>

### 3 Simple Isoquinoline Alkaloids

The chemistry of 4-hydroxy- and 4-oxo-1,2,3,4-tetrahydroisoquinolines has been reviewed.<sup>56</sup> A short chapter on the synthesis of isoquinoline derivatives has appeared.<sup>57</sup>

<sup>47</sup> M. F. Roberts, *J. Pharm. Pharmacol.*, 1973, **25**, Suppl., 115P.

<sup>48</sup> R. J. Borgman, M. R. Baylor, J. J. McPhillips, and R. E. Stitzel, *J. Medicin. Chem.*, 1974, **17**, 427.

<sup>49</sup> J. A. Manner, J. A. Cook, jun, and B. G. Ramsey, *J. Org. Chem.*, 1974, **39**, 1199.

<sup>50</sup> G. D. Cherayil, *J. Pharm. Sci.*, 1973, **62**, 2054.

<sup>51</sup> R. Brus, Z. S. Herman, A. Sokola, and Z. Jamrozik, *Experientia*, 1974, **30**, 66.

<sup>52</sup> R. Katz and A. E. Jacobson, *Mol. Pharmacol.*, 1973, **9**, 495.

<sup>53</sup> S. B. Carter and M. Sandler, *Adv. Neurol.*, 1973, **3**, 143.

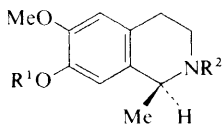
<sup>54</sup> T. Bican-Fister, B. Pavelic, and J. Merkas, *Acta Pharm. Jugoslav.*, 1973, **23**, 17.

<sup>55</sup> J. R. Watson, *J. Pharm. Sci.*, 1974, **63**, 96.

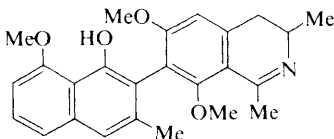
<sup>56</sup> J. M. Bobbitt, *Adv. Heterocyclic Chem.*, 1973, **15**, 99.

<sup>57</sup> R. C. Brown and S. F. Dyke, in 'Aromatic and Heteroaromatic Chemistry', ed. C. W. Bird and G. W. H. Cheeseman (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 1, p. 98.

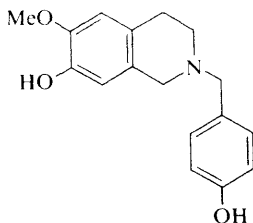
Salsolidine (18;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) has been isolated from *Alhagi pseudalhagi*.<sup>36</sup> A series of aracyl and aralkyl derivatives of salsolidine has been prepared.<sup>44</sup> The thermodynamics of the extraction of salsolidine, HCl from aqueous solutions in the form of ion associates with dyes have been reported.<sup>58</sup> The electrophoretic spectra of salsoline, HCl, as well as other diverse alkaloids, have been recorded and suitable conditions for their separation have been developed.<sup>59</sup> *Ancistrocladus heyneanus* yielded ancistrocladidine (19)<sup>60</sup> (cf. Vol. 2 of these Reports). (+)-1-Methylcorypalline (18;  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ) has been isolated for the first time as a natural product from *Corydalis ambigua*.<sup>61</sup> Corgoine (20) from *C. gortschakovii* has been synthesized by heating a mixture of 1,2,3,4-tetrahydro-6-methoxy-7-isoquinolinol and 4-hydroxybenzyl alcohol.<sup>62</sup> It was also obtained by the Pictet-Spengler cyclization of (21) with formaldehyde and subsequent debenzoylation by hydrogenation. 2-Methyl-6,7-dimethoxy-1(2H)-isoquinoline was found, together with benzyloisoquinoline, proaporphine, aporphine, berberine, and papaverrubine alkaloids, in *Papaver urbanianum*.<sup>63</sup>



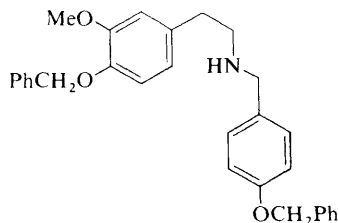
(18)



(19)



(20)



(21)

An alternative synthesis to the Pomeranz-Fritsch method has been developed for 7- and 5,7-substituted isoquinolines.<sup>64</sup> As an extension to the photolysis of

<sup>58</sup> G. L. Starobinets, D. E. Satarova, and S. F. Petrashkevich, *Doklady Akad. Nauk beloruss. S.S.R.*, 1973, **17**, 1021 (*Chem. Abs.*, 1974, **80**, 48 208c).

<sup>59</sup> L. V. Pesakhovich and S. P. Elovikova, *Fiz.-Khim. Probl. Sovrem. Biol. Med. Mater. Konf.*, ed. E. A. Zhukov, 1970, p. 175 (*Chem. Abs.*, 1974, **80**, 6989c).

<sup>60</sup> T. R. Govindachari, P. C. Parthasarathy, and H. K. Desai, *Indian J. Chem.*, 1973, **11**, 1190.

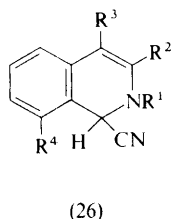
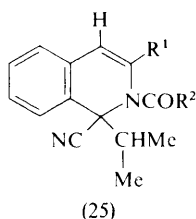
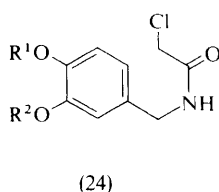
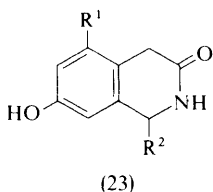
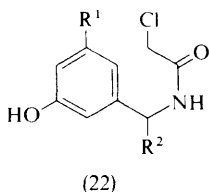
<sup>61</sup> S. Naruto and H. Kaneko, *Phytochemistry*, 1973, **12**, 3008.

<sup>62</sup> T. Kametani, K. Takahashi, C. Van Loc, and M. Hirata, *Heterocycles*, 1973, **1**, 247.

<sup>63</sup> V. Preininger and V. Tosnarova, *Planta Med.*, 1973, **23**, 233.

<sup>64</sup> M. Ikeda, K.-I. Hirato, Y. Okuno, and O. Yonemitsu, *Tetrahedron Letters*, 1974, 1181.

*N*-chloroacetyl- $\beta$ -phenethylamines, *N*-chloroacetylbenzylamines (22;  $R^1 = OH$ ,  $H$ ,  $R^2 = H$ ,  $Me$ , or  $CH_2Ph$ ) have been irradiated to give 3-oxo-1,2,3,4-tetrahydroisoquinolines (23;  $R^1 = OH$ ,  $H$ ;  $R^2 = H$ ,  $Me$ , or  $CH_2Ph$ ). Dimers were not detected in this reaction. However, *N*-chloroacetylbenzylamines (24;  $R^1 = Me$ ,  $R^2 = H$ ;  $R^1 = R^2 = Me$ ;  $R^1 + R^2 = CH_2$ ) without free hydroxy-groups provided only *N*-acetyl or *N*-hydroxyacetyl derivatives and not the cyclized products. The stereochemistry of 1-alkyl-2-acyl-1,2-dihydroisoquinolidonitriles of type (25) was studied by n.m.r.<sup>65</sup> The chemical shift differences of the diastereotopic groups in (25) revealed that the amide group configuration is the same in all cases and that the 1-alkyl substituent adopts a quasi-axial configuration. A similar study was carried out with Reissert compounds of general structure (26).<sup>66</sup> Long-range coupling observed in the n.m.r. of (26) suggested a quasi-axial configuration for the substituent at the saturated carbon centre. Hydrogenation of isoquinolines normally occurs preferentially in the nitrogen-containing ring to give 1,2,3,4-tetrahydroisoquinolines. It has now been reported that hydrogenation in a strongly acidic medium in the presence of platinum oxide leads to 5,6,7,8-tetrahydroisoquinoline derivatives in excellent yield.<sup>67</sup>



A stepwise aromatization of 1,2,3,4-tetrahydroisoquinolines (27) to (28) and (29) may be effected using Fremy's salt.<sup>68</sup> For example, tetrahydropapaverine [27;  $R^1 = OMe$ ,  $R^2 = 3,4-(OMe)_2C_6H_3CH_2$ ] gave 3,4-dihydroketopapaverine [28;  $R^1 = OMe$ ,  $R^2 = 3,4-(OMe)_2C_6H_3CO$ ]. The equilibrium constants for pseudobase formation of various *N*-substituted isoquinolinium cations have

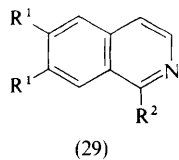
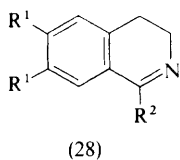
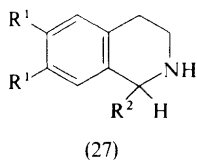
<sup>65</sup> H. W. Gibson, *J. Org. Chem.*, 1973, **38**, 2851.

<sup>66</sup> B. C. Uff, J. R. Kershaw, and S. R. Chhabra, *J. C.S. Perkin I*, 1974, 1146.

<sup>67</sup> F. W. Vierhapper and E. L. Eliel, *J. Amer. Chem. Soc.*, 1974, **96**, 2256.

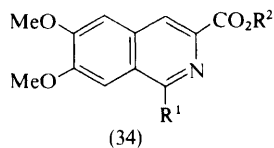
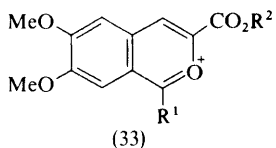
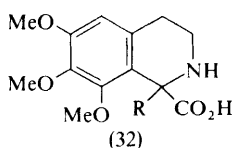
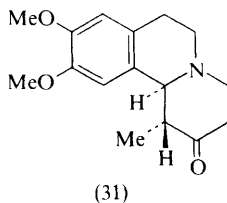
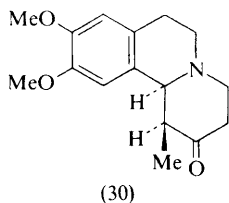
<sup>68</sup> P. A. Wehrli and B. Schaer, *Synthesis*, 1974, 288.





been obtained by n.m.r. and u.v. spectral analysis.<sup>69</sup> 1-Alkyl- or 1-arylamino-6,7-dimethoxy-3,4-dihydroisoquinolines have been prepared by Bischler-Napieralski reaction of thioamide derivatives.<sup>70,71</sup> A series of 4-amino-6,7-dimethoxyisoquinolines has been synthesized in order to evaluate their hypotensive properties.<sup>72</sup> The acylation of 2,3-diaminoisocarbostyrl has been studied.<sup>73</sup>

Treatment of 3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride with an excess of ethyl vinyl ketone gave the epimers (30) and (31) in variable proportions, depending on the pH of the reaction medium.<sup>74</sup> *O*-Methylpeyoxylic acid (32; R = H) and *O*-methylpeyoruvic acid (32; R = Me) have been prepared and identified as constituents of the amine fraction of peyote.<sup>75</sup> Acylation of 3,4-dimethoxyphenylpyruvic acid with anhydrides in the presence of perchloric acid yielded 2-benzopyrylium perchlorates (33), which were transformed into the corresponding isoquinolines (34) with ammonium acetate in glacial acetic acid.<sup>76</sup>



<sup>69</sup> J. W. Bunting and W. G. Meathiel, *Canad. J. Chem.*, 1974, **52**, 962.

<sup>70</sup> I. M. Roushdi, A. Omar, M. E. Mohsen, and A. A. B. Hazzaa, *Egypt. J. Pharm. Sci.*, 1973, **13**, 101 (*Chem. Abs.*, 1974, **80**, 59 839k); *ibid.*, p. 109 (*Chem. Abs.*, 1974, **80**, 59 838j).

<sup>71</sup> A. A. B. Hazzaa, A. Omar, M. E. Mohsen, and M. E. Ragab, *Pharmazie*, 1973, **28**, 364.

<sup>72</sup> G. C. Wright and R. P. Halliday, *J. Pharm. Sci.*, 1974, **63**, 149.

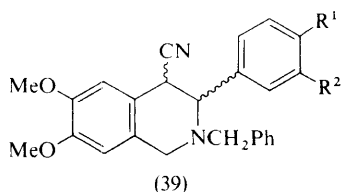
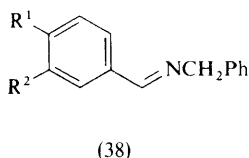
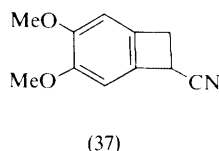
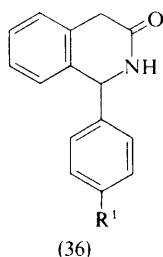
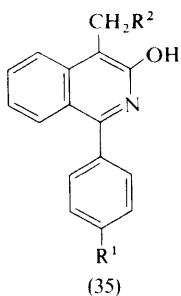
<sup>73</sup> S. Kimoto, M. Okamoto, T. Kawabata, and S. Ohta, *Yakugaku Zasshi*, 1973, **93**, 1581 (*Chem. Abs.*, 1974, **80**, 59 836g).

<sup>74</sup> A. Buzas, F. Cossais, J. P. Jacquet, L. Novak, and C. S. Szantay, *J. Heterocyclic Chem.*, 1974, **11**, 175.

<sup>75</sup> G. J. Kapadia, G. S. Rao, M. H. Hussain, and B. K. Chowdhury, *J. Heterocyclic Chem.*, 1973, **10**, 135.

<sup>76</sup> G. N. Dorofeenko, S. V. Krivun, and V. G. Korobkova, *Khim. geterotsikl. Soedinenii*, 1973, 1458 (*Chem. Abs.*, 1974, **80**, 70 649u).

3-Isoquinolinols of the type (35;  $R^1 = H, Me, Cl$ , or  $NHAc$ ,  $R^2 = aryl$  or  $alkyl-aryl$ ) have been prepared by treating 1,4-dihydro-1-aryl-3(2*H*)-isoquinolinones (36) with the appropriate aldehydes in the presence of sodium hydride.<sup>77</sup> Thermolysis of the benzocyclobutene (37) in the presence of Schiff bases (38;  $R^1 = OMe$ ,  $R^2 = H$ ) and (38;  $R^1 + R^2 = OCH_2O$ ) provides in modest yields the 4-cyano-3-aryltetrahydroisoquinoline derivatives (39;  $R^1 = OMe$ ,  $R^2 = H$ ) and (39;  $R^1 + R^2 = OCH_2O$ ) respectively, together with the dimer of (37).<sup>78</sup> This reaction may be formulated as a regiospecific intermolecular  $[4 + 2]\pi$  cycloaddition reaction. An attempt to effect this type of reaction between (37)



and aryl oximes failed. A new attempt to prepare the known 3,4'-di-isoquinoline (40) was thwarted at an early stage of the synthesis.<sup>79</sup> The reaction of diketene with isoquinoline has been shown to give (41), (41;  $\Delta^{1,9}$ ), and (42).<sup>80</sup> Spiro-compounds of the type (43) have been obtained from the reaction of 1,3-dioxo-tetrahydroisoquinoline derivatives with 1,5-diarylpentadienones.<sup>81</sup> The Beckmann rearrangement of 2-indanone oxime with  $PCl_5$  leads to a single product (44) in excellent yield.<sup>82</sup> The Friedel-Crafts reaction of 2-methyl-1(2*H*)-isoquinolinone

<sup>77</sup> G. Deak and L. Hazai, *Acta Chim. Acad. Sci. Hung.*, 1973, **79**, 113 (*Chem. Abs.*, 1974, **80**, 27 075s).

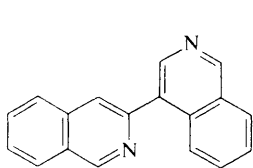
<sup>78</sup> T. Kametani, T. Takahashi, K. Ogasawara, and K. Fukumoto, *Tetrahedron*, 1974, **30**, 1047.

<sup>79</sup> J. Knabe and F. Renz, *Arch. Pharm.*, 1974, **307**, 372.

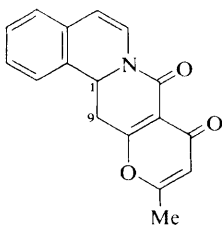
<sup>80</sup> A. A. Akhrem, A. M. Moiseenkov, and V. A. Krivoruchko, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 1800 (*Chem. Abs.*, 1974, **80**, 14 860u).

<sup>81</sup> H. H. Otto, *Arch. Pharm.*, 1974, **307**, 58.

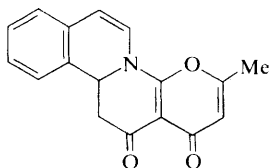
<sup>82</sup> R. E. Lyle and D. A. Walsh, *Org. Prep. Proced. Internat.*, 1973, **5**, 299.



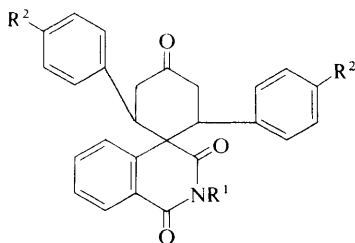
(40)



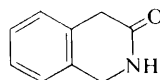
(41)



(42)



(43)



(44)

with different aliphatic acids produced mixtures of 4-, 5-, and 7-acylated derivatives.<sup>83</sup>

In continuation of previous work (see Vol. 4 of these Reports), the reaction of the carbinol amines cotarnine and hydrastinine with a variety of  $\alpha$ -diazocarbonyl derivatives has been shown to give a series of stable compounds (45;  $R^1 = H$  or OMe,  $R^2 = Me, OMe, OEt, Ph, CH_2Ph$ , or  $p\text{-MeOC}_6\text{H}_4$ )<sup>84</sup> together with minor amounts of the *E*- and *Z*-isomers of (46).<sup>85</sup> A number of new examples (47;  $R^1 = H$  or OMe,  $R^2 = CPh, 2\text{-thienyl}$ , or  $2\text{-furfuryl}$ ) of the general acid-catalysed rearrangement (47)  $\rightarrow$  (48) have been reported.<sup>86,87</sup> The reaction of 4-cyanoisoquinoline with Grignard reagents gives 1-substituted-4-cyano-1,2-dihydroisoquinoline derivatives.<sup>88</sup> Irradiation of 1-cyanoisoquinoline in benzene in the presence of propionic acid leads to a mixture of 1-ethylisoquinoline, 1-phenylisoquinoline, 1,4-diethylisoquinoline, and 1-cyano-4-ethylisoquinoline.<sup>89</sup>

<sup>83</sup> T. Tomisawa and R. Fujita, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2585.

<sup>84</sup> B. Goeber, G. Bauer, S. Pfeifer, G. Dube, G. Engelhardt, and H. Jancke, *Pharmazie*, 1973, **28**, 221.

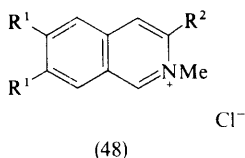
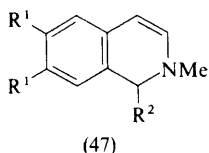
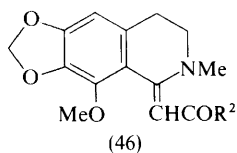
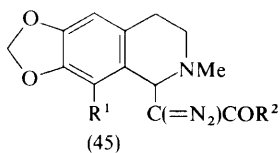
<sup>85</sup> B. Goeber, G. Bauer, S. Pfeifer, G. Dube, G. Engelhardt, and H. Jancke, *Pharmazie*, 1973, **28**, 310.

<sup>86</sup> J. Knabe and A. Frie, *Arch. Pharm.*, 1973, **306**, 592.

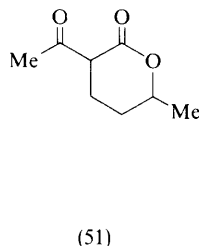
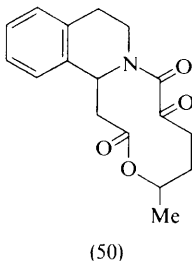
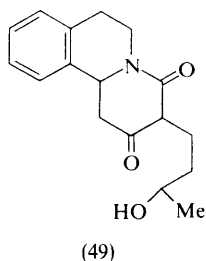
<sup>87</sup> J. Knabe and A. Frie, *Arch. Pharm.*, 1973, **306**, 648.

<sup>88</sup> K. Matsumori, A. Ide, and H. Watanabe, *Nippon Nogei Kagaku Kaishi*, 1973, **47**, 23 (*Chem. Abs.*, 1973, **79**, 5234v).

<sup>89</sup> A. Ide, H. Watanabe, and H. Watanabe, *Nippon Nogei Kagaku Kaishi*, 1973, **47**, 29 (*Chem. Abs.*, 1973, **79**, 5233u).



New reactions of isoquinoline derivatives include the following: 3,4-dihydroisoquinoline *N*-oxide with 2-acetylcycloalkane-1,3-diones,<sup>90,91</sup> Reissert compounds with stilbene and tolan derivatives,<sup>92</sup> isoquinoline with pyrrole derivatives<sup>93</sup> and with 2-methylfuran<sup>94</sup> (both in the presence of benzyl chloride), and the chromium trioxide oxidation of the benzo[*a*]quinolizidine (49) to give (50).<sup>95</sup> Compound (49) was prepared by the condensation of 3,4-dihydroisoquinoline with the  $\delta$ -lactone (51).<sup>96</sup> Further examples of a classical benzo[*a*]-



quinolizidine synthesis are available.<sup>97</sup> The preparation of a series of *N*-substituted 1-methyl-6,7-dimethoxytetrahydroisoquinolines has been

<sup>90</sup> A. A. Akhrem, A. M. Moiseenkov, V. A. Krivoruchko, and A. I. Poselenov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 710 (*Chem. Abs.*, 1973, **79**, 5240u).

<sup>91</sup> A. A. Akhrem, A. M. Moiseenkov, A. I. Poselenov, and V. A. Krivoruchko, *Doklady Akad. Nauk S.S.S.R.*, 1973, 210, 841 (*Chem. Abs.*, 1973, **79**, 66 140h).

<sup>92</sup> W. E. McEwen, P. E. Stott, and C. M. Zepp, *J. Amer. Chem. Soc.*, 1973, **95**, 8452.

<sup>93</sup> A. A. Deikalo, A. I. Zaitseva, and A. K. Sheinkman, *Metody Poluch. Khim. Reaktivov Prep.*, 1971, 26 (*Chem. Abs.*, 1973, **79**, 66 142k).

<sup>94</sup> A. A. Deikalo and A. K. Sheinkman, *Metody Poluch. Khim. Reaktivov Prep.*, 1971, 24 (*Chem. Abs.* 1973, **79**, 78 570m).

<sup>95</sup> A. A. Akhrem, A. M. Moiseenkov, and V. S. Malishevskii, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 1611 (*Chem. Abs.*, 1973, **79**, 105 055f).

<sup>96</sup> A. A. Akhrem, A. M. Moiseenkov, V. S. Malishevskii, and Yu. G. Chernov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 1308 (*Chem. Abs.*, 1973, **79**, 92 053b).

<sup>97</sup> A. Buzas, F. Cossais, J. P. Jacquet, and A. Merour, *Bull. Soc. chim. France*, 1973, 3476.

reported.<sup>98</sup> The following preparations and procedures may be of some interest: 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentane,<sup>99</sup> 4-hydroxy-1,2,3,4-tetrahydroisoquinolines,<sup>100,101</sup> 3-fluoro-1-fluoroalkyl-4-phenylisoquinoline,<sup>102</sup> and the reduction of isoquinoline with sodium hydride to give, after acylation, 1,2-dihydroisoquinoline derivatives.<sup>103</sup>

#### 4 Benzyloisoquinoline Alkaloids

Alkaloid isolation and structural elucidation studies are summarized in Table 3. 1,2,3,4-tetrahydroisoquinolines,<sup>100,101</sup> 3-fluoro-1-fluoroalkyl-4-phenylisoquinoline,

**Table 3** Isolation of benzyloisoquinoline alkaloids

Species	Alkaloid (Structure)	Ref.
<i>Argemone albiflora</i>	AA1 (52; R <sup>1</sup> , R <sup>2</sup> = H, Me)	104
<i>A. turnerae</i>	(+)-Armepavine	105
<i>Cocculus laurifolius</i>	Coclaurine	106
<i>Erythrina abyssinica</i>	Orientaline	107
<i>E. crista-galli</i>	N-Nororientaline	108
<i>E. orientalis</i>	L-Reticuline	109
<i>E. poeppigiana</i>	(+)-N-Nororientaline	107
<i>Eschscholtzia californica</i>	Escholinine = (+)-Romneine methohydroxide	110
<i>Papaver fugax</i>	Armepavine	111
<i>P. macrostomum</i>	Macrostomine (53)	112
	Sevanine (54)	112
<i>P. urbanianum</i>	(-)-Armepavine	63
	(-)-N-Norarmepavine	63
<i>Zanthoxylum clava-herculis</i>	Tembetarine	113

<sup>98</sup> L. Sh. Pirdzhanov, A. A. Agekyan, L. S. Papayan, and E. A. Markaryan, *Armenian. khim. Zhur.*, 1973, **26**, 667 (*Chem. Abs.*, 1974, **80**, 3360e).

<sup>99</sup> E. A. Markaryan, Zh. S. Arustamyan, L. P. Solomina, and L. Sh. Pirdzhanov, *Sin. geterotsikl. Soedinenii*, 1972, 39 (*Chem. Abs.*, 1973, **79**, 146 352u).

<sup>100</sup> M. A. Collins and F. J. Kernozek, *J. Heterocyclic Chem.*, 1972, **9**, 1437.

<sup>101</sup> M. A. Collins, *Ann. New York Acad. Sci.*, 1973, **215**, 92.

<sup>102</sup> D. P. Del'tsova, N. P. Gambaryan, and I. L. Knunyants, *Doklady Akad. Nauk S.S.S.R.*, 1973, **212**, 628 (*Chem. Abs.*, 1974, **80**, 3359m).

<sup>103</sup> M. Natsume, S. Kumadaki, Y. Kanda, and K. Kiuchi, *Tetrahedron Letters*, 1973, 2335.

<sup>104</sup> K. Haisova, J. Slavik, and L. Dolejs, *Coll. Czech. Chem. Comm.*, 1973, **38**, 3312.

<sup>105</sup> F. R. Stermitz, D. K. Kim, and K. A. Larson, *Phytochemistry*, 1973, **12**, 1355.

<sup>106</sup> L. Batllori, R. San Martin, and J. M. Secanell, *Rev. real Acad. Farm. Barcelona*, 1973, **29** (*Chem. Abs.*, 1974, **80**, 45 643e).

<sup>107</sup> 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.

<sup>108</sup> K. Ito, H. Furukawa, M. Haruna, and M. Ito, *Yakugaku Zasshi*, 1973, **93**, 1674 (*Chem. Abs.*, 1974, **80**, 68 391k).

<sup>109</sup> K. Ito, H. Furukawa, M. Haruna, and S.-T. Lu, *Yakagaku Zasshi*, 1973, **93**, 1671 (*Chem. Abs.*, 1974, **80**, 68 390j).

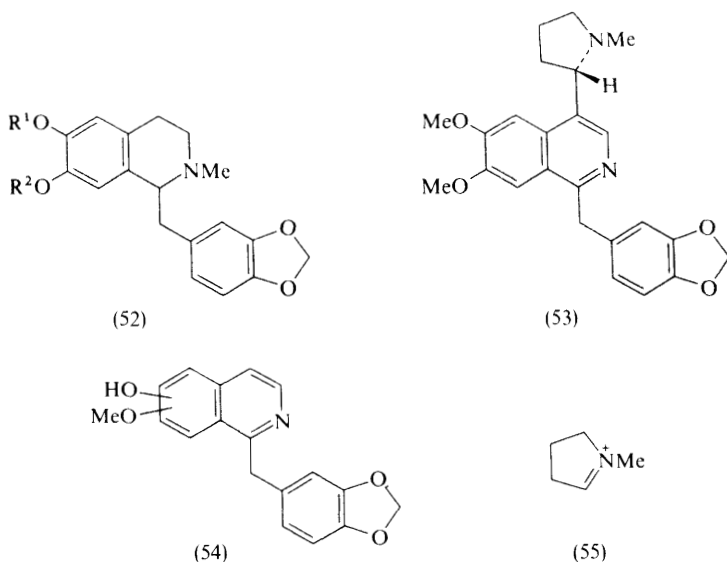
<sup>110</sup> J. Slavik and L. Dolejs, *Coll. Czech. Chem. Comm.*, 1973, **38**, 3514.

<sup>111</sup> J. D. Phillipson, G. Sariyar, and T. Baytop, *Phytochemistry*, 1973, **12**, 2431.

<sup>112</sup> V. A. Mnatsakanyan, V. Preininger, V. Simanek, A. Klasek, L. Dolejs, and F. Santavy, *Tetrahedron Letters*, 1974, 851.

<sup>113</sup> F. Fish and P. G. Waterman, *J. Pharm. Pharmacol.*, 1973, **25**, Suppl., 115P.

*Argemone albiflora* yielded an alkaloid AAl with partial structure (52;  $R^1$ ,  $R^2 = H$ , Me).<sup>104</sup> Armepavine has been found in *A. turnerae*;<sup>105</sup> the same alkaloid occurs also in *Papaver fugax*<sup>111</sup> and *P. urbanianum*.<sup>63</sup> The latter plant yields in addition *N*-norarmepavine. Only coclaurine was positively identified in the Menispermaceae species *Cocculus laurifolius*.<sup>106</sup> *Erythrina abyssinica*<sup>107</sup> contained orientaline, and *E. poeppigiana*<sup>107</sup> and *E. crista-galli*<sup>108</sup> yielded *N*-nororientaline. The quaternary alkaloid escholine from *Eschscholtzia californica*<sup>110</sup> was found to be identical with (+)-romneine methohydroxide. Macrostromine and sevanine, two new alkaloids from *Papaver macrostomum*, possess structures (53) and (54) respectively.<sup>112</sup> The novel structure (53) was assigned on the basis of spectroscopic analysis. Strong evidence for the presence of the *N*-methylpyrrolidine substituent in (53) was obtained from the mass spectrum, which showed the presence of a peak at  $m/e$  84 ( $C_5H_{10}N$ ) attributed to the fragment (55). The *S*-configuration in (53) was deduced on the basis of

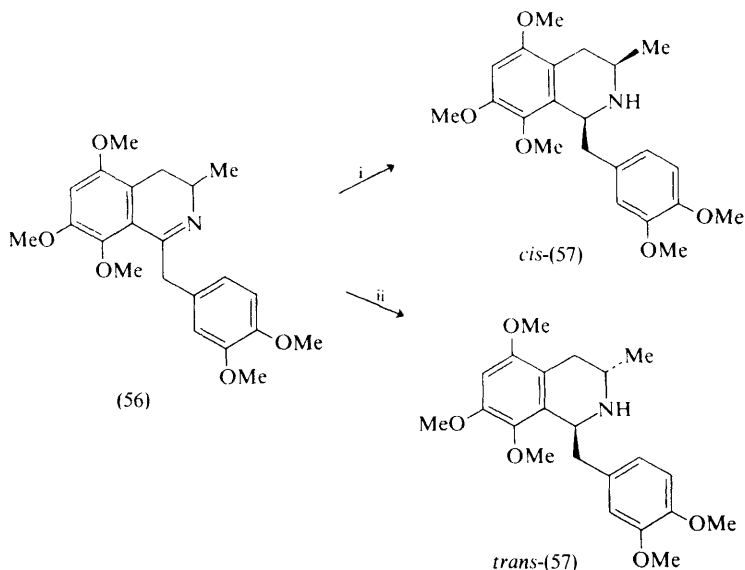


comparison of its Cotton effect with those of (*S*)-(-)-nicotine and (*S*)-(-)-brevicolline. Reticuline was detected in *Corydalis cava* in the course of biosynthetic experiments using radiolabelled amino-acid precursors.<sup>114</sup> The optimization of conditions for the extraction of alkaloids from *Fumaria officinalis* has been reported.<sup>115</sup>

<sup>114</sup> G. Blaschke, G. Waldheim, M. Von Schantz, and P. Peura, *Arch. Pharm.*, 1974, **307**, 122.

<sup>115</sup> L. G. Molokhova and B. N. Nazarov, *Farmatsiya (Moscow)*, 1974, **23**, 23 (*Chem. Abs.*, 1974, **80**, 149 053d).

The catalytic and chemical reduction of the 3-methyl-3,4-dihydrobenzylisoquinoline (56) has been studied (Scheme 2).<sup>116</sup> Catalytic hydrogenation of (56) in acidic ethanol gave the *cis*-1,2,3,4-tetrahydroisoquinoline, *cis*-(57), as the sole product whereas reduction with NaBH<sub>4</sub> produced a 25 : 1 mixture in favour of *trans*-(57). The same report also describes the Bischler–Napieralski cyclization of *N*-2-[1-(2,5-dimethoxy-4-methylphenyl)propyl]-3,4-dimethoxyphenylacetamide to give, in addition to the normal product (56), a number of neutral compounds which shed some light on the mechanism of this reaction.<sup>116</sup> One of



Reagents: i, H<sub>2</sub>-PtO<sub>2</sub>; ii, NaBH<sub>4</sub>-MeOH

Scheme 2

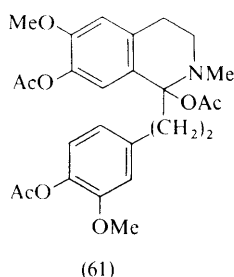
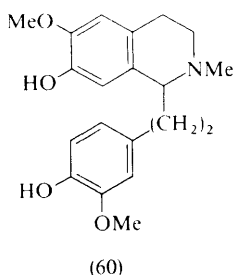
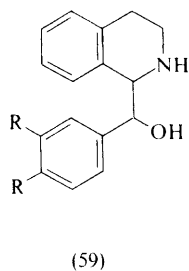
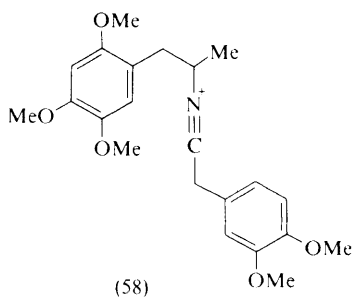
these is the von Braun product, 3,4-dimethoxybenzyl cyanide, whose isolation strongly suggests the intermediacy of (58) in the cyclization reaction.

Further utility of the 4-oxazolin-2-one as a protective group (see Vol. 2) is evidenced in the synthesis of the hydroxylated tetrahydrobenzylisoquinolines of the type (59).<sup>117</sup> An attempt to effect phenolic oxidative dimerization of homo-orientaline (60) gave instead, after acetylation, the 1-acetoxy-derivative (61) in low yield.<sup>118</sup> A series of 5-hydroxy-6-hydroxymethyl-, 6-hydroxy-7-hydroxymethyl-, and 7-hydroxy-6-hydroxymethyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-

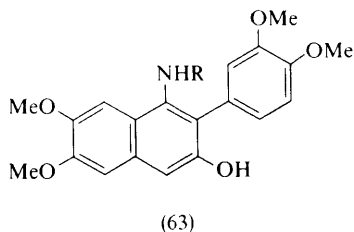
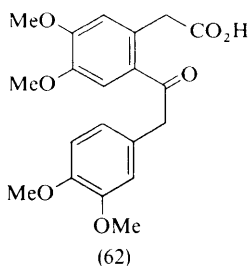
<sup>116</sup> J. Gal, R. J. Wienkam, and N. Castagnoli, jun., *J. Org. Chem.*, 1974, **39**, 418.

<sup>117</sup> J. L. Neumeyer and C. B. Boyce, *J. Org. Chem.*, 1973, **38**, 2291.

<sup>118</sup> T. Kametani, M. Mizushima, S. Takano, and K. Fukumoto, *Tetrahedron*, 1973, **29**, 2031.



tetrahydroisoquinolines, which may possess bronchodilator properties, has been prepared.<sup>119</sup> The reaction of the 2-acylphenylacetic acid derivative (62) with primary amines in acidic solution produced compounds (63) and the isomeric isoquinolones (64).<sup>120</sup> The intermediacy of (65) was suggested to account for the formation of the two products. Treatment of ( $\pm$ )-*N*-(6'-hydroxy-methyl)-1,2,3,4-tetrahydropapaverine with ethyl chloroformate provided the 3-phenylisochroman derivative (66).<sup>121</sup>

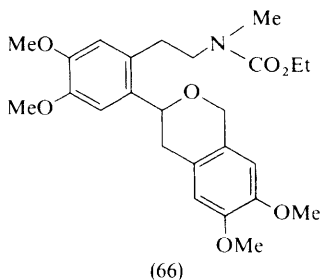
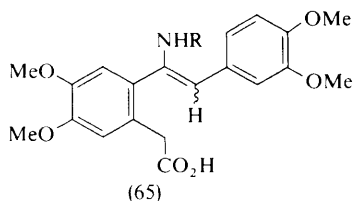
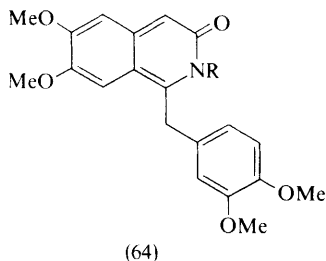


<sup>119</sup> S. F. Dyke, A. W. C. White, and D. Hartley, *Tetrahedron*, 1973, **29**, 857.

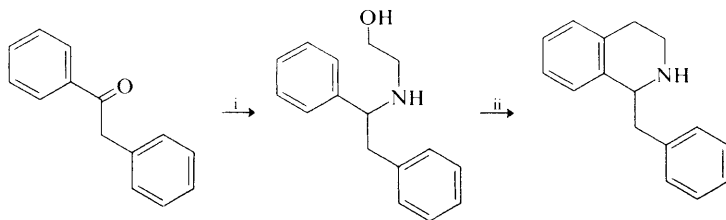
<sup>120</sup> W. E. Kreighbaum, W. F. Kavanaugh, and W. T. Comer, *J. Heterocyclic Chem.*, 1973, **10**, 317.

<sup>121</sup> W. Wiegand, H. Reinhardt, and J. Fricke, *Pharm. Acta Helv.*, 1973, **48**, 420 (*Chem. Abs.*, 1973, **79**, 105 446j).





A new simple synthesis of 1-benzyl-1,2,3,4-tetrahydroisoquinoline has been reported (Scheme 3).<sup>122</sup> Successful oxidative coupling reactions using *non-phenolic* precursors have been achieved for the first time.<sup>123</sup> Treatment of



Reagents: i,  $\text{NH}_2(\text{CH}_2)_2\text{OH}-\text{NaBH}_4$ ; ii,  $\text{HBr}-\text{AlCl}_3$

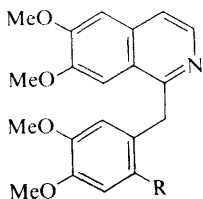
**Scheme 3**

papaverine (67;  $\text{R} = \text{H}$ ) with  $\text{VOF}_3$  in  $\text{CF}_3\text{CO}_2\text{H}$  afforded an 80% yield of an aryl-aryl coupled product (67;  $\text{R} = 6'$ -papaveryl). Intramolecularly coupled products were not observed in this reaction. On the other hand, similar oxidation of ( $\pm$ )-laudanosine (68;  $\text{R} = \text{Me}$ ), in which *N*-protonation would be expected to

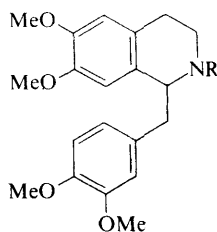
<sup>122</sup> L. W. Deady, N. H. Pirzada, R. D. Topsom, and J. M. Bobbitt, *Austral. J. Chem.*, 1973, **26**, 2063.

<sup>123</sup> S. M. Kupchan, A. J. Liepa, J. Andris, V. Kameswaran, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1973, **95**, 6861.

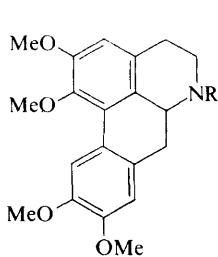
impart a smaller deactivation effect on the isoquinoline moiety compared with (67; R = H), resulted in intramolecular coupling to give ( $\pm$ )-glaucine (69; R = Me). Finally, ( $\pm$ )-*N*-formylnorlaudanosine (68; R = CHO) yielded a small amount of ( $\pm$ )-formylnorglaucine (69; R = CHO) the major product (55%) being the spirodienone (70), whose structure was established by *X*-ray analysis. Compound (70) may have important implications for the biosynthesis of the *Erythrina* alkaloids. The catalytic<sup>124</sup> and chemical<sup>125</sup> reduction of the 5,6,7,8-tetrahydroisoquinolinium salt (71) has been studied. The hydrogen



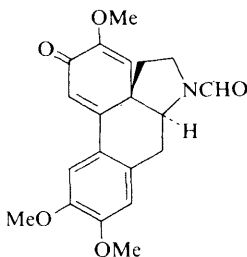
(67)



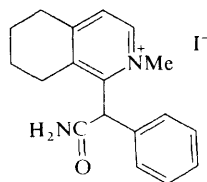
(68)



(69)



(70)



(71)

bromide-catalysed rearrangement of 3-phenylsulphonyl-3-benzazocin-6-one in the presence of phenol as bromine scavenger gave 1-*p*-hydroxyphenethyl-3,4-dihydroisoquinoline as well as a Hofmann-degradation product.<sup>126</sup> The synthesis of *N*-benzyl-4-spirobutane-1,2,3,4-tetrahydroisoquinoline has been described.<sup>127</sup> 1-Carboxyphenyl- and 1-carboxybenzyl-isoquinolines have been prepared for pharmacological testing.<sup>128,129</sup>

<sup>124</sup> E. Ochiai, Y. Kawazoe, and I. Kenkyusho, *Nempo*, 1971, 41 (*Chem. Abs.*, 1974, **80**, 3682m).

<sup>125</sup> M. Natsume, S. Kumadaki, and I. Kenkyusho, *Nempo*, 1971, 47 (*Chem. Abs.*, 1974, **80**, 3683n).

<sup>126</sup> W. T. Comer, J. D. Catt, W. L. Matier, C. M. Combs, and J. S. Dykstra, *J. Heterocyclic Chem.*, 1973, **10**, 519.

<sup>127</sup> E. A. Markaryan, Zh. S. Arustamyan, and S. S. Vasilyan, *Khim. geterotsikl. Soedinenii*, 1973, 679 (*Chem. Abs.*, 1973, **79**, 78 561j).

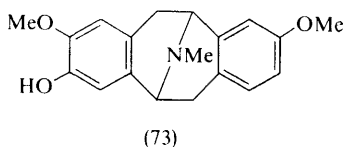
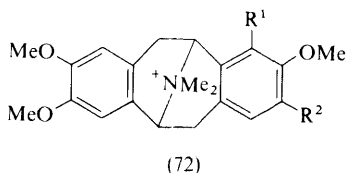
<sup>128</sup> L. Simon, G. Talpas, and M. Marosy, *Pharmazie*, 1974, **29**, 313.

<sup>129</sup> L. Simon and G. Talpas, *Pharmazie*, 1974, **29**, 314.

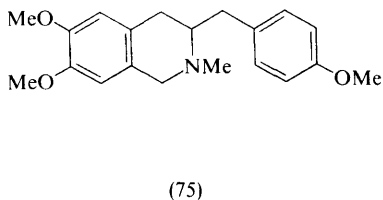
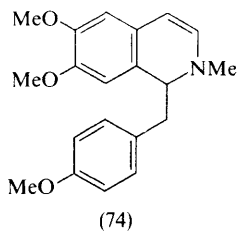
Several physical methods have been developed for the determination of papaverine, viz. spectrophotometry,<sup>130,131</sup> titration in non-aqueous media,<sup>132</sup> thin-layer chromatography,<sup>133</sup> electrophoresis,<sup>59</sup> planimetry,<sup>134</sup> and oscillopolarography.<sup>135</sup>

### 5 Pavine Alkaloids

The aerial parts of *Argemone platyceras* yielded the quaternary alkaloids (–)-platycerine methohydroxide (72; R<sup>1</sup> = OH, R<sup>2</sup> = H) and (–)-argemoneine methohydroxide (72; R<sup>1</sup> = H, R<sup>2</sup> = OMe).<sup>136</sup> *A. munita* subsp. *rotundata* has been shown to elaborate a new alkaloid, 3-hydroxy-2,9-dimethoxypavinane (73),



whose structure was confirmed by synthesis.<sup>137</sup> An attempt to prepare the methyl ether of (73) by formic–phosphoric acid-catalysed cyclization of (74) led instead to the rearrangement product (75). Although this is a general reaction of 1,2-dihydroisoquinolines,<sup>86,87</sup> it is the first time that it has been observed under



<sup>130</sup> F. E. Kagan and L. A. Kirichenko, *Farm. Zhur.* 1973, **28**, 34 (*Chem. Abs.*, 1974, **80**, 100 245d).

<sup>131</sup> F. E. Kagan and L. A. Kirichenko, *Farm. Zhur.* 1973, **28**, 64 (*Chem. Abs.*, 1974, **79**, 35 197c).

<sup>132</sup> Gh. Morait, *Farmacia (Bucharest)*, 1973, **21**, 29 (*Chem. Abs.*, 1973, **79**, 73 349m).

<sup>133</sup> M. Ono, M. Shimamine, and K. Takahashi, *Eisei Shikenjo Hokoku*, 1972, 73 (*Chem. Abs.*, 1973, **79**, 57 731z).

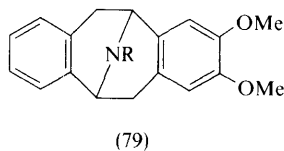
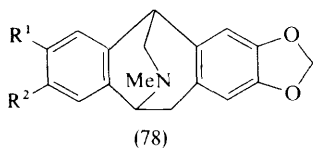
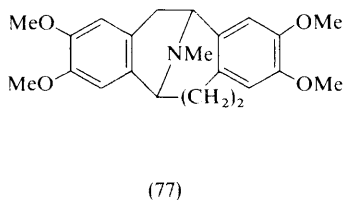
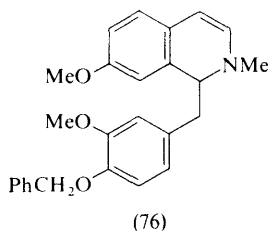
<sup>134</sup> Z. Blagojevic, M. Skrij, and V. Bulajic, *Arh. Farm.*, 1972, **22**, 97 (*Chem. Abs.*, 1973, **79**, 70 261r).

<sup>135</sup> I. F. Shcherbak, N. F. Tsareva, and Z. G. Shcherbak, *Fiz.-Khim. Probl. Sovrem. Biol. Med., Mater. Konf.*, ed. E. A. Zhukov, 1970, p. 190 (*Chem. Abs.*, 1974, **80**, 6990d).

<sup>136</sup> J. Slavik, L. Slavikova, and K. Haisova, *Coll. Czech. Chem. Comm.*, 1973, **38**, 2513.

<sup>137</sup> R. M. Coomes, J. R. Falck, D. K. Williams, and F. R. Stermitz, *J. Org. Chem.*, 1973, **38**, 3701.

conditions of a pavinane synthesis. The failure to effect the desired ring closure may be due to the fact that the cyclization must occur *meta* to the methoxy-group. This problem was circumvented by an alternative synthesis which utilized the key intermediate (76). Treatment of (76) with a mixture of formic and phosphoric acids gave directly the alkaloid (73). An analogous synthesis of  $(\pm)$ -*N*-methyl-homopavine [ $(\pm)$ -homoargemonine] (77) using the appropriate 1-phenethyl-1,2-dihydroisoquinoline derivative has been achieved.<sup>138</sup> Two other isopavines, (78;  $R^1 = OH$ ,  $R^2 = OMe$ ) and (78;  $R^1 = OMe$ ,  $R^2 = OH$ ), have been synthesized and the former has been found to be identical with the alkaloid reframoline.<sup>139</sup> A synthesis of  $(\pm)$ -eschscholtzidine has been reported.<sup>140</sup>



An important discovery which promises to improve the yields of most of the above syntheses has been recently described.<sup>141</sup> Since side reactions such as disproportionation and rearrangement [e.g. (74)  $\rightarrow$  (75)] observed in the crucial cyclization [e.g. (76)  $\rightarrow$  (73)] are bimolecular processes, it was reasoned that high-dilution conditions should favour the desired reaction. In the event, treatment of the appropriate dihydroisoquinolines with perchloric acid gave the corresponding pavinane derivatives (79;  $R = Me$ ,  $CH_2Ph$ ,  $p\text{-NO}_2C_6H_4CH_2$ , or  $2,6\text{-Cl}_2C_6H_3CH_2$ ) in 50–95% yield.

Using a previously devised ring-expansion reaction,<sup>142</sup> Kametani and co-workers have synthesized  $(\pm)$ -reframidine (82) (Scheme 4) as well as other isopavine derivatives.<sup>143,144</sup> Treatment of the hydrastinine derivative (80) with diazomethane gave the aziridinium salt (81), which when subjected to strong acid

<sup>138</sup> F. R. Stermitz and D. K. Williams, *J. Org. Chem.*, 1973, **38**, 2099.

<sup>139</sup> S. F. Dyke, A. C. Ellis, R. G. Kinsman, and A. W. C. White, *Tetrahedron*, 1974, **30**, 1193.

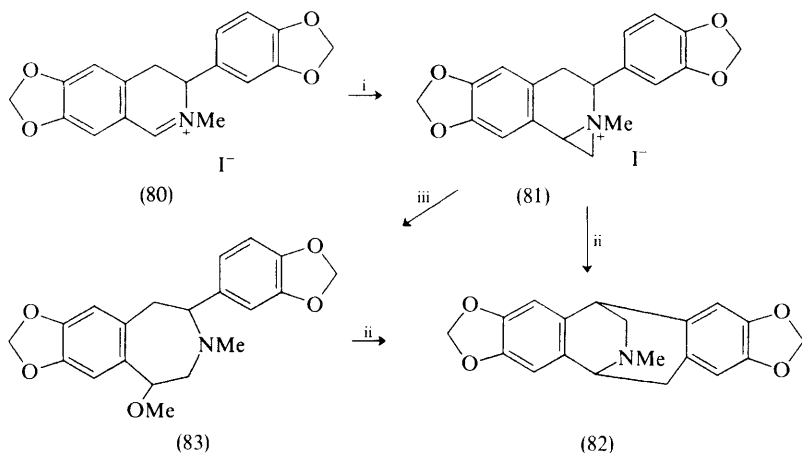
<sup>140</sup> M. S. Premila and B. R. Pai, *Indian J. Chem.*, 1973, **11**, 1084.

<sup>141</sup> D. S. Walsh and R. E. Lyle, *Tetrahedron Letters*, 1973, 3849.

<sup>142</sup> H. O. Bernhard and V. Snieckus, *Tetrahedron*, 1971, **27**, 2091.

<sup>143</sup> T. Kametani and K. Ogasawara, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 893.

<sup>144</sup> T. Kametani, S. Hirata, and K. Ogasawara, *J.C.S. Perkin I*, 1973, 1466.



Reagents: i,  $\text{CH}_2\text{N}_2$ -ether; ii, 6M-HCl, 20°C, 1 week; iii, 1% HCl-MeOH, reflux

**Scheme 4**

afforded ( $\pm$ )-reframidine (82) in 20% yield.<sup>144</sup> On the other hand, treatment of (81) with mild acid gave the 3-benzazepine derivative (83), which could also be transformed into (82). A similar sequence of reactions was effected on the corresponding *N*-benzyl salt of (80). The formation of (82) and (83) may be rationalized by the intermediacy of a common benzylic carbonium ion which undergoes either intramolecular cyclization or attack by external nucleophile depending on the reaction conditions. Lead tetra-acetate oxidation of 1-benzyl-tetrahydroisoquinolines gave C-4-hydroxylated products, which upon acid treatment provided isopavine derivatives.<sup>145</sup> In this manner, ( $\pm$ )-*O*-methyl-thalisopavine and ( $\pm$ )-reframine were synthesized in high yield. A series of argemone analogues has been prepared.<sup>146–148</sup>

## 6 Dibenzopyrrocoline Alkaloids

Treatment of ( $84; \text{R}^1 + \text{R}^2 = \text{CH}_2$ ) and ( $84; \text{R}^1 = \text{R}^2 = \text{Me}$ ) with sodium amide in liquid ammonia gave cryptowoline (85;  $\text{R}^1 + \text{R}^2 = \text{CH}_2$ ) and cryptaustoline (85;  $\text{R}^1 = \text{R}^2 = \text{Me}$ ) in addition to other products.<sup>149,150</sup> Under similar conditions, the unnatural dihydrodibenzopyrrocoline derivative (86;  $\text{R} = \text{H}$  or  $\text{Me}$ )

<sup>145</sup> O. Hoshino, M. Tata, and B. Umezawa, *Heterocycles*, 1973, **1**, 223.

<sup>146</sup> R. M. Lagidze, N. K. Iremadze, M. Sh. Vashakidze, and B. V. Rozynov, *Khim. prirod. Soedinenii*, 1973, **188** (*Chem. Abs.*, 1973, **79**, 5241v).

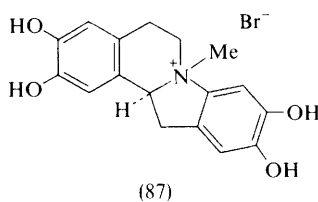
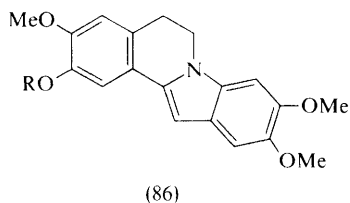
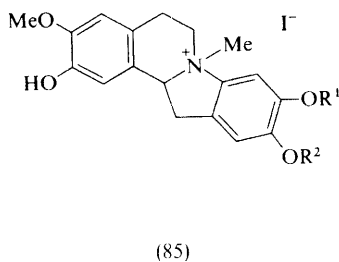
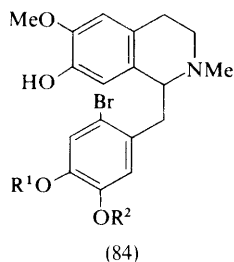
<sup>147</sup> R. M. Lagidze, A. I. Dvalishvili, L. P. Chigogidze, D. R. Lagidze, and R. R. Devdariani, *Soobshch. Akad. Nauk gruz. S.S.R.*, 1973, **69**, 597 (*Chem. Abs.*, 1973, **79**, 53 159w).

<sup>148</sup> R. M. Lagidze, *Doklady Vses. Konf. Khim. Atsetilena*, 4th, 1972, **1**, 253 (*Chem. Abs.*, 1973, **79**, 18910m).

<sup>149</sup> T. Kametani, A. Ujiie, K. Takahashi, T. Nakano, T. Suzuki, and F. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 768.

<sup>150</sup> S. V. Kessar, R. Randhawa, and S. S. Gandhi, *Tetrahedron Letters*, 1973, 2923.

have been prepared.<sup>151</sup> Horseradish peroxidase effected oxidative coupling of (*S*)-(+)-laudanoline hydrobromide and (*R*)-(-)-laudanoline methiodide to give the salt (87) and an aporphine derivative, respectively, in preparative amounts.<sup>152</sup>



## 7 Proaporphine, Aporphine, and Phenanthrene Alkaloids

The oxoaporphine alkaloids have been the subject of a recent review.<sup>153</sup> Table 4 presents new isolation and structural elucidation studies of this class of alkaloids.

**Table 4** Isolation of proaporphine, aporphine, and phenanthrene alkaloids

Species	Alkaloid (Structure) <sup>a</sup>	Ref.
<i>Cassytha filiformis</i>	Nantenine	154
<i>Erythrina abyssinica</i>	Isoboldine	107
<i>Eschscholtzia californica</i>	Escholine = Magnoflorine	110
<i>E. douglasii</i>	Escholine	110
<i>Glaucium flavum</i>	6,6a-Didehydronorglaucine <sup>b</sup> (88)	155
	1-Hydroxy-2,9,10-trimethoxyaporphine <sup>b</sup> (89; R <sup>1</sup> = OH, R <sup>2</sup> = OMe)	155
<i>Guatteria subsessilis</i>	Homoschatoline <sup>b</sup> (90; R <sup>1</sup> = OMe, R <sup>2</sup> = H)	156
	Subsessiline <sup>b</sup> (90; R <sup>1</sup> = OH, R <sup>2</sup> = OMe)	156

<sup>151</sup> T. Kametani, S. Shibuya, and S. Kano, *J.C.S. Perkin I*, 1973, 1212.

<sup>152</sup> A. Brossi, A. Ramel, J. O'Brien, and S. Teitel, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1839.

<sup>153</sup> M. Shamma and R. L. Castenson, ref. 1, p. 225.

<sup>154</sup> J. R. Merchant and H. K. Desai, *Indian J. Chem.*, 1973, **11**, 342.

<sup>155</sup> K. H. B. Duchevska, A. S. Orahovats, and N. M. Mollov, *Doklady bolg. Akad. Nauk*, 1973, **26**, 899 (*Chem. Abs.*, 1974, **80**, 27 410x).

<sup>156</sup> M. Hasegawa, M. Sojo, A. Lira, and C. Marquez, *Acta Cient. Venez.*, 1972, **23**, 165 (*Chem. Abs.*, 1973, **79**, 42 716z).

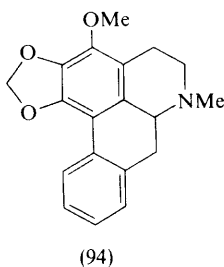
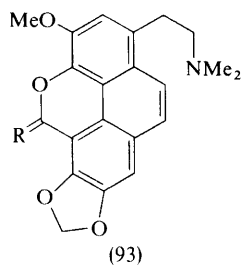
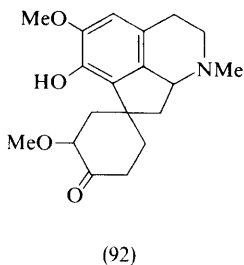
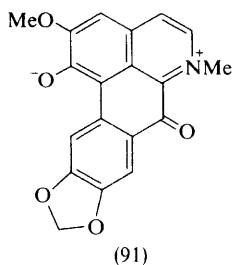
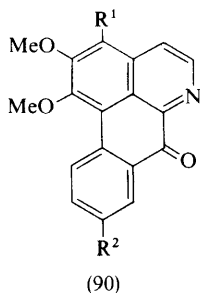
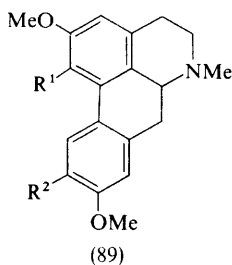
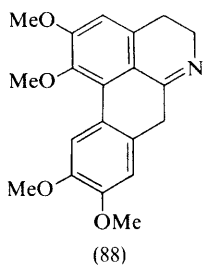
Table 4—continued

Species	Alkaloid (Structure) <sup>a</sup>	Ref.
<i>Legnephora moorei</i>	Magnoflorine	157
	Laurifoline	157
	Stepharine	157
<i>Liriodendron tulipifera</i>	Lirinine methyl ether <sup>b</sup> (89; R <sup>1</sup> = OMe, R <sup>2</sup> = H)	158
	Lirinine N-oxide <sup>b</sup> (89; R <sup>1</sup> = OH, R <sup>2</sup> = H; N $\rightarrow$ O)	158
<i>Nandina domestica</i>	Nandazurine (91) <sup>b</sup>	159, 160
	O-Methylndomesticine	160
<i>Neolitsea variabilima</i>	L-Hernovine	161
	L-Nandigerine	161
	N-Methylhernovine	161
<i>Ocotea puberula</i>	Thalicminine	162
<i>Papaver urbanianum</i>	(-)-Mecambrine	163
<i>Phoebe formosana</i>	Lauroilsine	163
	Roemerine	163
	Ushinsunine	163
	Oxoushinsunine (liliodenine)	163
	Roehybrine <sup>b</sup> (92)	164
<i>Roemeria hybrida</i>	Roehybrine <sup>b</sup> (92)	164
<i>Thalictrum dioicum</i>	(+)-Corydine	165
<i>T. longipedunculatum</i>	Thalicsine (93; R = 0)	166
<i>T. minus</i>	Magnoflorine	166a
<i>T. polygamum</i>	Thaliglucinone	167
	Magnoflorine	167
<i>Stephania dinklagei</i>	Corydine	168
	Norcorydine	168
	Stepharine	168
	Stephalagine <sup>b</sup> (94)	168
	Steporphine	168

<sup>a</sup> Structures of alkaloids for which no formulation appears may be found in the corresponding section of previous volumes of these Reports or in ref. 169.

<sup>b</sup> New alkaloid.

- <sup>157</sup> S. Campos Flor, N. J. Doorenbos, G. H. Svoboda, J. E. Knapp, and P. L. Schiff, jun., *J. Pharm. Sci.*, 1974, **63**, 618.
- <sup>158</sup> R. Ziyaev, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, **9**, 505 (*Chem. Abs.*, 1974, **80**, 60 055h).
- <sup>159</sup> J. Kunitomo, M. Juichi, Y. Yoshikawa, and H. Chikamatsu, *Experientia*, 1973, **29**, 518.
- <sup>160</sup> J. Kunitomo, M. Juichi, Y. Yoshikawa, and H. Chikamatsu, *Yakugaku Zasshi*, 1974, **94**, 97 (*Chem. Abs.*, 1974, **80**, 108 725f).
- <sup>161</sup> S.-T. Lu and T.-L. Su, *J. Chin. Chem. Soc. (Taipei)*, 1973, **20**, 75 (*Chem. Abs.*, 1973, **79**, 123 625w).
- <sup>162</sup> F. Baralle, N. Schvarzberg, M. J. Vernengo, G. Y. Moltrasio, and D. Giacomello, *Phytochemistry*, 1973, **12**, 948.
- <sup>163</sup> S.-T. Lu and T.-L. Su, *J. Chin. Chem. Soc. (Taipei)*, 1973, **20**, 87 (*Chem. Abs.*, 1973, **79**, 123 626x).
- <sup>164</sup> J. Slavik, L. Dolejs, and L. Slavikova, *Coll. Czech. Chem. Comm.*, 1974, **39**, 888.
- <sup>165</sup> M. Shamma and S. S. Salgar, *Phytochemistry*, 1973, **12**, 1505.
- <sup>166</sup> W. G. Chodschav, S. C. Majech, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, **441**.
- <sup>166a</sup> I. Ciulei and P. A. Ionescu, *Farmacia (Bucharest)*, 1973, **21**, 17 (*Chem. Abs.*, 1973, **79**, 123 633x).
- <sup>167</sup> S. A. Gharbo, J. L. Beal, R. W. Doskotch, and L. A. Mitscher, *Lloydia*, 1973, **36**, 349.
- <sup>168</sup> A. N. Tackie, D. Dnuma-Badu, P. A. Lartey, P. L. Schiff, jun., J. E. Knapp, and D. J. Slatkin, *Lloydia*, 1974, **37**, 6.
- <sup>169</sup> T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Elsevier, Amsterdam, 1969.

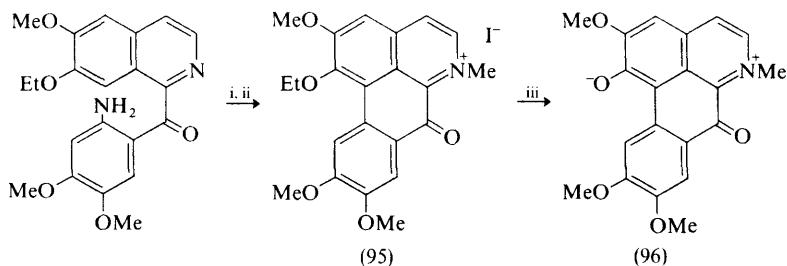


The alkaloid nantenine was isolated from *Cassytha filiformis* and its structure was confirmed by synthesis.<sup>154</sup> Alkaloids A and B from *Glaucium flavum* had structures (89;  $R^1 = \text{OH}$ ,  $R^2 = \text{OMe}$ ) and (88) respectively.<sup>155</sup> Homoschatoline (90;  $R^1 = \text{OMe}$ ,  $R^2 = \text{H}$ ) and subessiline (90;  $R^1 = \text{OH}$ ,  $R^2 = \text{OMe}$ ) are new examples of 7-oxoaporphines.<sup>156</sup> Nandazurine, a green-coloured alkaloid, was first isolated in 1925 from *Nandina domestica*.<sup>159,160</sup> The zwitterionic structure (91) was assigned on the basis of spectroscopic data and reduction to *dl*-domesticine. *Phoebe formosana* yielded nine alkaloids, four of which were identified as lauroilsine, roemerine, ushinsunine, and oxoushinsunine (liliodenine).<sup>163</sup> A further report on the constituents of *Liriodendron tulipifera* has appeared<sup>158</sup> (*cf.* Vol. 4). The tertiary bases of *Thalictrum minus* showed hypotensive properties and antispasmodic effects.<sup>166a</sup> The identity between the quaternary alkaloid escholine from *Eschscholtzia californica* and magnoflorine was established by n.o.e., mass spectral, and Hofmann degradation studies.<sup>110</sup> Structure (93);



R = O) has been proposed for thalicsine isolated from *Thalictrum longipedunculatum*;<sup>166</sup> it corresponds to that of thaliglucinone, which has been previously found in other *Thalictrum* species (see Vol. 3 of these Reports). Strong evidence for the methine structure of (93; R = O) was obtained from its mass spectrum, which showed  $m/e$  58 ( $\text{H}_2\text{C}=\text{NMe}_2^+$ ) as base peak. Thaliglucinone, isolated from *Thalictrum polygamum*, has been found to possess some antimicrobial activity.<sup>167</sup> The isolation of thalicminine from *Ocotea puberula* marks the first time that this alkaloid has been found in this species.<sup>162</sup> In addition, ocoteine and dehydro-ocoteine were obtained. The first report of a proaporphine alkaloid (stepharine) in *Stephania dinklagei* has appeared.<sup>168</sup> Based primarily on mass spectral data, structure (92) was assigned to roehybrine from *Roemeria hybrida*.<sup>164</sup> A 1-hydroxy-2-methoxy-12,13-dihydrobromoproaporphine skeletal structure was deduced for the alkaloid jolantamine<sup>170</sup> (see also Vol. 4 of these Reports).

Four major reactions (Pschorr, phenol oxidative coupling, photocyclization, and benzyne-mediated synthesis) continue to play key roles in the total synthesis of aporphine and proaporphine alkaloids. Coninnine (96) was synthesized according to Scheme 5, employing the Pschorr reaction as the key step.<sup>171</sup> An



Reagents: i, Pschorr reaction; ii, MeI; iii, DMF-PhH

**Scheme 5**

interesting selective dealkylation (95)  $\rightarrow$  (96) was achieved in refluxing DMF-benzene. ( $\pm$ )-Apomorphine, ( $\pm$ )-apocodeine, ( $\pm$ )-*N*-*n*-propylnorapomorphine, and ( $\pm$ )-*N*-*n*-propylnorapocodeine,<sup>172</sup> as well as ( $\pm$ )-9,10-dihydroxyaporphine, (+)-, (-)-, and ( $\pm$ )-1,2-dihydroxyaporphine, and (+)-1,2,9,10-tetrahydroxyaporphine<sup>173</sup> have been prepared *via* a modified Reissert alkylation-Pschorr cyclization reaction sequence. Some of these compounds

<sup>170</sup> 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, **79**, 79 010r).

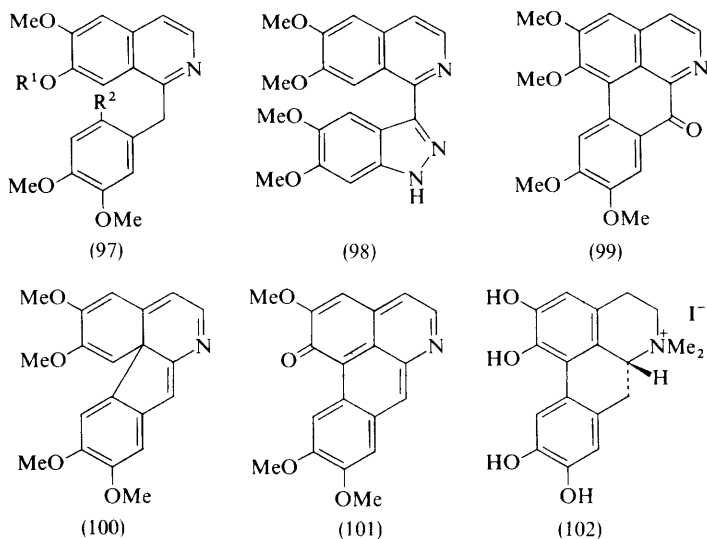
<sup>171</sup> I. Ribas, J. Saa, and L. Castedo, *Tetrahedron Letters*, 1973, 3617.

<sup>172</sup> J. L. Neumeyer, B. R. Neustadt, K. H. Oh, K. K. Weinhardt, and C. B. Boyce, *J. Medicin. Chem.*, 1973, **16**, 1223.

<sup>173</sup> J. L. Neumeyer, M. McCarthy, S. P. Battista, F. J. Rosenberg, and D. G. Teiger, *J. Medicin. Chem.*, 1973, **16**, 1228.

were shown to possess pharmacological activity quantitatively similar to that of their *laevo*-isomers, which were obtained from morphine by treatment with strong mineral acid.<sup>172</sup> Emetic and CNS activity was observed in aporphines with hydroxy-groups in the C-10 and C-11 positions.<sup>173</sup>

The diazotization of 6'-aminopapaverine (97;  $R^1 = \text{Me}$ ,  $R^2 = \text{NH}_2$ ) has been reinvestigated.<sup>174</sup> Formation of the diazonium salt in dilute sulphuric acid followed by treatment with copper provided a low yield of the desired oxidized Pschorr product (99), the major product being the indazole derivative (98). In contrast, diazotization of (97;  $R^1 = \text{Me}$ ,  $R^2 = \text{NH}_2$ ) in 46% sulphuric acid followed by Pschorr cyclization gave papaverine (97;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ), 1-oxopapaverine, and the unusual indenoisoquinoline (100). The last, upon acid treatment, rearranged almost quantitatively to the quinonoid oxoaporphine (101). Chemical conversion of (100) and (101) into the known aporphine alkaloids glaucine and thaliporphine respectively was also achieved in this work.<sup>174</sup> Interestingly, compound (101) was also obtained directly from (97;  $R^1 = \text{H}$ ,  $R^2 = \text{NH}_2$ ) under (presumably) somewhat different Pschorr cyclization conditions.<sup>175</sup> This reaction probably involves aerial oxidation of a phenolic aporphine intermediate and set the stage for the following surprising observation. Treatment of (97;  $R^1 = R^2 = \text{H}$ ) with ceric sulphate in acidic solution also gave the quinonoid oxoaporphine (101) in 25% yield. A variety of one-electron and two-electron oxidants was then investigated and it was found that the highest yields (62%) are achieved with  $\text{MoOCl}_4$  in trifluoroacetic acid-chloroform solution. Although mechanistically undefined, these smooth reactions of mono-

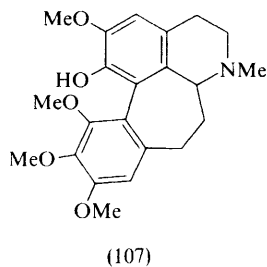
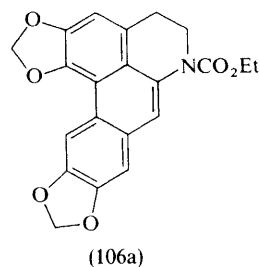
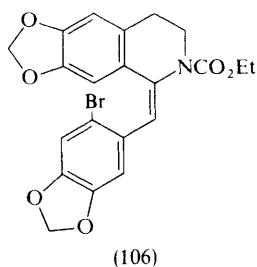
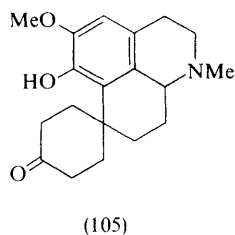
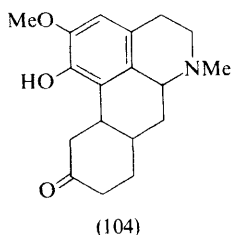
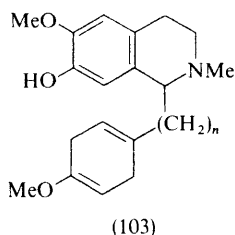


<sup>174</sup> M. P. Cava, I. Noguchi, and K. T. Buck, *J. Org. Chem.*, 1973, **38**, 2394.

<sup>175</sup> M. S. Kupchan and A. J. Liepa, *J. Amer. Chem. Soc.*, 1973, **95**, 4062.

phenolic benzylisoquinolines contrast starkly with previous intramolecular oxidative cyclizations of diphenolic benzyltetrahydroisoquinolines. Enzymatic oxidative coupling of (1S)-(+)-laudanoline methiodide yielded the quaternary aporphine derivative (102) with retention of absolute configuration.<sup>152</sup>

Treatment of the cyclohexadiene derivatives (103;  $n = 1$ ) and (103;  $n = 2$ ) with phosphoric acid afforded the aporphine (104) and ( $\pm$ )-tetrahydrohomoglaziovine (105) respectively.<sup>176</sup> The preference for six- over five- or seven-membered-ring formation may be noted. The catalytic hydrogenation of the homoaporphine alkaloid kreysiginone was thoroughly investigated using deuteriated derivatives.<sup>177</sup> ( $\pm$ )-Glaziovine was obtained in low yield in a reaction which may involve a nitrenium ion intermediate.<sup>178</sup> A key improvement in the non-oxidative photochemical synthesis of aporphine alkaloids has been discovered by Cava and co-workers.<sup>179</sup> Thus irradiation of the *o*-halogenobenzylidene-tetrahydroisoquinoline (106) in the presence of potassium *t*-butoxide provided *N*-ethoxycarbonylnorneolitsine (106a) in 72% yield. Using these conditions, dicentrine and cassameridine,<sup>179</sup> cassamedine,<sup>180</sup> corunnine, nandazurine, ( $\pm$ )-thalicmidine, ( $\pm$ )-domesticine, ( $\pm$ )-caaverine, HBr, and ( $\pm$ )-isoboldine<sup>181</sup> were prepared. Photolysis of 1-(2-bromo-3-hydroxy-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline gave the homoaporphine (107), which was found to be identical with the alkaloid CC-24



<sup>176</sup> W. V. Curran, *J. Heterocyclic Chem.*, 1973, **10**, 307.

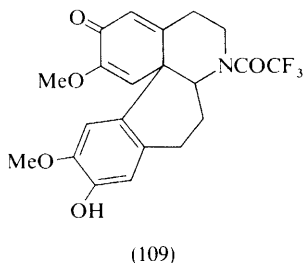
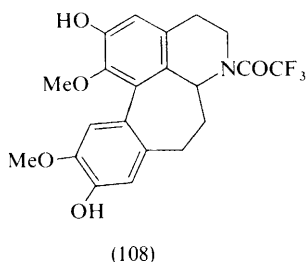
<sup>177</sup> T. Kametani, F. Satoh, K. Fukumoto, H. Sugi, and K. Kigasawa, *Heterocycles*, 1973, **1**, 47.

<sup>178</sup> T. Kametani, K. Takahashi, K. Ogasawara, and K. Fukumoto, *Tetrahedron Letters*, 1973, 4219.

<sup>179</sup> M. P. Cava, P. Stern, and K. Nakisaka, *Tetrahedron*, 1973, **29**, 2245.

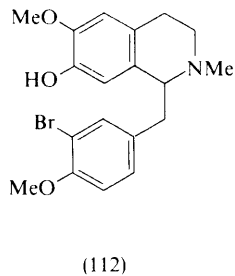
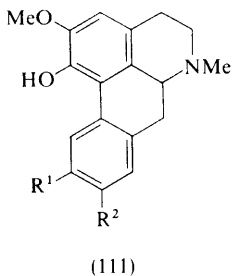
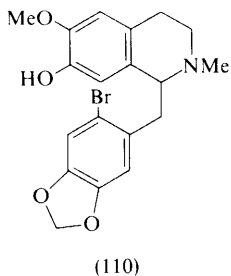
<sup>180</sup> M. P. Cava and S. S. Libsch, *J. Org. Chem.*, 1974, **39**, 577.

<sup>181</sup> S. M. Kupchan and F. P. O'Brien, *J.C.S. Chem. Comm.*, 1973, 915.



isolated from *Colchicum cornigerum*.<sup>182</sup> The homoaporphine (108) was obtained by  $\text{BF}_3$ -catalysed reaction of the dienone (109), which in turn was prepared by  $\text{VOCl}_3$  oxidative coupling of an appropriate tetrahydroisoquinoline precursor.<sup>183</sup>

Benzene reaction of (110) gave domesticine (111;  $\text{R}^1 + \text{R}^2 = \text{OCH}_2\text{O}$ ) in addition to three other products.<sup>149</sup> Thaliporphine (111;  $\text{R}^1 = \text{R}^2 = \text{OMe}$ ) was obtained similarly.<sup>149,151</sup> The intermediacy of a benzyne species was shown using the precursor (112), which gave the 1-hydroxyaporphine (111;  $\text{R}^1 = \text{OMe}$ ,



$\text{R}^2 = \text{H}$ ) in 20% yield. Compound (111;  $\text{R}^1 = \text{OMe}$ ,  $\text{R}^2 = \text{H}$ ) has also been synthesized by a conventional Pschorr cyclization route.<sup>184</sup> The photochemical oxidation of glaucine to 7-oxoglaucine has been reported.<sup>185</sup> Photochemical synthesis of the unusual aporphine alkaloid thalphenine (113;  $N\text{-MeI}$ ) has been achieved.<sup>186</sup> Irradiation of (114) under basic conditions gave directly (113), presumably *via* the intermediate quinone methide (115), which results from the initially formed aporphine precursor by elimination of the elements of methanol. Quaternization of (113) provided ( $\pm$ )-thalphenine (113;  $N\text{-MeI}$ ), whose Hofmann elimination gave the alkaloid thaliglucine (93;  $\text{R} = \text{H}_2$ ).

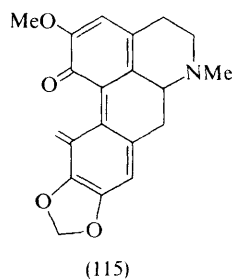
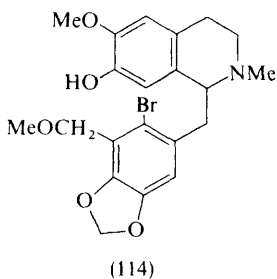
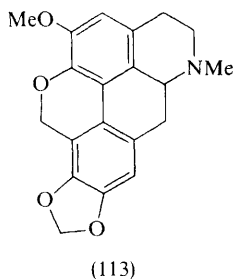
<sup>182</sup> T. Kametani, Y. Satoh, and K. Fukumoto, *Tetrahedron*, 1973, **29**, 2027.

<sup>183</sup> J. P. Marino and J. M. Samanen, *Tetrahedron Letters*, 1973, 4553.

<sup>184</sup> B. R. Pai and C. S. Swaminathan, *Indian J. Chem.*, 1973, **11**, 1086.

<sup>185</sup> A. S. Orakhovats, K. H. B. Duchevska, and N. M. Mollov, *Doklady bolg. Akad. Nauk*, 1973, **26**, 491 (*Chem. Abs.*, 1973, **79**, 53 643z).

<sup>186</sup> M. Shamma and D.-Y. Hwang, *Heterocycles*, 1973, **1**, 31.



The mass spectral behaviour of proaporphine alkaloids has been analysed.<sup>187</sup> Microcrystalloscopic determination of phenanthrene-isoquinolines using antimony acid complexes has been carried out.<sup>188</sup>

The metabolism of apocodeine to apomorphine and norapomorphine was shown to occur in rats.<sup>189</sup> The clinical application of apomorphine has been discussed.<sup>190</sup> The synthesis and pharmacological testing of several aporphine alkaloid analogues have been reported.<sup>191</sup> The pharmacology of liriodenine, thalicminine, corydine, and isocorydine hydrochloride has been investigated.<sup>192</sup>

The synthesis of tritium- and deuterium-labelled apomorphine has been reported.<sup>192a</sup> Under controlled conditions, exclusive introduction of label into the catechol ring of the molecule was achieved.

Spectrophotometric studies of two types of aporphine alkaloid and of benzyloisoquinolines isolated from *Peumus boldus* have been published.<sup>192b</sup>

## 8 Morphine and Morphinandienone Alkaloids

The capsules of Iranian *Papaver armeniacum* have been examined for alkaloids, and thebaine (116) has been identified as the major alkaloid by physical methods.<sup>193</sup> The roots of certain strains of *P. bracteatum* were shown to contain significant quantities of thebaine which could be used for the production of codeine and other opiates.<sup>193a</sup> Thebaine and other isoquinoline alkaloids have been shown to be present in the aerial parts of *P. fugax*.<sup>111</sup> The alkaloid content of the latex of *P. orientale* varied to a great extent during the day.<sup>194</sup> Pallidine (117) was

<sup>187</sup> L. Dolejs, *Coll. Czech. Chem. Comm.*, 1974, **39**, 571.

<sup>188</sup> T. P. Churina, *Fiz.-Khim. Probl. Sovrem. Biol. Med. Mater. Konf.*, ed. E. A. Zhukov, 1970, p. 216 (*Chem. Abs.*, 1974, **80**, 7004q).

<sup>189</sup> R. V. Smith and M. R. Cook, *J. Pharm. Sci.*, 1974, **63**, 161.

<sup>190</sup> A. Tagliamonte, R. Gessa, and G. L. Gessa, *Rivista Farmacol. e Terapia*, 1973, **4**, 3.

<sup>191</sup> F. Schneider, M. Gerold, and K. Bernauer, *Helv. Chim. Acta*, 1973, **56**, 759.

<sup>192</sup> S. Fakhutdinov and M. B. Sultanov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, **118** (*Chem. Abs.*, 1974, **80**, 91 212m).

<sup>192a</sup> J. Z. Ginos, A. LoMonte, G. C. Cotzias, A. K. Bose, and R. J. Brambilla, *J. Amer. Chem. Soc.*, 1973, **95**, 2991.

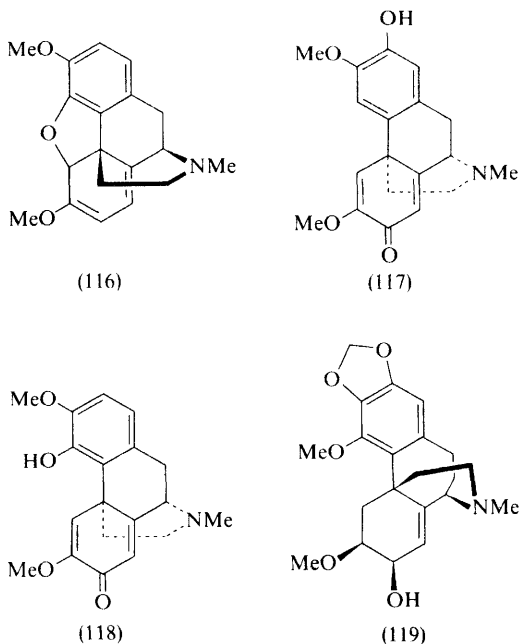
<sup>192b</sup> M. Vanhaelen, *J. Pharm. Belgique*, 1973, **28**, 291 (*Chem. Abs.*, 1973, **79**, 134 317y).

<sup>193</sup> J. D. Phillips, *J. Pharm. Pharmacol.*, 1973, **25**, Suppl., 113P.

<sup>193a</sup> J. W. Fairbairn and F. Hakim, *J. Pharm. Pharmacol.*, 1973, **25**, 353.

<sup>194</sup> D. Vagujfalvi, *Acta Bot.*, 1973, **18**, 391 (*Chem. Abs.*, 1974, **80**, 105 913e).

isolated from *Thalictrum dioicum*.<sup>165</sup> The phenolic base isolated from *Nandina domestica* was shown to be sinoacutine (118).<sup>160</sup> The structure and absolute configuration (119) have been assigned to the alkaloid CC-2 isolated from



*Colchicum cornigerum* on the basis of an X-ray analysis of its methiodide.<sup>195</sup> A review on the opium poppy *Papaver somniferum* describing its diverse uses and effects has appeared.<sup>196</sup> Apparently the positive identification of morphine, codeine, thebaine, papaverine, and narcotine in unknown resins and powders may be taken as evidence that they are derived from *P. somniferum*.<sup>197</sup> The yield and alkaloid content of *P. somniferum* capsules upon fertilization has been determined.<sup>198</sup>

Synthetic work on morphine and morphinandienone alkaloids continues unabated. Amurine<sup>149,150</sup> and *O*-methylflavinantine<sup>149</sup> have been obtained by the benzyne reaction of appropriate benzyloisoquinoline precursors. A review concerning new synthetic derivatives of dihydrocodeinone is not readily available.<sup>199</sup> Codeine has been prepared in 98% yield from morphine using

<sup>195</sup> A. F. Cameron and C. Hannaway, *J.C.S. Perkin II*, 1973, 1002.

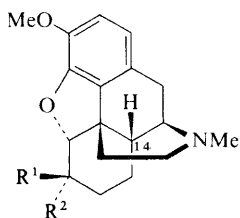
<sup>196</sup> J. A. Duke, *Econ. Bot.*, 1973, 27, 390.

<sup>197</sup> P. C. Maiti, A. Chatterjee, and S. Mookherjee, *J. Indian Acad. Forensic Sci.*, 1973, 12, 19 (*Chem. Abs.*, 1974, 80, 141 560w).

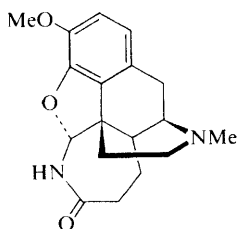
<sup>198</sup> K. Kuzminska, *Herba Pol.*, 1973, 19, 256 (*Chem. Abs.*, 1974, 80, 119 558e).

<sup>199</sup> R. Bogner, G. Gaal, G. Horvath, P. Kerekes, and Z. Dobany, *Acta Pharm. Hung.*, 1973, 43, 169 (*Chem. Abs.*, 1974, 80, 15 092g).

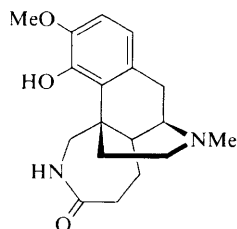
phenyltrimethylammonium methoxide as a methylating agent.<sup>200</sup> The available methods for the preparation of tosyloxy- and mesyloxy-derivatives of morphine and its analogues have been reviewed.<sup>201</sup> The morphinandenone alkaloids (+)-amurine, (+)-flavinantine, and (+)-pallidine have been synthesized by anodic oxidation using  $\text{HBF}_4$  as the electrolyte.<sup>202</sup> This procedure represents an improvement on the electrochemical synthesis of this class of compound previously reported by Miller (see Vol. 4 of these Reports). Dihydrocodeinone (120;  $\text{R}^1 + \text{R}^2 = \text{O}$ ) upon treatment with diazomethane gave the epoxide (120;  $\text{R}^1 + \text{R}^2 = \text{CH}_2\text{O}$ ), which upon lithium aluminium hydride reduction provided (120;  $\text{R}^1 = \text{OH}$ ,  $\text{R}^2 = \text{Me}$ ). On the other hand, treatment of dihydrocodeinone with methyl-lithium yielded the epimer (120;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{OH}$ ).<sup>203</sup> The Beckmann rearrangement of dihydrocodeinone oxime (120;  $\text{R}^1 + \text{R}^2 = \text{NOH}$ ) gave the c-homo-6-azamorphinan (121) whereas the Schmidt reaction of dihydrothebainone afforded the phenol (122).<sup>204,205</sup>



(120)

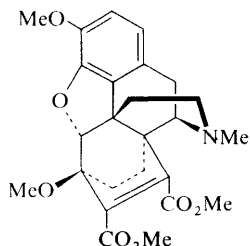


(121)

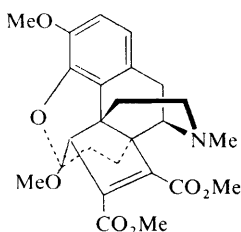


(122)

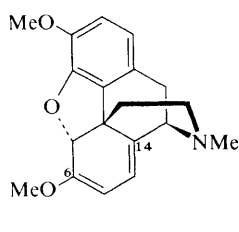
Photolysis of the adduct (123) gave the rearranged product (124), which was subjected to a number of chemical transformations.<sup>206</sup> (See also Vol. 4 for photochemistry of a similar adduct.) Treatment of thebaine (125) with 4-phenyl-



(123)



(124)



(125)

<sup>200</sup> K. Ikonomovski, *Acta Pharm. Jugoslav.*, 1973, **23**, 169 (*Chem. Abs.*, 1973, **79**, 137 324j).

<sup>201</sup> S. Makleit, *Acta Phys. Chim. Debrecina*, 1973, **18**, 265 (*Chem. Abs.*, 1974, **80**, 108 717e).

<sup>202</sup> T. Kotani and S. Tobinaga, *Tetrahedron Letters*, 1973, 4759.

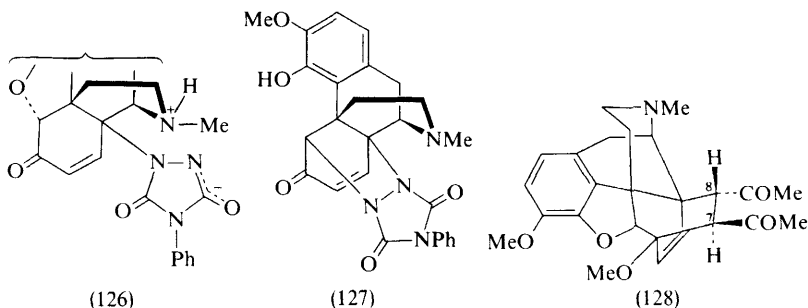
<sup>203</sup> G. Horvath, P. Kerekes, G. Gaal, and R. Bogнар, *Magyar Kém. Folyóirat*, 1973, **79**, 429 (*Chem. Abs.*, 1974, **80**, 27 406a).

<sup>204</sup> R. Bogнар, S. Makleit, L. Radies, and I. Seki, *Magyar Kém. Folyóirat*, 1973, **79**, 250 (*Chem. Abs.*, 1973, **79**, 53 638b).

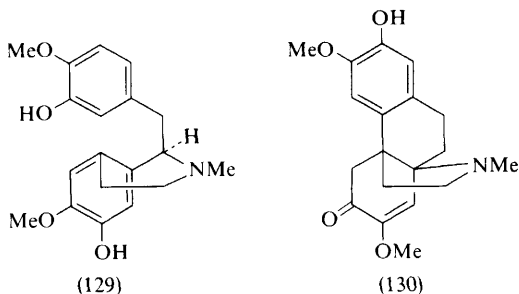
<sup>205</sup> R. Bogнар, S. Makleit, L. Radies, and I. Seki, *Org. Prep. Proced. Internat.*, 1973, **5**, 49.

<sup>206</sup> R. Rubinstein, R. Giger, and D. Ginsburg, *Tetrahedron*, 1973, **29**, 2383.

1,2,4-triazoline-3,5-dione gave the expected C-6, C-14-cycloaddition product,<sup>207</sup> which, when subjected to reaction with acid, yielded the betaine (126).<sup>208</sup> This compound was converted into the new adduct (127). Thebaine (125) was also shown to undergo Diels-Alder reactions with *trans*-disubstituted ethylenes containing relatively bulky groups.<sup>209</sup> *cis*-Disubstituted ethylenes were also used for the cycloaddition reactions and the two sets of results were correlated. For example, the product from (125) and *trans*-diacetylene was established to be the 7 $\beta$ ,8 $\alpha$ -diacetyl compound (128) by spectrometric methods. The downfield



shift observed in the n.m.r. spectrum for H-8 in the *N*-oxide and protonated forms of (128) constituted strong evidence for the stereostructure as written. Reductions, Grignard reactions, and base-catalysed rearrangements of the adducts [e.g. (128)] were also described.<sup>209</sup>



Reticuline (129) has been converted into the cephamine-type compound (130) using a phenol oxidative coupling reaction as the key step.<sup>210</sup> The Hofmann degradation of flavothebaone trimethyl ether  $\psi$ -methine (131) has been re-examined and shown to give (133) as the major product, presumably formed *via*

<sup>207</sup> R. Giger, R. Rubinstein, and D. Ginsburg, *Tetrahedron*, 1973, **29**, 2387.

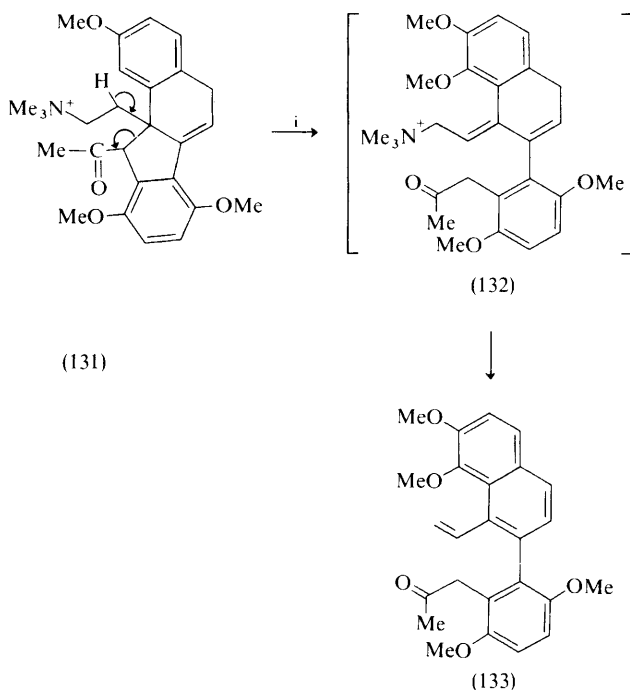
<sup>208</sup> R. Giger, R. Rubinstein, and D. Ginsburg, *Tetrahedron*, 1973, **29**, 2393.

<sup>209</sup> R. Rubinstein, F. Haviv, and D. Ginsburg, *Tetrahedron*, 1974, **30**, 1201.

<sup>210</sup> T. Kametani, T. Kobari, K. Shishido, and K. Fukumoto, *Tetrahedron*, 1974, **30**, 1059.



the intermediacy of (132) (Scheme 6).<sup>211</sup> The structure of (133) was deduced by  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. analysis. The dimeric structure (134) has been proposed for the product from the reaction of morphine with formaldehyde in sulphuric acid on the basis of spectroscopic data.<sup>212</sup> The 2,4,5-trimethylpyrrole-3-carboxylic acid ester of codeine has been synthesized by a mixed-anhydride procedure.<sup>32</sup>



Reagent: i, KOH-cyclohexanol, reflux

**Scheme 6**

The search for new pharmacologically active morphine derivatives continues to produce a voluminous synthetic literature. Part morphine-like compounds (135)<sup>213</sup> and (136)<sup>214</sup> have been prepared. Compound (136) has analgesic properties. A number of homobenzomorphan derivatives have been synthesized in order to probe into structure-activity relationships with respect to their analgesic activity.<sup>215</sup> New dibenzomorphan derivatives have been prepared.<sup>216</sup>

<sup>211</sup> K. W. Bentley, I. A. Selby, and C. A. Young, *J.C.S. Perkin I*, 1974, 682.

<sup>212</sup> H. Auterhoff and D. Braun, *Arch. Pharm.*, 1973, **306**, 866.

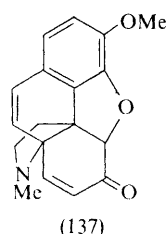
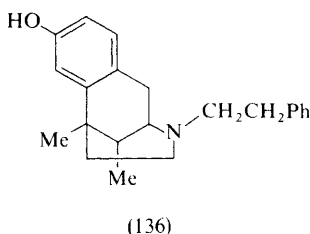
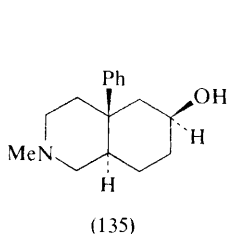
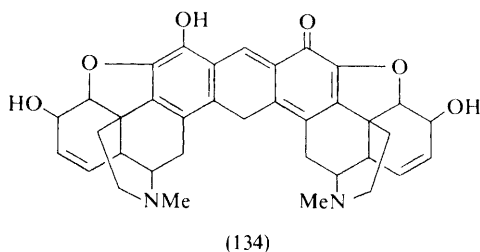
<sup>213</sup> N. Finch, L. Blanchard, R. T. Puckett, and L. H. Werner, *J. Org. Chem.*, 1974, **39**, 1118.

<sup>214</sup> T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, and H. Sugi, *J. Heterocyclic Chem.*, 1973, **10**, 313.

<sup>215</sup> S. Shotani and T. Kametani, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1053.

<sup>216</sup> A. Surana, D. Kishore, and B. C. Joshi, *Naturwiss.*, 1973, **60**, 388.

The sodium borohydride reduction of '9,10-dehydroindolinocodeine' (137) has been studied.<sup>217</sup> 3-Sulphopropyl and 4-sulphobutyl salts<sup>218</sup> and ethynyl derivatives<sup>219</sup> of morphine have been synthesized.



The proceedings of a symposium entitled 'Alcoholism and the Central Nervous System' contain a section which summarizes recent work on the possible role of morphine and related alkaloids in alcohol addiction.<sup>220</sup> Further information regarding pharmacological and toxicological properties of morphine and its analogues is available.<sup>221</sup>

A simple procedure for the preparation of C-15 and C-16 <sup>3</sup>H-labelled oripavine has been described.<sup>222</sup> Tritium-labelled morphine has been obtained using microwave discharge activation of tritium gas.<sup>223</sup>

Mass spectral, o.r.d., and c.d. studies have been carried out on unnatural B/C *trans*-fused morphine derivatives.<sup>224</sup> Characteristic differences between m.s. fragmentation patterns of C-14 epimeric derivatives were observed which should have diagnostic value. Mass spectral investigations were also used in structural and stereochemical assignments of benzomorphan derivatives.<sup>225</sup> The <sup>13</sup>C n.m.r. spectrum of codeine has been analysed.<sup>226</sup> A method for selective

<sup>217</sup> H. Bartsch and F. Vieboeck, *Monatsh.*, 1974, **105**, 213.

<sup>218</sup> I. Zeid, A. Saleh, and I. Ismail, *Chem. and Ind.*, 1973, 1001.

<sup>219</sup> P. Kerekes, R. Bognar, G. Gaal, and G. Horvath, *Magyar Kém. Folyóirat*, 1973, **79**, 401 (*Chem. Abs.*, 1974, **80**, 27 408c).

<sup>220</sup> F. A. Seixas, *Ann. New York Acad. Sci.*, 1973, **215**, 89.

<sup>221</sup> J. Knoll, S. Furst, and K. Kelemen, *J. Pharm. Pharmacol.*, 1973, **25**, 929.

<sup>222</sup> J. W. Lewis, M. J. Rance, and G. R. Young, *J. Medicin. Chem.*, 1974, **17**, 465.

<sup>223</sup> J. Fishman, B. I. Norton, and W. Hembree, *J. Labelled Compounds*, 1973, **9**, 563.

<sup>224</sup> H. Inoue, M. Takeda, and H. Kugita, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2004.

<sup>225</sup> D. P. Vaughan and A. H. Beckett, *J. Pharm. Pharmacol.*, 1973, **25**, 845.

quaternary-carbon  $^{13}\text{C}$  n.m.r. signal enhancement in dihydrothebaine has been developed.<sup>226a</sup>

New developments in analytical chemistry have centred around the application of combined physical methods involving mass spectrometry as the key component. For example, computerized g.c.-m.s. has been used in forensic analysis of opium,<sup>227</sup> and mass fragmentography has made it possible to detect normorphine in urine after codeine intake.<sup>228</sup> Direct mass spectral analysis of opium alkaloid mixtures has also been reported.<sup>229</sup> Other methods used in the analysis and separation of opium mixtures during the past year are: t.l.c.,<sup>230,231</sup> ion-exchange chromatography,<sup>232</sup> high-speed liquid chromatography (thebaine),<sup>233</sup> spectrophotometry,<sup>234,235</sup> electrophoresis (codeine),<sup>59</sup> complexometry,<sup>236</sup> and non-aqueous protometry.<sup>237</sup> The extraction of alkaloids with solutions of fatty acids<sup>238</sup> and the separation of the main opium alkaloids using a new eluent<sup>239</sup> have been described. The mechanism of adsorption of morphine alkaloids upon chromatography has been studied.<sup>240</sup> The preparation of decavanadates of codeine hydrochloride has been reported.<sup>241</sup>

Studies on the effect of phosphorus<sup>242</sup> and boron<sup>243</sup> on the yield and quality of oil poppy capsules have been carried out.

## 9 Colchicine Alkaloids

A new synthesis of ( $\pm$ )-colchicine (138; R = Me) has been reported using an elegant methylene-transfer reaction as the key step (Scheme 7).<sup>243a</sup> Reduction of the spirodienone (139) gave an epimeric mixture of alcohols (140), which upon

<sup>226</sup> F. W. Wehrli, *J.C.S. Chem. Comm.*, 1973, 379.

<sup>226a</sup> I. H. Sadler, *J.C.S. Chem. Comm.*, 1973, 809.

<sup>227</sup> R. M. Smith, *J. Forensic Sci.*, 1973, **18**, 327.

<sup>228</sup> W. O. R. Ebbighausen, J. Mowat, and P. Vestergaard, *J. Pharm. Sci.*, 1973, **62**, 146.

<sup>229</sup> Y. Suzuki, H. Hojo, M. Mizugaki, and M. Uchiyama, *Eisei Kagaku*, 1973, **19**, 212 (*Chem. Abs.*, 1974, **80**, 34 199p).

<sup>230</sup> A. Gyeresi and G. Racz, *Rev. Med. (Tirgu-Mures, Rom.)* 1973, **19**, 384 (*Chem. Abs.*, 1974, **80**, 124 801h).

<sup>231</sup> C. Guven and B. Aran, *Eczacilik Bul.*, 1973, **95**, 28 (*Chem. Abs.*, 1973, **79**, 97 023b).

<sup>232</sup> J. H. Knox and J. Jurand, *J. Chromatog.*, 1973, **82**, 398.

<sup>233</sup> D. W. Smith, T. H. Beasley, R. L. Charles, and H. W. Ziegler, *J. Pharm. Sci.*, 1973, **62**, 1691.

<sup>234</sup> H. J. Uhlmann, *Pharm. Ztg.*, 1973, **118**, 2029.

<sup>235</sup> A. Dzhumashev and G. B. Aimukhanedova, *Lek. Veshchestva Rast. Syr'ya Kirg.*, 1972, 102 (*Chem. Abs.*, 1973, **79**, 35 194z).

<sup>236</sup> M. Gajewska, *Chem. analit.*, 1973, **18**, 313 (*Chem. Abs.*, 1973, **79**, 97 016b).

<sup>237</sup> E. Galfalvi and V. Molnar, *Rev. Med. (Tirgu-Mures, Rom.)*, 1973, **19**, 147 (*Chem. Abs.*, 1974, **80**, 52 420h).

<sup>238</sup> L. Jusiak, *Acta Polon. Pharm.*, 1973, **30**, 49 (*Chem. Abs.*, 1973, **79**, 18 905q).

<sup>239</sup> A. Gyeresi and G. Racz, *Pharmazie*, 1973, **28**, 271.

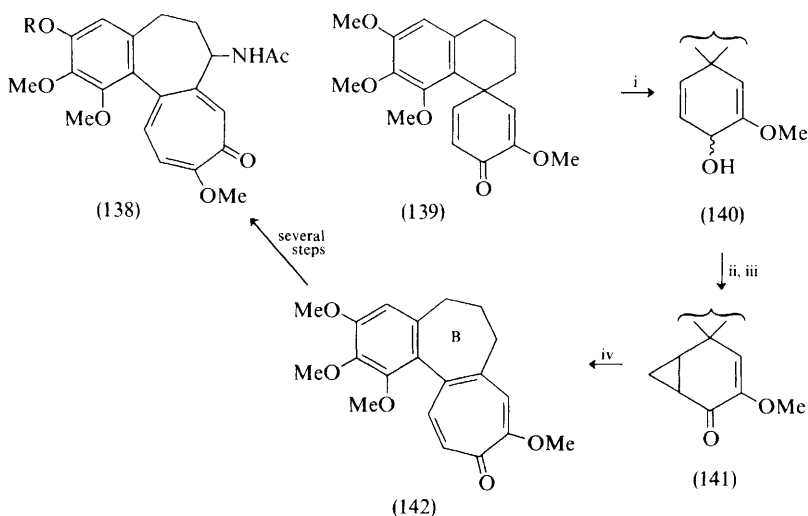
<sup>240</sup> M. Petkovic, *Acta Pharm. Jugoslav.*, 1973, **23**, 23 (*Chem. Abs.*, 1973, **79**, 9936y).

<sup>241</sup> V. Sucha and L. Zurkova, *Acta Fac. Rerum Natur. Univ. Comenianae, Chim.*, 1973, 27 (*Chem. Abs.*, 1974, **80**, 48 213a).

<sup>242</sup> G. E. Naumova and V. V. Sheberstov, *Sbornik Nauchn. Rab., Vses. Nauchn.-Issled. Inst. Lek. Rast.*, 1971, **3**, 105 (*Chem. Abs.*, 1974, **80**, 58 845x).

<sup>243</sup> L. I. Arsyukhina, *Sbornik Nauchn. Rab., Vses. Nauchn.-Issled. Inst. Lek. Rast.*, 1971, **3**, 112 (*Chem. Abs.*, 1974, **80**, 58 846y).

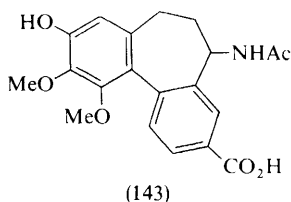
<sup>243a</sup> E. Kotani, F. Miyazaki, and S. Tobinaga, *J.C.S. Chem. Comm.*, 1974, 300.



Reagents: i,  $\text{NaBH}_4$ ; ii, Simmons-Smith; iii, Jones reagent; iv,  $\text{Ac}_2\text{O}-\text{H}_2\text{SO}_4$

**Scheme 7**

treatment with Simmons-Smith reagent followed by oxidation yielded the cyclopropyl ketone (141). The desired rearrangement of (141) took place in excellent yield to give (142), which had been previously converted into colchicine. The acid-catalysed hydrolysis of colchicine and several of its derivatives has been studied.<sup>244</sup> Desmethylocolchicine (138;  $\text{R} = \text{H}$ ) yielded desmethyallolocchicine (143) upon treatment with sodium methoxide.<sup>245</sup> Colchicine and other minor



alkaloids were obtained from galenical formulations by t.l.c. separation.<sup>246</sup> Luminescence and u.v. spectra of colchicine have been recorded and analysed.<sup>247</sup> In the course of a continuing search for tumour inhibitors of plant origin, a

<sup>244</sup> T. J. Fitzgerald, *Z. Naturforsch.*, 1973, **28c**, 228.

<sup>245</sup> M. K. Yusupov, Kh. Turdikulov, Kh. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1973, 194 (*Chem. Abs.*, 1973, **79**, 32 144x).

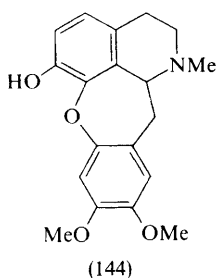
<sup>246</sup> M. Haag-Berrurier and M. C. Mathis, *Ann. pharm. franc.*, 1973, **31**, 457.

<sup>247</sup> H. Roigt and R. M. Leblanc, *Canad. J. Chem.*, 1973, **51**, 2821.

reinvestigation of *Colchicum speciosum* has been undertaken and demecolcine, colchicine, and desmethylcolchicine (138; R = H) have been isolated.<sup>248</sup> Desmethylcolchicine showed significant antileukaemic activity.

### 10 Cularine Alkaloids

A conventional synthesis of ( $\pm$ )-cularidine (144) has been reported.<sup>249</sup>



### 11 Protoberberine Alkaloids

Table 5 shows that isolation and structural elucidation work on this group has not diminished.

**Table 5** Isolation of protoberberine alkaloids

Species	Alkaloid (Structure)	Ref.
<i>Argemone albiflora</i> <sup>a</sup>	(-)-Scoulerine (145; R = H)	104
	(-)- $\beta$ -Scoulerine methohydroxide	104
	Berberine	105
	Coptisine	105
<i>A. brevicornuta</i>	Berberine	105
<i>A. ochroleuca</i>	Berberine	250
	(-)-Cheilanthesifoline	250
	(-)- $\alpha$ -Canadine methohydroxide	250
	(-)- $\alpha$ -Tetrahydropalmatine methohydroxide	250
	(-)-Stylopine methohydroxide	250
	Coptisine	250
<i>A. platyceras</i> <sup>b</sup>	(-)-Stylopine methoperchlorate	136
<i>A. turnerae</i>	(-)-Tetrahydropalmatine (145; R = Me)	105
<i>Berberis lycium</i>	Berberine chloroform <sup>c</sup> (146; R <sup>1</sup> + R <sup>2</sup> = CH <sub>2</sub> , R <sup>3</sup> = H, CCl <sub>3</sub> )	251
	Palmatine chloroform <sup>c</sup> (146; R <sup>1</sup> = R <sup>2</sup> = Me, R <sup>3</sup> = H, CCl <sub>3</sub> )	251
	Oxyberberine (146; R <sup>1</sup> + R <sup>2</sup> = CH <sub>2</sub> , R <sub>3</sub> = O)	251

<sup>248</sup> S. M. Kupchan, R. W. Britton, C. K. Chiang, N. Noyanalpan, and M. F. Ziegler, *Lloydia*, 1973, **36**, 338.

<sup>249</sup> H. Ida, H.-C. Hsu, and T. Kikuchi, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1001.

<sup>250</sup> K. Haisova and J. Slavik, *Coll. Czech. Chem. Comm.*, 1973, **38**, 2307.

<sup>251</sup> G. A. Miana, *Phytochemistry*, 1973, **12**, 1822.

Table 5—continued

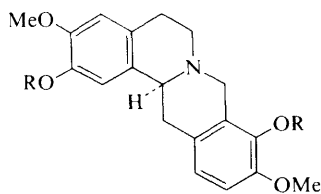
Species	Alkaloid (Structure)	Ref.
<i>Chelidonium majus</i>	Berberine	252
<i>Corydalis ambigua</i>	Cavidine	61
	Dehydrothalictrifoline	61
<i>C. incisa</i>	Corydamine (147)	253
<i>C. koidzumiana</i>	Corydalidine (148; R = H)	254
<i>Erythrina orientalis</i>	Scoulerine	109
	(+)-Coreximine	109
<i>Legnephora moorei</i>	Dehydrocorydalmine	157
<i>Papaver rhoeas</i>	(-)-N-Methylstylopinium chloride	255
<i>P. urbanianum</i>	Palmatine	63
<i>Phellodendron wilsonii</i>	Berberine	256
<i>Roemeria hybrida</i>	(-)-Isocorypalmine	164
	Coptisine	164
<i>Thalictrum minus</i>	Berberine	166a
<i>T. polygamum</i>	Berberine	167
	Berberrubine	167
	Deoxythalidastine chloride	167
	Thalifendine chloride	167

<sup>a</sup> An unknown alkaloid, AA-3, was also isolated.

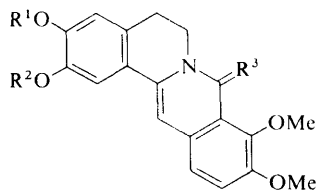
<sup>b</sup> An unknown alkaloid, AP1, was also isolated.

<sup>c</sup> Artefact.

Scoulerine (145; R = H), the main constituent of *Argemone albiflora*, had not been previously obtained from *Argemone* species.<sup>104</sup> The previously named alkaloid HF 1 isolated from *Hunnemannia fumariaefolia* was found to be identical with (-)-scoulerine. The co-occurrence of (-)-tetrahydropalmatine (145; R = Me) and (+)-armepavine in *Argemone turnerae* has been established for the first time.<sup>105</sup> The isolation and characterization of two artefact alkaloids, berberine chloroform (146; R<sup>1</sup> + R<sup>2</sup> = CH<sub>2</sub>; R<sup>3</sup> = H, CCl<sub>3</sub>) and palmatine chloroform (146; R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = H, CCl<sub>3</sub>), from *Berberis lycium* have



(145)



(146)

<sup>252</sup> K. Michels-Nyomarkay, *Ann. Univ. Sci. Budapest, Sect. Biol.*, 1971, **13**, 127 (*Chem. Abs.*, 1974, **80**, 130 517m).

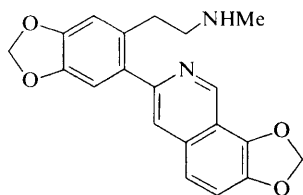
<sup>253</sup> N. Takao and K. Iwasa, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1587.

<sup>254</sup> C. Tani, N. Nagakura, and S. Hattori, *Tetrahedron Letters*, 1973, 803.

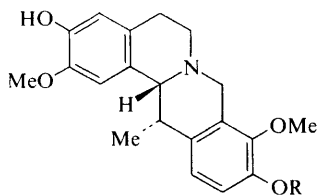
<sup>255</sup> V. Preininger, V. Simanek, L. Dolejs, O. Gasic, A. Nemeckova, and F. Santavy, *Coll. Czech. Chem. Comm.*, 1973, **38**, 3662.

<sup>256</sup> Y.-C. Lin, T'ai-Wan Yao Hsueh Tsa Chih, 1972, **24**, 1 (*Chem. Abs.*, 1974, **80**, 124 654n).

been described.<sup>251</sup> Corydamine (147), an alkaloid isolated from *Corydalis incisa*, has also been synthesized from ( $\pm$ )-tetrahydrocoptisine.<sup>253</sup> Corydalidine (148; R = H), isolated from *C. koidzumiana*, represents a demethyl analogue of corybulbine (148; R = Me).<sup>254</sup> A synthesis of corydalidine was also accomplished.



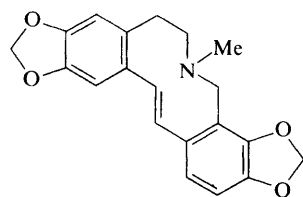
(147)



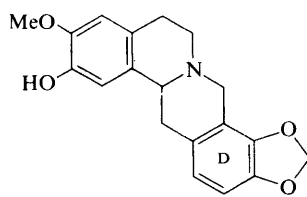
(148)

The isolation of (–)-*N*-methylstylopinium chloride from *Papaver rhoeas* represents the first time that a quaternary tetrahydroprotoberberine alkaloid has been isolated from the *Papaver* genus.<sup>255</sup> Treatment of this alkaloid with base in DMSO solution gave the Hofmann product (149). This type of product has not been obtained by Hofmann degradation of *N*-methyltetrahydroberberinium or *N*-methyltetrahydropseudoprotoberberinium alkaloids. Of the alkaloids isolated from *Thalictrum polygamum*, only berberine was shown to exhibit weak antimicrobial activity.<sup>167</sup> The alkaloid content of *Chelidonium majus* was studied as a function of the drying procedure of the plant.<sup>252</sup>

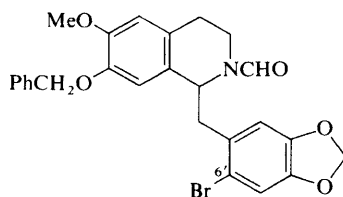
( $\pm$ )-Cheilanthifoline (150) has been synthesized.<sup>257</sup> The key step involved the acid-catalysed cyclization of the C-6'-bromo-substituted tetrahydrobenzylisoquinoline (151), which provided a precursor for cheilanthifoline with the correct



(149)



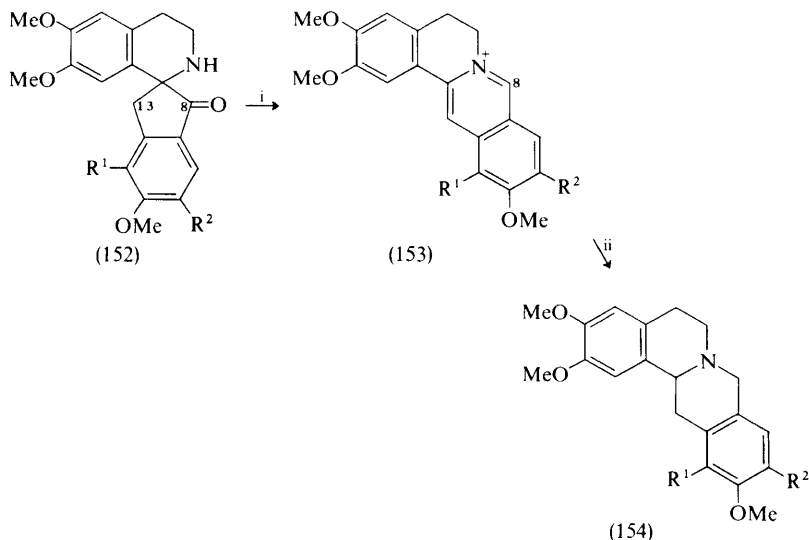
(150)



(151)

<sup>257</sup> C. Tani, S. Takao, H. Endo, and E. Oda, *Yakugaku Zasshi*, 1973, **93**, 268 (*Chem. Abs.*, 1973, **79**, 5478c).

orientation of the ring D substituents. The spiroisoquinolines (152;  $R^1 = H$ ,  $R^2 = OMe$ ) and (152;  $R^1 = OMe$ ,  $R^2 = H$ ) have been converted into xylopinine (154;  $R^1 = H$ ,  $R^2 = OMe$ ) and tetramethoxyxyberberine (154;  $R^1 = OMe$ ,  $R^2 = H$ ) respectively by a two-step procedure which involves a novel photochemical rearrangement (152)  $\rightarrow$  (153) (Scheme 8).<sup>258</sup> This reaction, for which mechanistic information is not available, occurs in high yield and with a high degree of stereoselectivity in that only the product of C-8 to N migration is observed.



Reagents: i, high-pressure Hg lamp, THF-N<sub>2</sub>; ii, NaBH<sub>4</sub>-EtOH

**Scheme 8**

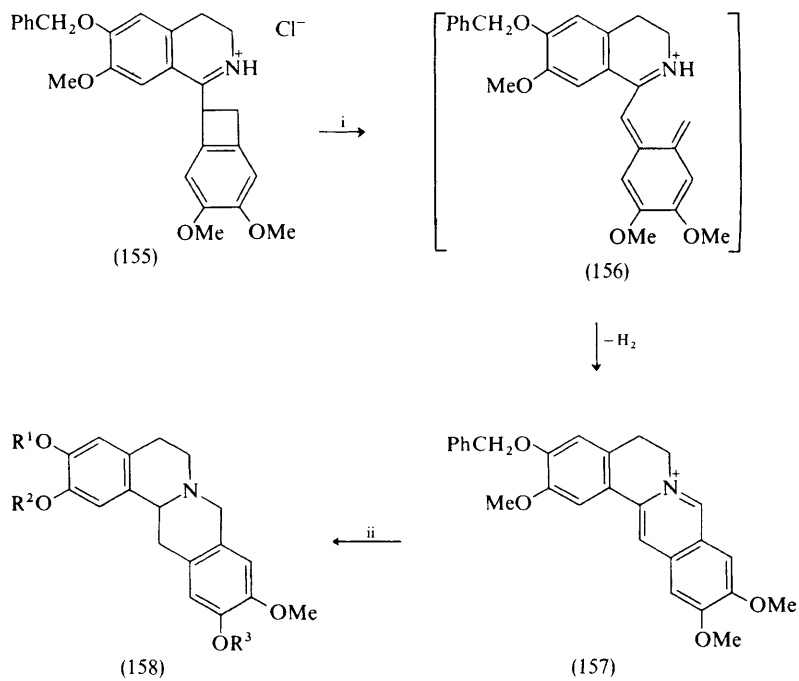
The usefulness of benzocyclobutenyl derivatives for the synthesis of isoquinoline alkaloids (see Vols. 2—4 of these Reports) has been extended to the preparation of the protoberberine bases (Schemes 9 and 10). In one case (Scheme 9), compound (155) was thermolysed to afford the protoberberinium salt (157), the reaction plausibly proceeding *via* the *ortho*-quinonoid intermediate (156), which then undergoes electrocyclization and dehydrogenation to give the product.<sup>259,260</sup> Reduction of (157) then provided the protoberberine (158;  $R^1 = H$ ,  $R^2 = R^3 = Me$ ). This route was used for the synthesis of ( $\pm$ )-discretine (158;  $R^1 = H$ ,

<sup>258</sup> H. Irie, K. Akagi, S. Tani, K. Yabusaki, and H. Yamane, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 855.

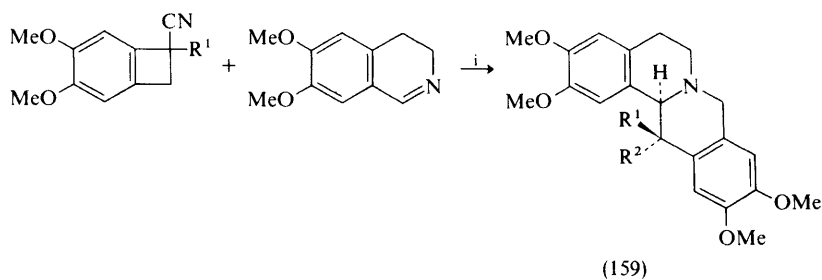
<sup>259</sup> T. Kametani, Y. Hirai, F. Satoh, K. Ogasawara, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 907.

<sup>260</sup> T. Kametani, M. Takemura, K. Ogasawara, and K. Fukumoto, *J. Heterocyclic Chem.*, 1974, **11**, 179.





Reagents: i, 160—170 °C, PhBr, 20 min,  $\text{N}_2$ ; ii,  $\text{PtO}_2\text{-H}_2$

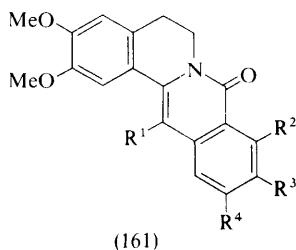
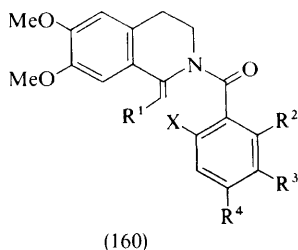
**Scheme 9**

Reagents: i, 150—160 °C, PhBr, 15 min; or 25 °C, 2 months; or  $\text{SiO}_2\text{-CH}_2\text{Cl}_2$

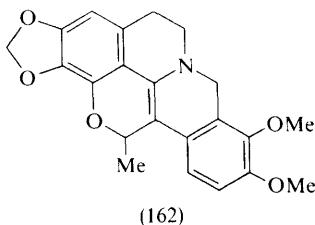
**Scheme 10**

$R^2 = R^3 = \text{Me}$ )<sup>259</sup> and ( $\pm$ )-coreximine (158;  $R^1 = \text{Me}$ ,  $R^2 = R^3 = \text{H}$ ).<sup>260</sup> An intermolecular version of this sequence was used for the synthesis of the two sets of stereoisomers (159;  $R^1 = \text{H}$  or  $\text{Me}$ ,  $R^2 = \text{CN}$ ) and (157;  $R^1 = \text{CN}$ ,  $R^2 = \text{H}$  or  $\text{Me}$ ) (Scheme 10).<sup>261</sup> The regioselectivity of the cycloaddition reaction was discussed.

The enamide photocyclization reaction has been widely exploited for the synthesis of protoberberine and other alkaloids (see Vol. 4 of these Reports and ref. 7). It has now been found that enamides of the type (160;  $X = \text{OMe}$ ) undergo photochemical elimination of methanol to produce in good yield protoberberine precursors of the type (161).<sup>262,263</sup> For example, compounds (161;  $R^1 = R^2 = \text{H}$ ,  $R^3 = R^4 = \text{OMe}$ ),<sup>262</sup> (161;  $R^1 = R^4 = \text{H}$ ,  $R^2 + R^3 = \text{OCH}_2\text{O}$ ), and (161;



$R^1 = \text{Me}$ ,  $R^2 + R^3 = \text{OCH}_2\text{O}$ ,  $R^4 = \text{H}$ )<sup>263</sup> were prepared by this method. The last two compounds were easily converted into ( $\pm$ )-sinactine and ( $\pm$ )-cavidine. A number of other substituents (160;  $X = \text{OAc}$ ,  $\text{Cl}$ , or  $\text{Br}$ ) were also shown to be useful for the photoelimination reaction.<sup>262</sup> The dealkylation of N-substituted protoberberinium salts on a semi-industrial scale has been described.<sup>264</sup> ( $\pm$ )-Mecambridine has been synthesized along conventional lines.<sup>265</sup> New protoberberine derivatives of the type (162) have been synthesized<sup>266</sup> (see also Vol. 3).



<sup>261</sup> T. Kametani, T. Takahashi, T. Honda, K. Ogasawara, and K. Fukumoto, *J. Org. Chem.*, 1974, **39**, 447.

<sup>262</sup> G. R. Lenz, *Tetrahedron Letters*, 1973, 1963.

<sup>263</sup> I. Ninomiya, H. Takasugi, and T. Naito, *Heterocycles*, 1973, **1**, 17.

<sup>264</sup> T. Kametani, E. Taguchi, K. Yamaki, A. Kozuka, and T. Terui, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1124.

<sup>265</sup> T. Kametani, A. Ujije, and K. Fukumoto, *Heterocycles*, 1974, **2**, 55.

<sup>266</sup> V. Simanek and A. Klasek, *Coll. Czech. Chem. Comm.*, 1973, **38**, 1614.

Four papers describe the synthesis of a large number of protoberberine derivatives for the purpose of testing them as hypotensive agents.<sup>267–270</sup> In one of these, the Mannich reaction of benzyloisoquinolines was explored in detail.<sup>267</sup> The influence of tetrahydropprotoberberine on experimental psychosis has been studied.<sup>271</sup>

## 12 Protopine Alkaloids

Recent sources of known protopine alkaloids are: *Argemone albiflora*,<sup>104,105</sup> *A. mexicana*, growing in Vietnam<sup>272</sup> and Sudan, U.S.S.R., and North Vietnam,<sup>273</sup> *A. ochroleuca*,<sup>250</sup> and *Corydalis ambigua*.<sup>61</sup> Protopine and cryptopine as well as six as yet unidentified alkaloids have been isolated from *Fumaria officinalis*.<sup>274</sup> The yield of alkaloids from this species as a function of the drying technique has been studied.<sup>275</sup> *Papaver urbanianum* has been shown to yield muramine and protopine.<sup>63</sup> Apparently, no structurally new protopine alkaloids have been isolated during the past year nor has any synthetic work been carried out.

α,β-Allocryptopine has been shown to possess significant antiarrhythmic effects<sup>276</sup> while protopine has been reported to affect the cardiovascular system.<sup>277</sup>

## 13 Benzophenanthridine Alkaloids

Results of new isolation work are summarized in Table 6.

**Table 6** Isolation of benzophenanthridine alkaloids

Species	Alkaloid (Structure)	Ref.
<i>Argemone albiflora</i>	Chelerythrine	104
	Sanguinarine	104, 105
<i>A. mexicana</i>	Heletrine (= Heleritrine?)	272, 273
	Heleritrine	272
	Sanguinarine	272

<sup>267</sup> T. Kametani, E. Taguchi, K. Yamaki, A. Kozuka, and T. Terui, *Yakugaku Zasshi*, 1973, **93**, 529 (*Chem. Abs.*, 1973, **79**, 79 005t).

<sup>268</sup> T. Kametani, K. Nyu, S. Ikeda, T. Tominaga, and R. Iwaki, *Yakugaku Zasshi*, 1973, **93**, 1116 (*Chem. Abs.*, 1973, **79**, 137 330h).

<sup>269</sup> T. Kametani, K. Nyu, S. Ikeda, T. Tominaga, and R. Iwaki, *Yakugaku Zasshi*, 1973, **93**, 1120 (*Chem. Abs.*, 1973, **79**, 137 331j).

<sup>270</sup> T. Kametani, K. Nyu, S. Ikeda, and R. Iwaki, *Yakugaku Zasshi*, 1973, **93**, 899 (*Chem. Abs.*, 1973, **79**, 105 451g).

<sup>271</sup> B. L. Danilevskii, N. Tulyaganov, and F. Sadritdinov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 136 (*Chem. Abs.*, 1974, **80**, 103 861n).

<sup>272</sup> T. Y. Bui and D. A. Murav'eva, *Farmatsiya (Moscow)*, 1973, **22**, 32 (*Chem. Abs.*, 1973, **79**, 113 201r).

<sup>273</sup> T. Y. Bui and D. A. Murav'eva, *Rast. Resur.*, 1973, **9**, 200 (*Chem. Abs.*, 1973, **79**, 15 820x).

<sup>274</sup> J. Hermansson and F. Sandberg, *Acta Pharm. Suecica*, 1973, **10**, 520.

<sup>275</sup> B. A. Figurkin, *Nauchn. Trudy, perm. farm. Inst.*, 1971, No. 4, 128 (*Chem. Abs.*, 1973, **79**, 23 540w).

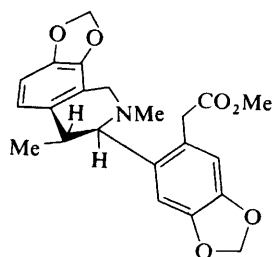
<sup>276</sup> Kh. U. Aliev and M. B. Akbarov, *Farmacol. Alkaloidov Ikh Proizvod.*, 1972, 133 (*Chem. Abs.*, 1974, **80**, 103 860m).

<sup>277</sup> Kh. U. Aliev, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 126 (*Chem. Abs.*, 1974, **80**, 103 859l).

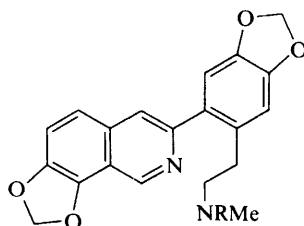
Table 6—continued

Species	Alkaloid (Structure)	Ref.
<i>A. ochroleuca</i>	Chelerythrine	250
	Sanguinarine	250
<i>A. platyceras</i>	Chelerythrine	136
	Corysamine	136
<i>Chelidonium majus</i>	Chelidonine	252, 278
	Chelerythrine	252, 278
	Homochelidonine	278
	Sanguinarine	252, 278
<i>Corydalis incisa</i>	Corydalic acid methyl ester (163)	279
	Corydamine hydrochloride (164; R = H)	280
	(+)-14-Epicorynoline (165)	280
	N-Formylcorydamine (164; R = CHO)	281
<i>Fagara xanthoxyloides</i>	Fagaridine (166)	282
<i>Zanthoxylum clava-herculis</i>	Chelerythrine	113
	Nitidine	113
<i>Z. rubescens</i>	Dihydrochelerythrine	283
<i>Z. tsianimposa</i>	Chelerythrine	284
	Dihydrochelerythrine	284

Corydalic acid methyl ester (163), isolated from *Corydalis incisa* only when the plant is in the vegetative stage, represents a new structural type which is formally derived from a ring C-cleaved benzophenanthridine nucleus.<sup>279</sup> It is of interest that two other alkaloids possessing a similar structure, corydamine hydrochloride (164; R = H) and N-formylcorydamine (164; R = CHO), are obtained from the same plant.<sup>280,281</sup> Biogenetic considerations would suggest that these alkaloids originate from a protoberberine skeleton.<sup>279</sup>



(163)



(164)

<sup>278</sup> W. Debska and R. Walkowiak, *Farm. Pol.*, 1973, **29**, 695 (*Chem. Abs.*, 1974, **80**, 63 784f).

<sup>279</sup> G. Nonaka, T. Koderu, and I. Nishioka, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1020.

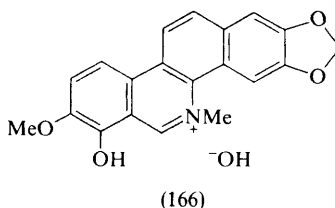
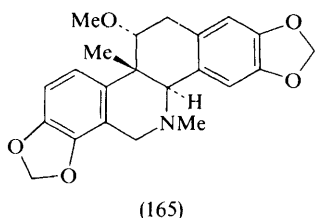
<sup>280</sup> G. Nonaka and I. Nishioka, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1410.

<sup>281</sup> N. Takao, H. W. Bersch, and S. Takao, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1096.

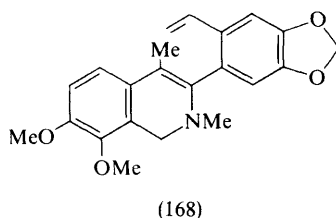
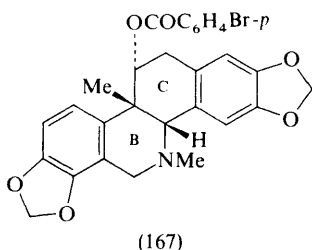
<sup>282</sup> F. G. Torto and I. A. Mensah, *Phytochemistry*, 1973, **12**, 2315.

<sup>283</sup> F. Fish, A. I. Gray, and P. G. Waterman, *Planta Med.*, 1973, **25**, 281.

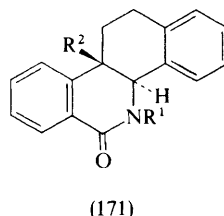
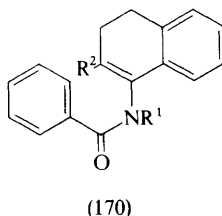
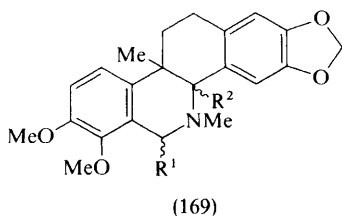
<sup>284</sup> N. Weber, *Chem. Ber.*, 1973, **106**, 3769.



The determination of the crystal structure of corynoline *p*-bromobenzoate (167) has revealed a *cis* B/C ring fusion with rings B and C in half-chair and twist-boat conformations respectively.<sup>285</sup>



Photolysis of the methine base (168) derived from berberine chloride gives the two isomeric tetrahydrochelerythrine derivatives (169;  $R^1 = OH$ ,  $R^2 = H$ ) and (169;  $R^1 = H$ ,  $R^2 = OH$ ).<sup>286</sup> The *cis* B/C ring junction in (169;  $R^1 = OH$ ,  $R^2 = H$ ) was determined by n.o.e. measurements. Details of the stereoselective photocyclization of the enamides (170) to *trans*-tetrahydrobenzo[*c*]phenanthridones (171) for a variety of substituents ( $R^1 = H$ , Me, or  $CH_2Ph$ ,  $R^2 = H$  or Me) have appeared.<sup>287</sup> Allonitidine and 5,6-dihydro-6-methoxyallonitidine have

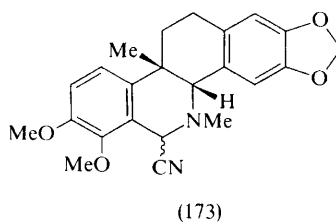
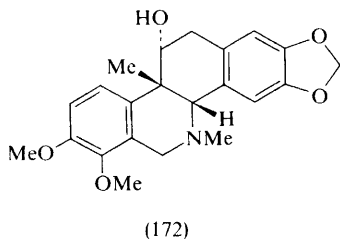


<sup>285</sup> T. Kametani, T. Honda, M. Ihara, H. Shimanouchi, and Y. Sasada, *J.C.S. Perkin II*, 1973, 1605.

<sup>286</sup> M. Onda, K. Yuasa, J. Okada, K. Katoaka, and K. Abe, *Chem. and Pharm. Bull. (Japan)*, 1973, 21, 1333.

<sup>287</sup> I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, *J.C.S. Perkin I*, 1973, 1696.

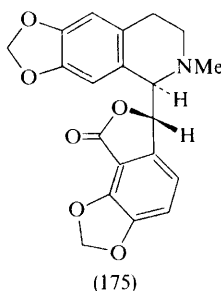
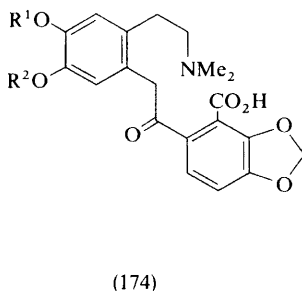
been synthesized.<sup>288</sup> An analogue of corynoline (172) has been prepared in seven steps starting with the  $\psi$ -cyanide (173), which had previously been obtained from berberine.<sup>289</sup>



Structural relations among cytotoxic and antitumour benzophenanthridine alkaloid derivatives have been discussed.<sup>290</sup>

#### 14 Phthalideisoquinoline Alkaloids

The presence of narcotine as well as of a number of other isoquinoline alkaloids in the aerial parts of *Papaver fugax* of Turkish origin has been established.<sup>111</sup> Adlumidiceine (174;  $R^1 + R^2 = CH_2$ ), adlumiceine (174;  $R^1 = R^2 = Me$ ), and the enol lactone of adlumidiceine are new alkaloids of the narceine type obtained from *Corydalis sempervirens* and *Papaver rhoeas*.<sup>291</sup> The occurrence of these alkaloids raises the possibility that these species also elaborate quaternary phthalideisoquinoline alkaloids.



The crystal and molecular structures of bicuculline (175) have been determined by *X*-ray analysis.<sup>292</sup> N.m.r. studies of the *N*-methylbicuculline cation indicate that the *N*-containing ring is in a half-chair conformation and that the phthalide ring adopts a pseudo-axial arrangement staggered with the *N*-methyl function.<sup>293</sup>

<sup>288</sup> K. Y. Zee-Cheng and C. C. Cheng, *J. Heterocyclic Chem.*, 1973, **10**, 867.

<sup>289</sup> M. Onda, K. Yuasa, and J. Okada, *Heterocycles*, 1973, **1**, 27.

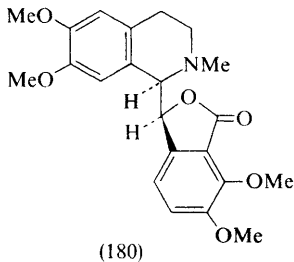
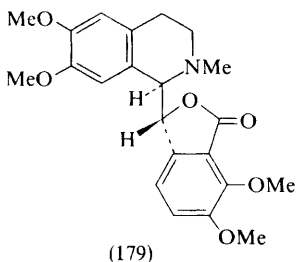
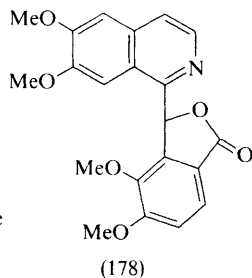
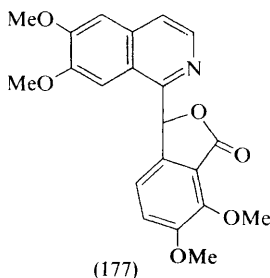
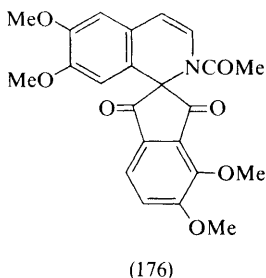
<sup>290</sup> F. R. Stermitz, K. A. Larson, and D. K. Kim, *J. Medicin. Chem.*, 1973, **16**, 939.

<sup>291</sup> V. Preininger, V. Simanek, O. Gasic, and F. Santavy, *Phytochemistry*, 1973, **12**, 2513.

<sup>292</sup> C. Gorinsky and D. S. Moss, *J. Cryst. Mol. Structure*, 1973, **3**, 299.

<sup>293</sup> P. R. Andrews and G. A. R. Johnston, *Nature New Biol.*, 1973, **243**, 29.

Alkyl ethers of narcotoline have been prepared.<sup>294,295</sup> A new route to the phthalideisoquinoline system has been developed.<sup>296</sup> It was found that acid treatment of (176) (*cf.* Vol. 4) results in an interesting rearrangement to give the isomeric phthalideisoquinolines (177) and (178). Compound (177) was further converted into cordrastine I (179) and cordrastine II (180).



The pharmacology of *d*- $\beta$ -hydrastine has been studied.<sup>297</sup>

## 15 Rhoeadine and Papaverrubine Alkaloids

Alpinigenine has been isolated from the dried latex of *Papaver bracteatum*.<sup>298</sup> Rhoeadine, as well as other isoquinoline alkaloids, has been found in the aerial parts of *P. fugax* of Turkish origin.<sup>111</sup> *P. urbanianum* has been shown to produce papaverrubine B.<sup>63</sup> A thin-layer chromatographic procedure on talc has been developed for the separation of papaverrubines A, D, and E from *P. rhoeas*.<sup>299</sup>

Details concerning attempts to correlate results of c.d. studies of rhoeadine and related alkaloids (*cf.* Vol. 4) with those obtained by the aromatic chirality and

<sup>294</sup> P. Gorecki and T. Kubala, *Herba Pol.*, 1973, **19**, 152 (*Chem. Abs.*, 1973, **79**, 146 709r).

<sup>295</sup> P. Gorecki and T. Kubala, *Herba Pol.*, 1973, **19**, 195 (*Chem. Abs.*, 1974, **80**, 133 665u).

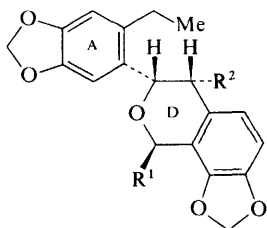
<sup>296</sup> V. Smula, N. E. Cundasawmy, H. L. Holland, and D. B. MacLean, *Canad. J. Chem.*, 1973, **51**, 3287.

<sup>297</sup> I. Khamdamov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 139 (*Chem. Abs.*, 1974, **80**, 103 862p).

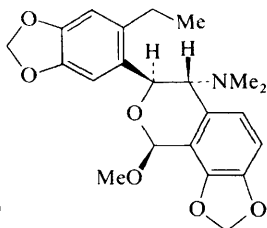
<sup>298</sup> I. Lalezari, A. Shafiee, and P. Nasseri-Nouri, *J. Pharm. Sci.*, 1973, **62**, 1718.

<sup>299</sup> A. Cvejic, O. Gasic, M. Pergal, and V. Canic, *Zbornik prir. Nauke, Matica Srp.*, 1972, No. 43, 185 (*Chem. Abs.*, 1973, **79**, 42 717a).

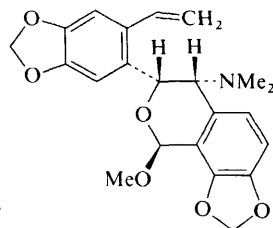
X-ray crystallographic methods are now available.<sup>300</sup> For the purpose of these studies, a number of ring B- and/or D-cleaved derivatives of these alkaloids, *e.g.* (181;  $R^1 = OH$ ,  $R^2 = NMe_2$ ), (181;  $R^1 = OMe$ ,  $R^2 = H$ ), (182), (183), (184), and (185) were prepared.



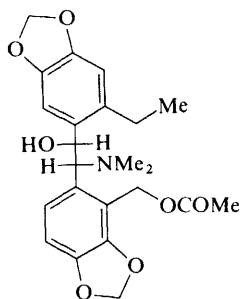
(181)



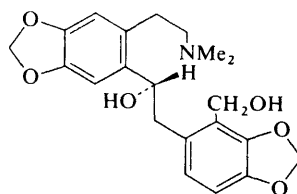
(182)



(183)

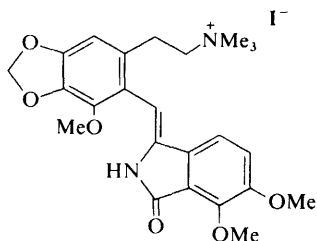


(184)

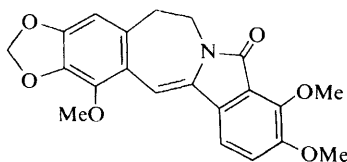


(185)

Treatment of the methiodide of narceine imide (186) with aqueous potassium hydroxide solution provided a low yield of the benzazepine derivative (187),



(186)

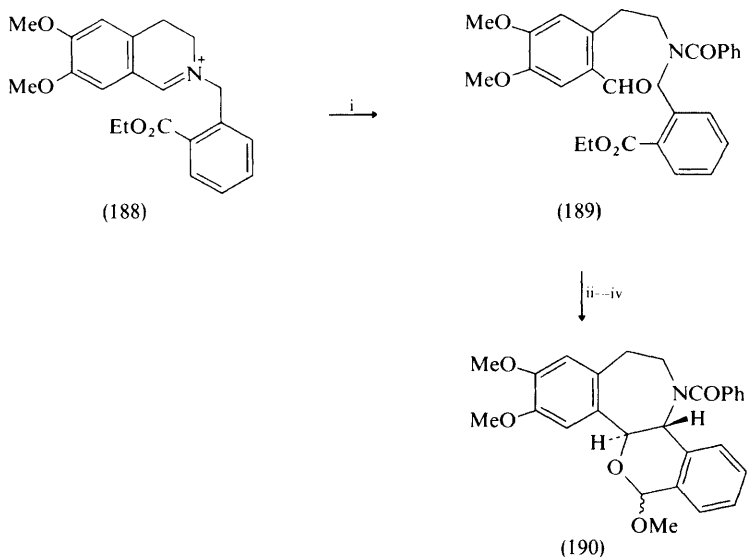


(187)

<sup>300</sup> J. Hrbek, jun., K. Hruban, V. Simanek, F. Santavy, and G. Snatzke, *Coll. Czech. Chem. Comm.*, 1973, **38**, 2799.



which was converted into an analogue of Schoepf-Schweikert amine VI (see Vols. 3 and 4).<sup>301</sup> An interesting and convenient route for the elaboration of the rhoeadan skeleton has been developed (Scheme 11).<sup>302</sup> Advantage was taken of



Reagents: i,  $\text{PhCOCl-NaOH}$ ; ii,  $\text{KOBu}^t\text{-DMSO}$ ; iii,  $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OMe})_2\text{-C}_5\text{H}_5\text{N}$ ; iv,  $\text{HC(OMe)}_3$

**Scheme 11**

the carbinolamine reactivity of (188) in aqueous base in order to prepare the benzaldehyde derivative (189). This compound was then converted in three steps into the rhoeadan (190) in good overall yield. A different approach to *cis*-fused rhoeadine alkaloids, as exemplified by the synthesis of ( $\pm$ )-*cis*-alpinigenine (193), has also been published (Scheme 12).<sup>303</sup> The key step involves the photo-sensitized oxidation of the enamino-ketone (191) to give the spiro lactone (192). The latter was converted into ( $\pm$ )-*cis*-alpinigenine (193) according to procedures previously developed in yet another synthesis of the rhoeadine alkaloids (*cf.* Vols. 3 and 4).

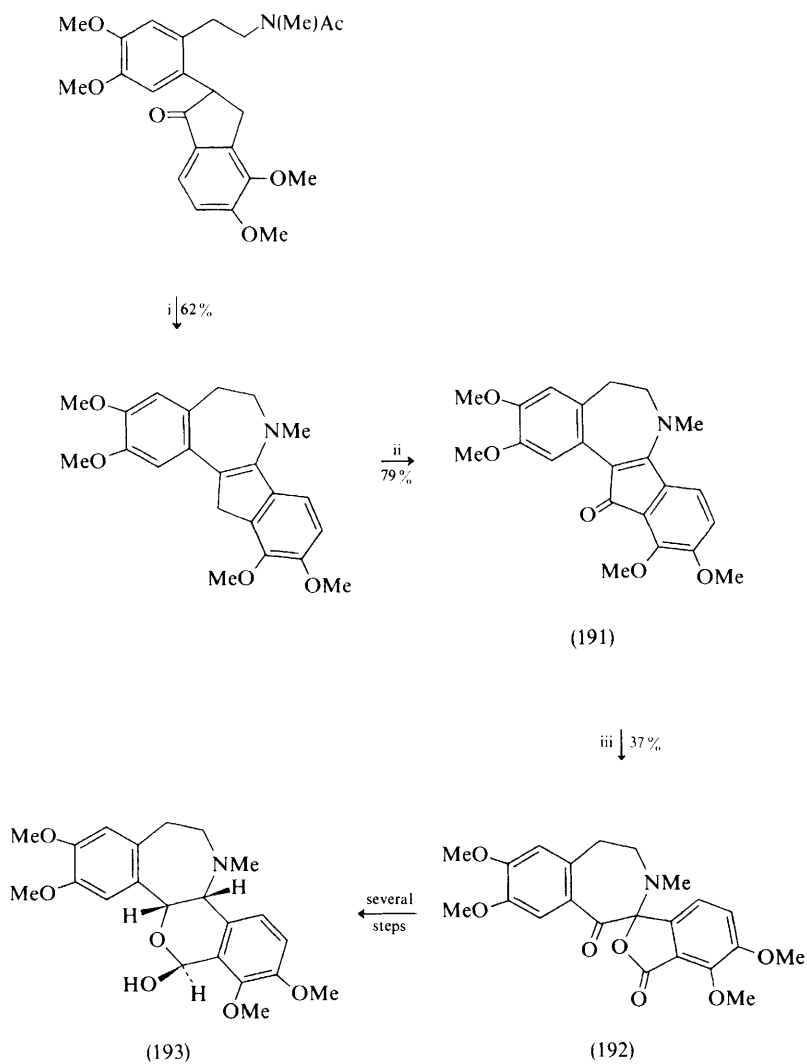
Details concerning the protoberberine  $\rightarrow$  spirobenzylisoquinoline  $\rightarrow$  di-benzocyclopent[*b*]azepine rearrangement [(194)  $\rightarrow$  (195)  $\rightarrow$  (196)] (see Vol. 3) have appeared.<sup>304</sup>

<sup>301</sup> Z. Vesely, J. Holubek, and J. Trojanek, *Chem. and Ind.*, 1973, 740.

<sup>302</sup> M. Shamma and L. Toke, *J.C.S. Chem. Comm.*, 1973, 740.

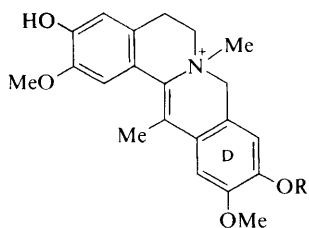
<sup>303</sup> K. Orito, R. H. Manske, and R. Rodrigo, *J. Amer. Chem. Soc.*, 1974, **96**, 1944.

<sup>304</sup> M. Shamma and J. F. Nugent, *Tetrahedron*, 1973, **29**, 1265.

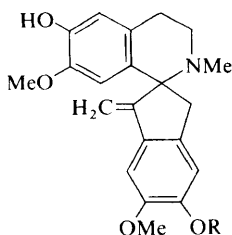


Reagents: i, KOH-EtOH-H<sub>2</sub>O, reflux; ii, Triton B, C<sub>5</sub>H<sub>5</sub>N-O<sub>2</sub>; iii, *hν*, O<sub>2</sub>, Rose Bengal

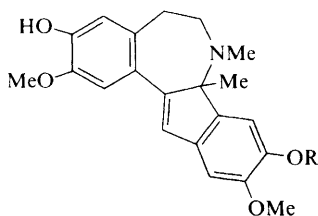
**Scheme 12**



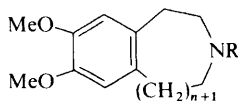
(194)



(195)



(196)



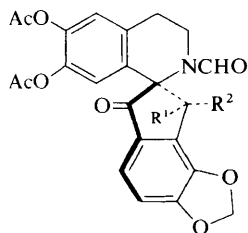
(197)

3-Benzazocines and higher homologues (197;  $n = 1-4$ ) have been synthesized.<sup>305</sup>

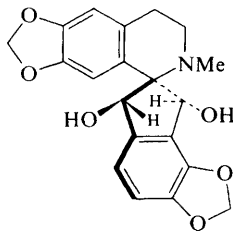
### 16 Spirobenzylisoquinoline Alkaloids

A recent review on the structural elucidation and synthesis of this class is not readily available.<sup>306</sup>

Several new synthetic reports are worthy of mention. The indanone approach has been used for the preparation of the bromo-derivative (198;  $R^1 = \text{Br}$ ,  $R^2 = \text{H}$ ), which was converted into the hydroxy-ketone (199;  $R^1 = \text{H}$ ,  $R^2 = \text{OH}$ ), the overall methodology thus allowing for a distinction between the two oxygen functions in the spiro-ring.<sup>307</sup> This approach led to a stereoselective synthesis of



(198)



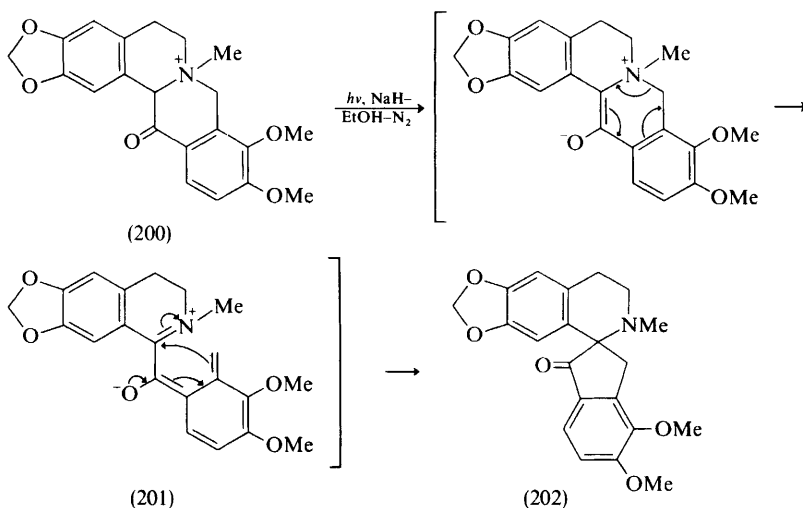
(199)

<sup>305</sup> B. Pecherer, F. Humiec, and A. Brossi, *Synth. Comm.*, 1973, **3**, 153.

<sup>306</sup> H. Irie, *Farumashia*, 1973, **9**, 472 (*Chem. Abs.*, 1973, **79**, 137 322g).

<sup>307</sup> S. McLean and J. Whelan, *Canad. J. Chem.*, 1973, **51**, 2457.

( $\pm$ )-ochrobirine (199). The photolytic rearrangement (200)  $\rightarrow$  (202) (Scheme 13) under basic conditions represents an elegant entry into the spirobenzylisoquinoline alkaloids.<sup>308</sup> This reaction may be envisaged to proceed via a retro-Diels–Alder intermediate (201) similar to that proposed for the direct base-catalysed protoberberine  $\rightarrow$  spirobenzylisoquinoline rearrangement (194)  $\rightarrow$  (195). Details concerning the synthesis of alkaloids *via* the thermal rearrangement of benzocyclobutenyl derivatives (see Vol. 4) have appeared.<sup>309</sup>



**Scheme 13**

### 17 Ipecacuanha Alkaloids

The arenesulphonic acid salt of emetine has been prepared for qualitative analysis.<sup>310</sup>

### 18 Dimeric Benzylisoquinoline Alkaloids

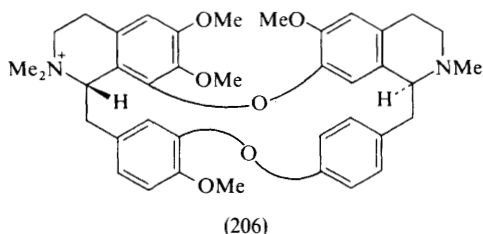
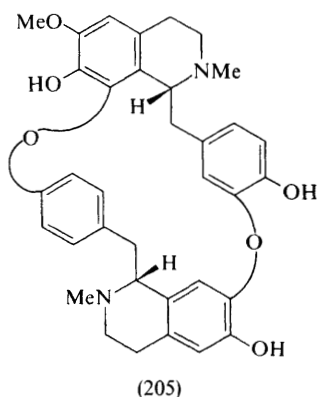
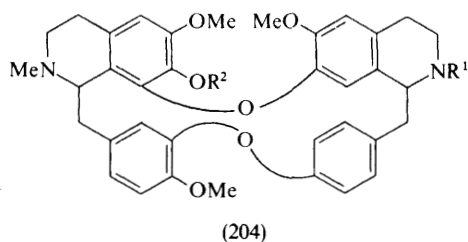
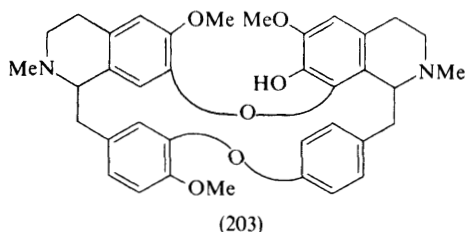
Five new bisbenzylisoquinoline alkaloids, cycleapeltine (203; 1-*S*, 1'-*S*), cycleadrine (204;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ), cycleacurine (205), cycleanorine (204;  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Me}$ , 1-*S*, 1'-*S*), and cycleahomine chloride (206) have been isolated from *Cyclea peltata*.<sup>311</sup> Three related compounds which proved to be artefacts were

<sup>308</sup> B. Nalliah, R. H. F. Manske, R. Rodrigo, and D. B. MacLean, *Tetrahedron Letters*, 1973, 2795.

<sup>309</sup> T. Kametani, T. Takahashi, and K. Ogasawara, *J.C.S. Perkin I*, 1973, 1464.

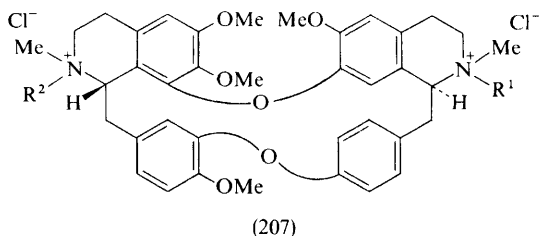
<sup>310</sup> Z. Zakrzewski and J. Jarzebinski, *Farm. Pol.*, 1973, **29**, 517 (*Chem. Abs.*, 1973, **79**, 118 289k).

<sup>311</sup> S. M. Kupchan, A. J. Liepa, R. L. Baxter, and H. P. J. Hintz, *J. Org. Chem.*, 1973, **38**, 1846.

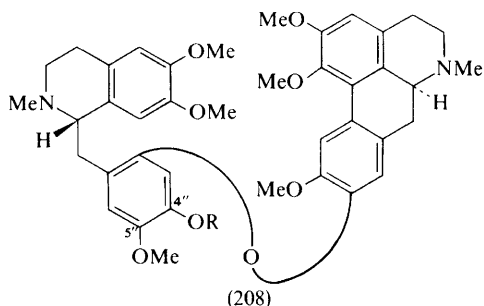


also obtained. The presence of dauricine in *Cocculus laurifolius* remains doubtful.<sup>106</sup> According to chemotaxonomic studies, the plant referred to as Krung Kha Mao (Menispermaceae) and previously thought to be the same as *Cissampelos pareira* may in fact be identical with *Cyclea barbata*.<sup>312</sup> This species elaborates a monoquaternary berbamine-type alkaloid, monomethyl-tetrandrinium chloride (207;  $R^1 = H$ ,  $R^2 = Me$  or  $R^1 = Me$ ,  $R^2 = H$ ). The location of the tertiary and quaternary nitrogen centres was not established and raises problems similar to those encountered in the structural elucidation of (+)-tubocurarine (see Vol. 2). Partial synthesis of (207;  $R^1 = H$ ,  $R^2 = Me$  or  $R^1 = Me$ ,  $R^2 = H$ ) from tetrandrine was achieved.

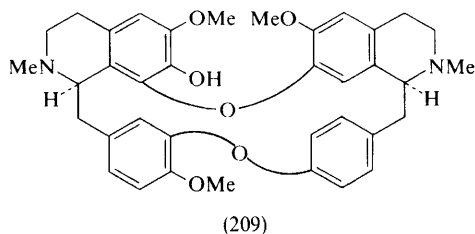
<sup>312</sup> B. Hoffstadt, D. Moecke, P. Pachaly, and F. Zymalkowski, *Tetrahedron*, 1974, **30**, 307.



Thalidoxine (208;  $R = H$ ) is a new aporphine-benzylisoquinoline alkaloid isolated from *Thalictrum dioicum*.<sup>313</sup> Methylation with diazomethane gave the known thalicarpine (208;  $R = Me$ ). The site of the phenolic OH was established at C-4'' rather than at C-5'' by n.m.r. studies of the acetate (208;  $R = Ac$ ). The



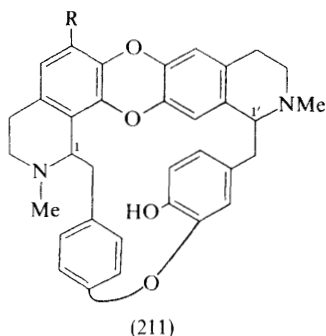
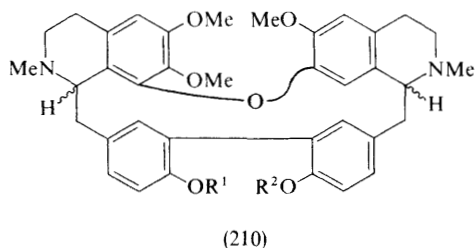
n.m.r. spectra of a number of aporphine-benzylisoquinoline alkaloids were also studied and several reassignments of methoxy resonances in particular alkaloids were made. Thalicarpine has been isolated from *T. polygnum* and has been shown to exhibit antimicrobial activity.<sup>167</sup> The same species also yielded a new alkaloid, thaligine (209).<sup>314</sup> Funiferine, previously obtained from *Tiliacora funifera*, has been shown to possess the revised structure (210;  $R^1 = H$ ,  $R^2 = Me$ ).<sup>315</sup> Funiferine is thus an *O*-methyl positional isomer of rodiasine (210;



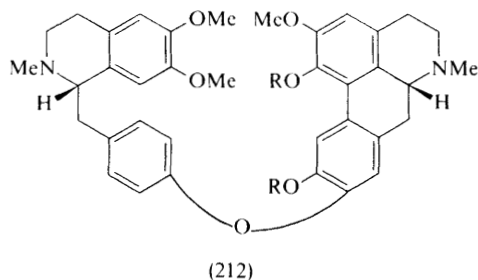
<sup>313</sup> M. Shamma, S. S. Salgar, and J. L. Moniot, *Tetrahedron Letters*, 1973, 1859.

<sup>314</sup> M. Shamma and S. Y. Yao, *Experientia*, 1973, **29**, 517.

<sup>315</sup> A. N. Tackie, D. Dwuma-Badu, J. E. Knapp, and P. L. Schiff, jun., *Lloydia*, 1973, **36**, 66.



$R^1 = \text{Me}, R^2 = \text{H}$ ). The Menispermaceae plant *Triclisia gillettii* has been shown to elaborate two new phenolic dimeric bases, efrine (211;  $R = \text{H}$ )<sup>316</sup> and trigilletine (211;  $R = \text{OMe}$ )<sup>317</sup> in addition to the known alkaloids stebisimine, isotetrandrine, and cocsuline.<sup>318</sup> The code-named alkaloids TGS-1, TGL-3, and TGL-4 were also isolated but not fully characterized.<sup>318</sup> *T. patens* was shown to produce the known bases phaeanthine, pycnamine, and cocsuline, as well as TGS-1.<sup>318</sup> Fangchinoline<sup>318</sup> and tricordatine (211;  $R = \text{OH}$ )<sup>317,318</sup> have been obtained from *T. subcordata*. The optical activity of the methylation products of trigilletine (211;  $R = \text{OMe}$ ) and tricordatine (211;  $R = \text{OH}$ ) suggested that these alkaloids possess stereochemistry identical with that of the known isotrilobine (1*S*,1'*S*).<sup>317</sup> A full account of the structural elucidation of pakistanine (212;  $R = \text{H}$ ) and pakistanamine (213), aporphine-benzylisoquinoline and proaporphine-benzylisoquinoline dimers respectively, isolated from *Berberis baluchistanica* (see Vol. 3), is now available.<sup>319</sup> Biogenetic speculation is provided partially on the basis of the acid-catalysed dienone-phenol rearrangement of

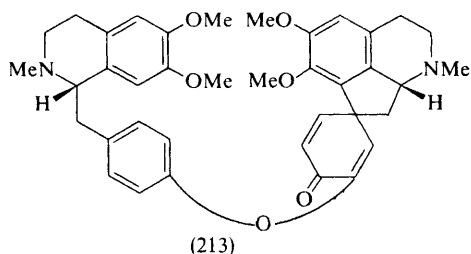


<sup>316</sup> R. Huls and C. Detry, *Bull. Soc. roy. Sci. Liège*, 1973, **42**, 73 (*Chem. Abs.*, 1973, **79**, 32 156c).

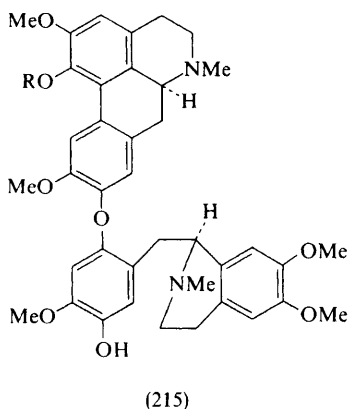
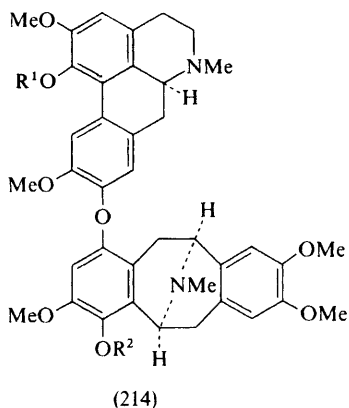
<sup>317</sup> A. N. Tackie, D. Dwuma-Badu, T. Okarter, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, jun., *Phytochemistry*, 1973, **12**, 2509.

<sup>318</sup> A. N. Tackie, D. Dwuma-Badu, T. Okarter, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, jun., *Lloydia*, 1974, **37**, 1.

<sup>319</sup> M. Shamma, J. L. Moniot, S. Y. Yao, G. A. Miana, and M. Ikram, *J. Amer. Chem. Soc.*, 1973, **95**, 5742.



(213), which, after methylation, gives rise to compound (212; R = Me). Two examples of a new group of dimeric alkaloids have been discovered in *Thalictrum polygamum*.<sup>320</sup> The porphine-pavine dimers pennsylvavine (214; R<sup>1</sup> = Me, R<sup>2</sup> = H) and pennsylvavoline (214; R<sup>1</sup> = R<sup>2</sup> = H) have been isolated and structurally elucidated, mainly on the basis of n.m.r. and mass spectral studies. Two additional alkaloids belonging to the thalicarpine series, (+)-pennsylvanine (215; R = Me) and (+)-pennsylvanamine (215; R = H), were also isolated from *T. polygamum*.<sup>320</sup>



Structural elucidation work on the cencentrine alkaloids has been concisely reviewed.<sup>321</sup> A biogenetic proposal for these unusual morphine-cularine dimers was also advanced.

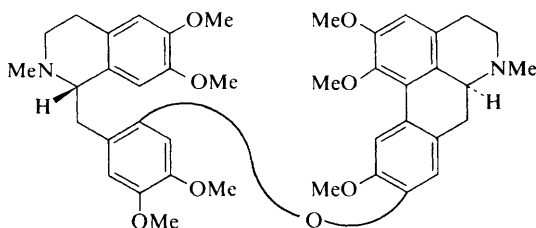
Thalicarpine (216) is presently in clinical trial as a tumour-inhibitory agent. In view of the probable need of this alkaloid in large quantities, synthetic work had been undertaken some time ago by Kupchan and his collaborators (see Vols. 3 and 4). Details and modifications of this work are now available.<sup>322</sup> The same

<sup>320</sup> M. Shamma and J. L. Moniot, *J. Amer. Chem. Soc.*, 1974, **96**, 3338.

<sup>321</sup> R. Rodrigo, ref. 1, p. 407.

<sup>322</sup> S. M. Kupchan, A. J. Liepa, V. Kameswaran, and K. Sempuku, *J. Amer. Chem. Soc.*, 1973, **95**, 2995.





(216)

group has also synthesized ( $\pm$ )-*O*-methyldauricine in connection with general studies aimed at delving into structure–tumour-inhibitory activity relationships of dimeric benzylisoquinoline alkaloids.<sup>323</sup>

The effects of hyatine methochloride and (+)-tubocurarine chloride on the autonomic ganglia of cats have been studied.<sup>324</sup> The cardiovascular action of thalicarpine has been investigated.<sup>325</sup> Fetidine has been shown to possess anti-inflammatory activity.<sup>326</sup> *Thalictrum* alkaloids in general have been shown to exhibit antitubercular activity.<sup>327</sup>

<sup>323</sup> S. M. Kupchan and H. W. Altland, *J. Medicin. Chem.*, 1973, **16**, 913.

<sup>324</sup> G. K. Patnaik, S. N. Pradhan, and M. M. Vohra, *Indian J. Exp. Biol.*, 1973, **11**, 89 (*Chem. Abs.*, 1974, **80**, 103 855p).

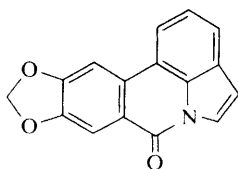
<sup>325</sup> E. H. Herman and D. P. Chadwick, *Pharmacology*, 1973, **10**, 178.

<sup>326</sup> F. Sadritdinov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 154 (*Chem. Abs.*, 1974, **80**, 91 211k).

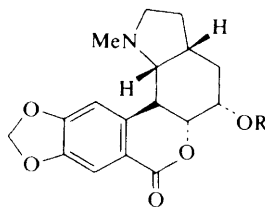
<sup>327</sup> Sh. U. Ismailov and D. A. Asadov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, 171 (*Chem. Abs.*, 1974, **80**, 103 857r).

Progress in this area during the past two to three years has been reviewed in the new MTP International Review of Science series.<sup>1</sup>

In addition to a large number of known alkaloids, *Lycoris sanguinea* has been shown to elaborate the highly dehydrogenated compound (1).<sup>2</sup> Poetinate (2; R = OCEt), a new alkaloid obtained from *Narcissus poeticus* var. *ornatus*, is a simple variant of clivonine (2; R = H).<sup>3</sup> Efficient isolation of lycorine from *Ungernia severtzovii* by the use of an ion-exchange method has been described.<sup>4</sup>



(1)



(2)

The <sup>13</sup>C n.m.r. spectra of examples of all Amaryllidaceae structural types have been recorded and fully assigned with the aid of proton-decoupling, lanthanide shift reagents, and empirical calculations.<sup>5</sup>

The crystal structure of lycorine has been determined.<sup>6</sup>

A number of stimulating and instructive synthetic achievements have been reported. A convenient synthesis of 1-desoxylycorinone (10), a degradation product of lycorine, has been announced (Scheme 1).<sup>7</sup> The oxazolone (3), readily prepared from piperonal and hippuric acid in the presence of acetic anhydride and sodium acetate, was treated with the sodium salt of dimethyl 3-oxoglutarate

<sup>1</sup> P. W. Jeffs, in 'Alkaloids', ed. K. Wiesner (MTP International Review of Science), Organic Chemistry, Series One, Vol. 9, Butterworths, London, 1973, p. 273.

<sup>2</sup> S. Takagi and M. Yamaki, *Yakugaku Zasshi*, 1974, **94**, 617 (*Chem. Abs.*, 1974, **81**, 74 924y).

<sup>3</sup> W. Doepeke and T. D. Nguyen, *Z. Chem.*, 1974, **14**, 57.

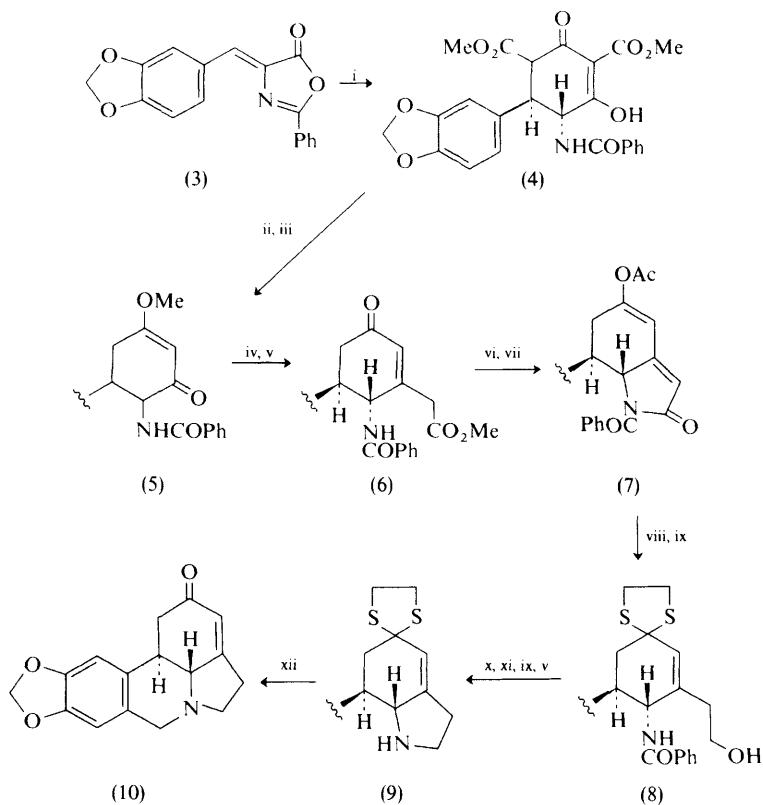
<sup>4</sup> T. Sadikov, I. N. Zatorskaya, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1974, **10**, 110 (*Chem. Abs.*, 1974, **81**, 68 419w).

<sup>5</sup> L. Zetta, G. Gatti, and C. Fuganti, *J.C.S. Perkin II*, 1973, 1180.

<sup>6</sup> R. Roques, J. Piquion, R. Fourme, and D. Andre, *Acta Cryst.*, 1974, **30B**, 296.

<sup>7</sup> H. Muxfeldt, J. P. Bell, J. A. Baker, and U. Cuntze, *Tetrahedron Letters*, 1973, 4587.

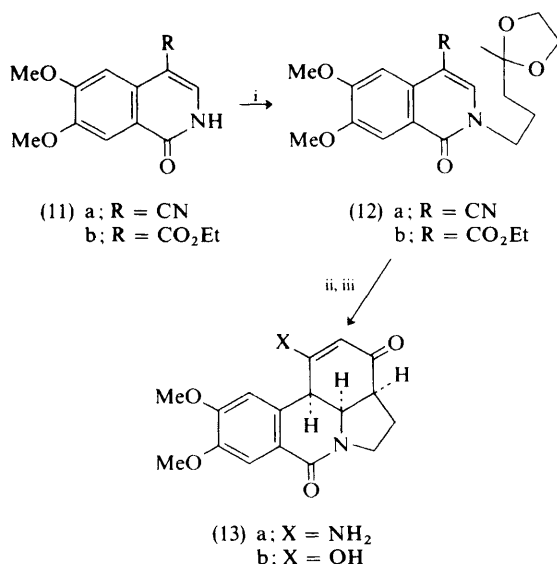
to give the cyclohexenone (4) in quantitative yield. This reaction has been previously generalized for the preparation of 4-aminocyclohexane-1,3-diones. Compound (4) was hydrolysed and decarboxylated and the resulting product was dissolved in methanol to give a mixture of enol ethers from which the major isomer (5) could be readily isolated. Compound (5) was subjected to the Reformatsky reaction to give, after acidic work-up, the enone (6). Cyclization led to (7); thioketalization followed by selective reduction led to the primary alcohol (8). Mesylation followed by base-catalysed cyclization and reductive debenzoylation gave the amine (9) which, upon Pictet–Spengler reaction with formaldehyde, gave 1-deoxy-lycorinone (10). The facile dethioketalization which accompanied the last reaction was interpreted as a transthioetherification with formaldehyde acting as the acceptor.



**Reagents:** i, Na salt of  $\text{MeO}_2\text{CCH}_2\text{COCH}_2\text{CO}_2\text{Me}$ , THF; ii,  $\text{Ba}(\text{OH})_2$ ; iii, MeOH; iv,  $\text{BrCH}_2\text{CO}_2\text{Me}$ , Zn; v,  $\text{H}^+$ ; vi, base; vii,  $\text{Ac}_2\text{O}$ ; viii,  $\text{H}^+$ ,  $\text{HSCH}_2\text{CH}_2\text{SH}$ ; ix,  $\text{LiAlH}_4$ ; x,  $\text{MeSO}_2\text{Cl}$ ; xi, NaH, DMF; xii,  $\text{CH}_2\text{O}$ , HCl, HOAc

Scheme 1

A short synthesis of the tetracyclic  $\gamma$ -lycorane derivatives (13a) and (13b) from isocarbostyrils has been reported (Scheme 2).<sup>8</sup> N-Alkylation of (11a) and (11b) with 5-bromo-2-pentanone ethylene ketal gave the ketals (12a) and (12b), respectively. Acid hydrolysis provided the corresponding ketones which upon base-catalysed cyclization yielded compounds (13a) and (13b), respectively.



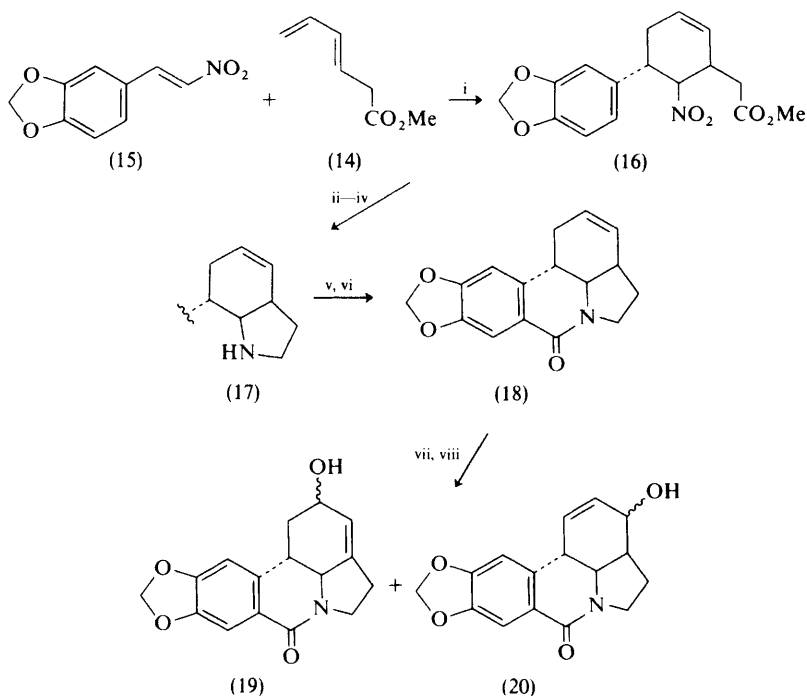
Reagents: i, Br(CH<sub>2</sub>)<sub>3</sub>C(OCH<sub>2</sub>)<sub>2</sub>Me, K<sub>2</sub>CO<sub>3</sub>, DMF; ii, 2% HCl, THF; iii, KOBu<sup>t</sup>, HOBu<sup>t</sup>

**Scheme 2**

Epimeric mixtures of the lycorine derivatives (19) and (20) which appear to be suitable for further elaboration to Amaryllidaceae alkaloids have been prepared (Scheme 3).<sup>9</sup> Deconjugation of methyl sorbate with lithium di-isopropylamide-HMPA in THF solution gave (14) which, upon treatment with (15), gave the Diels-Alder adduct (16). Three successive reduction steps were necessary to obtain the amine (17) which was subjected to Bischler-Napieralski reaction to give the lactam (18). Epoxidation followed by oxidative rearrangement using the Sharpless phenyl selenide reagent gave a mixture from which the epimeric (19) and (20) could be separated by preparative t.l.c. in the ratio 3 : 1 (overall yield 30% from the epoxide intermediate).

<sup>8</sup> E. Wenkert, H. P. S. Chawla, and F. M. Schell, *Synthetic Comm.*, 1973, 3, 381.

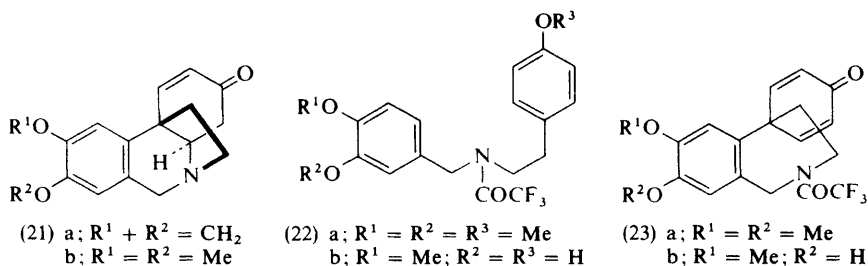
<sup>9</sup> K. Torsell, *Tetrahedron Letters*, 1974, 623.



Reagents: i,  $\Delta$ ; ii, Zn,  $H_2SO_4$ , MeOH- $CHCl_3$ ; iii,  $LiAlH_4$ ; iv, Fe,  $H_2SO_4$ , MeOH; v,  $ClCO_2Et$ ; vi,  $POCl_3$ ; vii,  $m-ClC_6H_4CO_3H$ ;  $CH_2Cl_2$ ; viii,  $PhSe^-$

**Scheme 3**

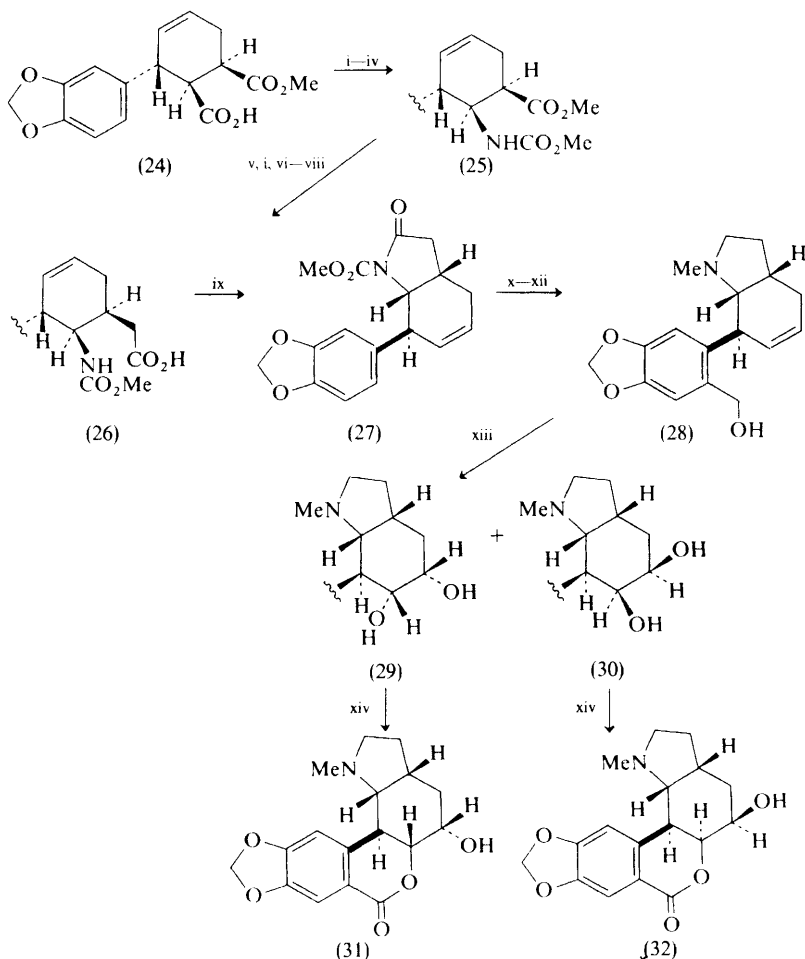
Biogenetic-type syntheses of ( $\pm$ )-oxocrinine (21a) and ( $\pm$ )-oxomaritidine (21b) by an anodic oxidation procedure have been achieved.<sup>10</sup> Thus oxidation of the trifluoroacetyl derivative (22a) in acetonitrile solution using platinum electrodes and fluoroboric acid electrolyte gave the spirodienone (23a) in 62% yield. Compound (23a) was readily converted into ( $\pm$ )-oxomaritidine (21b) by known procedures. This represents the highest observed yield of a phenol oxidative



<sup>10</sup> E. Kotani, N. Takeuchi, and S. Tobinaga, *J.C.S. Chem. Comm.*, 1973, 550.

coupling reaction for the 5,10-ethanophenanthridine system. An alternative synthesis of (21b) *via* the oxidative coupling reaction (22b)  $\rightarrow$  (23b) (35% yield) using a new iron-DMF complex has also been reported.<sup>11</sup>

Irie and co-workers have adapted the initial steps of their synthesis of dihydrocorine (see Vol. 2 of these Reports) to the preparation of ( $\pm$ )-clivonine (31) and ( $\pm$ )-clividine (32) (Scheme 4).<sup>12</sup> Thus the half-ester (24), obtained by a Diels-



Reagents: i,  $\text{SOCl}_2$ ; ii,  $\text{NaN}_3$ ; iii,  $\Delta$ ,  $\text{C}_6\text{H}_6$ ; iv,  $\text{MeOH}$ ; v,  $\text{HCl-HOAc}$ ; vi,  $\text{CH}_2\text{N}_2$ ; vii,  $\text{Ag}_2\text{O}$ ,  $\text{MeOH}$ ; viii,  $\text{H}^+$ , ix,  $\text{Ac}_2\text{O}$ ; x,  $\text{ClCH}_2\text{OMe}$ ,  $\text{ZnCl}_2$ ,  $\text{HOAc}$ ; xi,  $\text{AgOAc}$ ,  $\text{HOAc}$ ,  $\text{Ac}_2\text{O}$ ; xii,  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ; xiii,  $\text{OsO}_4$ ,  $\text{Et}_2\text{O}$ ; xiv,  $\text{MnO}_2$ ,  $\text{CHCl}_3$

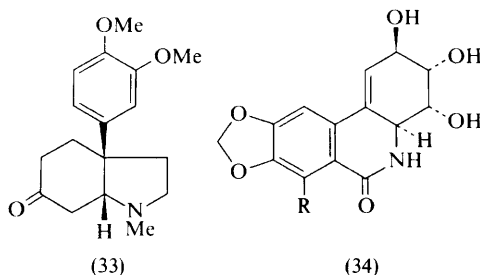
**Scheme 4**

<sup>11</sup> E. Kotani, N. Takeuchi, and S. Tobinaga, *Tetrahedron Letters*, 1973, 2735.

<sup>12</sup> H. Irie, Y. Nagai, K. Tamoto, and H. Tanaka, *J.C.S. Chem. Comm.*, 1973, 302.

Alder route, was converted into the urethan (25) by a series of unexceptional steps. Arndt-Eistert homologation of (25) provided the carboxylic acid (26) which, upon treatment with acetic anhydride, readily gave the lactam (27). Introduction of a one-carbon unit into the aromatic ring was achieved with chloromethyl methyl ether, and further reductive and hydrolytic modification afforded the amino-alcohol (28). Osmium tetroxide oxidation of (28) yielded the stereoisomeric triols (29) (20%) and (30) (22%) which were separated and oxidized to ( $\pm$ )-clivonine (31) and ( $\pm$ )-clividine (32), respectively.

Details of the interesting asymmetric synthesis of unnatural (+)-mesembrine (33) using an L-proline enamine intermediate (see Vol. 3 of these Reports) have appeared.<sup>13</sup> Details are also available<sup>14</sup> regarding the photochemical synthesis of ( $\pm$ )-crinan, a compound possessing the basic skeleton of the alkaloid crinine (see Vol. 2 of these Reports).



Lycorine<sup>15</sup> and lycoricidinol (34; R = OH) and lycoricidine (34; R = H)<sup>16</sup> have been shown to possess plant-growth inhibiting properties. A crude alkaloid extract from *Narcissus tazetta* shows inhibition of purified DNA polymerase from avian myeloblastosis virus.<sup>17</sup> Furthermore, extracts containing pseudolycorine have been shown to exhibit anticancer activity.<sup>18,19</sup> Narwedine continues to be the subject of pharmacological studies.<sup>20</sup>

<sup>13</sup> G. Otani and S. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2130.

<sup>14</sup> I. Ninomiya, T. Naito, and T. Kiguchi, *J.C.S. Perkin I*, 1973, 2261.

<sup>15</sup> P. De Leo, G. Dalessandro, A. De Santis, and O. Arrigoni, *Plant Cell Physiol.*, 1973, **14**, 487.

<sup>16</sup> T. Okamoto, Y. Torii, and Y. Isogai, in 'Plant Growth Substances, Proceedings of the Seventh International Conference, 1970', ed. D. J. Carr, Springer, New York, 1972, p. 311.

<sup>17</sup> T. S. Papas, L. Sandhaus, M. A. Chirigos, and E. Furusawa, *Biochem. Biophys. Res. Comm.*, 1973, **52**, 88.

<sup>18</sup> N. Suzuki, S. Tani, S. Furusawa, and E. Furusawa, *Proc. Soc. Exp. Biol. Med.*, 1974, **145**, 771.

<sup>19</sup> E. Furusawa, N. Suzuki, S. Tani, S. Furusawa, G. Y. Ishioka, and J. Motobu, *Proc. Soc. Exp. Biol. Med.*, 1973, **143**, 33.

<sup>20</sup> E. D. Bazhenova, Kh. U. Aliev, and U. B. Zakirov, *Farmakol. Alkaloidov Ikh Proizvod.*, 1972, **74** (*Chem. Abs.*, 1974, **80**, 103 864r).

### 1 Erythrina and Homoerythrina Alkaloids

A recent review on the topic of chemotaxonomy of alkaloids deals in part with the *Erythrina* group.<sup>1</sup>

A series of detailed accounts of structural elucidation studies by Ito and co-workers has appeared.<sup>2-8</sup> Aside from a number of known bases, the new alkaloids erythrinine (1;  $R^1 + R^2 = CH_2$ ,  $R^3 = OH$ ,  $X = H_2$ ) and erybidine (2) (previously reviewed in Vol. 3 of these Reports) have been obtained from *Erythrina bidwillii*.<sup>2-4</sup> The structures of (1;  $R^1 + R^2 = CH_2$ ,  $R^3 = OH$ ,  $X = H_2$ ) and (2) rest on spectral and chemical data;<sup>2,3</sup> furthermore, (2) was synthesized from the known erysodienol (3).<sup>4</sup> Erybidine was subsequently also isolated from *E. orientalis*,<sup>5</sup> *E. crista-galli*,<sup>6</sup> and *E. arborescens*,<sup>7,8</sup> and erythrinine was obtained from *E. crista-galli*.<sup>6</sup> *E. arborescens* has also been shown to elaborate the new alkaloids erythrabine (4), erysotramidine (1;  $R^1 = R^2 = Me$ ,  $R^3 = H$ ,  $X = O$ ), and 11-hydroxyerysotrine (1;  $R^1 = R^2 = Me$ ,  $R^3 = OH$ ,  $X = H_2$ ) in addition to other known bases.<sup>7,8</sup>

An important paper by Rinehart and co-workers describes the utility of combined gas chromatography-mass spectrometry (g.c.-m.s.) for the resolution and direct identification of *Erythrina* alkaloids in crude mixtures.<sup>9</sup> The mixture is treated with *NO*-bis(trimethylsilyl)acetamide in order to convert the hydroxylic alkaloids into their trimethylsilyl ethers. The hydroxylic alkaloids (most of the

<sup>1</sup> J. A. Mears and T. J. Mabry, in 'Alkaloids in the Leguminosae', ed. J. B. Harborne, D. Boulter, and B. L. Turner, Academic Press, London, 1971, p. 73.

<sup>2</sup> K. Ito, H. Furukawa, and H. Tanaka, *Yakugaku Zasshi*, 1973, **93**, 1211 (*Chem. Abs.*, 1973, **79**, 146 713n).

<sup>3</sup> K. Ito, H. Furukawa, and H. Tanaka, *Yakugaku Zasshi*, 1973, **93**, 1215 (*Chem. Abs.*, 1973, **79**, 146 715q).

<sup>4</sup> K. Ito, H. Furukawa, H. Tanaka, and T. Rai, *Yakugaku Zasshi*, 1973, **93**, 1218 (*Chem. Abs.*, 1973, **79**, 146 714p).

<sup>5</sup> K. Ito, H. Furukawa, M. Haruna, and S.-T. Lu, *Yakugaku Zasshi*, 1973, **93**, 1671 (*Chem. Abs.*, 1974, **80**, 68 390j).

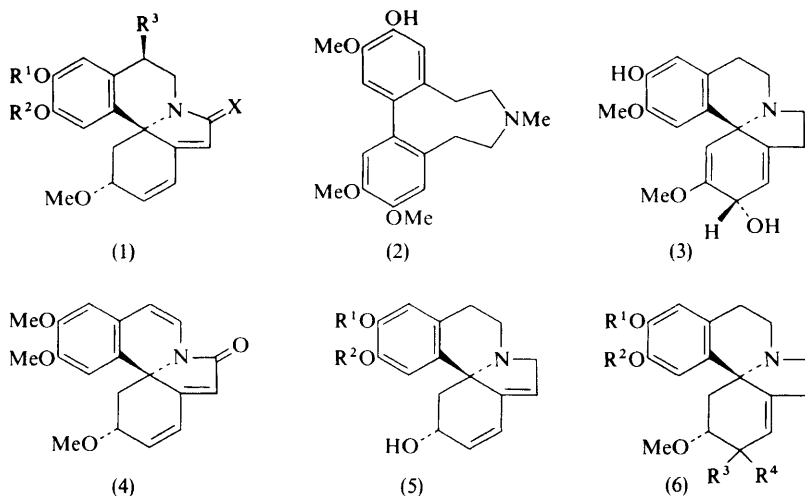
<sup>6</sup> K. Ito, H. Furukawa, M. Haruna, and M. Ito, *Yakugaku Zasshi*, 1973, **93**, 1674 (*Chem. Abs.*, 1974, **80**, 68 391k).

<sup>7</sup> K. Ito, H. Furukawa, and M. Haruna, *Yakugaku Zasshi*, 1973, **93**, 1611 (*Chem. Abs.*, 1974, **80**, 68 387p).

<sup>8</sup> K. Ito, H. Furukawa, and M. Haruna, *Yakugaku Zasshi*, 1973, **93**, 1617 (*Chem. Abs.*, 1974, **80**, 48 212z).

<sup>9</sup> D. S. Millington, D. H. Steinman, and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1974, **96**, 1909.





known *Erythrina* bases) are then readily distinguished from those containing no hydroxy-group by the appearance of a strong peak at  $m/e$  73 ( $\text{Me}_3\text{Si}^+$ ) in their mass spectra. The mass spectra of a large number of pure alkaloids as their trimethylsilyl derivatives were analysed. Application of the combined g.c.-m.s. method to extracts from *E. folkersii* led to the identification of the new alkaloids erysoline (5;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ) and erythravine (5;  $\text{R}^1 = \text{R}^2 = \text{Me}$ ) as well as a number of known bases. Similarly, the new alkaloids, erysosalvine (6;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{R}^3, \text{R}^4 = \text{H}$ , OH), erysflorinone (6;  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3\text{R}^4 = \text{O}$ ) and erysosalvinone (6;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{R}^3\text{R}^4 = \text{O}$ ) have been identified in *E. salviiflora*. Finally, erysotine (6;  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Me}$ ,  $\text{R}^3, \text{R}^4 = \text{H}$ , OH) and erysotinone (6;  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Me}$ ,  $\text{R}^3\text{R}^4 = \text{O}$ ), previously known only as synthetic (racemic) intermediates, were also obtained from *E. salviiflora*. In most cases, initial g.c.-m.s. identification was accompanied by full characterization using other spectral methods and chemical interconversions. This study<sup>9</sup> has increased the number of known *Erythrina* alkaloids by 40%. It is clear therefore that the combined g.c.-m.s. method should prove valuable in future chemical and chemotaxonomic studies on this class of alkaloids.

It appears that the combined g.c.-m.s. method for analysis of crude natural product mixtures can be improved by using it in conjunction with high-resolution field-ionization m.s. studies.<sup>10</sup> Such studies on the crude mixture from *E. princeps* (formerly known as *E. lysistemon*) have allowed the tentative structural assignments of several new *Erythrina* alkaloids.<sup>11</sup>

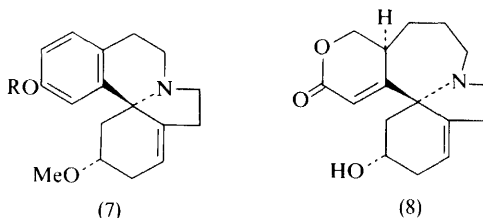
The structure and absolute configuration of cocculine (7;  $\text{R} = \text{H}$ ) have been conclusively established by an X-ray crystallographic study of its hydrobromide

<sup>10</sup> H. D. Beckey, in 'Biochemical Application of Mass Spectrometry', ed. G. R. Waller, Wiley, New York, 1972, p. 795.

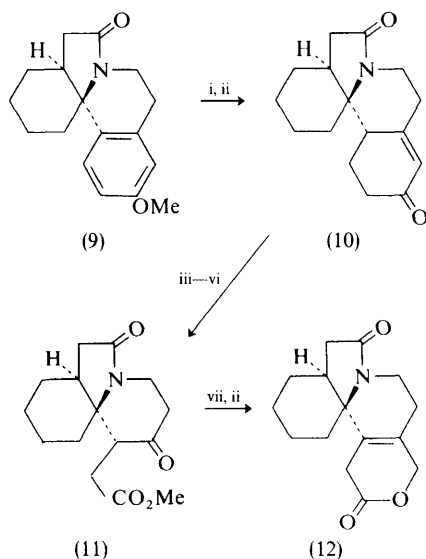
<sup>11</sup> D. E. Games, A. H. Jackson, and D. S. Millington, *Tetrahedron Letters*, 1973, 3063.

derivative.<sup>12,13</sup> O.r.d. studies of cocculine and cocculidine (7; R = Me) allowed also the assignment of absolute configuration to the latter alkaloid.<sup>12</sup>

The structure and relative configuration of phellibiline (8), a homoerythrina alkaloid, has been established by direct X-ray crystallographic analysis.<sup>14</sup>



An interesting conversion of an erythrinan (9) into a  $\beta$ -erythroidine derivative (12) has been reported (Scheme 1).<sup>15</sup> Birch reduction of (9) followed by hydrolysis gave a good yield of the conjugated enone (10), which upon successive treatment with benzaldehyde, ozone, hydrogen peroxide, and diazomethane provided the



Reagents: i, Li, liq.  $\text{NH}_3$ , EtOH; ii, HCl-MeOH; iii, PhCHO, piperidine, HOAc; iv,  $\text{O}_3$ ,  $\text{CHCl}_3$ ,  $-20^\circ\text{C}$ ; v,  $\text{H}_2\text{O}_2$ , NaOH; vi,  $\text{CH}_2\text{N}_2$ ; vii,  $\text{Me}_2\text{SOCH}_2$ , DMSO

**Scheme 1**

<sup>12</sup> R. Razakov, S. Yu. Yunusov, S. M. Nasirov, A. N. Chekhlov, V. G. Andrianov, and Yu. T. Struchkov, *J.C.S. Chem. Comm.*, 1974, 150.

<sup>13</sup> R. Razakov, S. Yu. Yunusov, S. M. Nasirov, V. G. Andrianov, and Yu. T. Struchkov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1974, 218 (*Chem. Abs.*, 1974, **80**, 108 727h).

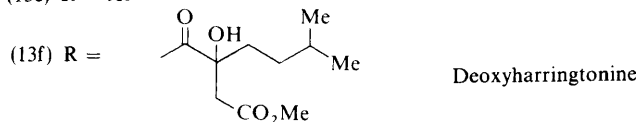
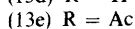
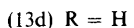
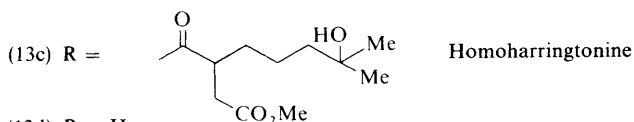
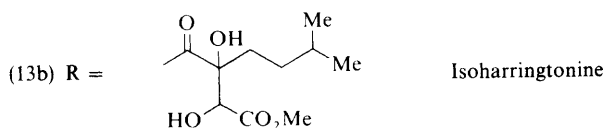
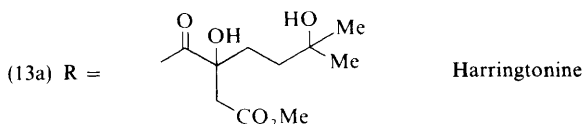
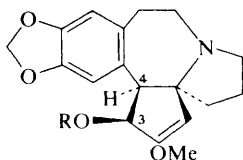
<sup>14</sup> C. Riche, *Acta Cryst.*, 1974, **30B**, 1386.

<sup>15</sup> T. Kitahara and M. Matsui, *Agric. and Biol. Chem. (Japan)*, 1974, **38**, 171.

keto-ester (11). Application of Corey's oxiran synthesis using methyl sulphoxonium methylide followed by acid treatment afforded the  $\beta$ -erythroidine derivative (12).

## 2 *Cephalotaxus* Alkaloids

Intense structural-elucidation and synthetic activity has continued, no doubt as a consequence of the significant antitumour activity of this class of alkaloids. A pilot-plant extraction of harringtonine (13a), isoharringtonine (13b), and homoharringtonine (13c) from *Cephalotaxus harringtonia* using counter-current distribution has been described.<sup>16</sup> This method provides 36 g of the three alkaloids in pure form from 455 kg of plant material.

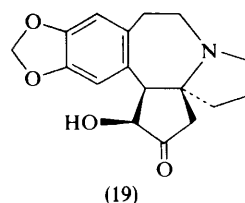
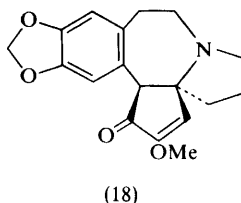
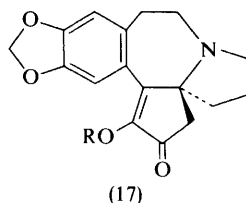
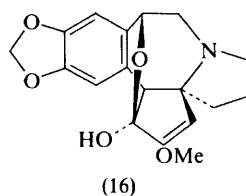
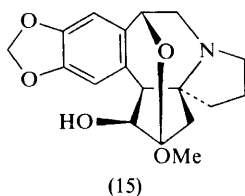
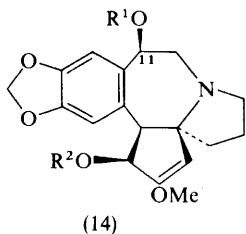


Details regarding the structural assignment of 11-hydroxycephalotaxine (14;  $R^1 = R^2 = H$ ) and drupacine (15), isolated from *C. harringtonia* var.

<sup>16</sup> R. G. Powell, S. P. Rogovin, and C. R. Smith, jun., *Ind. and Eng. Chem. (Product Res. and Development)*, 1974, 13, 129.

*drupacea* (formerly referred to as *C. drupacea*), are now available.<sup>17</sup> The structures follow from spectral data and chemical interrelationships. For example, treatment of (14;  $R^1 = R^2 = H$ ) under mild acidic conditions provided (15), while its Oppenauer oxidation gave the hemiketal (16). Furthermore, hydrolysis of the diacetate (14;  $R^1 = R^2 = Ac$ ) in aqueous dioxan at ambient temperatures resulted in epimerization at C-11. All these reactions are best accommodated by the proposed stereochemical formulation (14;  $R^1 = R^2 = H$ ) for 11-hydroxycephalotaxine. Interestingly, this formulation represents the most hindered of four possible geometric isomers. The alkaloids (14;  $R^1 = R^2 = H$ ) and (15) are unique to *C. harringtonia* var. *drupacea*. It is not yet clear if drupacine (15) is identical with Alkaloid IV obtained by Asada during an extensive reinvestigation of *Cephalotaxus* species.<sup>18</sup>

Desmethylcephalotaxinone (17;  $R = H$ ) has been isolated from *C. harringtonia* var. *harringtonia*.<sup>19</sup> Its structure has been conclusively established by spectral means and by chemical interrelation with cephalotaxine (13d). Thus treatment of (17;  $R = H$ ) with dimethoxypropane in the presence of sulphuric acid gave cephalotaxinone (18) and a minor amount of isocephalotaxinone (17;  $R = Me$ ).<sup>19</sup> Sodium borohydride reduction of (18) proceeded stereoselectively to give cephalotaxine (13d). Isolation of cephalotaxinone (18) from *C. harringtonia* var. *harringtonia*<sup>19</sup> and *C. fortunei*<sup>20</sup> confirms that it is a naturally occurring material. Acetylcephalotaxine (13e),<sup>20</sup> epicephalotaxine (13d; epimeric at C-3)<sup>20</sup>, and desmethylcephalotaxine (19)<sup>19,20</sup> have been identified as minor constituents of the above species.



<sup>17</sup> R. G. Powell, R. V. Madrigal, C. R. Smith, jun., and K. L. Mikolajczak, *J. Org. Chem.*, 1974, **39**, 676.

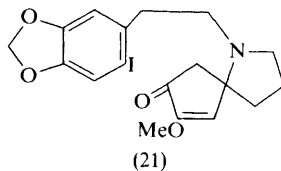
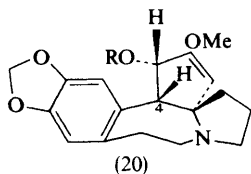
<sup>18</sup> S. Asada, *Yakugaku Zasshi*, 1973, **93**, 916 (*Chem. Abs.*, 1973, **79**, 123 699y).

<sup>19</sup> R. G. Powell and K. L. Mikolajczak, *Phytochemistry*, 1973, **12**, 2987.

<sup>20</sup> W. W. Paudler and J. McKay, *J. Org. Chem.*, 1973, **38**, 2110.

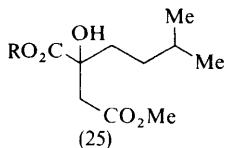
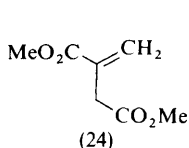
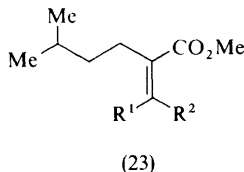
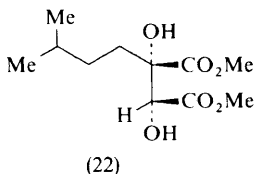
An *X*-ray crystallographic study of the *p*-bromobenzoate of cephalotaxine has verified the constitution and relative stereochemistry of this alkaloid and its esters (13a—c) and has established for the first time the 4*S* absolute configuration as depicted by (20; R = COC<sub>6</sub>H<sub>4</sub>-*p*-Br).<sup>21</sup>

Most of the synthetic efforts during the past year have appertained to the preparation of the ester portion of harringtonine (13a) and analogues related to it. As far as the synthesis of the basic alkaloid skeleton is concerned, an improvement in the transformation of the iodo-ketone (21) into cephalotaxinone (18) (see Vol. 4 of these Reports) has been achieved.<sup>22</sup> Three sets of conditions were explored for this transformation, of which by far the best (94% yield) was irradiation of (21) in refluxing liquid ammonia in the presence of excess of potassium *t*-butoxide.



The *erythro* configuration has been shown<sup>23</sup> for the dimethyl ester diol (22) previously obtained from isoharringtonine (13b). The readily available maleic and fumaric diesters (23; R<sup>1</sup> = H, R<sup>2</sup> = CO<sub>2</sub>Me) and (23; R<sup>1</sup> = CO<sub>2</sub>Me, R<sup>2</sup> = H) were hydroxylated with osmium tetroxide–hydrogen peroxide to give stereospecifically the *erythro*-diol (22) and the corresponding diastereomeric *threo*-diol, respectively. Diol (22) was found to be identical, except for optical activity, with the product obtained by transesterification of isoharringtonine (13b) with sodium methoxide in methanol solution.

A short synthesis of the dimethyl ester (25; R = Me), produced similarly by transesterification of deoxyharringtonine (13f), has been achieved.<sup>24</sup> Commercially



<sup>21</sup> S. K. Arora, R. B. Bates, R. A. Grady, and R. G. Powell, *J. Org. Chem.*, 1974, **39**, 1269.

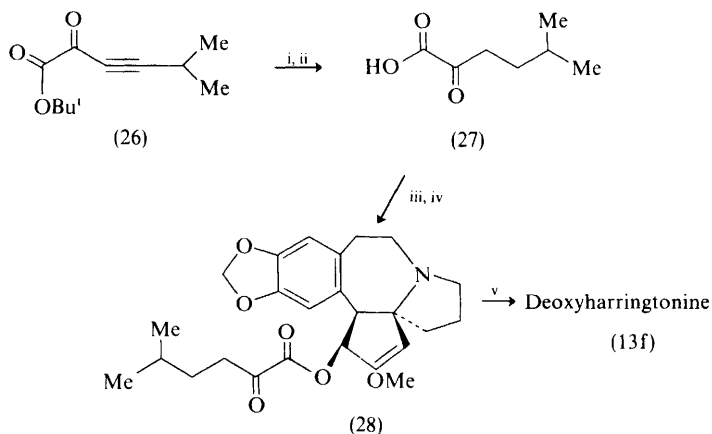
<sup>22</sup> M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, *Tetrahedron Letters*, 1973, 4519.

<sup>23</sup> T. Ipakchi and S. M. Weinreb, *Tetrahedron Letters*, 1973, 3895.

<sup>24</sup> J. Auerbach, T. Ipakchi, and S. M. Weinreb, *Tetrahedron Letters*, 1973, 4561.

available dimethyl itaconate (24) was converted with  $\text{CF}_3\text{CO}_3\text{H}$  into the corresponding epoxide, which upon treatment with lithium di-isobutylcuprate gave the diester (25;  $\text{R} = \text{Me}$ ), identical with material derived from deoxyharringtonine. The corresponding acid (25;  $\text{R} = \text{H}$ ) was obtained by hydrogenolysis of the benzyl ester (25;  $\text{R} = \text{CH}_2\text{Ph}$ ), which, in turn, was available by a similar synthesis. Although the mono-acid (25;  $\text{R} = \text{H}$ ) could be resolved using ephedrine, attempts to esterify (25;  $\text{R} = \text{H}$ ) with cephalotaxine (13d) failed, presumably owing to serious steric hindrance.

The problem of deoxyharringtonine (13f) synthesis from cephalotaxine (13d) has been solved in an interesting way (Scheme 2).<sup>25</sup> Treatment of ethyl t-butyl



Reagents: i,  $\text{H}_2$ ,  $\text{Pd/C}$ ; ii,  $\text{CF}_3\text{CO}_2\text{H}$ ,  $0^\circ\text{C}$ ; iii,  $(\text{COCl})_2$ ; iv, cephalotaxine (13d),  $\text{C}_5\text{H}_5\text{N}$ ; v,  $\text{LiNPr}_2$ ,  $\text{MeCO}_2\text{Me}$ ,  $-78^\circ\text{C}$

Scheme 2

oxalate with the lithium acetylide of 3-methylbut-1-yne gave the acetylenic  $\alpha$ -keto-ester (26), which upon hydrogenation and hydrolysis provided the saturated acid (27). The acid chloride of (27) prepared under normal conditions was treated with natural cephalotaxine (13d) to give the desired ester (28) in 50–80% yield. Treatment of (28) with the lithium salt of methyl acetate, generated by Rathke's useful method, gave a mixture of diastereomers, one of which proved to be identical with deoxyharringtonine (13f). The last step in this synthesis was also used on an appropriately modified  $\alpha$ -keto-ester to prepare the dimethyl ester resulting from transesterification of harringtonine (13a).<sup>26</sup>

<sup>25</sup> K. L. Mikolajczak, C. R. Smith, jun., D. Weisleder, T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Letters*, 1974, 283.

<sup>26</sup> T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Letters*, 1973, 3501.

## 1 Introduction

Several\* of the chapters in volume XIV<sup>2</sup> of the Manske series 'The Alkaloids' are of relevance to indole alkaloid chemistry; thus, as well as the chapter<sup>2a</sup> on unclassified alkaloids and those of unknown structure, there are reviews of oxindole alkaloids,<sup>2b</sup> alkaloids of *Mitragyna*<sup>2c</sup> and related genera, *Picalima* and *Alstonia* species,<sup>2d</sup> and *Cinchona*<sup>2e</sup> and *Elaeocarpus*<sup>2f</sup> alkaloids.

Reviews have been published on *Rhazya*<sup>3</sup> and indoline *Vinca*<sup>4a</sup> alkaloids, and a book<sup>4b</sup> has been devoted to the chemistry, botany, folklore, and biological activities associated with *Vinca* species. A table surveys<sup>5</sup> all the Rutaceae species so far studied and lists the alkaloids obtained therefrom; canthinone, euxylophorine, and pyrano-carbazoles of the murrayacine-mahanimbine series have been obtained from this family.

Of relevance from a practical point of view are publications dealing with the t.l.c.-quantitative analysis of twelve *Rauwolfia* bases,<sup>6a</sup> t.l.c.-colour reactions for analysis<sup>6b</sup> of 38 indole alkaloids from some *Vinca* species, the quantitative determination of *Cinchona* quinoline alkaloids by t.l.c.-differential spectrophotometry,<sup>6c</sup> and the high-speed liquid-liquid chromatography of ergot alkaloids<sup>7a</sup> and *Mitragyna* alkaloids.<sup>7b</sup>

<sup>1</sup> (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. 212; (c) *ibid.*, p. 216; (d) *ibid.*, p. 230; (e) *ibid.*, p. 233; (f) *ibid.*, p. 239.

<sup>2</sup> (a) R. H. F. Manske, 'The Alkaloids', Academic Press, New York, 1973, Vol. XIV, Chap. 9; (b) *ibid.*, Chap. 2; (c) *ibid.*, Chap. 3; (d) *ibid.*, Chap. 4; (e) *ibid.*, Chap. 5; (f) *ibid.*, Chap. 8.

<sup>3</sup> A. Chatterjee, J. Banerji, and A. Banerji, *J. Indian Chem. Soc.*, 1974, **51**, 156.

<sup>4</sup> (a) A. M. Aliev and N. A. Babaev, *Farmatsiya (Moscow)* 1973, **22**, 82 (*Chem. Abs.*, 1973, **78**, 148 095); (b) W. I. Taylor and N. R. Farnsworth, 'The Vinca Alkaloids', Marcel Dekker, New York, 1973.

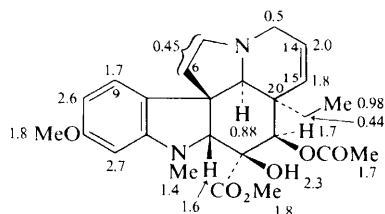
<sup>5</sup> I. Mester, *Fitoterapia*, 1973, **44**, 123.

<sup>6</sup> (a) W. E. Court and M. S. Habib, *J. Chromatog.*, 1973, **80**, 101; (b) V. U. Vachnadze, V. M. Malikov, Kh. T. Il'yasova, K. S. Mudhiri, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, **9**, 72 (*Chem. Abs.* 1973, **79**, 5483); (c) M. Vincze-Vermes and Z. Vincze, *Acta Pharm. Hung.*, 1973, **43**, 49 (*Chem. Abs.*, 1973, **79**, 5481).

<sup>7</sup> (a) R. A. Heacock, K. R. Langille, J. D. MacNeil, and R. W. Frei, *J. Chromatog.*, 1973, **77**, 425; (b) G. H. Jolliffe and E. J. Shellard, *ibid.*, 1973, **81**, 150.

\* Following this first section detailing reviews and publications of general interest, the remainder of this chapter is sub-divided according to the different alkaloid structural types. For the order within each sub-group see Ref. 1a.

Using a Fourier transform technique, an improvement<sup>8</sup> on a previous determination<sup>9a</sup> which used a selective audiofrequency pulse technique, has enabled the hydrogen nuclear relaxation times of all the protons in vindoline (1) to be



(1) Vindoline (hydrogen nuclear relaxation times in seconds)

determined. Although the application of such a technique to structural work is very much in its infancy, it is clear from this study that one can discern useful differences between differently sterically situated hydrogen atoms. Thus protons 'in the middle' of the molecule and hence closest to others have shorter relaxation times than those directed towards the periphery. The figures given in seconds on (1) illustrate this; thus, the lower value for H-9 than for the other aromatic protons derives from the closeness of only H-9 to the protons on C-6. Again, the lower value for H-15 than for H-14 is considered to reflect the proximity of the C-20 ethyl group to H-15.

A technique<sup>10</sup> which must certainly now be regarded as moving out of its infancy in its applicability to the complex indole alkaloids is <sup>13</sup>C n.m.r.; indeed,

<sup>8</sup> L. D. Hall and C. M. Preston, *Canad. J. Chem.*, 1974, **52**, 829.

<sup>9</sup> (a) J. A. Joule, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3, p. 208; (b) *ibid.*, p. 188; (c) *ibid.*, p. 189; (d) *ibid.*, p. 211; (e) *ibid.*, p. 203; (f) *ibid.*, p. 204; (g) *ibid.*, p. 199; (h) *ibid.*, p. 197; (i) *ibid.*, p. 212; (j) *ibid.*, p. 209; (k) *ibid.*, p. 202; (l) *ibid.*, p. 216; (m) *ibid.*, p. 221.

<sup>10</sup> (a) A. Ahond, M.-M. Janot, N. Langlois, G. Lukacs, P. Potier, P. Rasoanaivo, M. Sangaré, N. Neuss, M. Plat, J. Le Men, E. W. Hagaman, and E. Wenkert, *J. Amer. Chem. Soc.*, 1974, **96**, 633; (b) A. Cavé, J. Bruneton, A. Ahond, G. L. Nelson, H.-P. Husson, C. Kan, G. Lukacs, and P. Potier, *Tetrahedron Letters*, 1973, 5081; (c) N. Neuss, H. E. Boaz, J. L. Occolowitz, E. Wenkert, F. M. Schell, P. Potier, C. Kan, M.-M. Plat, and M. Plat, *Helv. Chim. Acta*, 1973, **56**, 2660; (d) E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Accounts Chem. Res.*, 1974, **7**, 46; (e) R. H. Levin, J.-Y. Lallemand, and J. D. Roberts, *J. Org. Chem.*, 1973, **38**, 1983; (f) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Amer. Chem. Soc.*, 1973, **95**, 4990; (g) R. G. Parker and J. D. Roberts, *J. Org. Chem.*, 1970, **35**, 996; (h) G. W. Gribble, R. B. Nelson, G. C. Levy, and G. L. Nelson, *J.C.S. Chem. Comm.*, 1972, 703; (i) G. Lukacs, M. De Bellefor, L. Le Men-Olivier, J. Lévy, and J. Le Men, *Tetrahedron Letters*, 1974, 487; (j) J. Le Men, G. Lukacs, L. Le Men-Olivier, J. Lévy, and M. J. Hoizey, *ibid.*, p. 483; (k) P. Yates, F. N. MacLachlan, I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, M. P. Cava, M. Behforouz, M. V. Lakshmikantham, and W. Zieger, *J. Amer. Chem. Soc.*, 1973, **95**, 7842; (l) R. E. Moore and H. Rapoport, *J. Org. Chem.*, 1973, **38**, 215; (m) E. Wenkert, C.-J. Chang, A. O. Clouse, and D. W. Cochran, *Chem. Comm.*, 1970, 961; (n) C. Kan-Fan, G. Massiot, A. Ahond, B. C. Das, H.-P. Husson, P. Potier, A. I. Scott, and C. C. Wei, *J.C.S. Chem. Comm.*, 1974, 164; (o) E. Wenkert, C.-J. Chang, D. W. Cochran, and R. Pellicciari, *Experientia*, 1972, **28**, 377; (p) W. O. Crain, W. C. Wildman, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 990; (q) R. J. Pugmire, D. M. Grant, M. J. R. Robins, and R. K. Robins, *ibid.*, 1969, **91**, 6381; (r) N. J. Bach, H. E. Boaz, E. C. Kornfeld, C.-J. Chang, H. G. Floss, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, 1974, **39**, 1272.



this year sees a revision of structure<sup>10a</sup> (see p. 214) which would have been difficult to achieve simply by any chemical or other spectroscopic methods, and also structure determinations<sup>10b,c,f,n</sup> largely based on analyses of <sup>13</sup>C spectra (see pp. 212, 214, 224, 226). A relevant review<sup>10d</sup> covers *Nicotiana* and tropane types as well as *Corynanthe* and *Cinchona* groups.

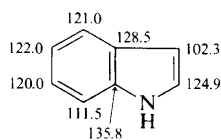
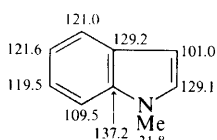
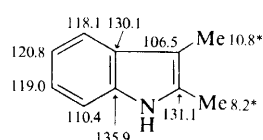
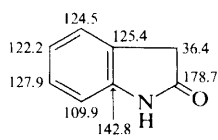
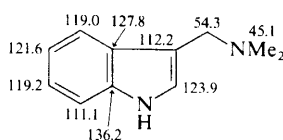
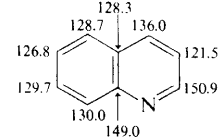
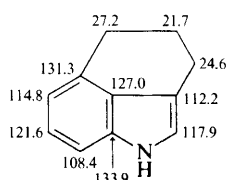
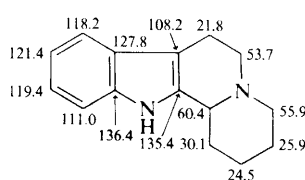
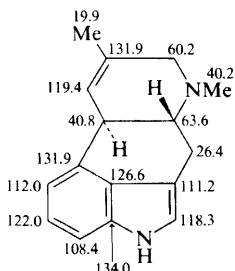
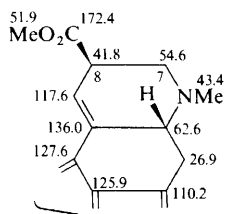
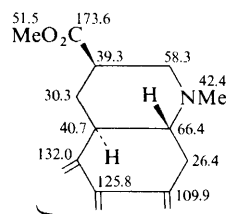
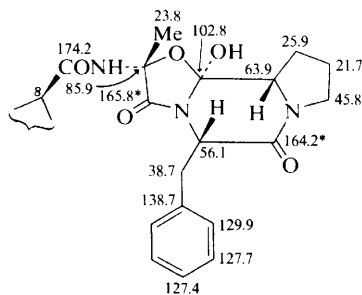
Since it is now clear that the <sup>13</sup>C chemical shifts for carbons in typical indole alkaloid environments have reliably characteristic values, it seemed worthwhile at this stage to gather together, as has been done in the Table of structures (2)–(39) and chemical shifts which follows, a relevant selection of data from those so far available on typical alkaloids, derivatives, and simple model compounds. The values given are for 0.2–2.0 mol l<sup>-1</sup> solutions in chloroform or deuteriochloroform unless otherwise specified, and are  $\delta$  values in p.p.m. downfield from tetramethylsilane. There is not yet a generally used system for reporting <sup>13</sup>C chemical shifts, thus  $\delta$  values relative to benzene, downfield from chloroform, and upfield from carbon disulphide, as well as downfield from tetramethylsilane, are currently to be found in the literature.

Where ambiguity exists in assignments, the pairs of undifferentiated signals are marked \* or †. Partial structures are used in the Table in some cases for compounds which differ only slightly from the preceding example; in these cases it can be assumed that the chemical shifts for the carbons in the unspecified portion of the molecule are identical with the corresponding ones on the preceding structure, or as close as to make no difference.

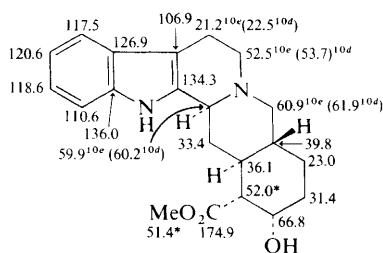
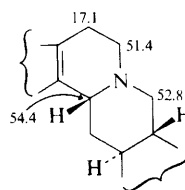
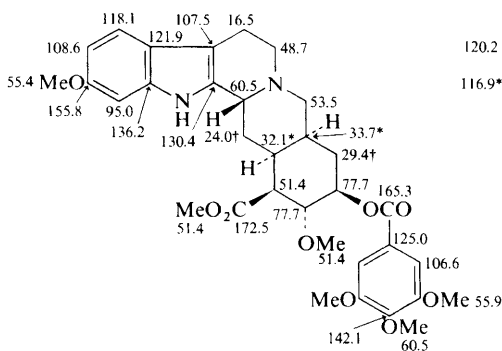
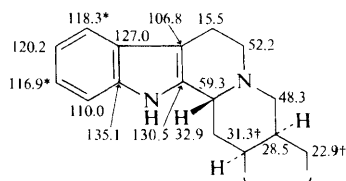
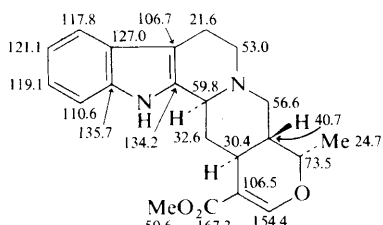
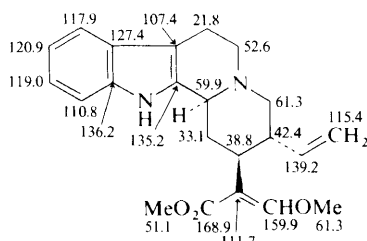
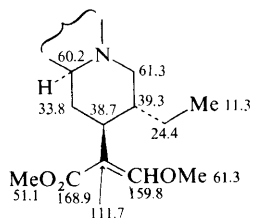
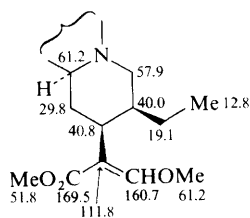
In arriving at signal assignments use has usually been made of a combination of information gained from some or all of the following: (i) proton resonance decoupling to detect chemical shift values; (ii) noise off-resonance decoupling for the differentiation of signals from quaternary carbons from those from carbons carrying hydrogen(s); (iii) single frequency off-resonance decoupling (SFORD) to distinguish between methyl, methylene, and methine carbons; and (iv) comparisons with the chemical shifts of carbons in simple model compounds. Derivatization and the subsequent comparison of the spectra of those derivatives with starting materials has also proved useful on occasions. Wenkert has recommended<sup>10d</sup> *N*<sub>b</sub>-oxides as suitable derivatives, being easily formed and often, if necessary, easily removed, and having significantly different chemical shifts for carbon atoms close to the nitrogen; the spectra of quinine (38) and its *N*-oxide (39) illustrate this. Roberts has shown<sup>10e</sup> that addition of lanthanide chelate shift reagents can be used to separate overlapping signals; the six methoxy carbons of reserpine (16) were resolved in this way. Wenkert has pointed out<sup>10f</sup> that, when using the SFORD technique, the observed multiplicity of a methylene carbon signal where the two hydrogens are magnetically non-equivalent, often the case in complex molecules, can depend on the radiation frequency.

In general it is possible, as a preliminary, to divide a <sup>13</sup>C spectrum into two regions, above *ca.* 90 p.p.m. for multiply-bound carbon and below that figure for the saturated carbons.

Perusal of the Table reveals considerable consistency both in the absolute magnitude and in the relative order of chemical shifts for the aromatic carbons in

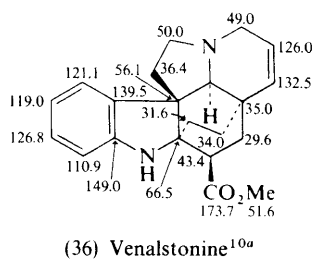
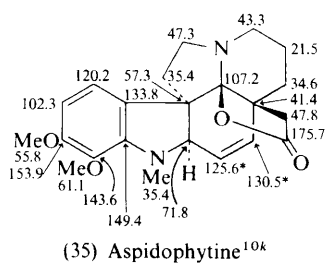
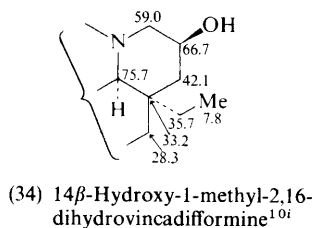
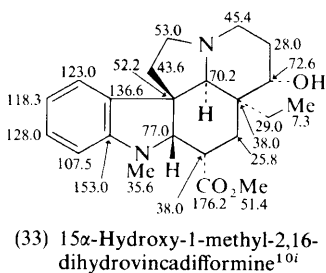
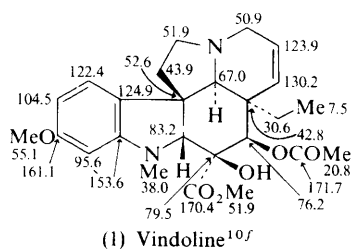
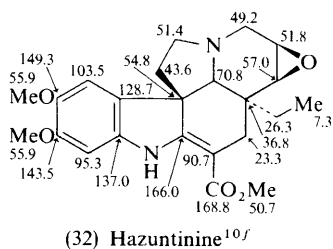
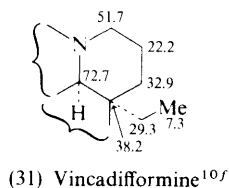
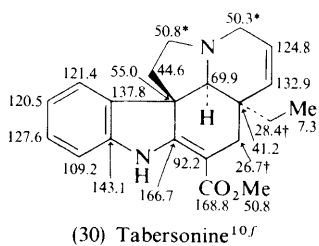
**Table**  $^{13}\text{C}$  Nuclear magnetic resonance data(2)  $^{10g}$  (in dioxan)(3)  $^{10g}$  (in dioxan)(4)  $^{10g}$  (in dioxan)(5)  $^{10m}$ (6)  $^{10d}$ (7)  $^{10q}$  (neat)(8)  $^{10r}$ (9)  $^{10d, 10h}$ (10) Agroclavine $^{10r}$   
(in  $[\text{}^2\text{H}_5]$ pyridine)(11) Methyl lysergate $^{10r}$ (12) Methyl 9,10-dihydrolysergate $^{10r}$   
(in  $[\text{}^2\text{H}_6]$ DMSO)(13) Ergotamine $^{10r}$  (in  $[\text{}^2\text{H}_6]$ DMSO)

Table—(cont.)

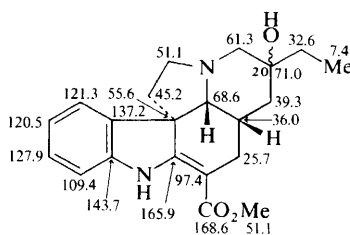
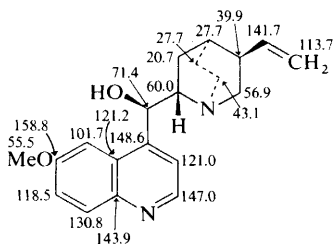
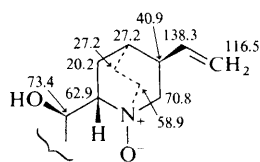
(14) Yohimbine<sup>10e,10d</sup>(15) Pseudoyohimbine<sup>10d</sup>(16) Reserpine<sup>10e</sup>(17) Deserpidine<sup>10e</sup>(18) Ajmalicine<sup>10e</sup>(19) Corynantheine<sup>10d</sup>(20) Dihydrocorynantheine<sup>10d</sup>(21) Corynantheidine<sup>10d</sup>

(29) 14,15-Dehydro-16-epivincine<sup>10c</sup>

Table—(cont.)



Table—(cont.)

(37) Pandoline<sup>10j</sup>(38) Quinine<sup>10d, 10p</sup>(39) Quinine N-oxide<sup>10d</sup>

indole, oxindole, and indoline alkaloids. In order of increasing field, alkaloid indoles (not carrying a substituent on the homoaromatic ring) follow the order (monoterpenoid indole alkaloid numbering) C-13  $\approx$  C-2, C-8, C-10, C-11, C-9 (C-11 and C-9 are reversed in simple indoles), C-12, C-7, whereas oxindoles, indolines, and, it is assumed,<sup>10f</sup> alkaloids with the anilino-acrylate chromophore, follow the order C-13, C-8, C-11, C-9, C-10, C-12 (C-8 and C-11 are reversed in oxindole itself). The basis for the assumption that the relative order for oxindoles and anilino-acrylate systems is the same is two-fold. Firstly the anilino-acrylate chromophore can be looked on as a vinylogous oxindole type (though their u.v. absorptions are quite different) and secondly the absolute chemical shift values for the aromatic carbons of the anilino-acrylate alkaloids measured so far do parallel those for oxindoles quite well.

Aromatic methoxy-substitution has a predictable effect,<sup>10e</sup> illustrated by the pairs reserpine (16)/deserpidine (17) and vindoline (1)/15-hydroxy-2,16-dihydro-1-methylvincadifformine (33). A methoxy-group shifts a *para* carbon *ca.* 7 p.p.m. to higher field and an *ortho* carbon *ca.* 15 p.p.m. in the same direction (9 p.p.m. if the *ortho* carbon also carries a substituent) while the methoxy-bearing carbon moves some 31 p.p.m. downfield. In rings carrying more than one methoxy-group, the observed effects are approximately the sum of their contributions; *cf.* the values for tabersonine (30) and hazuntinine (32).

It is usually easy to pick out those saturated carbon atoms which are also attached to a heteroatom as they resonate at the lower-field end of this portion of the <sup>13</sup>C n.m.r. spectrum. This knowledge can sometimes be used in assignments

of structures which are of a standard type for which typical values are known but which additionally carry, say, a hydroxy-group (see p. 215).

Substitution of hydrogen for another group can give an effect at the substitution site ( $\alpha$ -effect), the neighbouring carbon ( $\beta$ -effect), and the centre one more carbon removed ( $\gamma$ -effect). The magnitude of these effects varies according to whether the group is a heteroatom or an alkyl group and to its stereochemical orientation. The way in which hydroxy-substitution modifies the resonance positions in an aspidosperma system can be seen by comparing the data for vincadifformine (31) with those for the epoxide (32) and the alcohols (33) and (34).

Wenkert recognised an unanticipated 'endocyclic homoallylic effect'<sup>10f</sup> shown, by examination of several other analogous systems, to be general, which came to light in comparisons of the spectra of pairs of alkaloids, one having and the other not having a double bond in a piperidine ring. The homoallylic carbon in the unsaturated compound is shielded, and examples of this to be found in the Table are the pairs vincadifformine (31)/tabersonine (30), vincamine (27)/14,15-dehydrovincine (28), C-21 being the carbon in question in each case, and methyl lysergate (11)/methyl 9,10-dihydrolysergate (12), where C-7 is the carbon concerned.

Two pieces of stereochemical information which, it is claimed,<sup>10d</sup> can be gained easily from <sup>13</sup>C n.m.r. spectroscopy are worthy of specific comment. The spectra of rhynchophylline (22) and isorhynchophylline (23) illustrate how the relative stereochemistry at the spiro C-7 affects the chemical shifts of C-3 and C-9 in the epimeric pair. The differences are said to be sufficient to allow a distinction to be made; the Reporter is less than convinced that such small changes form a reliable basis on which to assign the stereochemistry at C-7.

The conformation of the C/D ring-junction in yohimbine types can be determined by inspection of the chemical shifts of carbons in the immediate vicinity of the ring-junction. The data shown on pseudo-yohimbine (15), in which the C/D ring-junction is constrained to be *cis*, show that these carbons are appreciably different from those in, for example, yohimbine (14) itself.

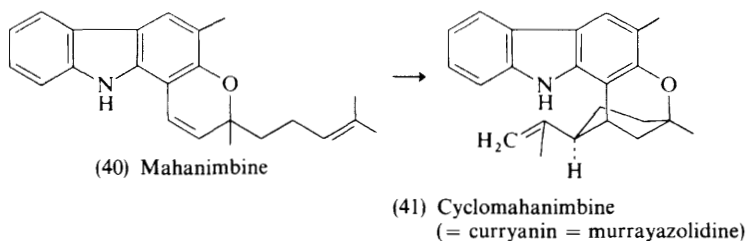
## 2 Simple Alkaloids

**Non-tryptamines.**—Details<sup>11</sup> have been given of the X-ray analysis of dibromocannabicyclol which led to the revision<sup>9b</sup> of the structures of bicyclomahanimbine and bicyclomahanimbicine. Crombie and Whiting have also reported<sup>11</sup> that treatment of ( $\pm$ )-mahanimbine (40) with an acidic ion-exchange resin converts it into ( $\pm$ )-cyclomahanimbine (41) (Scheme 1); further spectral data are presented<sup>11</sup> for this structure. It seems likely<sup>11</sup> that curryanin<sup>13</sup> and murrayazolidine,<sup>12a</sup> both of which had been formulated as (42), actually have the structure (41). Further evidence for this revised structure for murrayazolidine (? =

<sup>11</sup> W. M. Bandaranayake, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Perkin I*, 1974, 998.

<sup>12</sup> (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. 153; (c) *ibid.*, p. 154; (d) *ibid.*, p. 158; (e) *ibid.*, p. 162; (f) *ibid.*, p. 164; (g) *ibid.*, p. 174; (h) *ibid.*, p. 172.

<sup>13</sup> N. L. Dutta, C. Quasim, and M. S. Wadia, *Indian J. Chem.*, 1969, 7, 1168.

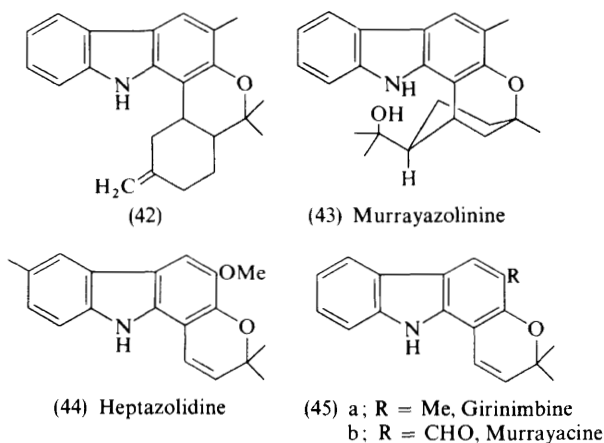


Reagent: Dowex-50W-X8(H<sup>+</sup>) resin-benzene-heat-6 days

Scheme 1

curryanin ? = cyclomahanimbine) is provided by Indian workers who claim the formation of some (41) in the condensation of 3-methyl-2-hydroxycarbazole with citral to form mahanimbine: no (41) was observed<sup>11</sup> by the British workers in their synthesis of mahanimbine by the same route. Chakraborty<sup>14</sup> also dehydrated murrayazolinine (43) to give a mixture which contained some (41).

3-Formyl-1-methoxycarbazole (murrayanine) and 3-methylcarbazole (for the first time from natural sources) have been isolated from *Clausena heptaphylla*.<sup>15,16</sup> Heptazolidine,<sup>17</sup> a new alkaloid from the same source, has been given the structure (44). Its dihydro-derivative has a u.v. absorption said to be similar to that of 2,3-dimethoxycarbazole.



Girinimbine (45a) has been converted<sup>18</sup> into murrayacine (45b) by oxidation of the aromatic methyl with dicyanodichloroquinone. In a synthesis<sup>19</sup> (Scheme 2)

<sup>14</sup> D. P. Chakraborty, P. Bhattacharyya, and A. R. Mitra, *Chem. and Ind.*, 1974, 260.

<sup>15</sup> P. Bhattacharyya and D. P. Chakraborty, *Phytochemistry*, 1973, **12**, 1831.

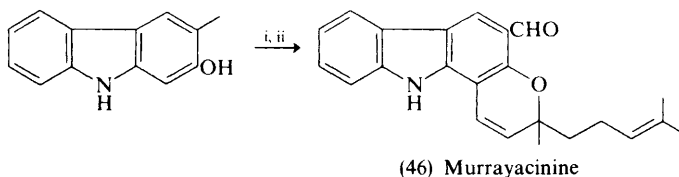
<sup>16</sup> S. Roy, P. Bhattacharyya, and D. P. Chakraborty, *Phytochemistry*, 1974, **13**, 1017.

<sup>17</sup> D. P. Chakraborty, P. Bhattacharyya, A. Islam, and S. Roy, *Chem. and Ind.*, 1974, 303.

<sup>18</sup> F. Anwer, A. S. Masaldan, R. S. Kapil, and S. P. Popli, *Indian J. Chem.*, 1973, **11**, 1314.

<sup>19</sup> D. P. Chakraborty, P. Bhattacharyya, A. Islam, and S. Roy, *Chem. and Ind.*, 1974, 165.

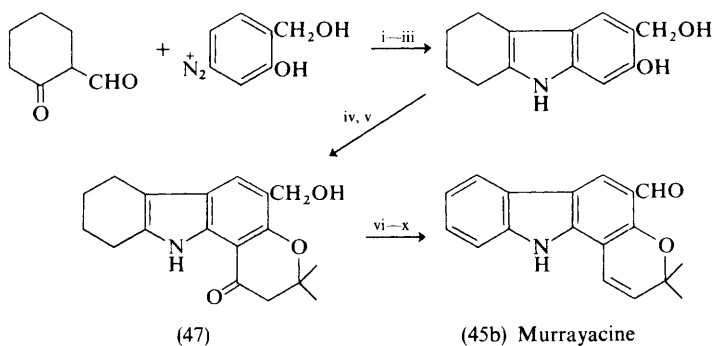




Reagents: i,  $\text{CrO}_2\text{Cl}_2$ ; ii, citral-pyridine

**Scheme 2**

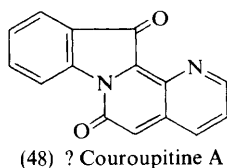
of a new alkaloid murrayacinine (46), chromyl chloride was employed for the analogous purpose. A total synthesis<sup>20</sup> of murrayacine (45b), shown in Scheme 3, used a Fries rearrangement to insert the C-1 carbon substituent [ $\rightarrow$  (47)].



Reagents: i, aq.  $\text{NaOAc-MeOH}$ ; ii,  $\text{AcOH-conc. HCl-heat}$ ; iii,  $\text{N}_2\text{H}_4\text{-KOH-heat}$ ; iv,  $\text{Me}_2\text{C:CHCOCl-pyridine}$ ; v,  $\text{AlCl}_3\text{-R.T.-3 days}$ ; vi,  $\text{Pd/C-200 } ^\circ\text{C}$ ; vii,  $\text{NaBH}_4$ ; viii,  $\text{TsCl-pyridine}$ ; ix,  $\text{collidine-heat}$ ; x,  $\text{MnO}_2$

**Scheme 3**

The inclusion of couroupitine A in this sub-section may well be as unjustified as is the structure (48) at present suggested<sup>21</sup> for this yellow alkaloid from mature fruits of *Couroupita guianensis*. The u.v. absorption reported is neither that of a yellow compound nor that of a pseudo-indoxyl, as is claimed, though a structure such as (48) would be expected not to have a straightforward pseudo-indoxyl



<sup>20</sup> D. P. Chakraborty, A. Islam, and P. Bhattacharyya, *J. Org. Chem.*, 1973, **38**, 2728.

<sup>21</sup> A. K. Sen, S. B. Mahato, and N. L. Dutta, *Tetrahedron Letters*, 1974, 609.

absorption. Since the only other evidence advanced for the structure is the presence of carbonyl bands at 1725 and 1680  $\text{cm}^{-1}$ , the loss of both one and two carbon monoxide units and a hydrogen cyanide and two carbon monoxide units in the mass spectrometer, and the presence of ABX, singlet and homoaromatic signals in the region  $\tau$  1.4—2.8 as the only n.m.r. signals, the structure (48) must remain as yet open to considerable doubt. Couroupitine B, a red compound which gave an acetyl derivative with molecular weight 304, was also isolated in this study.

**Non-isoprenoid Tryptamines.** The stems of *Picrasma ailanthoides*, from which plant canthine derivatives had previously been obtained, has now yielded<sup>22</sup> 1-methoxycarbonyl- and 1-hydroxymethyl- $\beta$ -carboline. The molecular shape of eserine (=physostigmine) in the crystal has been determined.<sup>23</sup> The new evidence fits in well with information, summarized previously,<sup>12b</sup> from n.m.r. NOE measurements. More alkylations at the C-1 methyl of harmaline<sup>9c</sup> have been reported.<sup>24</sup> The  $N_a$ -methyl derivative<sup>25</sup> of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine<sup>9c,12c</sup> has been isolated from cranberries.

An ingenious method<sup>26</sup> for the synthesis of the epidithiodiketopiperazine system forms the basis for Kishi's delightful syntheses of ( $\pm$ )-dehydrogliotoxin (49)<sup>27</sup> and ( $\pm$ )-sporidesmin A (50a)<sup>28a</sup> and ( $\pm$ )-sporidesmin B (50b).<sup>28b</sup>

The synthesis<sup>27</sup> (Scheme 4) of dehydrogliotoxin began with the introduction [(51)  $\rightarrow$  (52)] of an aromatic ring, for the prospective indoline, on to a piperazine-2,5-dione nucleus. Insertion of the two sulphur atoms, by bromination and displacement with thioacetate, gave (53) and this was then transformed into a mixture of anisaldehyde thioacetal epimers (54). Transformations on the benzene ring ester substituent then provided a benzyl halide, in the pair of epimers (55), to serve as an internal alkylating agent for the piperazinedione ring and thus provide the means for forming the indoline hetero-ring. Now, in the model work, it had been found<sup>27</sup> that the relative stereochemistry at the thioacetal carbon determines which of the two bridgehead hydrogens is the more acidic and consequently which of the two bridgehead positions can be preferentially alkylated. Thus when the mixture of stereoisomers (55) was treated with base, only one underwent internal alkylation, the other being recovered overall unchanged, because from it the alternative bridgehead hydrogen had been removed. The unreacted isomer could be used, however, one way being to equilibrate at the acetal carbon to give a mixture containing the desired isomer in the ratio 3 : 2.

<sup>22</sup> Y. Kondo and T. Takemoto, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 837.

<sup>23</sup> P. Pauling and T. J. Petcher, *J.C.S. Perkin II*, 1973, 1342.

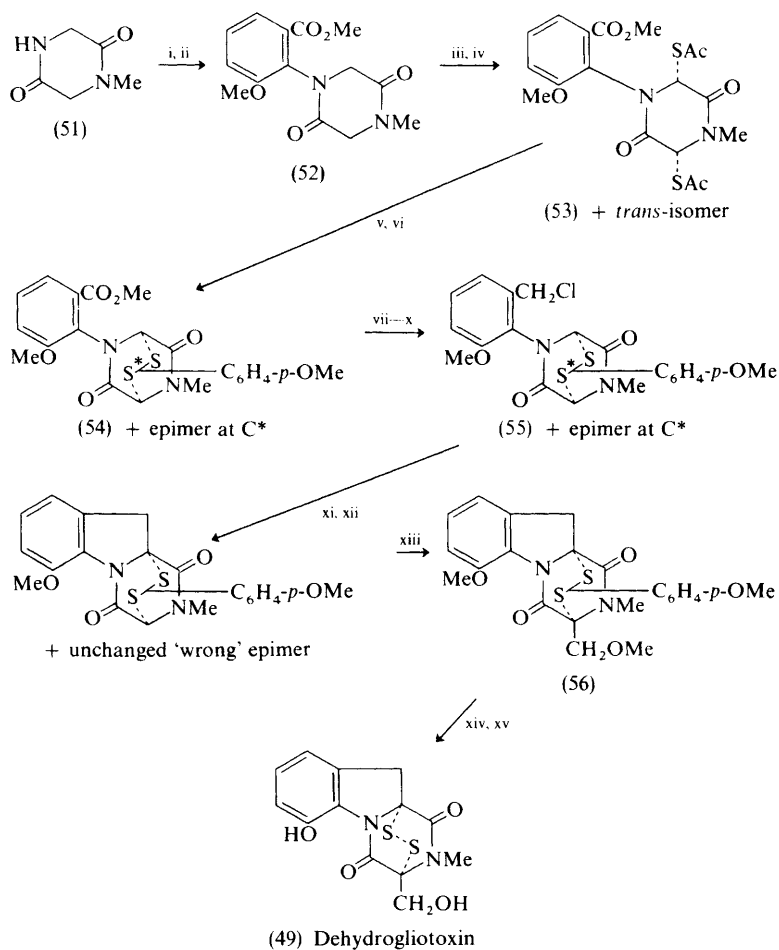
<sup>24</sup> Atta-ur-Rahman and F. Zehra, *Pakistan J. Sci. Ind. Res.*, 1972, **15**, 266 (*Chem. Abs.*, 1973, **79**, 53 651).

<sup>25</sup> K. Jankowski, S. Godin, and N. E. Cundasawmy, *Canad. J. Chem.*, 1974, **52**, 2064.

<sup>26</sup> Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, 1973, **95**, 6490.

<sup>27</sup> Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, 1973, **95**, 6492.

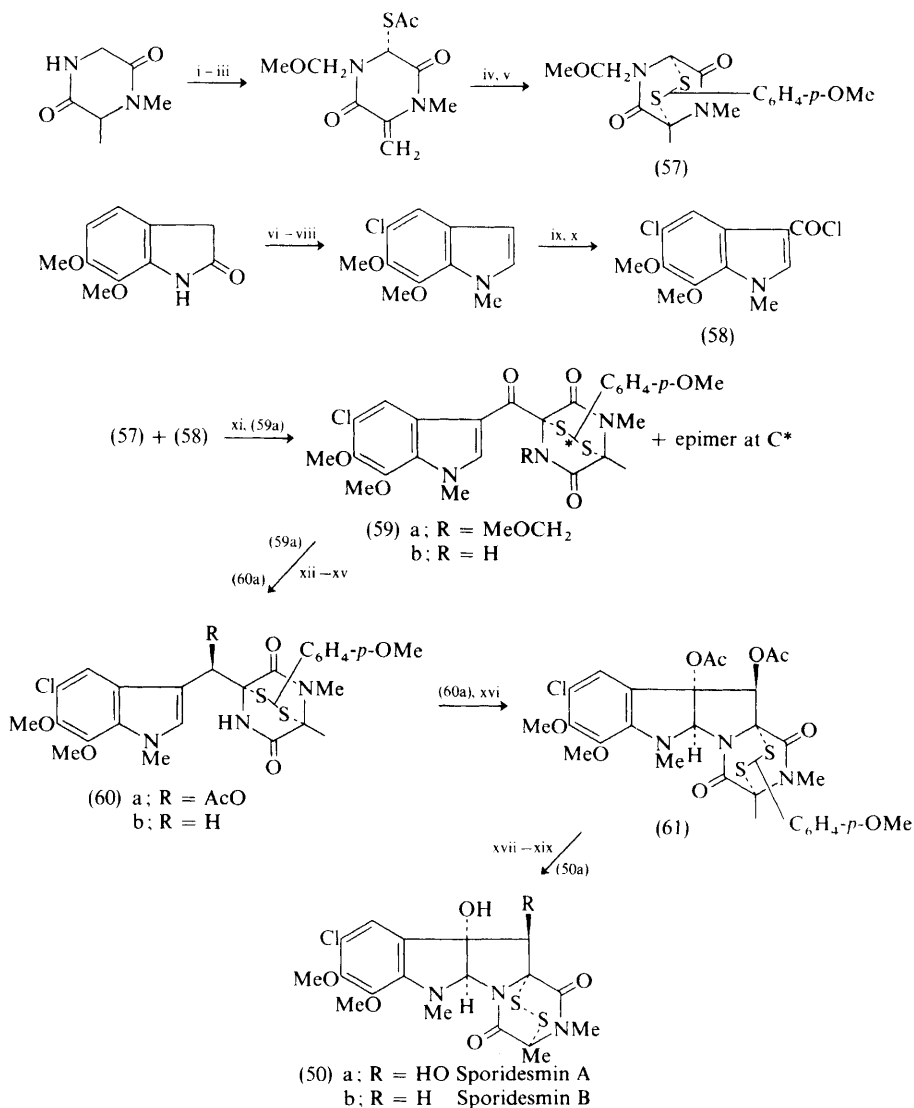
<sup>28</sup> (a) Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *ibid.*, p. 6495; (b) S. Nakatsuka, T. Fukuyama, and Y. Kishi, *Tetrahedron Letters*, 1974, 1549.



Reagents: i, 2-iodo-3-methoxybenzoic acid-CuI-K<sub>2</sub>CO<sub>3</sub>-PhNO<sub>2</sub>-170°C; ii, CH<sub>2</sub>N<sub>2</sub>; iii, NBS-(PhCO<sub>2</sub>)<sub>2</sub>; iv, MeCOSK; v, HCl-MeOH; vi, *p*-MeOC<sub>6</sub>H<sub>4</sub>CHO-BF<sub>3</sub>; vii, aq. NaOH-dioxan; viii, *NN'*-carbonyl di-imidazole-THF; ix, 0°C-LiBH<sub>4</sub>; x, (n-C<sub>8</sub>H<sub>17</sub>)<sub>3</sub>P-CCl<sub>4</sub>-RT; xi, -110°C-BuLi; xii, AcOH; xiii, -78°C-BuLi-MeOCH<sub>2</sub>Cl; xiv, *m*-ClC<sub>6</sub>H<sub>4</sub>CO<sub>3</sub>H-CH<sub>2</sub>Cl<sub>2</sub>; xv, 0°C-BCl<sub>3</sub>-CH<sub>2</sub>Cl<sub>2</sub>

Scheme 4

The second bridgehead substituent was introduced in a protected form [ $\rightarrow$  (56)] and this intermediate subjected to the sequence of steps worked out<sup>26</sup> for the construction of the disulphide bridge. Thus oxidation to a sulphoxide followed by reaction with a Lewis acid, also in this case usefully cleaving the two methyl ethers, afforded dehydrogliotoxin (49).

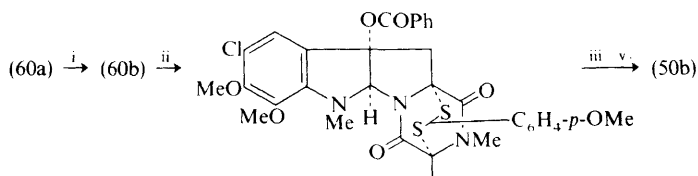


Reagents: i, Bu<sup>t</sup>OK-Bu<sup>t</sup>OH-MeOCH<sub>2</sub>Cl; ii, NBS-(PhCO<sub>2</sub>)<sub>2</sub>; iii, MeCOSK-CH<sub>2</sub>Cl<sub>2</sub>; iv, HCl-MeOH; v, trithian derivative of *p*-MeOC<sub>6</sub>H<sub>4</sub>CHO-BF<sub>3</sub>-CH<sub>2</sub>Cl<sub>2</sub>; vi, Cl<sub>2</sub>-aq. MeOH-R.T.; vii, MeI-NaH-xylene-heat; viii, -78 °C-Bu<sup>t</sup><sub>2</sub>AlH-Et<sub>2</sub>O; ix, (COCl)<sub>2</sub>-Et<sub>2</sub>O; x, 120 °C-CH<sub>2</sub>Cl<sub>2</sub>; xi, 1 mol BuLi-110 °C; xii, conc. HCl-70 °C; xiii, separate isomers; xiv, -78 °C-Bu<sup>t</sup><sub>2</sub>AlH-THF; xv, Ac<sub>2</sub>O-pyridine; xvi, iodosobenzene diacetate-MeCN-Me<sub>2</sub>S; xvii, aq. NaOH-MeOH-R.T.; xviii, *m*-ClC<sub>6</sub>H<sub>4</sub>CO<sub>3</sub>H; xix, BF<sub>3</sub>-Et<sub>2</sub>O-CH<sub>2</sub>Cl<sub>2</sub>-R.T.

Scheme 5

In the synthesis (Scheme 5)<sup>28a</sup> of sporidesmin A, the bicyclic epidithiodiketopiperazine precursor (57) was acylated with the appropriate indolyl acid chloride (58). Stereoselective reduction of the ketone carbon was effected, after removal of the methoxymethyl *N*-protecting group, by reaction with di-isobutylaluminum hydride. This reduction probably involves initial reaction of the reagent at the amide *N*-hydrogen in (59b) since the methoxymethyl precursor (59a) was not reduced, even by lithium aluminium hydride. With the reagent thus complexed, hydride is likely to be delivered to a conformation in which indole and thioacetal units are as far apart as possible, leading to the desired product. The key step in the synthesis then followed in the formation of the C ring by a process which is shown in (60a)  $\rightarrow$  (61). Here, what must happen<sup>9d</sup> is electrophilic acetoxylation at the indole  $\beta$ -position followed by intramolecular nucleophilic addition by the apposite amide nitrogen; the required stereochemistry was again realized in this step.

Sporidesmin B, one of the minor toxic metabolites of *Pithomyces chartarum*, was obtained (Scheme 6)<sup>28b</sup> by reducing the intermediate (60a) to (60b) and then by a sequence of steps which parallel those used for sporidesmin A.



Reagents: i,  $\text{NaB}(\text{CN})\text{H}_3$ -AcOH-R.T.; ii,  $(\text{PhCO}_2)_2-(\text{CH}_2\text{OMe})_2$ -trace 4,4'-thiobis(6-*t*-butyl-3-methylphenol); iii, aq. KOH-THF-MeOH-0 °C; iv, *m*- $\text{ClC}_6\text{H}_4\text{CO}_3\text{H}$ - $\text{CH}_2\text{Cl}_2$ -0 °C; v,  $\text{BF}_3$ - $\text{Et}_2\text{O}$ - $\text{CH}_2\text{Cl}_2$ -R.T.

Scheme 6

### 3 Isoprenoid Tryptamine and Tryptophan Alkaloids

**Non-terpenoid Alkaloids.**—Full details<sup>29</sup> have been given of the structural work<sup>12d</sup> on neoechinulin. Some or all of the ergoline alkaloids agroclavine, chanoclavine-I, chanoclavine-II, racemic chanoclavine-II, elymoclavine, festuclavine, lysergene, lysergol, isolysergol, molliclavine, penniclavine, setoclavine, isosetoclavine, ergine, isoergine, ergometrine, ergometrinine, lysergic acid  $\alpha$ -hydroxyethylamide, and isolysergic acid  $\alpha$ -hydroxyethylamide occur<sup>30</sup> in *Argyrea barnesii*, *A. capitata*, *A. cureata*, *A. bizoninsis*, *A. mollis*, *A. maingayi*, *A. nervosa*, *A. obtusifolia*, *A. philippinensis*, *A. reticulata*, *A. ridleyi*, *A. rubicunda*, *A. splendens*, *Stictocardia tiliafolia*, and *Rivea corymbosa*.

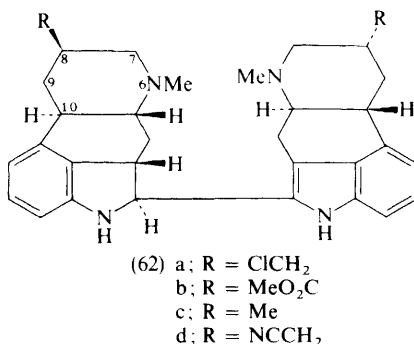
The  $^1\text{H}$  and  $^{13}\text{C}$  (see p. 186) n.m.r. spectra of ergot alkaloids have been examined;<sup>10r</sup> the revised  $^1\text{H}$  signal and coupling constant assignments are now

<sup>29</sup> G. Casnati, A. Pochini, and R. Ungaro, *Gazzetta*, 1973, **103**, 141.

<sup>30</sup> J.-M. Chao and A. H. Der Marderosian, *Phytochemistry*, 1973, **12**, 2435.

consistent with the *trans* stereochemistry of the C/D ring-junction. The fluorescence and phosphorescence characteristics of lysergic acid diethylamide and related ergolines have been studied.<sup>31</sup>

Lysergic acid amides can be prepared<sup>32</sup> easily by reaction of the acid, the amine, and phosphorus oxychloride at room temperature for a short while. Treatment<sup>33</sup> of methyl 9,10-dihydrolysergate *N*-oxide with acetic anhydride introduces unsaturation into the piperidine ring at C-7—C-8 presumably *via* the N-6—C-7 immonium salt. In the course of chlorinating 9,10-dihydrolysergol with phosphorus oxychloride a dimeric product was obtained to which the structure (62a) was given, mainly on the basis of the mixed indole/indoline u.v. absorption. It was further shown<sup>34</sup> that such dimers [e.g. (62b, c, and d)] could be prepared from a variety of ergot alkaloids and derivatives in good yield using boron trifluoride etherate–trifluoroacetic acid. Hydrogenation<sup>35</sup> of elymoclavine leads to some hydrogenolysis of the N-6—C-7 bond.



The tryptophan tetramic acid (63) has been isolated<sup>36</sup> from *Penicillium cyclopium*; it thus seems certain that the biosynthetic sequence leading to cyclopiazonic acid<sup>1b</sup> involves C-4 dimethylallylation of (63), *i.e.* that the formation of the tetramic acid unit from tryptophan and acetoacetate occurs first.

A 4-(4-hydroxy-3-methylbut-2-enyl)-tryptophan (double bond geometry not known) was shown<sup>37</sup> to be present in cultures of *Claviceps purpurea*. Barrerine,<sup>38</sup> from *Barreria verticillata*, is 2-methyl-1-(2-methylprop-2-enyl)-1,2,3,4-tetrahydro- $\beta$ -carboline; a dimer of barrerine was also isolated.

A bitter principle, isolated from bacterial proteinase casein hydrolysate, and originally thought to be a cyclic tetrapeptide, has been now shown<sup>39</sup> to have the

<sup>31</sup> A. Bawd, J. B. Hudson, and J. H. Turnbull, *J.C.S. Perkin II*, 1973, 1312.

<sup>32</sup> F. N. Johnson, I. E. Ary, D. G. Teiger, and R. J. Kassel, *J. Medicin. Chem.*, 1973, **16**, 532.

<sup>33</sup> P. Stütz and P. A. Stadler, *Tetrahedron Letters*, 1973, 5095.

<sup>34</sup> N. J. Bach and E. C. Kornfeld, *Tetrahedron Letters*, 1973, 3315.

<sup>35</sup> R. Voigt and P. Zier, *Pharmazie*, 1973, **28**, 486 (*Chem. Abs.*, 1973, **79**, 137 338).

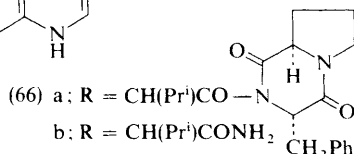
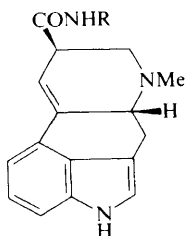
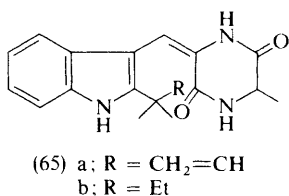
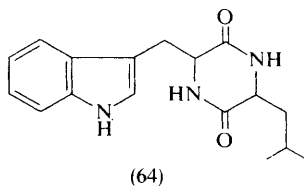
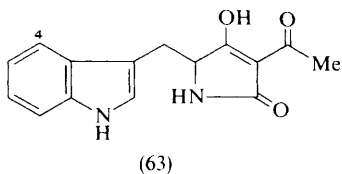
<sup>36</sup> R. M. McGrath, P. S. Steyn, and N. P. Ferreira, *J.C.S. Chem. Comm.*, 1973, 812.

<sup>37</sup> J. A. Anderson and M. S. Saini, *Tetrahedron Letters*, 1974, 2107.

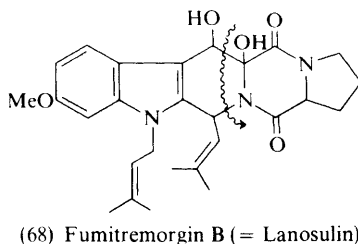
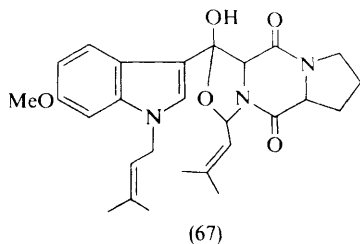
<sup>38</sup> J.-L. Pousset, J. Kerharo, G. Maynard, X. Monseur, A. Cavé, and R. Goutarel, *Phytochemistry*, 1973, **12**, 2308.

<sup>39</sup> T. Shiba and K. Nunami, *Tetrahedron Letters*, 1974, 509.

structure (64). The indole (65a) and its dihydro-derivative (65b) were obtained<sup>40</sup> from *Aspergillus ruber* infecting oil cakes. New alkaloids are represented by (66a)<sup>41</sup> from the mycelium of *Claviceps purpurea* and (66b)<sup>42</sup> 'from ergot'.



A tremorgenic toxic metabolite isolated<sup>43</sup> from *Aspergillus fumigatus* and given the name fumitremorgin B is said to be identical with lanosulin, which was recently assigned<sup>44a</sup> the structure (67); however, the Japanese workers conclude<sup>43</sup> that the newly isolated compound has structure (68). Both groups of workers agree on the presence of a tryptophan-proline diketopiperazine and that the



<sup>40</sup> H. Itokawa, Y. Akita, and M. Yamazaki, *Yakugaku Zasshi*, 1973, **93**, 1251 (*Chem. Abs.*, 1974, **80**, 70 634).

<sup>41</sup> P. Stütz, R. Brunner, and P. A. Stadler, *Experientia*, 1973, **29**, 936.

<sup>42</sup> A. N. Ban'kovskaya, V. I. Sheichenko, A. I. Ban'kovskii, L. D. Vechkanova, and V. S. Kabanov, *Khim. prirod. Soedinenii*, 1973, **9**, 134 (*Chem. Abs.*, 1973, **78**, 159 955).

<sup>43</sup> M. Yamazaki, K. Sasago, and K. Miyaki, *J.C.S. Chem. Comm.*, 1974, 408.

<sup>44</sup> (a) J. A. Joule, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4, p. 289; (b) *ibid.*, p. 295; (c) *ibid.*, p. 292; (d) *ibid.*, p. 294; (e) *ibid.*, p. 303; (f) *ibid.*, p. 305; (g) *ibid.*, p. 309; (h) *ibid.*, p. 307; (i) *ibid.*, p. 306; (j) *ibid.*, p. 315; (k) *ibid.*, p. 318.

indole carries a methoxy-group at C-6 and a dimethylallyl unit on the nitrogen. The negative Ehrlich reaction which the Japanese workers declare for fumitremorgin B, together with the lack (presumably—though this absence is not specifically mentioned in either communication) of an indole  $\alpha$ -hydrogen n.m.r. signal and the presence of a mass spectral base peak at  $m/e$  311, which, with a formula of  $C_{20}H_{25}NO_2$ , implies an indole fragment carrying six of the carbons and one of the oxygens of the aliphatic portion of the molecule [see curly arrows on (68)], speak strongly in favour of the second formulation (68), though more evidence would be needed before this structure could be made certain.

**Monoterpenoid Alkaloids.**—*Yohimbine–Corynantheine–Heteroyohimbine (and Related Oxindoles) Group.* Ajmalicine, yohimbine, rescinnamine, and serpentine were obtained from the root bark of *Rauwolfia macrophylla*.<sup>45a</sup> Serpentine was also obtained from the leaves of *R. caffra*<sup>45b</sup> and yohimbine from the roots<sup>45c</sup> of the same plant, from which aricine and renoxidine were also isolated;  $\alpha$ -yohimbine and an unidentified yohimbine stereoisomer were isolated from the aerial parts of *Vinca pusilla*.<sup>45d</sup> Tetrahydroalstonine has also been found in the root bark of *Voacanga chaloniana*<sup>45e</sup> and the leaves of *Amsonia tabernaemontana*.<sup>45f</sup> *Strychnos usambarensis*<sup>45g</sup> contains 6,7-dihydroflavopereirine and the bark of *Alstonia venenata*<sup>45h</sup> is yellow largely owing to the presence in it of 3,4-dehydroalstovenine. A detailed description<sup>45i</sup> of work on the quaternary bases from the bark of *Hunteria eburnea* describes the isolation of antirhine and dihydroantirhine  $\beta$ -metho-salts and pleiocarpamine metho-salt. 3,4,5,6-Tetrahydroalbotine and 5,6-dehydroalbotine and methyl deformyltalbotinate are new bases obtained from the leaves of *Pleiocarpa talbotii*.<sup>45j</sup> The C-11, C-12 location of the two methoxy-groups in majdine and isomajdine has been confirmed<sup>45k</sup> by NOE measurements. Pteropodine, isopteropodine, speciophylline, mitraphylline, isomitraphylline, and uncarine F, together with the *N*-oxides of all save the last, were isolated<sup>45l</sup> from the leaves of *Uncaria longiflora*. The leaves of *U. macrophylla* yielded<sup>45m</sup> corynoxine, corynoxine B, rhynchophylline, and isorhynchophylline; the stem bark of *Bleekeria vitiensis*<sup>45n</sup> gave carapanaubine and *Mitragyna tubulosa*<sup>45o</sup> gave ciliaphylline *N*-oxide.

The crystal structure and absolute configuration of yohimbine hydrochloride have been reported.<sup>46</sup> Sulphovanadic oxidation proves to be a good method<sup>47</sup>

<sup>45</sup> (a) P. Timmins and W. E. Court, *Phytochemistry*, 1974, 13, 281; (b) M. S. Habib and W. E. Court, *ibid.*, p. 661; (c) *ibid.*, 1971, 12, 1821; (d) A. Chatterjee, G. K. Biswas, and A. B. Kundu, *Indian J. Chem.*, 1973, 11, 7; (e) B. Gabetta, E. M. Martinelli, and G. Mustich, *Fitoterapia*, 1974, 45, 32; (f) B. Zsádon, J. Tamas, and M. Szilasi, *Magyar Kém. Folyóirat*, 1973, 79, 341 (*Chem. Abs.*, 1973, 79, 115 755); (g) L. Angenot and A. Denoel, *Planta Med.*, 1973, 23, 226 (*Chem. Abs.*, 1973, 79, 18 924); (h) A. B. Ray and S. C. Dutta, *Experientia*, 1973, 29, 1337; (i) R. H. Burnell, A. Chapelle, and M. F. Khalil, *Canad. J. Chem.*, 1974, 52, 2327; (j) M. Pinar, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1973, 56, 2719; (k) M. R. Yagudaev, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 9, 70 (*Chem. Abs.*, 1973, 78, 159 954); (l) J. D. Phillipson and S. R. Hemingway, *Phytochemistry*, 1973, 12, 2791; (m) *ibid.*, p. 2795; (n) S. Kanji and M. Sainsbury, *ibid.*, 1974, 13, 503; (o) J. D. Phillipson, D. Rungsiyakul, and E. J. Sheppard, *ibid.*, 1973, 12, 2043.

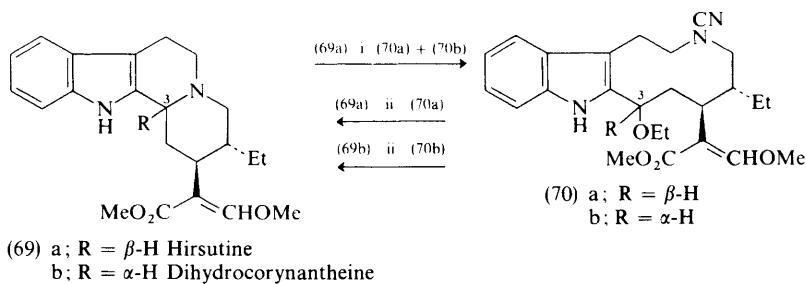
<sup>46</sup> G. Ambady and G. Kantha, *J. Cryst. Mol. Structure*, 1973, 3, 37.

<sup>47</sup> R. Stainer, H.-P. Husson, and C. L. Lapiere, *J. Pharm. Belg.*, 1973, 28, 307 (*Chem. Abs.*, 1973, 79, 79 018).



for the oxidation of yohimbine types to the corresponding 3,4-dehydro-immonium salts.

Venenatic and rauwolfscinic acids, but not yohimbic or  $\beta$ -yohimbic acids, are converted,<sup>48</sup> albeit in very small yields, into lactams in which N-4 is bonded to C-22, C-3 carries an acetoxy-group, and the C-3—N-4 bond is cleaved, by heating with acetic anhydride–sodium acetate. A further study<sup>49</sup> of the cyanogen bromide–ethanol cleavage of the C-3—N-4 bond in yohimbine<sup>12e</sup> has shown that both 3*R*- and 3*S*-ethoxy-3,4-seco-cyanamides can be obtained, more 3*R*-isomer resulting from the use of higher molar proportions of ethanol. It was further shown that the 3*R*- and 3*S*-isomers could be stereospecifically ring-closed with acetic acid to yohimbine and pseudoyohimbine respectively, apparently with retention of the configuration at C-3 in the seco-derivatives. Exactly analogous results were obtained with hirsutine (69a) (Scheme 7).



Reagents: i, CNBr–EtOH–CHCl<sub>3</sub>–K<sub>2</sub>CO<sub>3</sub>; ii, AcOH–heat

**Scheme 7**

Full details<sup>50</sup> have been given of the iminoether–borohydride–acetic acid method<sup>9e</sup> for the transformation of oxindole alkaloids into the corresponding indoles.

This year sees the addition by Brown of two further<sup>44b</sup> tryptophan-derived 5-carboxy-alkaloids<sup>51,52</sup> including one<sup>52</sup> in which the 'extra' carboxy-group is involved in the alkaloid ring structure.

5 $\beta$ -Carboxytetrahydroalstonine (71),<sup>51</sup> the first 5-carboxy-heteroyohimbine base to be isolated, was obtained from *Adina rubescens*. The location of the carboxy-group was confirmed by the observation of modified  $\beta$ -carboline-containing mass spectral fragments. The absolute stereochemistry at C-3 was established in the usual way by c.d. measurements and the relative stereochemistry at C-19 and C-20 in the following way. It was first noted, from their large coupling constant, that H-19 and H-20 are *trans* diaxially related; the

<sup>48</sup> A. Banerji, P. L. Majumder, and A. Chatterjee, *Indian J. Chem.*, 1973, **11**, 1057.

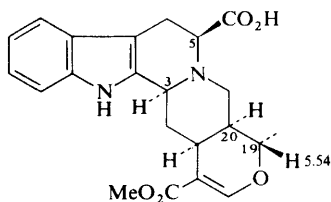
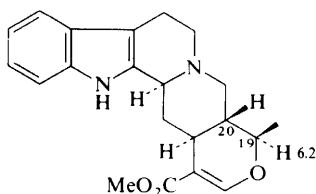
<sup>49</sup> S. Sakai, A. Kubo, K. Katano, N. Shinma, and K. Sasago, *Yakagaku Zasshi*, 1973, **93**, 1165 (*Chem. Abs.*, 1973, **79**, 137 336).

<sup>50</sup> N. Aimi, E. Yamanaka, J. Endo, S. Sakai, and J. Haginiwa, *Tetrahedron*, 1973, **29**, 2015.

<sup>51</sup> R. T. Brown and A. A. Charalambides, *Tetrahedron Letters*, 1974, 1649.

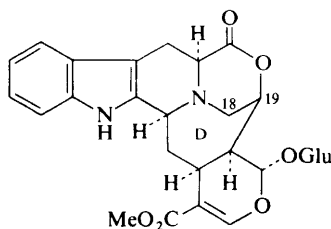
<sup>52</sup> R. T. Brown and A. A. Charalambides, *J.C.S. Chem. Comm.*, 1973, 765.

choice between the two *trans*-possibilities was made by reference to the empirical observation that the chemical shift of the H-19 proton in the heteroyohimbine types lies between  $\tau 6.2$ – $6.5$  in the  $19\alpha,20\beta$ -series, *e.g.* 19-epiajmalicine (72), and in the range  $\tau 5.5$ – $5.8$  in the  $19\beta,20\alpha$ -types as in the present case (71). This useful generalization applies equally to alkaloids with a  $\beta$ -hydrogen at C-3 and to heteroyohimbine oxindoles.

(71) 5 $\beta$ -Carboxytetrahydroalstonine

(72) 19-Epi-ajmalicine

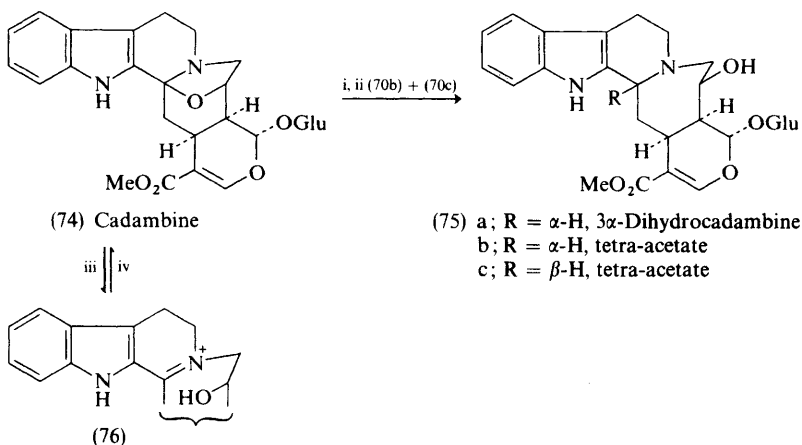
In the structure of rubenine (73)<sup>52</sup> isolated from the same plant the 5-carboxy-group forms part of a lactone. The alkaloid can be viewed as a derivative of 5-carboxystricoidine, in which the vinyl carbons, C-18 and C-19, have become linked, respectively, to N-4 and the C-5-carboxylate, thus giving a skeleton with a seven-membered ring D.



(73) Rubenine

The same type of seven-membered D ring occurs in cadambine (74)<sup>53a</sup> and 3 $\alpha$ -dihydrocadambine (75a)<sup>53</sup> (which was shown<sup>53b</sup> to be identical with the glycosidic alkaloid reported<sup>44c</sup> from *Nauclea diderrichii*) from *Anthocephalus cadamba* and in nauclechine.<sup>44c</sup> The relationship between cadambine and dihydrocadambine was established (Scheme 8) by the sodium borohydride-acetic acid reduction of the tetra-acetate of the former to a mixture of 3 $\alpha$ -dihydrocadambine (75a) tetra-acetate corresponding to the natural isomer, and its 3 $\beta$ -epimer (major product). The C-3 carbinolamine ether system in cadambine was diagnosed by the u.v. spectral shift observed in acidic solution. Reversible, acid-catalysed cleavage of the N—C—O system led to the well-known, characteristic chromophore (76).

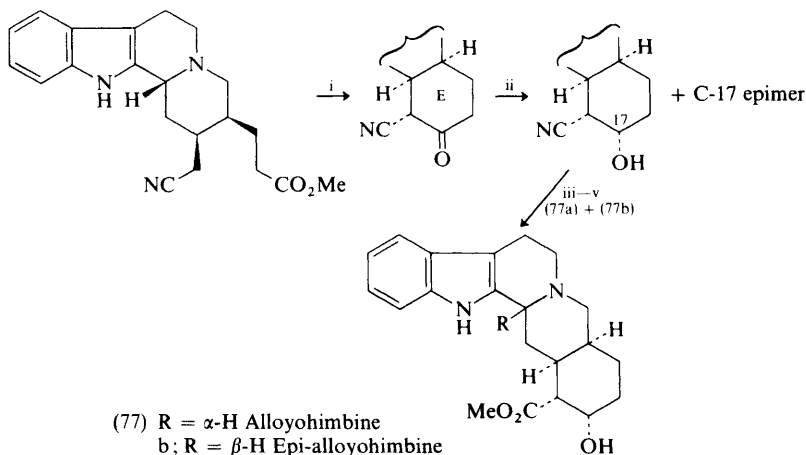
<sup>53</sup> (a) R. T. Brown and S. B. Fraser, *Tetrahedron Letters*, 1974, 1957; (b) G. I. Dimitrienko, D. G. Murray, and S. McLean, *ibid.*, p. 1961.



Reagents:  $\text{Ac}_2\text{O}$ ; ii,  $\text{NaBH}_4$ -AcOH; iii, AcOH; iv, base

Scheme 8

Extension<sup>54</sup> of the Szantay approach to the yohimbine system has now resulted in syntheses of ( $\pm$ )-alloyohimbine, ( $\pm$ )- $\alpha$ -yohimbine, and epimers thereof. Scheme 9 shows one route<sup>54a</sup> to alloyohimbine (77a). This total synthesis now necessitates the revision of the structures of the isomers allo- (77a) and epiallo-yohimbine (77b).

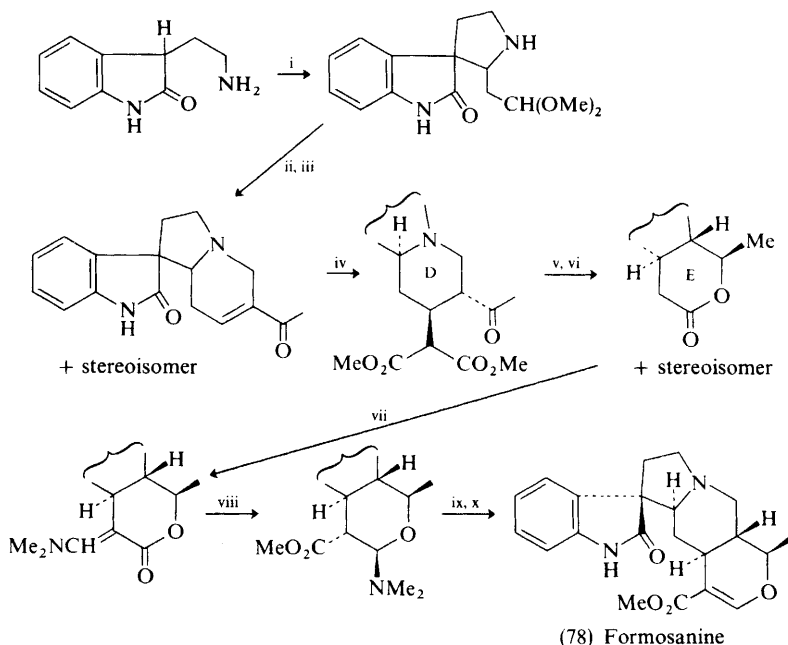


Reagents: i,  $\text{Bu}^t\text{OK}$ -DMSO-R.T.; ii,  $\text{NaBH}_4$ -DMF-MeOH; iii,  $\text{NaOH}$ - $\text{H}_2\text{O}_2$ ; iv, 18%  $\text{HCl}$ -heat; v,  $\text{CH}_2\text{N}_2$

Scheme 9

<sup>54</sup> (a) L. Töke, K. Honty, L. Szabó, G. Blaskó, and C. Szántay, *J. Org. Chem.*, 1973, **38**, 2496; (b) L. Töke, Z. Gombos, G. Blaskó, K. Honty, L. Szabó, J. Tamás, and C. Szántay, *ibid.*, p. 2501.

Ban's synthetic route to rhynchophylline<sup>9f</sup> has been extended now to provide a synthesis<sup>55</sup> of the pentacyclic oxindoles ( $\pm$ )-formosanine (78), ( $\pm$ )-isoformosanine, ( $\pm$ )-mitraphylline, and ( $\pm$ )-isomitraphylline. Scheme 10 reviews the synthesis of the first of these.



Reagents: i,  $(\text{MeO})_2\text{CHCH}_2\text{CHO}$ ; ii,  $\text{MeCOCH}=\text{CH}_2$ ; iii, 10%  $\text{HCl}-\text{AcOH}$ ; iv,  $(\text{MeO}_2\text{C})_2\text{CH}_2-0.5\text{eq. MeONa}-\text{MeOH}$ ; v,  $\text{H}_2-\text{Pt}$ ; vi, dil.  $\text{H}_2\text{SO}_4-\text{AcOH}$ -heat; vii,  $(\text{Me}_2\text{N})_2\text{CHOBu}^t-\text{DMF}-100^\circ\text{C}$ ; viii,  $\text{MeOH}-\text{HCl}$ ; ix, aq. dioxan-heat; x,  $\text{PPA}-\text{DME}$

Scheme 10

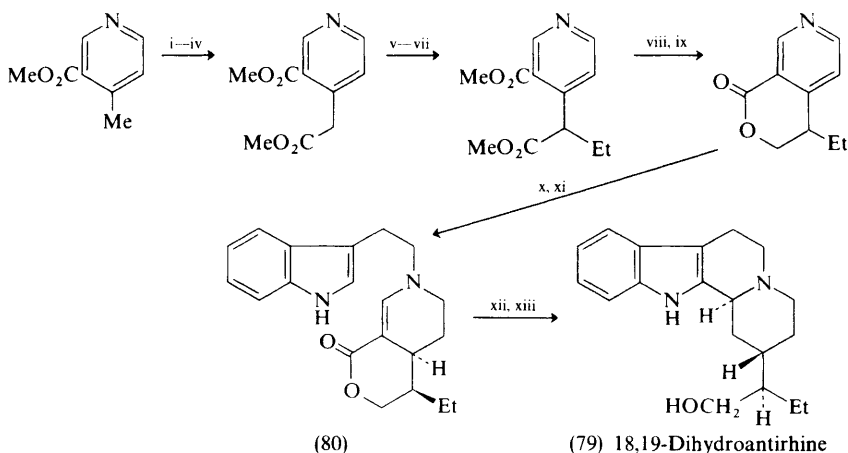
In a synthesis<sup>56</sup> (Scheme 11) of ( $\pm$ )-18,19-dihydroantirrhine (79), Wenkert employs as a key step his method for the formation of immonium salts within a piperidine ring by the decarboxylation of a 3-carboxy-1,4,5,6-tetrahydropyridine. One feature to note is the production of stereoisomer (80) in the hydrogenation of the precursor pyridinium salt; this governs the production of the finally required stereoisomer (79).

A possible clue to the explanation of the enigma of the biosynthetic use of vincoside, with a  $\beta$ -hydrogen at C-3, in making alkaloids with a C-3  $\alpha$ -configuration, was one of the results to come out of Brown's study<sup>57</sup> of the *in vitro* conversion (Scheme 12) of secologanin into corynantheine types. Condensation of

<sup>55</sup> Y. Ban, N. Taga, and T. Oishi, *Tetrahedron Letters*, 1974, 187.

<sup>56</sup> E. Wenkert, P. W. Sprague, and R. L. Webb, *J. Org. Chem.*, 1973, **38**, 4305.

<sup>57</sup> R. T. Brown and C. L. Chapple, *J.C.S. Chem. Comm.*, 1973, 886.



Reagents: i,  $(\text{CO}_2\text{Et})_2\text{-Bu}^t\text{OK-DME}$ ; ii, aq. KOH; iii,  $0^\circ\text{C-30\% H}_2\text{O}_2$ ; iv,  $\text{MeOH-HCl}$ ; v,  $\text{MeCHO-Bu}^t\text{OK-DME}$ ; vi,  $\text{MeOH-HCl}$ ; vii,  $\text{H}_2\text{-Pt-MeOH-R.T.-atm. press.}$ ; viii,  $\text{LiAlH}_4\text{-Et}_2\text{O-heat}$ ; ix,  $\text{MnO}_2$ ; x,  $\text{indol-3-yl-CH}_2\text{CH}_2\text{Br}$ ; xi,  $\text{H}_2\text{-Pd/C-Et}_3\text{N-atm. press.}$ ; xii, aq. KOH-MeOH-R.T.; xiii,  $10\% \text{HCl-R.T.}$

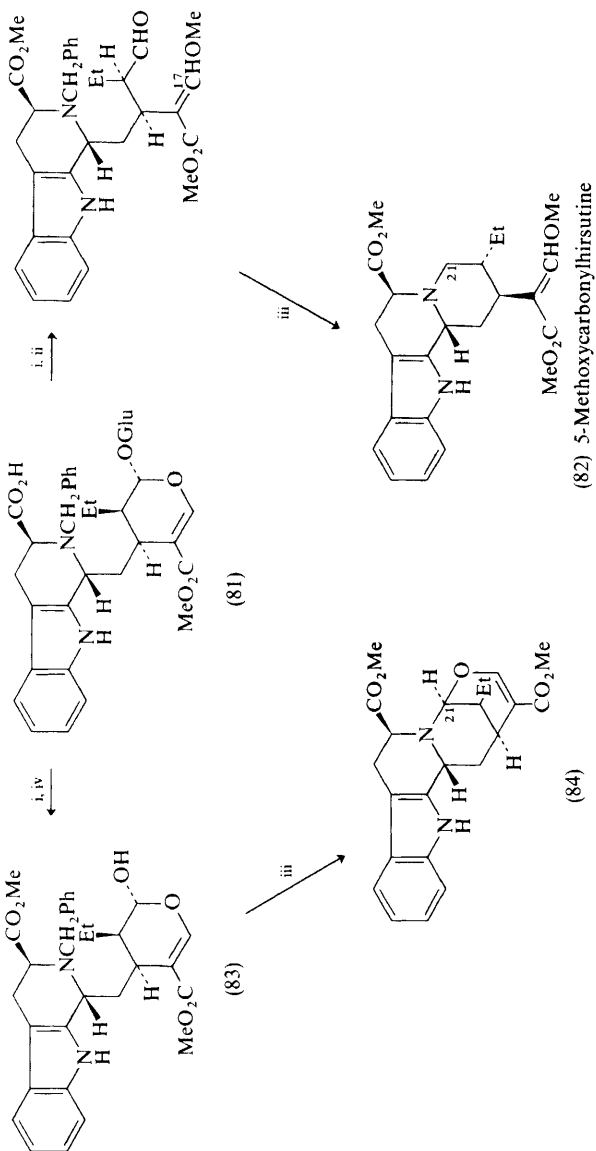
Scheme 11

$N_b$ -benzyl-L-tryptophan with dihydrosecologanin in the usual way<sup>9g,12f</sup> gave an intermediate (81) having a blocking group on the basic nitrogen. This prevented formation of vallesiachotamine types, as usually happens,<sup>9h</sup> on removal of the sugar unit. Subsequent opening of ring E by the formation of an enol ether at C-17, which also discouraged nitrogen attack at that position, thus allowed the required N-4—C-21 bonding to take place when the N-protecting group was removed; 5 $\beta$ -methoxycarbonylhirsutine (82) resulted.

Removal of the *N*-benzyl protection from the partially methylated hemi-acetal (83) gave the novel (84) in which N-4—C-21 bonding had occurred but presumably without opening of the E-ring, because the result of such an opening would almost certainly have been the formation of a vallesiachotamine type. It is suggested<sup>57</sup> that a structure such as that of (84) may be necessarily involved in the biosynthetic sequence which leads to alkaloids having an N-4—C-21 bond and that it is because the ring structure of (84) is sterically much more favourable than an isomer having a 3 $\alpha$ -hydrogen that Nature chooses to employ vincoside and not the C-3 epimer strictosidine.

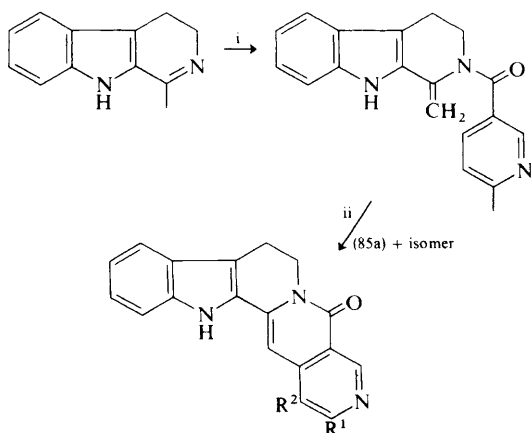
Considerable efforts<sup>58</sup> have been made in the synthesis of the *Strychnos angustiflora* alkaloids reviewed last year.<sup>44d</sup> A photochemical cyclization lies at the heart of a neat synthesis<sup>58a</sup> of angustidine (85a) (Scheme 13). 18,19-Dihydroangustine (85b) has been prepared<sup>58b</sup> from vincoside lactam tetra-

<sup>58</sup> (a) I. Ninomiya, H. Takasugi, and T. Naito, *J.C.S. Chem. Comm.*, 1973, 732; (b) R. T. Brown and A. A. Charalambides, *Tetrahedron Letters*, 1973, 4837; (c) A. Shafiee and E. Winterfeldt, *Chem. Ber.*, 1974, 107, 966.



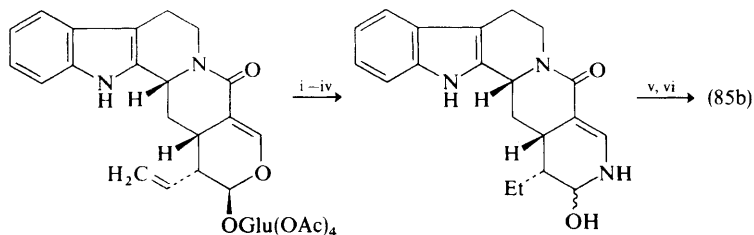
Reagents: i,  $\beta$ -glucosidase; ii, 'prolonged methylation treatment'  $\text{CH}_2\text{N}_2$ ; iii,  $\text{H}_2$ -Pd/C-MeOH-AcOH; iv, brief  $\text{CH}_2\text{N}_2$

**Scheme 12**



Reagents: i, 6-methyl-pyrid-3-yl-COCl; ii,  $h\nu$ -MeOH

**Scheme 13**



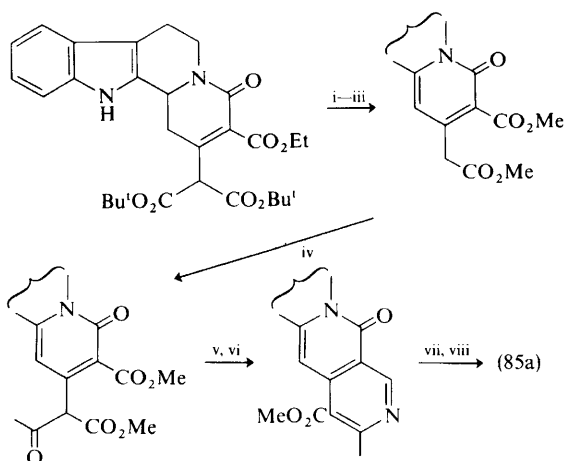
Reagents: i,  $\text{H}_2$ -Pt; ii, MeONa; iii,  $\beta$ -glucosidase; iv, conc. aq.  $\text{NH}_3$ ; v, S-xylene-heat; vi,  $\text{O}_2$ -TFA-R.T.

**Scheme 14**

acetate (Scheme 14), using the potential 1,5-dicarbonyl system in ring E to make a dihydropyridine intermediate. Winterfeldt has reported<sup>58c</sup> syntheses of angustidine (Scheme 15) and 18,19-dihydroangustine.

**Sarpagine-Ajmaline-Picraline Group.** Sarpagine has been found<sup>45c</sup> in *Rauwolfia caffra* and 10-deoxysarpagine (= normacusine B) in stem bark of *Strychnos medeola*<sup>59a</sup> and *Pleiocarpa talbottii*.<sup>45j</sup> 3-Hydroxyvoachalotine occurs in *Voacanga chaltotiana*<sup>45e</sup> and vobasine and dregamine in the stems of *Pandaca mauritiana*.<sup>59b</sup> Ajmaline has been isolated from *Rauwolfia macrophylla*<sup>45a</sup> and *R. caffra*.<sup>45b</sup> Picrinine has been reported<sup>59c</sup> as more abundant in wild than in cultivated *Vinca minor*.

<sup>59</sup> (a) G. B. Marini-Bettolo, S. E. Giuffra, C. Galeffi, and E. M. delle Monache, *Gazzetta*, 1973, **103**, 591; (b) F. Picot, F. Lallemand, P. Boiteau, and P. Potier, *Phytochemistry*, 1974, **13**, 660; (c) E. Grossman and P. Šefčović, *Phytochemistry*, 1973, **12**, 2058.

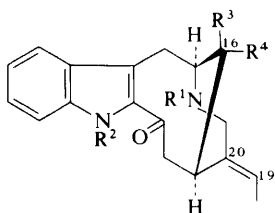


Reagents: i,  $\text{SOCl}_2$ ; ii,  $\text{CF}_3\text{CO}_2\text{H}$ ; iii,  $\text{MeOH-H}_2\text{SO}_4$ ; iv,  $\text{NaH-DMF-Ac}_2\text{O}$ ; v,  $-70^\circ\text{C}$ ;  $\text{Bu}'_2\text{AlH}$ ; vi,  $\text{NH}_3$ ; vii, aq.  $\text{KOH-MeOH}$ ; viii, quinoline-heat

Scheme 15

The absolute configurations of several 2-acylindole alkaloids (86a—g) have been confirmed as being all in the same series by c.d. measurements.<sup>60</sup>

Full details have been given<sup>61</sup> of the structural work<sup>12g</sup> on gardnerine, gardnutine and 18-hydroxygardnutine. Gardnerine (87) could be converted<sup>49</sup> into vobasine types as shown, for example, in Scheme 16.

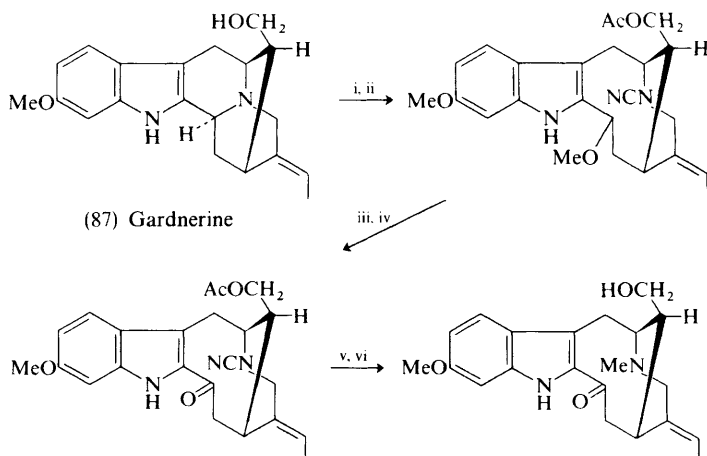


	$\text{R}^1$	$\text{R}^2$	$\text{R}^3$	$\text{R}^4$	
(86) a;	Me	H	$\text{MeO}_2\text{C}$	H,	Vobasine
b;	Me	H	$\text{MeO}_2\text{C}$	H,	
c;	Me	H	$\text{MeO}_2\text{C}$	H,	
d;	H	H	$\text{MeO}_2\text{C}$	H,	Perivine
e;	CHO	H	$\text{MeO}_2\text{C}$	H,	Periformyline
f;	Me	Me	$\text{MeO}_2\text{C}$	H,	Ochropamine
g;	Me	Me	H	$\text{MeO}_2\text{C}$ ,	16-Epi-ochropamine

<sup>60</sup> K. Blaha and J. Trojanek, *Coll. Czech. Chem. Comm.*, 1973, **38**, 929.

<sup>61</sup> S. Sakai, A. Kubo, T. Hamamoto, M. Wakabayashi, K. Takahashi, H. Ohtani, and J. Haginiwa, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1783.





Reagents: i,  $\text{Ac}_2\text{O}$ ; ii,  $\text{CNBr-MeOH-CHCl}_3\text{-Na}_2\text{CO}_3$ ; iii,  $\text{Bu}^t\text{OCl-Et}_3\text{N}$ ; iv,  $\text{H}_2\text{O}$ ; v, 5% aq.  $\text{AcOH-NH}_4\text{OAc-heat}$ ; vi,  $\text{HCHO-dioxan-H}_2\text{-Pd/C}$

Scheme 16

Standard aromatic electrophilic substitution reactions have been carried out<sup>62</sup> with ajmaline and isoajmaline; the substituent enters at C-10.

The structure of ervatamine (88a) has been confirmed by X-ray analysis of the methanol solvate.<sup>63a</sup> In an earlier review<sup>1c</sup> of the structural work on ervatamine a relationship to vallesiachotamine was suggested and the implied numbering used in the discussion. Potier has now demonstrated<sup>63b</sup> in a beautifully conceived interconversion the transformation of tabernaemontanine (86c) into ervatamine and of dregamine (86b) into 20-*epi*-ervatamine (88b). Incidentally, because of the X-ray-established stereochemistry at C-20 in ervatamine, the interconversions necessitate revisions (shown) of the stereochemistry at C-20 in tabernaemontanine and dregamine. Scheme 17 shows how the transformations were achieved, a reasonable mechanistic rationalization being included. This *in vitro* transformation must make the Reviewer's original suggestion the less likely of the two possibilities for the biosynthetic origin of the D ring in ervatamine.

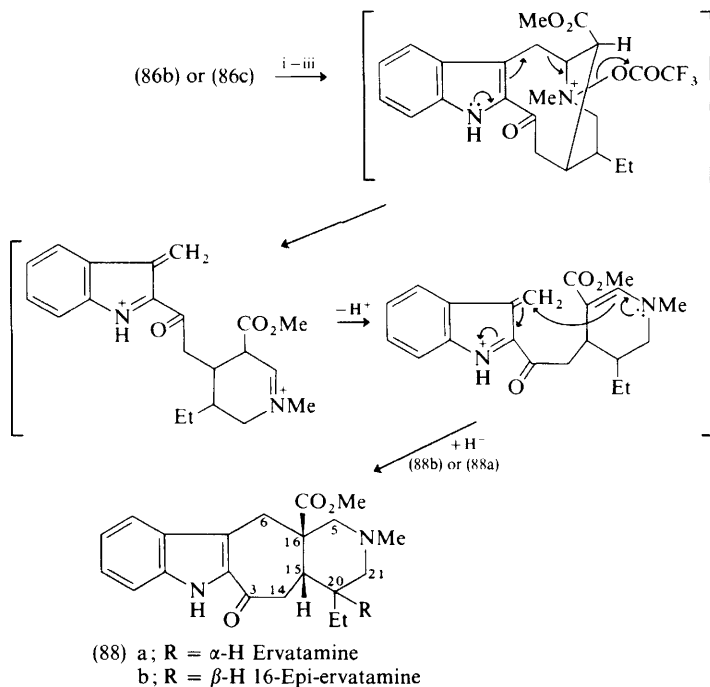
*Strychnine-Akuammicine-Condyllocarpine-Ellipticine Group.* Full details<sup>45i</sup> have been given of structural work on hunteracine chloride<sup>12h</sup> and of Le Goffic's synthesis<sup>64</sup> of ellipticine reviewed<sup>44e</sup> in Volume 4. It has been shown<sup>65</sup> that the so-called strychnicine, isolated from leaves of *Strychnos ignatii* and *S. nuxvomica* many years ago, is probably vomicine. 11-Methoxydiabolone occurs

<sup>62</sup> V. Ahmad and A. Basha, *Pakistan J. Sci. Ind. Res.*, 1972, **15**, 249 (*Chem. Abs.*, 1973, **79**, 53 652).

<sup>63</sup> (a) C. Riche, *Acta Cryst.*, 1974, **B30**, 610; (b) A. Husson, Y. Langlois, C. Riche, H.-P. Husson, and P. Potier, *Tetrahedron*, 1973, **29**, 3095.

<sup>64</sup> F. Le Goffic, A. Gouyette, and A. Ahond, *Tetrahedron*, 1973, **29**, 3357.

<sup>65</sup> N. G. Bisset and J. D. Phillipson, *Phytochemistry*, 1973, **12**, 2049.



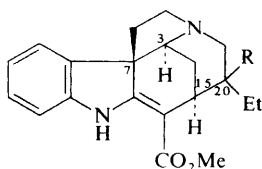
Reagents: i,  $H_2O_2$ - $CHCl_3$ -EtOH; ii,  $0^\circ C$ -( $CF_3CO$ ) $_2$ O- $CH_2Cl_2$ ; iii, NaBH $_4$

Scheme 17

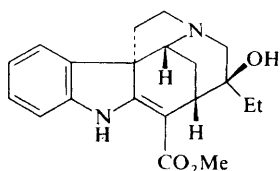
in root bark of *S. medeola*.<sup>59a</sup> The fruit pulp and pericarp of *S. nux-vomica* are now reported<sup>66a</sup> as containing *N*-methyl-*sec*-pseudo- $\beta$ -colubrine, which is a new variation, together with strychnine *N*-oxide, 12-hydroxystrychnine,  $\beta$ -colubrine, strychnine, brucine, pseudostrychnine, and pseudobrucine. The last four, together with *N*-cyano-*sec*-pseudostrychnine and *N*-cyano-*sec*-pseudo- $\beta$ -colubrine, were isolated from *S. ignatii*<sup>66b</sup> stem bark. *S. wallichiana*<sup>66c</sup> seeds also have strychnine and brucine and, in addition, 12-hydroxystrychnine, vomicine, novacine, 12-hydroxy-11-methoxystrychnine, and 12-hydroxy-11-methoxy-*N*-methyl-*sec*-pseudostrychnine. The leaves of the same plant<sup>66d,e</sup> have novacine again but also pseudostrychnine, icajine, and *N*-cyano-*sec*-pseudostrychnine and *N*-cyano-*sec*-pseudobrucine, *N*-methyl-*sec*-pseudo- $\beta$ -colubrine, 15-hydroxy-icajine, 15-hydroxynovacine and icajine *N*-oxide; the last two are new. A further seven alkaloids now obtained from *S. icaja* leaves<sup>66f</sup>

<sup>66</sup> (a) N. G. Bisset and A. K. Choudhury, *Phytochemistry*, 1974, 13, 265; (b) N. G. Bisset and M. D. Walker, *ibid.*, p. 525; (c) N. G. Bisset and J. D. Phillipson, *J. Pharm. Pharmacol.*, 1973, 25, 563; (d) N. G. Bisset, A. K. Choudhury, and M. D. Walker, *Phytochemistry*, 1974, 13, 255; (e) N. G. Bisset and A. K. Choudhury, *ibid.*, p. 259; (f) N. G. Bisset, B. C. Das, and J. Parello, *Tetrahedron*, 1973, 29, 4137.

are 3-hydroxystrychnine, 19,20- $\alpha$ -epoxy-12-hydroxy-11-methoxy-*N*-methyl-*sec*-pseudostrychnine, 19,20- $\alpha$ -epoxy-12-hydroxy-*N*-methyl-*sec*-pseudostrychnine, 19,20- $\alpha$ -epoxy-10-methoxy-*N*-methyl-*sec*-pseudostrychnine, 19,20- $\alpha$ -epoxy-15-hydroxy-*N*-methyl-*sec*-pseudostrychnine, 19,20- $\alpha$ -epoxy-12,15-dihydroxy-*N*-methyl-*sec*-pseudostrychnine, and 15-hydroxy-*N*-methyl-*sec*-pseudostrychnine. Tubotaiwine occurs in the stems and leaves of *Pandaca mauritiana*.<sup>59b</sup>

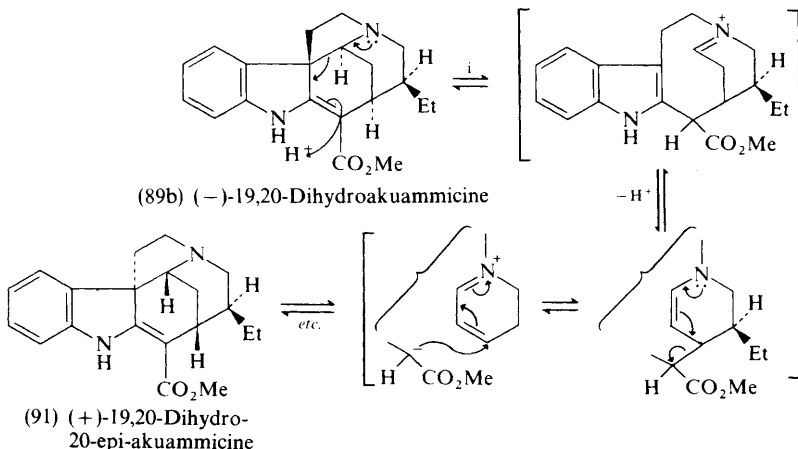


(89) a; R =  $\beta$ -OH, (-)-Lochneridine  
b; R =  $\alpha$ -H, (-)-19,20-Dihydroakuammicine



(90) (+)-20-Epi-lochneridine

Prompted by the natural occurrence of both (-)-lochneridine (89a) and (+)-20-epi-lochneridine (90), diastereoisomers in which C-3, C-7, and C-15 are opposite but C-20 has the same absolute configuration, and noting that an interconversion involving epimerization at only C-3, C-7 and C-15 could also explain the occurrence of both enantiomeric forms of akuammicine (which does not have an asymmetric C-20), Scott has devised<sup>67</sup> an *in vitro* model reaction which does bring about precisely these changes. Thus (-)-19,20-dihydro-akuammicine (89b) heated in methanol gave a mixture of starting material (65%) and its diastereoisomer (91) (15%), in which the absolute stereochemistry at C-20 was unchanged and the other centres had epimerized. Scheme 18 shows the rationalization which is offered for this reaction.

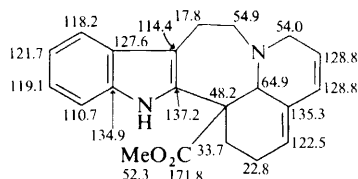


Conditions: i, degassed absolute methanol-95 °C-sealed tube-50 h

Scheme 18

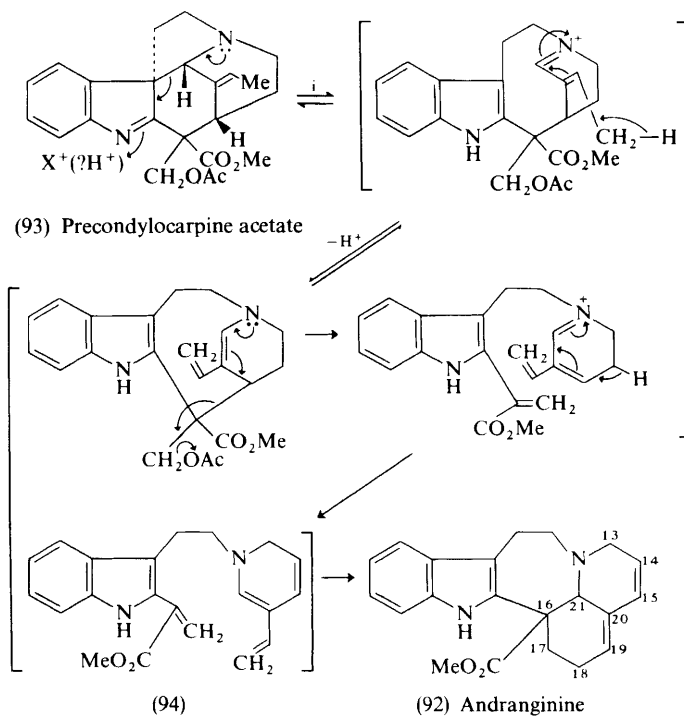
<sup>67</sup> A. I. Scott and C. L. Yeh, *J. Amer. Chem. Soc.*, 1974, **96**, 2273.

( $\pm$ )-Andranginine<sup>10n</sup> (92) from *Craspidospermum verticillatum* has a skeleton of an entirely novel type. Its inclusion in this sub-section is based on its partial synthesis from precondylocarpine acetate (93). The evidence so far advanced for the structure is a simple statement of <sup>1</sup>H and <sup>13</sup>C [given on (92)] n.m.r., u.v.,



(92) Andranginine, <sup>13</sup>C n.m.r. data

m.s., and i.r. data for the alkaloid and the <sup>13</sup>C measurements for its lithium aluminium hydride reduction product. All these are consistent with the structure proposed and inconsistent with alternative Diels–Alder additions in (94) or isomers of it, by which the compound might conceivably arise in partial synthesis.

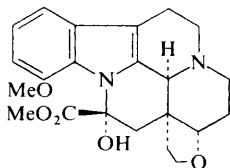


Reagent: i, EtOAc–100 °C

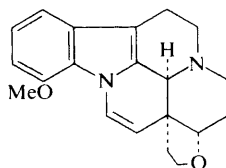
Scheme 19

This partial synthesis of andranginine is presented in Scheme 19 together with a mechanistic rationalization for this transformation which is reported as proceeding in the remarkably high yield of 28%.

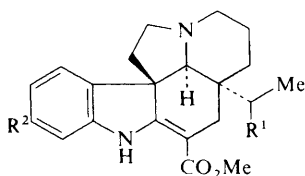
*Eburnamine-Aspidospermine Group.* Full details<sup>68a,b</sup> have been given of Ziegler's syntheses of tabersonine<sup>91</sup> and minovine,<sup>1d</sup> and of structural work<sup>69</sup> on cimicine and cimicidine. 14,15-Dehydroeburnamine occurs<sup>70a</sup> together with (–)-tabersonine in *Melodinus celastroides*. 14,15-Dehydrovincamine and beninine were isolated<sup>45e</sup> from *Voacanga chaltotiana*, together with two new alkaloids cuanzine (95) and decarbomethoxyapocuanzine (96), the supporting evidence for which is to be published later. (–)-Tabersonine has also been reported<sup>70b</sup> from *Pandaca retus* and here it co-occurs with voaphylline and pachysiphine. The root bark of *Aspidosperma fendleri* contains<sup>70c</sup> quebrachamine, fendli-spermine, fendlerine, and aspidolimidine. Lochnericine is reported<sup>45f</sup> from *Amsonia tabernaemontana* and vindoline and its 11-demethoxy-analogue from *Vinca pusilla*.<sup>45d</sup> Echitovenaldine (97a)<sup>70d</sup> is an alkaloid from the leaves of *Alstonia venenata* and echitoserpidine (97b) a base from the fruits<sup>70e</sup> of this plant.



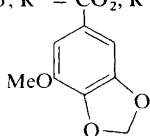
(95) Cuanzine



(96) Decarbomethoxyapocuanzine



(97) a;  $R^1 = \text{AcO}$ ,  $R^2 = \text{MeO}$ , Echitovenaldine  
 b;  $R^1 = \text{CO}_2$ ,  $R^2 = \text{H}$ , Echitoserpidine

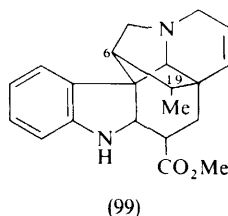
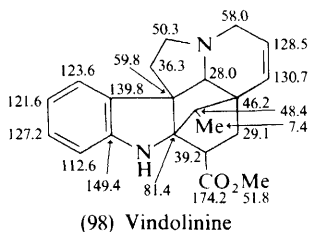


<sup>68</sup> (a) F. E. Ziegler and G. B. Bennett, *J. Amer. Chem. Soc.*, 1973, **95**, 7458; (b) F. E. Ziegler and E. B. Spitzner, *ibid.*, p. 7146.

<sup>69</sup> M. P. Cava, M. V. Lakshmikantham, S. K. Talapatra, P. Yates, I. D. Rae, M. Rosenberger, A. G. Szabo, B. Douglas, and J. A. Weisbach, *Canad. J. Chem.*, 1973, **51**, 3102.

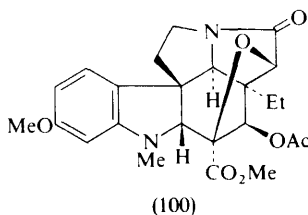
<sup>70</sup> (a) A. Rabaron, M. Plat, and P. Potier, *Phytochemistry*, 1973, **12**, 2537; (b) L. Le Men-Olivier, B. Richard, and J. Le Men, *ibid.*, 1974, **13**, 280; (c) J. D. Medina, J. Hurtado, and R. H. Burnell, *Rev. Latinoamer. Quim.*, 1973, **4**, 73 (*Chem. Abs.*, 1974, **80**, 27 419); (d) P. L. Majumder, T. K. Chandra, and B. N. Dinda, *Chem. and Ind.*, 1973, 1032; (e) P. L. Majumder and B. N. Dinda, *Phytochemistry*, 1974, **13**, 645.

The  $^{13}\text{C}$  n.m.r. spectrum of vindolinine enabled the structure to be corrected<sup>10a</sup> to (98). Formerly a structure (99) in which C-19 is attached to C-6 was thought to be correct. The chemical shifts in the n.m.r. spectrum [figures on (98)] of vindolinine compared well with those for venalstonine (36) (see p. 189). More importantly it could be shown that the spectrum had one more non-aromatic, non-protonated carbon and one less non-aromatic methine signal than required by the old structure, and that the 'extra' quaternary carbon had a chemical shift appropriate for C-2, an amino carbon, and the methylene carbon one appropriate for C-6.



The original structural assignment based on an analysis of the mass spectral fragmentation was used as a pattern for the structural examinations of tuboxenine, 19-epi-tuboxenine, pseudokopsinine, melobaline, and 19-epi-melobaline<sup>44f</sup> and the dimeric alkaloids pycnanthine and pleiomutinine, and hence the structures for all these alkaloids may well also need analogous revisions.

Exposure of vindoline to microbiological conversion using *Streptomyces* cultures has given<sup>71</sup> several metabolites. Those so far fully characterized are deacetylvindoline, 11-methoxycathanine,<sup>9a</sup> 3-acetonil-11-methoxycathanine, and 16-dehydroxy-14,15-dihydro-15, 16-epoxy-14-oxo-3-norvindoline (100).



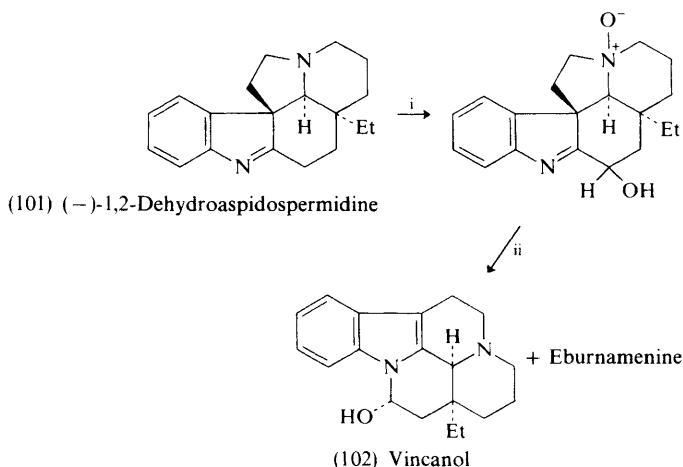
In continuation of their studies<sup>1e,44g</sup> of aspidosperma  $\rightarrow$  eburnea rearrangements, Lévy and Le Men have transformed<sup>72</sup> 1,2-dehydroaspidospermidine (101) into vincanol (102) (main product) and eburnamenine (Scheme 20).

The structure of vincarodine (103) has been elucidated<sup>10c,73</sup> independently by two groups, though they come to opposite conclusions regarding the absolute

<sup>71</sup> N. Neuss, D. S. Fukuda, G. E. Mallett, D. R. Brannon, and L. L. Huckstep, *Helv. Chim. Acta*, 1973, **56**, 2418.

<sup>72</sup> G. Hugel, B. Gourdier, J. Lévy, and J. Le Men, *Tetrahedron Letters*, 1974, 1597.

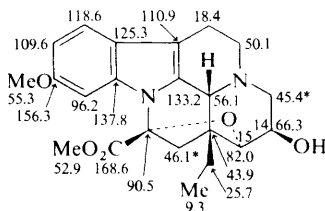
<sup>73</sup> G. A. Cordell, S. G. Weiss, and N. R. Farnsworth, *J. Org. Chem.*, 1974, **39**, 431.



Reagents: i,  $p\text{-O}_2\text{NC}_6\text{H}_4\text{CO}_3\text{H}$ -cold-24 h; ii,  $\text{Ph}_3\text{P}$ -AcOH-cold-2 days

Scheme 20

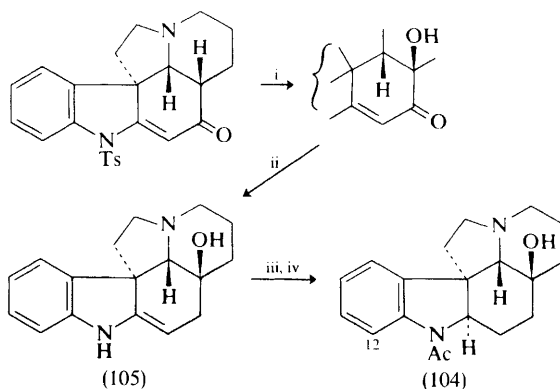
configuration of the alkaloid; that shown follows Farnsworth.<sup>73</sup> Both C-14 and C-15 can be shown by  $^{13}\text{C}$  n.m.r. to carry oxygen. The hydroxy-bearing carbon was identified most simply by noting the coupling, in the derived acetate, of the C-14 hydrogen to both a methylene and a methine.



Comparison,<sup>10f</sup> in a straightforward way, of the chemical shifts for the carbons of the new *Aspidosperma* alkaloids vandrikidine, vandrikine, and hazuntinine with those of tabersonine and vincadifformine and the application of the aromatic methoxyl shift rules (see p.190) lead inevitably to the structures 19-hydroxy-11-methoxytabersonine, 15,18-epoxy-11-methoxyvincadifformine, and 14,15-epoxy-10,11-dimethoxyvincadifformine respectively. Thus for example, compare the data on (32), hazuntinine, with those for (31) (p.189).

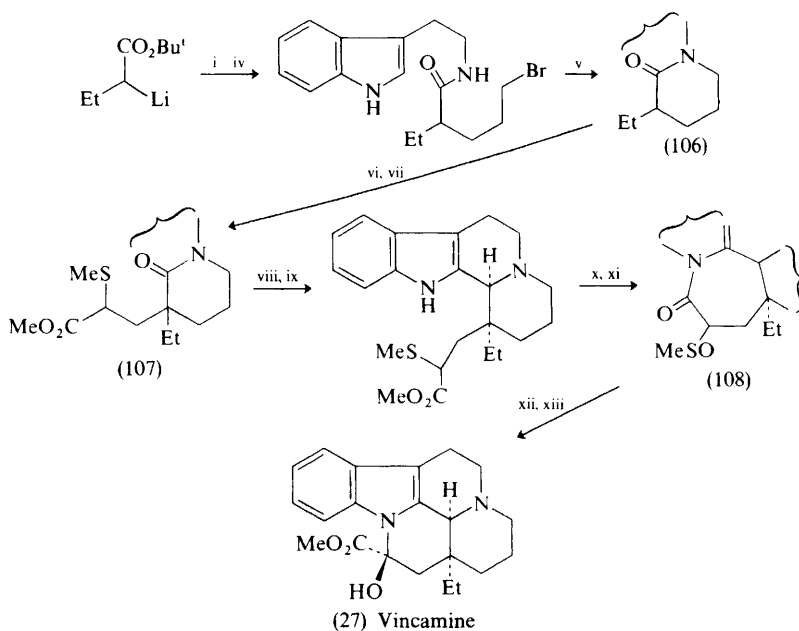
Using an intermediate, the synthesis of which was discussed<sup>44h</sup> previously, Ban has now produced (Scheme 21)<sup>74</sup> ( $\pm$ )-12-demethoxyaspidodispermine (104). Intermediate (105) apparently exists, as shown, as an enamine tautomer, which is surprising.

<sup>74</sup> T. Ohnuma, K. Seki, T. Oishi, and Y. Ban, *J.C.S. Chem. Comm.*, 1974, 296.



Reagents: i,  $-78^{\circ}\text{C}-\text{O}_2-(\text{EtO})_3\text{P}-\text{NaH}-\text{Bu}^t\text{OH}-\text{DMF}$ ; ii,  $\text{LiAlH}_4-\text{DME}-\text{heat}$ ; iii,  $\text{AcCl}-5\% \text{ NaOH}$ ; iv,  $\text{H}_2-\text{Pt}-\text{EtOH}-\text{dil. HCl}-56 \text{ psi}$

Scheme 21



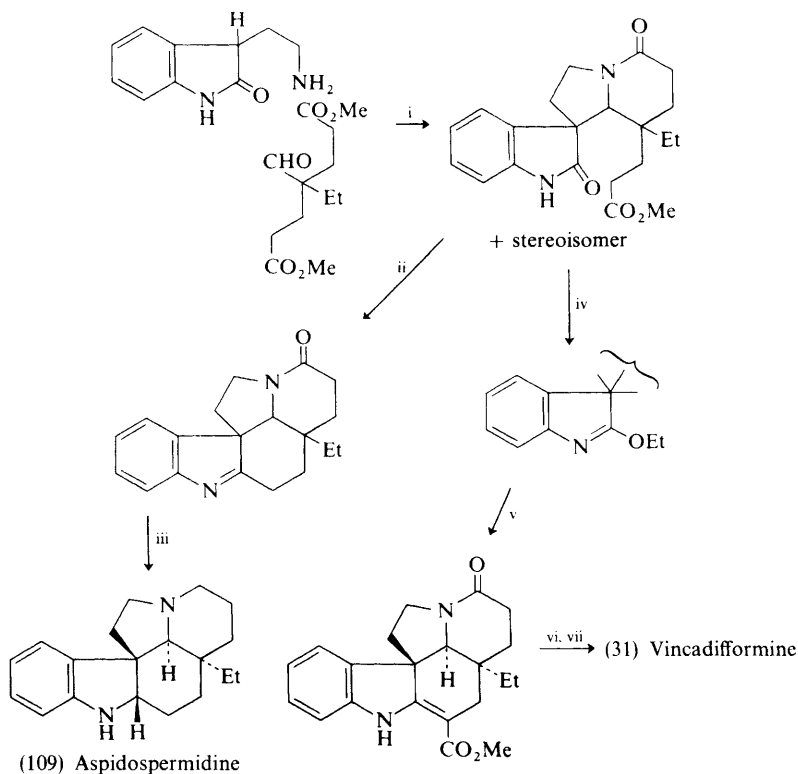
Reagents: i,  $\text{Br}(\text{CH}_2)_3\text{Br}$ ; ii,  $\text{TsOH}-\text{PhH}-\text{heat}$ ; iii,  $(\text{COCl})_2-\text{PhH}$ ; iv,  $\text{indol-3-yl}-\text{CH}_2\text{CH}_2-\text{NH}_2\cdot\text{HCl}-\text{LiH}$ ; v,  $\text{KH}-\text{THF}$ ; vi,  $-78^{\circ}\text{C}-\text{Pr}^t_2\text{NLi}$ ; vii,  $\text{CH}_2=\text{C}(\text{SMe})\text{CO}_2\text{Me}$ ; viii,  $\text{POCl}_3-\text{MeCN}-\text{heat}$ ; ix,  $0^{\circ}\text{C}-\text{Li}(\text{Bu}^t\text{O})_3\text{AlH}-\text{THF}$ ; x,  $m\text{-ClC}_6\text{H}_4\text{CO}_2\text{H}-\text{CH}_2\text{Cl}_2$ ; xi,  $2 \times \text{NaH}-\text{THF}$ ; xii,  $0^{\circ}\text{C}-2 \times \text{AcCl}$ ; xiii,  $4 \times \text{MeONa}-\text{MeOH}$

Scheme 22



A new total synthesis<sup>75</sup> of ( $\pm$ )-vincamine (27) is shown in Scheme 22. Points of particular interest are the C-mono-alkylation [ $\rightarrow$  (107)] of the dianion [NH and C(O)CH] resulting from the intermediate (106) and the final steps [108]  $\rightarrow$  (27)], which are believed to proceed by way of an  $\alpha$ -acetoxysulphide in turn converted by methoxide into an  $\alpha$ -keto-lactam, opening and reclosure of which gives the product.

As in the route described in Volume 4,<sup>44i</sup> tryptamine oxindole serves as the starting material for a now even shorter route<sup>76</sup> to the aspidosperma ring system. Scheme 23 shows the construction of ( $\pm$ )-aspidospermidine (109) and of ( $\pm$ )-vincadifformine using this approach.



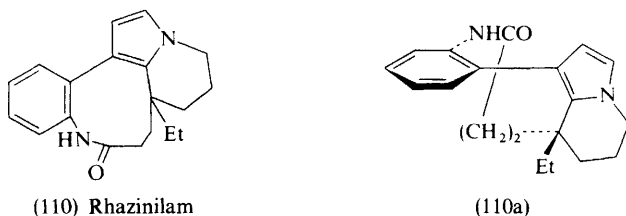
Reagents: i, PhH-heat; ii, PPA-heat; iii,  $\text{LiAlH}_4$ ; iv,  $\text{Et}_3\text{O}^+\text{BF}_4^-$ ; v, NaH-DMSO-heat; vi,  $\text{P}_2\text{S}_5$ -THF; vii,  $\text{H}_2$ -Ni

Scheme 23

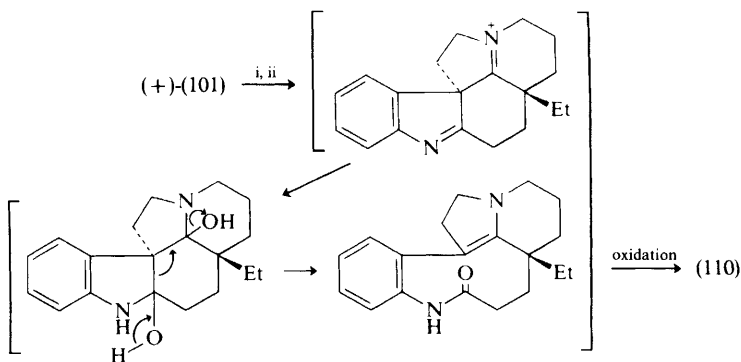
<sup>75</sup> J. L. Herrman, R. J. Cregge, J. E. Richman, C. L. Semmelhack, and R. H. Schlessinger, *J. Amer. Chem. Soc.*, 1974, **96**, 3702.

<sup>76</sup> J.-Y. Laronze, J. Laronze-Fontaine, J. Lévy, and J. Le Men, *Tetrahedron Letters*, 1974, 491.

( $\pm$ )-Rhazinilam (110)<sup>9j</sup> has been the subject of a total synthesis<sup>77</sup> which is as different in conception in the indole alkaloid synthetic area as the alkaloid's structure is amongst its peers. (–)-Rhazinilam has been obtained,<sup>77</sup> by a route



which suggests that rhazinilam may well be an oxidative artifact, from 1,2-dehydroaspidospermidine, thus incidentally establishing the absolute configuration of (–)-rhazinilam as that shown in (110a). Scheme 24 gives an indication of what probably occurs during the reaction.



Reagents: i,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$ ; ii, aq.  $\text{FeSO}_4$

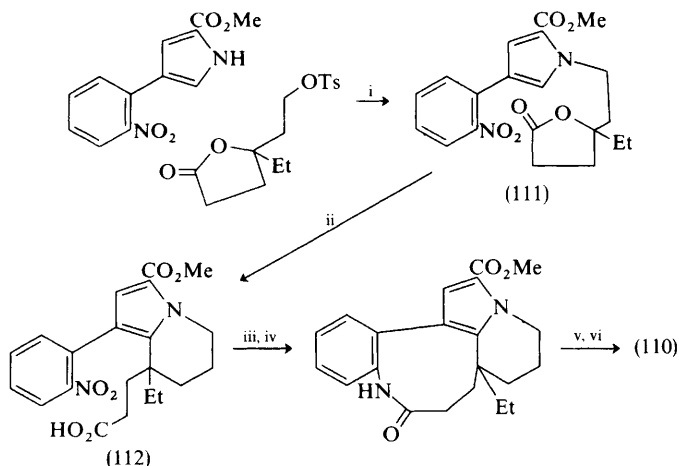
Scheme 24

The total synthesis (Scheme 25) of ( $\pm$ )-rhazinilam was achieved by viewing the alkaloid as a derivative of a 3-phenylpyrrole. Thus 2-methoxycarbonyl-4-(2-nitrophenyl)pyrrole was first synthesized and then the aliphatic portion of the molecule introduced by alkylation at the pyrrole nitrogen [ $\rightarrow$  (111)] and the carbon skeleton completed by intramolecular Friedel–Crafts alkylation [ $\rightarrow$  (112)] at the only available pyrrole  $\alpha$ -position.

**Ibogamine–Cleavamine Group.** Voacangine has been isolated from *Pandaca retusa* seeds<sup>70b</sup> and leaves and trunk bark<sup>78a</sup> and from *Voacanga thouarsii*.<sup>78b</sup> The seeds of *Pandaca retusa* also have coronaridine, the leaves and bark also

<sup>77</sup> A. H. Ratcliffe, G. F. Smith, and G. N. Smith, *Tetrahedron Letters*, 1973, 5179.

<sup>78</sup> (a) F. Picot, P. Boiteau, B. C. Das, and P. Potier, *Phytochemistry*, 1973, 12, 2517; (b) Y. Rolland, G. Croquelois, N. Kunesch, P. Boiteau, M. Debray, J. Pecher, and J. Poisson, *Phytochemistry*, 1973, 12, 2039.



Reagents: i, 'as sodium salt'; ii,  $\text{AlCl}_3\text{-MeNO}_2$ ; iii,  $\text{H}_2\text{-Pt-EtOAc}$ ; iv,  $\text{DCC-THF}$ ; v, aq.  $\text{MeOH-NaOH}$ ; vi,  $240^\circ\text{C-0.05 mmHg}$

**Scheme 25**

contain coronaridine and in addition heyneanine, three isomers of heyneanine, 3-oxovoacangine, and voacristine. From *V. thouarsii*, ibogaine and voacristine were also isolated. *V. chalongensis* yielded<sup>45a</sup> voachalotine and dehydrovoachalotine.

The structure of pandoline (37), isolated from *Pandaca calcarea* and *P. debrayi*, has been established<sup>10j</sup> as (37) and confirmed<sup>79</sup> by chemical interrelationship with catharanthine. Here again the structure assignment<sup>10j</sup> relied heavily on  $^{13}\text{C}$  n.m.r. evidence; comparisons of the data (p. 190) on (37) with those for the aspidosperma alkaloid vincadifformine (31) will illustrate this point. Thus, for example, the chemical shift of C-20, being 49 p.p.m. downfield from its position in (31), showed this to be the hydroxy-bearing carbon; that this carbon was also shown to be quaternary confirmed the presence of the ethyl at this same position.

#### 4 Biogenetically Related Quinoline Alkaloids

Chemical, synthetic, and clinical studies concerned with camptothecin have been reviewed,<sup>80a</sup> another review<sup>80b</sup> deals just with the nine total syntheses so far published. Full details of Sugawara's synthesis<sup>44j</sup> have been given.<sup>81</sup>

The Hofmann degradation of deoxydihydro-quinene and -quinidene has been described.<sup>82</sup>

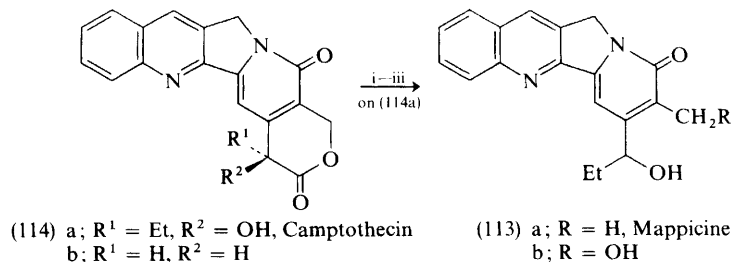
<sup>79</sup> M.-J. Hoizey, C. Sigaut, M.-J. Jacquier, L. Le Men-Olivier, J. Lévy, and J. Le Men, *Tetrahedron Letters*, 1974, 1601.

<sup>80</sup> (a) A. G. Schultz, *Chem. Rev.*, 1973, 73, 385; (b) B. Danieli and G. Palmisano, *Fito-terapia*, 1974, 45, 87.

<sup>81</sup> T. Sugawara, T. Toyoda, and K. Sasakura, *Chem. and Pharm. Bull. (Japan)*, 1974, 22, 771.

<sup>82</sup> H. Zielinski, *Acta Pharm. Polon.*, 1973, 30, 271 (*Chem. Abs.*, 1974, 80, 3350).

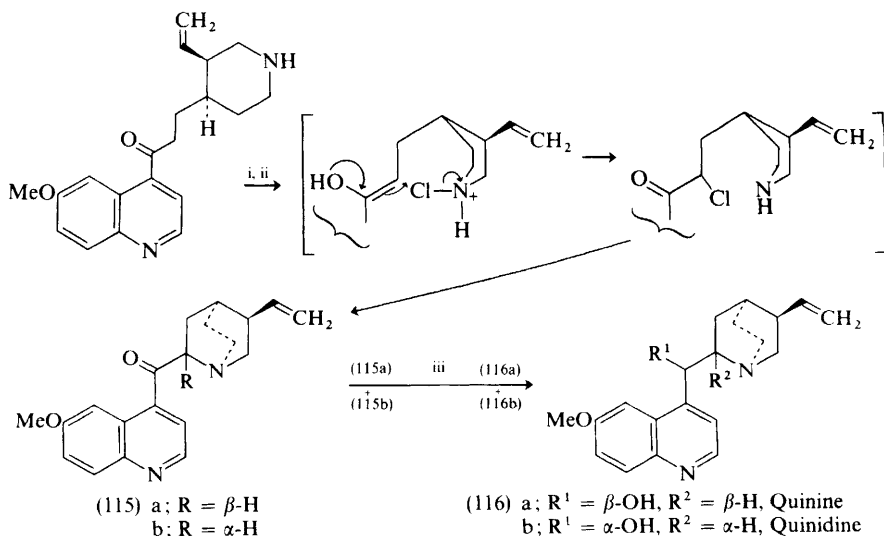
Mappicine, a minor alkaloid of *Mappia foetida*, has the structure (113a). This was confirmed<sup>83</sup> by converting camptothecin (114a) into the new alkaloid (Scheme 26).



Reagents: i,  $\text{NaBH}_4$ ; ii,  $\text{Pb}(\text{OAc})_4$ ; iii,  $\text{NaBH}_4$ -MeOH-heat

Scheme 26

A re-investigation<sup>84</sup> of the early work on the total synthesis of quinine (116a) has provided more efficient methods. In particular, and following earlier work,<sup>9k</sup> Uskoković has prepared the requisite vinylpiperidine intermediate by introducing unsaturation into an ethyl-precursor using the Hofmann-Löffler-Freytag reaction. Other improvements are the addition of the quinoline ring<sup>84a</sup>



Reagents: i, aq.  $\text{NaOCl-CH}_2\text{Cl}_2$ ; ii, 100%  $\text{H}_3\text{PO}_4\text{-CH}_2\text{Cl}_2$ ; iii,  $\text{Bu}^i_2\text{AlH-PhH}$

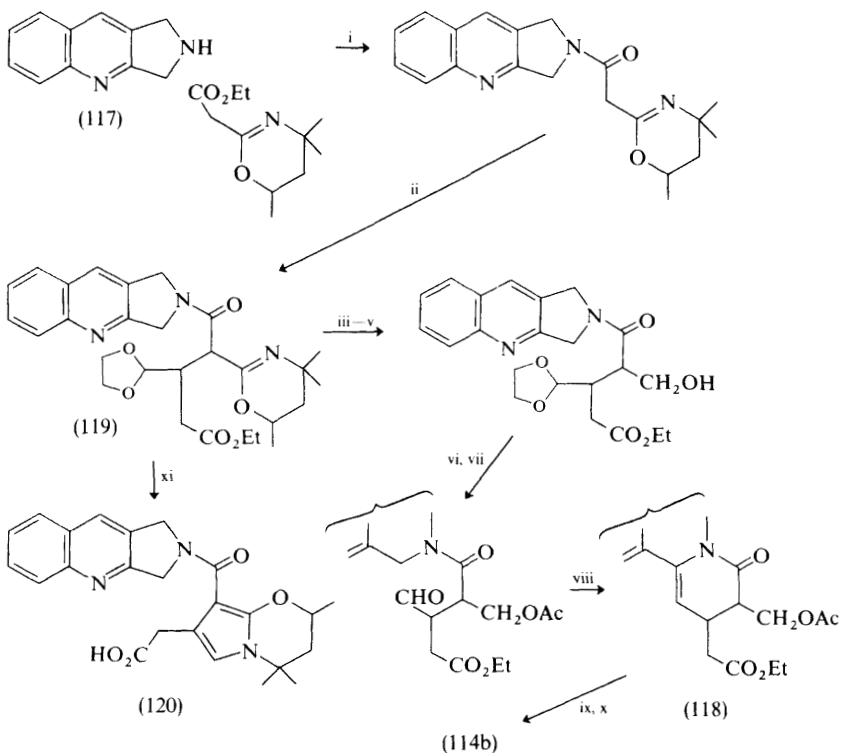
Scheme 27

<sup>83</sup> T. R. Govindachari, K. R. Ravindranath, and N. Viswanathan, *J.C.S. Perkin I*, 1974, 1215.

<sup>84</sup> (a) G. Grethe, H. L. Lee, T. Mitt, and M. R. Uskoković, *Helv. Chim. Acta*, 1973, **56**, 1485; (b) J. Gutzwiller and M. R. Uskoković, *ibid.*, p. 1494.

by means of a 4-lithioquinoline,<sup>91</sup> the formation of the quinuclidine ring<sup>84b</sup> by intramolecular C-chlorination *via* a transient N-chloroammonium ion, and final stage stereoselective reduction. The last few steps are summarized in Scheme 27.

As well as the syntheses<sup>85a</sup> of isocamptothecin, an unnatural isomer having ring E laterally transposed, and compounds having camptothecin part structures,<sup>85b</sup> yet two more formal total syntheses<sup>86,87</sup> (bringing the total so far to nine!), have been published in the year under review. Both syntheses produce de-ethyl-deoxycamptothecin (114b), which had previously<sup>9m</sup> been converted into the alkaloid.



Reagents: i, heat-DMF; ii,  $(\text{CH}_3\text{O})_2\text{CHCH}=\text{CHCO}_2\text{Et}$ -EtOH-EtONa-140 °C-sealed tube; iii, -45 °C- $\text{NaBH}_4$ -EtOH-pH 5; iv, aq.  $\text{NH}_4\text{Cl}$ -heat; v, 0 °C- $\text{NaBH}_4$ -EtOH; vi, 0 °C- $\text{AcCl}$ -pyridine; vii, -78 °C- $\text{BF}_3$ -Et<sub>2</sub>O- $\text{CH}_2\text{Cl}_2$ ; viii,  $\text{Ac}_2\text{O}$ -PhH-heat; ix, DDQ-PhH; x, 10 %  $\text{H}_2\text{SO}_4$ -EtOH-heat; xi, TsOH-PhH- $\text{H}_2\text{O}$

Scheme 28

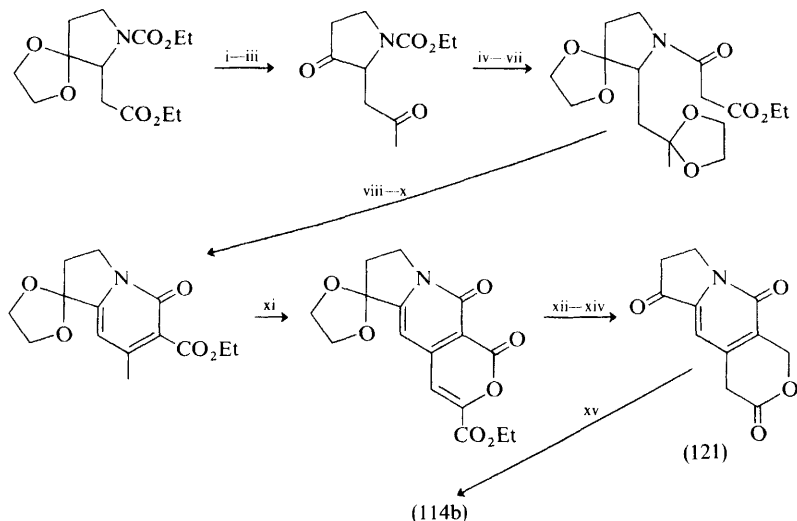
<sup>85</sup> (a) S. Danishefsky and R. Volkmann, *Tetrahedron Letters*, 1973, 2521; (b) S. Danishefsky and J. Quick, *ibid.*, p. 2525.

<sup>86</sup> A. I. Meyers, R. L. Nolen, E. W. Collington, T. A. Narwid, and R. C. Strickland, *J. Org. Chem.*, 1973, **38**, 1974.

<sup>87</sup> M. Shamma, D. A. Smithers, and V. St. Georgiev, *Tetrahedron*, 1973, **29**, 1949.

Meyers,<sup>86</sup> with the tricyclic (117) as a starting point, used the reactivity of the quinoline  $\alpha$ -methylene to make a dihydropyridone intermediate (118) (Scheme 28). The main difficulties in the synthesis were concerned with the selective release of one protected aldehyde from intermediates such as (119), and unwanted cyclizations such as that [ $\rightarrow$  (120)] which resulted from treatment of (119) with non-selective hydrolytic conditions.

Shamma's synthesis (Scheme 29)<sup>87</sup> leaves the formation of the quinoline ring to a late stage, building up a tricyclic pyridone-ketone (121) which is then subjected to a Friedländer quinoline ring synthesis.



Reagents: i, 1M-KOH-EtOH-R.T.-N<sub>2</sub>; ii, (COCl)<sub>2</sub>-PhH; iii, NaCH(CO<sub>2</sub>Me)<sub>2</sub> then H<sub>2</sub>O-H<sup>+</sup> (decarbomethoxylation); iv, (CH<sub>2</sub>OH)<sub>2</sub>-TsOH-PhH-heat; v, aq. KOH-EtOH-heat-N<sub>2</sub>; vi, HCl to form salt; vii, EtO<sub>2</sub>CCH<sub>2</sub>COCI-K<sub>2</sub>CO<sub>3</sub>-CHCl<sub>3</sub>; viii, 50% aq. AcOH; ix, 0°C-EtONa-EtOH; x, DDQ-PhH-heat; xi, (CO<sub>2</sub>Et)<sub>2</sub>-PhH-EtONa; xii, NaBH<sub>4</sub>-EtOAc; xiii, O<sub>2</sub>-Pt-EtOAc; xiv, (CO<sub>2</sub>H)<sub>2</sub>-EtOH-H<sub>2</sub>O-heat; xv, *o*-H<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CHO-NaOH-EtOH

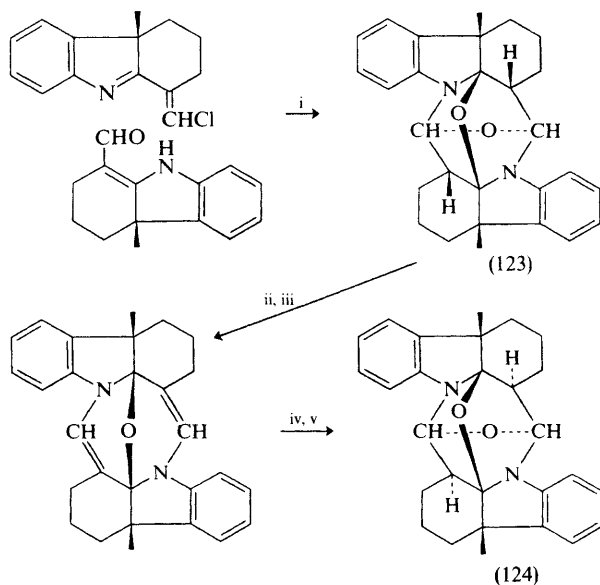
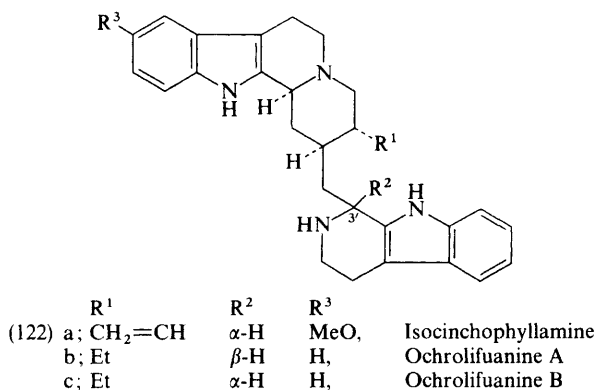
Scheme 29

## 5 Bisindole Alkaloids

An amorphous dimer, molecular weight 644, was isolated<sup>59b</sup> from *Pandaca mauritiana*. Full details<sup>88</sup> of work on verticillin A<sup>1f</sup> have been given. Two other metabolites are discussed; each is a dimer of the same type as verticillin A, but verticillin B has a hydroxymethyl instead of one of the methyl groups and verticillin C is an S<sub>3</sub>-bridged analogue of verticillin B with one of the two S<sub>2</sub>-bridges enlarged.

<sup>88</sup> H. Minato, M. Matsumoto, and T. Katayama, *J.C.S. Perkin I*, 1973, 1819.

Details of the *X*-ray analysis of hodgekinsine trimethiodide have been given.<sup>89</sup> The full paper<sup>90</sup> establishing the relative stereochemistry<sup>44k</sup> of the roxburghines has appeared; it also includes a detailed analysis of the <sup>1</sup>H n.m.r. spectra, which enables preferred conformations to be assigned to the four isomers.



Reagents: i, 2M-HCl-R.T.; ii, 0.1M-MeOH-HCl; iii,  $\text{Et}_3\text{N}$ ; iv, conc. HCl; v, 4M-NaOH

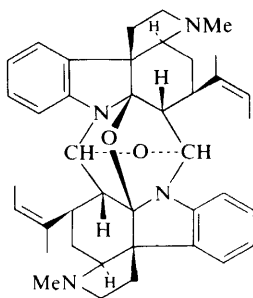
**Scheme 30**

<sup>89</sup> J. Fridrichson, M. F. MacKay, and A. McL. Mathieson, *Tetrahedron*, 1974, **30**, 85.

<sup>90</sup> C. Cistaro, L. Merlini, R. Mondelli, and G. Nasini, *Gazzetta*, 1973, **103**, 153.

The structure of isocinchophyllamine has been confirmed<sup>91</sup> as (122a) by an *X*-ray analysis of its methanol solvate. The stereochemistry, relative and absolute, of ochrolifuanines A and B (122b and c) has been settled<sup>92</sup> by partial synthesis involving condensations of dihydrocorynantheal and corynantheidal with tryptamine to give C-3' isomeric pairs, which were separated and one in each case shown to be identical with the natural alkaloid. C.d. measurements then settled the stereochemistry at the C-3' centres.

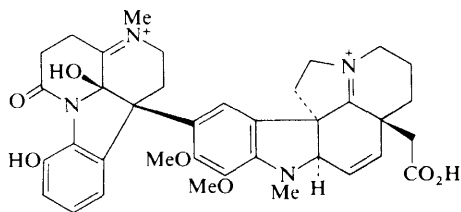
The synthesis (Scheme 30) of compounds (123) and (124) from optically active starting materials allows them to be used as chiroptical models to assign configurational types.<sup>93</sup> Thus, for example, the 'indoline-base-VII', a degradation product of C-curarine I, can now be given structure (125).



(125)

The <sup>13</sup>C n.m.r. spectrum of leurosine and comparisons with those from vinblastine and vindoline strongly support<sup>10f</sup> the view that leurosine has a 15',20'-epoxide unit.

The chemistry and spectra of haplophytine and derivatives have been described<sup>10k</sup> in detail, and although the structure given to haplophytine dihydrobromide (126) some while ago by *X*-ray analysis must stand, that (127) originally



(126) Haplophytine dihydrobromide

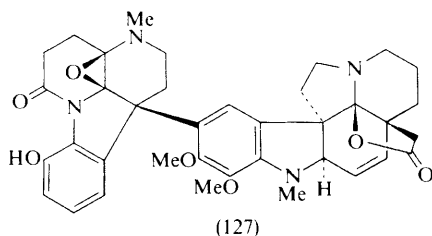
suggested for haplophytine free base, which is certainly the obvious possibility given that of the salt, has now been revised to (128). The <sup>13</sup>C n.m.r. spectrum of haplophytine has now clearly demonstrated the presence of *three* carbonyl

<sup>91</sup> J. Guilhem, *Acta Cryst.*, 1974, **B30**, 742.

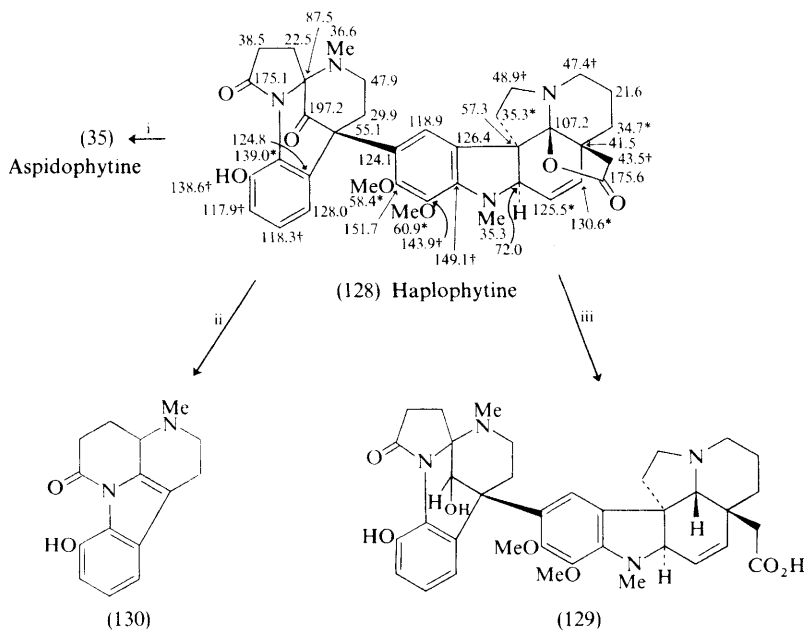
<sup>92</sup> M. Koch, M. Plat, and N. Préaux, *Bull. Soc. chim. France*, 1973, 2868.

<sup>93</sup> H. Fritz and R. Oehl, *Annalen*, 1973, 1628.





carbon atoms. The ketonic carbonyl group was not recognized in earlier i.r. studies owing to the overlapping of ketone and lactone carbonyl stretching bands. The position of the newly revealed carbonyl group is based on the reduction of haplophytine to a tetrahydro-derivative (129), which was a secondary alcohol, the  $\text{CH}(\text{OH})$  of which was not further coupled. The structures of acid and zinc-acid cleavage products (Scheme 31) of the alkaloid salt were fully established by spectroscopy and in the case of (130) by synthesis.



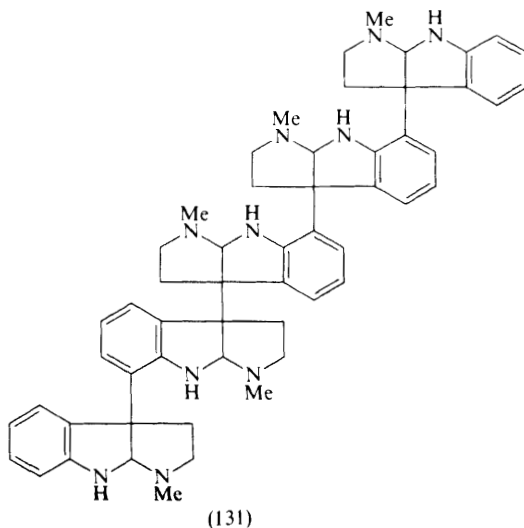
Reagents: i, conc.  $\text{HCl}$ -heat; ii,  $\text{Zn}$ -dil.  $\text{HCl}$ -heat; iii,  $\text{NaBH}_4$

**Scheme 31**

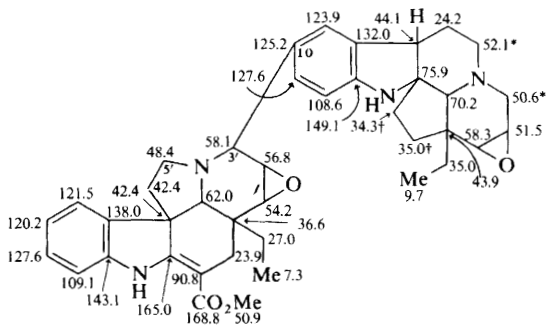
From the leaves of *Psychotria beccarioides* there has been isolated<sup>94</sup> an alkaloid with the formula  $\text{C}_{55}\text{H}_{62}\text{N}_{10}$ . It is a pentameric (!) analogue of the

<sup>94</sup> N. K. Hart, S. R. Johns, J. A. Lamberton, and R. E. Summons, *Austral. J. Chem.*, 1974, 27, 639.

tetrameric quadrigemines<sup>95a</sup> and the trimeric hodgekinsine.<sup>89,95b</sup> Structure (131) has been provisionally assigned mainly on the basis of mass spectral measurements.



Criophylline (132)<sup>10b</sup> from the leaves of *Crioceras dipladeniiflorus* contains an epoxyvincadifformine unit linked to an epoxyvallesamidine portion. The structure is based almost completely on <sup>13</sup>C n.m.r. spectroscopy. The method of linking of the two halves was based on noting that all of the carbons of the 'top' half gave signals identical in chemical shift with those in andrangine, a new base with the 'top half' structure; the multiplicities were also identical with those in the monomer with the exception of that of the indoline C-10, which thus represents one point of attachment. The spectrum showed only three aminomethylene

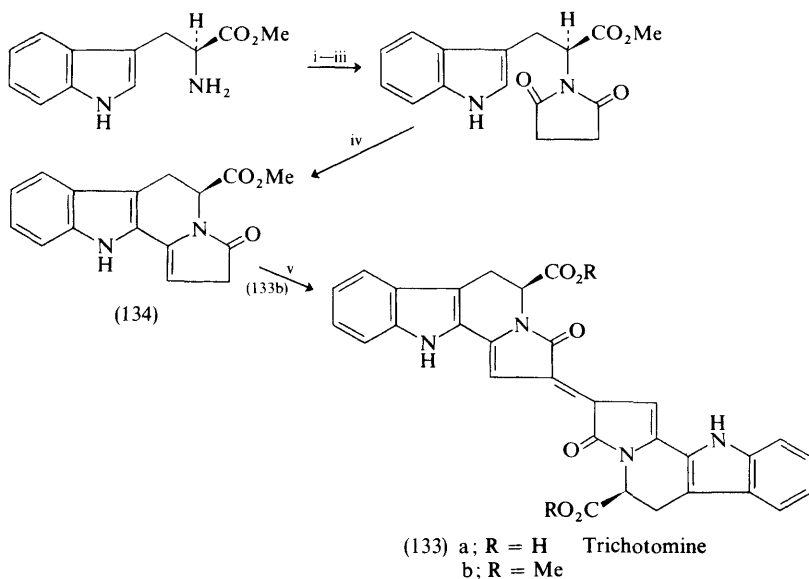


<sup>95</sup> (a) A. A. Gorman, M. Hesse, and H. Schmid, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports). The Chemical Society, London, 1971, Vol. 1, p. 207; (b) *ibid.*, p. 205.

carbons. It follows that either C-5' or C-3' must represent the other end of the link. The provisional assignment to C-3' rests, less securely, on the addition of effects to be expected on the shifts of adjacent carbons in the two alternatives.

The isomeric 7-chloroindoline-2,16-enamines, derived from the methoxycarbonyl cleavamines by reaction with *N*-chlorobenzotriazole, react with vindoline to give 15,20-anhydrovinblastine.<sup>96</sup>

The intriguing tryptophan derivative trichotomine, isolated<sup>97</sup> from the fruits of *Clerodendron trichotomum*, is a novel type of blue pigment. That catalytic reduction gave hexahydrotrichotomine, an indole having five-membered lactam carbonyl i.r. absorption, taken with the presence of two olefinic singlets and signals for two ABX systems in the <sup>1</sup>H n.m.r. spectrum of trichotomine itself, led to the postulation<sup>97a</sup> of structure (133), which was confirmed<sup>97b</sup> by an X-ray analysis of the *NN'*-di-*p*-bromobenzoyl derivative. Interestingly, although there must be extensive conjugation throughout the system, the two indole rings are not in a plane, but at a dihedral angle of 38.6°. Trichotomine has been synthesized<sup>97c</sup> (Scheme 32) starting with tryptophan methyl ester and succinic anhydride, components which may well also represent the biosynthetic precursors of the pigment. Cyclization to (134) was followed by a remarkably easy oxidative dimerization.



Reagents: i, succinic anhydride-PhH-heat; ii, CH<sub>2</sub>N<sub>2</sub>; iii, 200 °C; iv, P<sub>2</sub>O<sub>5</sub>-PhH-heat; v, -90 °C-O<sub>2</sub>-Bu<sup>n</sup>OH

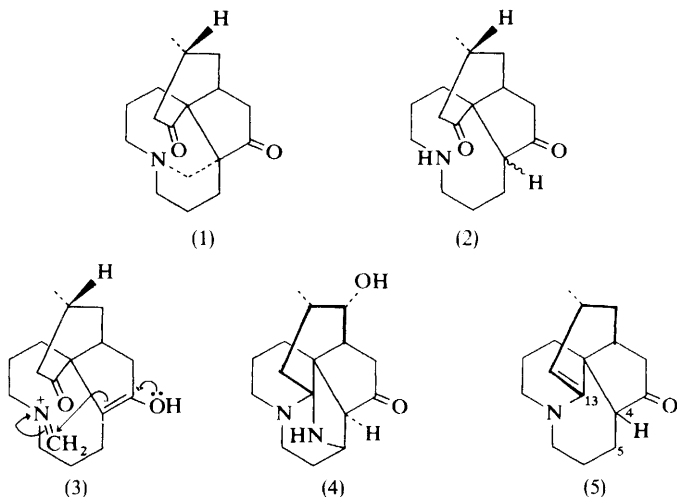
Scheme 32

<sup>96</sup> Atta-ur-Rahman, *Pakistan J. Sci. Ind. Res.*, 1971, **14**, 487 (*Chem. Abs.*, 1972, **77**, 62 204).

<sup>97</sup> (a) S. Iwadare, Y. Shizuri, K. Sasaki, and Y. Hirata, *Tetrahedron Letters*, 1974, 1051; (b) K. Sasaki, S. Iwadare, and Y. Hirata, *ibid.*, p. 1055; (c) S. Iwadare, Y. Shizuri, K. Yamada, and Y. Hirata, *ibid.*, p. 1177.

Two comprehensive reviews summarizing recent progress in the structural elucidation, synthesis, and biosynthesis have been prepared by Canadian workers, who have contributed widely and significantly to this field.<sup>1,2</sup>

Lycoflexine (1), isolated from *Lycopodium clavatum* var. *inflexum*, is a representative of a new skeleton hitherto not encountered in this group of alkaloids.<sup>3</sup> Lycoflexine showed in its mass spectrum a base peak at  $m/e$  84 which had not been previously encountered in mass spectra of *Lycopodium* alkaloids. The structure was solved by X-ray crystallographic analysis of its hydrobromide derivative. Lycoflexine may be biogenetically related to the known fawcettimine (2), which also occurs in *L. clavatum* var. *inflexum*, by invoking an intramolecular Mannich reaction on an initially formed immonium salt (3).



<sup>1</sup> D. B. MacLean, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1973, vol. 14, p. 347.

<sup>2</sup> W. A. Ayer, in 'Alkaloids', ed. K. Wiesner (MTP International Review of Science), Organic Chemistry, Series One, Vol. 9, Butterworths, London, 1973, p. 1.

<sup>3</sup> W. A. Ayer, Y. Fukazawa, P. P. Singer, and B. Altenkirk, *Tetrahedron Letters*, 1973, 5045.

A further alkaloid, Base R, obtained from *L. fawcettii*, has been shown to possess the novel structure (4) by *X*-ray analysis of its perchlorate derivative.<sup>4</sup> O.r.d. data indicate the absolute stereochemistry as depicted in (4). Base R is biogenetically related to fawcettidine (5) by the insertion of an NH-bridge between C-5 and C-13, a process that necessitates an inversion of configuration at C-4.

<sup>4</sup> R. H. Burnell, A. Chapelle, J. Fischer, and L. Ricard, *J.C.S. Chem. Comm.*, 1974, 391.

# 13

## The Diterpenoid Alkaloids: Chemistry and Synthesis

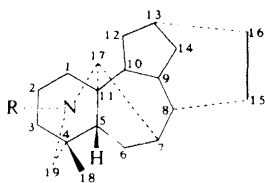
BY S. W. PELLETIER AND S. W. PAGE

### 1 Introduction

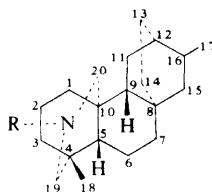
Only a moderate amount of work in diterpenoid alkaloid chemistry has been reported during the past year. A detailed report on the structure and chemistry of heteratisine has been published. The most active area has been that of the syntheses of these complex bases by Professor Karel Wiesner's group at the University of New Brunswick. Among their notable achievements have been the total syntheses of napelline and talatisamine.

No new work on the *Daphniphyllum* alkaloids has appeared since the last Report.<sup>1</sup> An excellent review of the chemistry of this class of diterpenoid alkaloids was included in Professor Yoshima Hirata's report presented in May 1974 at the I.U.P.A.C. 9th International Symposium on Natural Products in Ottawa.

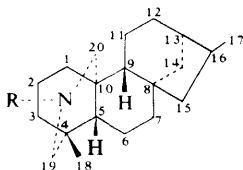
The numbering systems for the lycoctonine, atisine, and veatchine skeletons discussed in this Report are indicated in structures A, B, and C, respectively.



(A) Lycoctonine skeleton



(B) Atisine skeleton

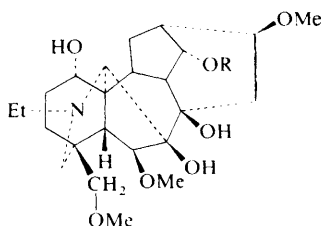


(C) Veatchine skeleton

<sup>1</sup> S. W. Pelletier and S. W. Page, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4, Ch. 14.

## 2 Structural Investigations

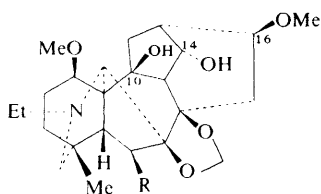
**Alkaloids of *Delphinium ajacis*.**—Waller, Sastry, and Kinneberg<sup>2</sup> have reported mass spectral studies of the alkaloidal components of the seeds of *Delphinium ajacis*. Delcosine (1), acetyldecosine (2), and delsoline (3) were identified by mass spectral comparisons.



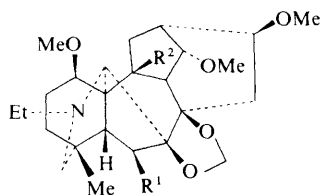
Delcosine	(1) R = H
Acetyldecosine	(2) R = Ac
Delsoline	(3) R = Me

**Dictyocarpine.**—The structure of this alkaloid isolated from *D. dictyocarpum*<sup>3</sup> has been determined by n.m.r. spectral analyses.<sup>4</sup> Comparison of the n.m.r. spectra of dictyocarpine (4), deltaline (eldeline) (5), deltamine (eldelidine) (6), dehydroacetyldepheline (7), dehydrodepheline (8), acetyldepheline (9), and depheline (10) allowed assignment of the hydroxy-groups to C-10 and C-14 on the basis of deshielding effects.

Acetyldeltaline (11) was pyrolysed at 210–220 °C for 30 minutes to yield dehydroacetyldepheline (7). Catalytic hydrogenation afforded acetyldepheline (9), which was hydrolysed to depheline (10).



Dictyocarpine	(4) R = OAc
Dictyocarpine (12)	R = OH



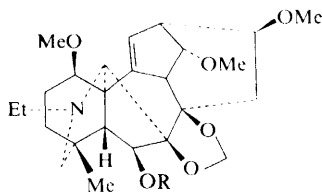
Deltaline (Eldeline)	(5) R <sup>1</sup> = OAc; R <sup>2</sup> = OH
Deltamine (Eldelidine)	(6) R <sup>1</sup> = R <sup>2</sup> = OH
Acetyldepheline	(9) R <sup>1</sup> = OAc; R <sup>2</sup> = H
Depheline	(10) R <sup>1</sup> = OH; R <sup>2</sup> = H
Acetyldeltaline	(11) R <sup>1</sup> = R <sup>2</sup> = OAc

<sup>2</sup> G. R. Waller, S. D. Sastry, and K. F. Kinneberg, *Proc. Oklahoma Acad. Sci.*, 1973, 53, 92.

<sup>3</sup> A. S. Narzullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, 8, 498.

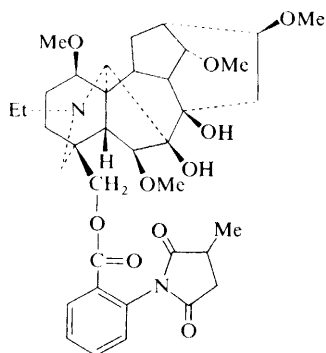
<sup>4</sup> A. S. Narzullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 9, 443.

Acetylation of dictyocarpine (12), the alkaline hydrolysis product of dictyocarpine (4), afforded a triacetyl derivative identical with the diacetyl derivative of deltamine (6). This confirms the presence of a methoxy-group at C-16 in dictyocarpine.

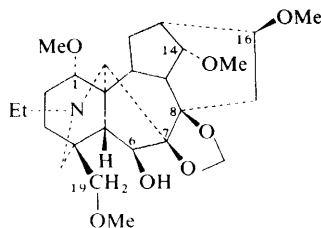


Dehydroacetyldepheline (7) R = Ac  
Dehydrodelpheline (8) R = H

**Alkaloids of *Delphinium corumbosum*.**—A recent report on the investigation of the alkaloid components of the aerial parts of *Delphinium corumbosum* (*D. corymbosum* Regel) has appeared.<sup>5</sup> Chloroform extraction yielded 0.51% total alkaloids from which were isolated methyl-lycoctonine (13), a new alkaloid delcorine (14), and a base, m.p. 93–95 °C.



Methyl-lycoctonine (13)



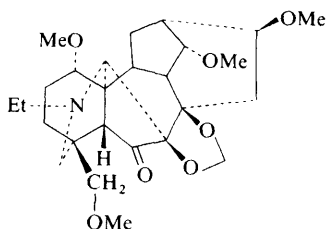
Delcorine (14)

Delcorine,  $C_{26}H_{41}NO_7$ , m.p. 200–202 °C, forms a monoacetyl derivative on treatment with acetyl chloride. The i.r. and n.m.r. spectral data indicate the presence of one hydroxy-, an *N*-ethyl, a methylenedioxy-, and four methoxy-groups. Oxidation of delcorine with chromium trioxide affords dehydrodelcorine (15). Comparison of the i.r. and n.m.r. spectra of delcorine and dehydrodelcorine with those of deltamine (6) and dictyocarpine (4) and their dehydroderivatives located the hydroxy-group at C-6 and the methylenedioxy function at C-7 and C-8. On heating delcorine (14) with aqueous sulphuric acid, the

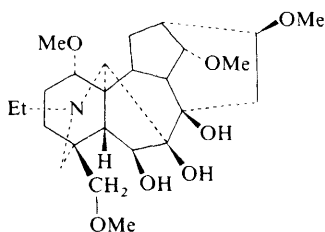
<sup>5</sup> A. S. Narzullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 9, 497.



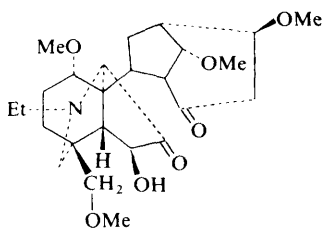
acetal was hydrolysed to yield compound (16). Oxidation of the latter with periodic acid afforded compound (17). The  $\beta$ -methoxy-group was shown to be present at C-16 by treatment of (17) with sulphuric acid; methanol was eliminated smoothly to yield the olefin (18). A methoxy function was assigned to C-19 on the basis of acetylation and oxidation reactions and n.m.r. spectral data. The positions of the additional methoxy-groups at C-1 ( $\alpha$ ) and C-14 ( $\alpha$ ) were assigned by n.m.r. and mass spectral comparisons. From these data, structure (14) was assigned to delcorine. The base, m.p. 93–95 °C, has a molecular weight of 463 by mass spectral analysis. Preliminary spectral data indicate the presence of an *N*-ethyl, a methylenedioxy-, and four methoxy-groups.



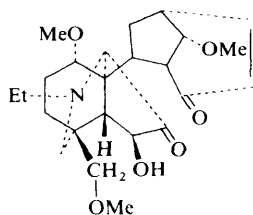
Dehydrodelcorine (15)



(16)



(17)



(18)

**Heteratisine.**—A detailed report on the chemical elucidation of the structure and stereochemistry of heteratisine (19) has appeared.<sup>6</sup> This lactone diterpenoid alkaloid has been isolated along with its monobenzoyl ester from the roots of *Aconitum heterophyllum* Wall.<sup>7,8</sup> Heteratisine has not been detected in any other plant. An earlier X-ray crystallographic analysis of the hydrobromide monohydrate of heteratisine indicated the identical structure.<sup>9</sup> Heteratisine thus bears a closer structural relationship to the highly toxic and polyoxygenated alkaloids of the lycotonine–aconitine type than to its companion bases atisine, atidine, and hetisine.

Heteratisine,  $C_{22}H_{33}NO_5$ , contains two hydroxy-groups, one methoxy-group, an *N*-ethyl function, and a lactone ring. Since treatment of heteratisine with

<sup>6</sup> R. Aneja, D. M. Locke, and S. W. Pelletier, *Tetrahedron*, 1973, **29**, 3297; cf. R. Aneja and S. W. Pelletier, *Tetrahedron Letters*, 1964, 669.

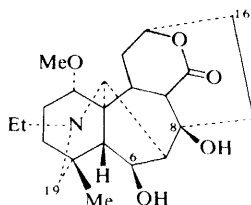
<sup>7</sup> W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, 1942, **143**, 605.

<sup>8</sup> S. W. Pelletier, R. Aneja, and K. W. Gopinath, *Phytochemistry*, 1968, **7**, 625.

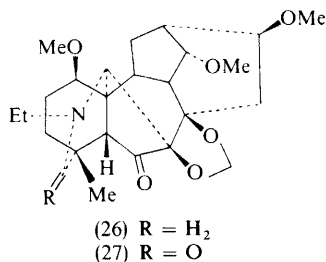
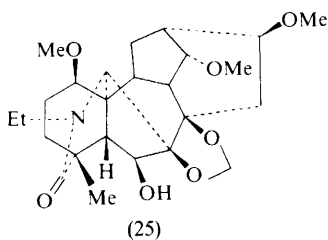
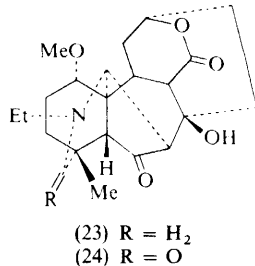
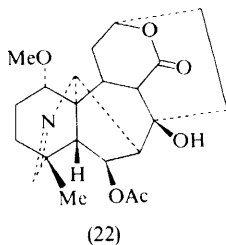
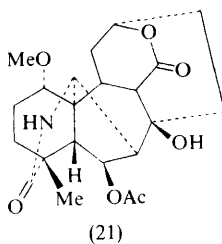
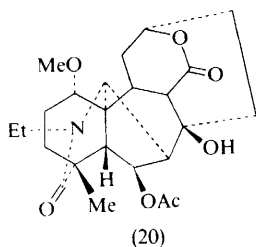
<sup>9</sup> M. Przybylska, *Canad. J. Chem.*, 1963, **41**, 2911.

acetic anhydride-pyridine affords only a basic monoacetate derivative, the presence of one secondary and one tertiary hydroxy-group is indicated, the nitrogen atom being tertiary and part of a ring.

Oxidation of heteratisine acetate with Sarett's reagent gives three products, 19-oxoheteratisine acetate (20) in a yield of 70—75%, *N*-desethyl-19-oxoheteratisine acetate (21), and the azomethine (22). Treatment of heteratisine and oxoheteratisine with chromium trioxide in acetic acid yields dehydroheteratisine (23) and oxodehydroheteratisine (24), respectively. Comparison of their i.r.

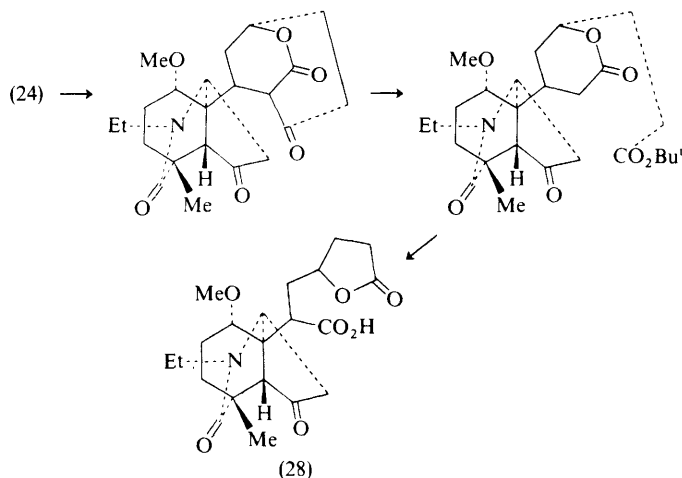


Heteratisine (19)



spectra and molar rotation changes with those of delpheline (10), oxodelpheline (25), and their dehydro-derivatives (26) and (27), suggested a  $\beta$ -hydroxy-group at C-6 in heteratisine. The location of the lactone system could be assigned from the n.m.r. spectra.

On treatment with hot aqueous alkali, only hydrolysis of the lactone ring occurs. However, on treatment of 19-oxodehydroheteratisine (24) with potassium t-butoxide in t-butyl alcohol, a  $\gamma$ -lactone carboxylic acid (28) was isolated. This product may be formed as indicated in the Scheme. The rearrangement to (28)



Scheme

indicates the presence of the tertiary hydroxyl at C-8,  $\beta$  to both the cyclopentanone and the  $\delta$ -lactone functions. The secondary methoxy-group was assigned to C-1. Biogenetic precedence suggests locations for this functionality at C-1 or C-16. However, a methoxyl at C-16 would be expected to undergo  $\beta$ -elimination readily during the treatment of (24) with strong base. The assignment of an  $\alpha$ -methoxy-group at C-1 is supported by the n.m.r. spectral data. The indicated absolute stereochemistry has been confirmed by earlier pyrolysis studies.<sup>10</sup> This structure for heteratisine is consistent with additional previously reported chemical studies.<sup>11</sup>

### 3 Diterpenoid Alkaloid Syntheses

**The Total Synthesis of Napelline.**—Following a series of model studies,<sup>12</sup> the Wiesner group has successfully completed a formal synthesis of napelline (29).<sup>13,14</sup>

<sup>10</sup> R. Aneja and S. W. Pelletier, *Tetrahedron Letters*, 1965, 215.

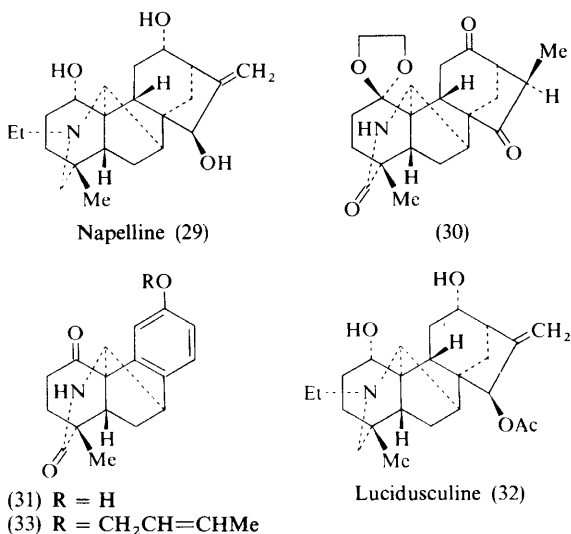
<sup>11</sup> O. E. Edwards and C. Ferrari, *Canad. J. Chem.*, 1964, **42**, 172.

<sup>12</sup> K. Wiesner, A. Deljac, T. Y. R. Tsai, and M. Przybylska, *Tetrahedron Letters*, 1970, 1145.

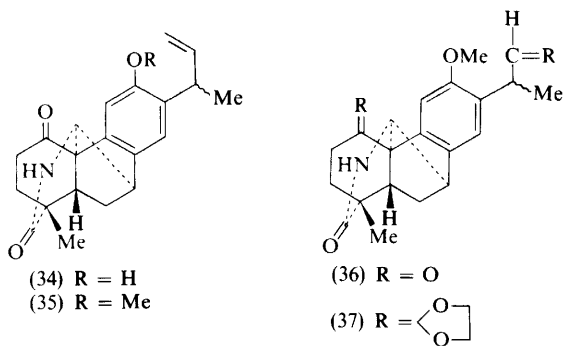
<sup>13</sup> K. Wiesner, Pak-tsun Ho, and C. S. J. Tsai, *Canad. J. Chem.*, 1974, **52**, 2353.

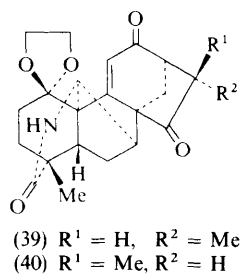
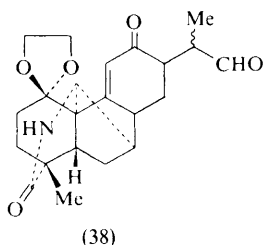
<sup>14</sup> K. Wiesner, Pak-tsun Ho, C. S. J. Tsai, and Yiu-Kuen Lam, *Canad. J. Chem.*, 1974, **52**, 2355.

The recent work describes the synthesis of the racemate (30) from the pentacyclic intermediate (31), and the conversion of lucidusculture (32) into the identical derivative (30). Using the optically active intermediate (30) as a relay, the synthesis of napelline was completed.

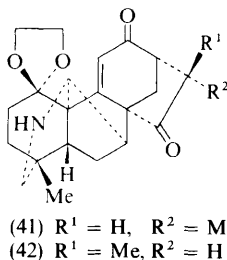


Treatment of (31) with crotyl chloride-potassium carbonate in DMF afforded (33), which was converted into (34) by heating in a sealed tube. Methylation of the phenol (34) with methyl iodide-potassium carbonate gave (35). Osmic acid-sodium periodate oxidation produced the keto-aldehyde (36). Acetalization by standard methods gave the diacetal (37). Reduction of (37) with lithium in liquid ammonia and subsequent toluene-*p*-sulphonic acid work-up afforded (38) in a yield of 50%. A vinylogous aldol condensation was effected with methanolic potassium hydroxide. The resulting mixture was oxidized with chromium





(39)  $R^1 = H$ ,  $R^2 = Me$   
 (40)  $R^1 = Me$ ,  $R^2 = H$

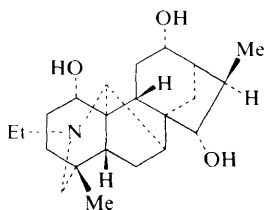


(41)  $R^1 = H$ ,  $R^2 = Me$   
 (42)  $R^1 = Me$ ,  $R^2 = H$

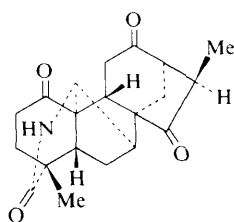
trioxide-pyridine in methylene chloride to yield four diketones (39)–(42). These were separable by chromatography. Napelline had previously been converted into (39), and the t.l.c. behaviour and mass and i.r. spectra of (39) derived from the two sources were identical. Hydrogenation of (40) with 10% palladium on charcoal gave the diketo-acetal (30), identical by t.l.c., i.r., n.m.r., and mass spectra with the corresponding optically active product derived from napelline.

In order to prepare the relay intermediate (30), lucidusculine was converted into napelline by hydride reduction. Dihydranapelline (43) was then prepared by hydrogenation with platinum oxide in acetic acid. Removal of the *N*-ethyl group by treatment with mercuric acetate in aqueous acetic acid followed by oxidation with chromium trioxide in pyridine afforded the triketolactam (44). This was converted into the diketo-acetal intermediate (30) by conventional methods.

The triketone (44) could be regenerated by treatment of (30) with 60% aqueous acetic acid. Reduction of (44) with lithium aluminium hydride gave a trihydroxy-

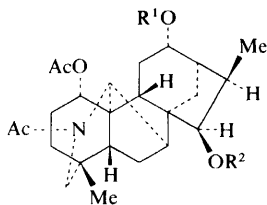


Dihydranapelline (43)



(44)

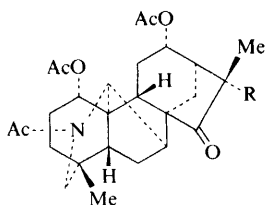
compound which was immediately acetylated with acetic anhydride-pyridine to yield (45). Partial hydrolysis of (45) to the dihydroxy-acetate (46) was accomplished with aqueous methanolic potassium carbonate. This compound was acetylated with acetic anhydride in pyridine for 7 hours at 5 °C to afford (47). Oxidation of (47) with chromium trioxide-pyridine in methylene chloride gave the ketone (48). Bromination of compound (48) with bromine-HCl in ether-chloroform gave the bromide (49). Dehydrobromination with lithium bromide-lithium carbonate resulted in the unsaturated ketone (50). Lithium aluminium hydride reduction of the latter yielded napelline (29).



(45)  $R^1 = R^2 = \text{Ac}$

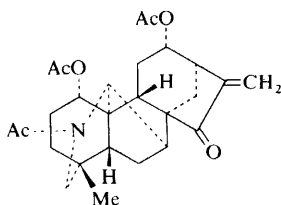
(46)  $R^1 = R^2 = \text{H}$

(47)  $R^1 = \text{Ac}, R^2 = \text{H}$



(48)  $R = \text{H}$

(49)  $R = \text{Br}$



(50)

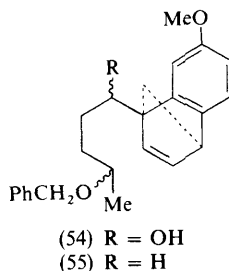
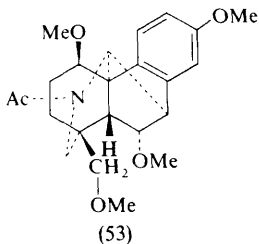
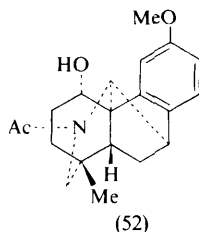
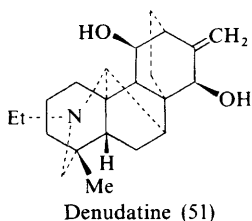
**The Synthesis of the Denudatine Skeleton.**—Wiesner and co-workers<sup>15</sup> have successfully elaborated the carbon skeleton of denudatine (51) in studies designed to develop methods for the construction of the C/D ring systems of the diterpenoid alkaloids from aromatic intermediates such as (52)<sup>16</sup> and (53).<sup>17</sup>

Starting with (54),<sup>16</sup> the hydroxy-group was removed by mesylation and subsequent reduction with lithium aluminium hydride. The resulting compound (55) was converted into the pentacyclic methyl ether (56) using the analogous reaction sequence employed for the previously described synthesis of (52).<sup>16</sup> Birch reduction of (56) and reacetylation yielded the enol ether (57). This compound was hydrolysed with dilute oxalic acid to the unsaturated ketone (58). Reduction with sodium borohydride followed by mesylation and treatment

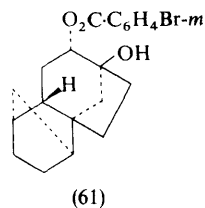
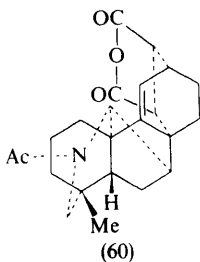
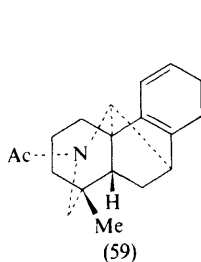
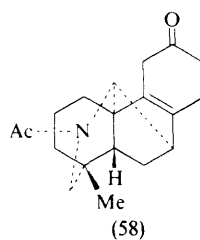
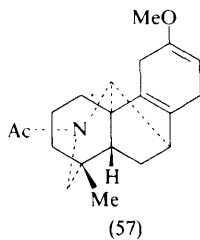
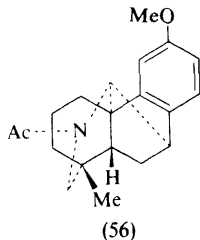
<sup>15</sup> K. Wiesner, Pak-tsun Ho, and S. Oida, *Canad. J. Chem.*, 1974, **52**, 1042.

<sup>16</sup> K. Wiesner, Pak-tsun Ho, D. Chang, Yiu-Kuen Lam, C. S. J. Pan, and W. Y. Ren, *Canad. J. Chem.*, 1973, **51**, 3978.

<sup>17</sup> K. Wiesner, Pak-tsun Ho, R. C. Jain, S. F. Lee, S. Oida, and A. Philipp, *Canad. J. Chem.*, 1973, **51**, 1448.



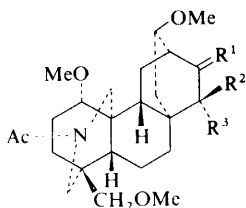
with potassium *t*-butoxide afforded the unstable diene (59). Reaction of the latter with maleic anhydride gave the desired adduct (60) in a yield of 60%.<sup>15</sup> The configuration of (60) was confirmed by n.m.r. analysis and an *X*-ray crystallographic study of a related system (61).



In order to utilize this reaction sequence for the construction of the appropriately substituted C/D ring systems, the cyclic diene system must contain functionalities which are or can be converted into the substituents of the desired final product.

**The Total Synthesis of Talatisamine.**—The atisine-type intermediate (62) has been used in the synthesis of talatisamine (63).<sup>18</sup> A key step in this synthetic route is the rearrangement of an atisine skeleton (structure B) to a lycoctonine skeleton (structure A). This type of rearrangement has been proposed in the biogenesis of alkaloids possessing the lycoctonine skeleton. Johnson and Overton<sup>19</sup> and Ayer and Deshpande<sup>20</sup> have previously reported studies of this process.

Benzoylation of (62) with sodium hydride and benzoyl peroxide afforded (64). Acetalization followed by alkaline hydrolysis of the benzoate group gave the hydroxy-acetal (65). The latter was oxidized to the ketone (66) by treatment with chromium trioxide-pyridine in methylene chloride. Borohydride reduction of the ketone (66) gave the alcohol (67), which was converted into the tosylate (68) using toluene-*p*-sulphonyl chloride and pyridine. The structure of this compound has been confirmed by an *X*-ray crystallographic analysis. On heating the tosylate (68) in dimethyl sulphoxide-tetramethylguanidine for 24 hours at 180 °C, the desired skeletal rearrangement to (69) was effected in yields of about 40%. In addition to some starting material, 40% of a product with a C-8—C-15 double bond was obtained. Lithium aluminium hydride reduction of the *N*-acetyl derivative (69) gave the corresponding *N*-ethyl compound (70).

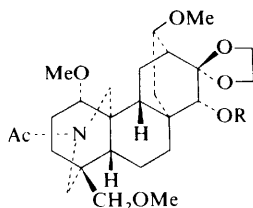


(62)  $R^1 = O, R^2 = R^3 = H$

(64)  $R^1 = O, R^2 = O_2CPh, R^3 = H$

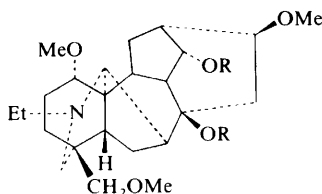
(65)  $R^1 = \begin{array}{c} \diagup \diagdown \\ O \end{array}, R^2 = OH, R^3 = H$

(66)  $R^1 = \begin{array}{c} \diagup \diagdown \\ O \end{array}, R^2 R^3 = O$



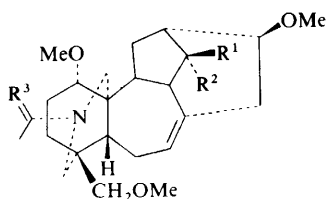
(67)  $R = H$

(68)  $R = Ts$



Talatisamine (63)  $R = H$

(71)  $R = Ac$



(69)  $R^1 R^2 = \begin{array}{c} \diagup \diagdown \\ O \end{array}, R^3 = O$

(70)  $R^1 R^2 = \begin{array}{c} \diagup \diagdown \\ O \end{array}, R^3 = H_2$

(72)  $R^1 R^2 = O, R^3 = H_2$

(73)  $R^1 = H, R^2 = OH, R^3 = H_2$

<sup>18</sup> K. Wiesner, T. Y. R. Tsai, K. Huber, and S. E. Bolton, *J. Amer. Chem. Soc.*, 1974, **96**, 4990.

<sup>19</sup> J. P. Johnston and K. H. Overton, *J.C.S. Perkin I*, 1972, 1490.

<sup>20</sup> W. A. Ayer and P. D. Deshpande, *Canad. J. Chem.*, 1973, **51**, 77.



The corresponding optically active derivative was prepared from talatisamine. Reductive cleavage of the diacetate (71) of talatisamine followed by Jones oxidation gave the ketone (72). Acetalization by standard methods afforded (70). The synthetic racemic compound and the optically active derivative were indistinguishable by i.r., mass, and n.m.r. spectroscopy. Deacetalization of (70) with aqueous methanolic HCl afforded the ketone (72). Reduction of the latter with sodium borohydride proceeded stereospecifically to yield the alcohol (73). Finally, oxidation of (73) with mercuric acetate furnished talatisamine (63).

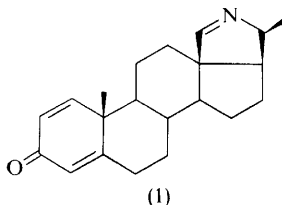
# Steroidal Alkaloids of the Apocynaceae, Buxaceae, Asclepiadaceae, and of the *Salamandra-Phyllobates* Group

BY F. KHUONG-HUU AND R. GOUTAREL

This subject has been reviewed recently by G. G. Habermehl.<sup>1</sup>

## 1 Alkaloids of the Apocynaceae

**Steroidal Alkaloids and Amines.**—*Phytochemistry*. Maingayne (1) was extracted from the bark of *Paravallis maingayi*. This represents the first reported isolation of an alkaloid of the conanine group from the genus *Paravallis*.<sup>2</sup>



Conamine (highest content), conessine, and isoconessimine were isolated from the seeds of *Holarrhena mitis* R. Br. Aminoglycosteroids and irehdiamine-type alkaloids were not characterized.<sup>3</sup>

Six alkaloids of the conanine group, conessine (main product), conessimine, isoconessimine, conarrhimine, conessidine, and conkurchine, and four alkaloidal derivatives of 3-amino- $\Delta^5$ -pregnene, holafebrine (main product), holaminol, holarrhimine, and holaphylline, were isolated from the bark of *Holarrhena febrifuga* Klotzsch.<sup>4</sup>

Malouetine and funtumafrine C have been extracted from *Malouetia brachyloba*,<sup>5</sup> an African plant from Yangambi (Katanga), showing that this species is a neighbour of *M. bequaertiana*.<sup>6</sup> Five conanine derivatives, latifolinine (main

<sup>1</sup> G. G. Habermehl, in 'Alkaloids', ed. K. Wiesner (MTP International Review of Science), Organic Chemistry Series One, Vol. 9, Butterworths, London, 1973, p. 235.

<sup>2</sup> J. B. Davis, K. Jewers, A. H. Manchanda, and A. B. Wood, *Chem. and Ind.*, 1970, 627.

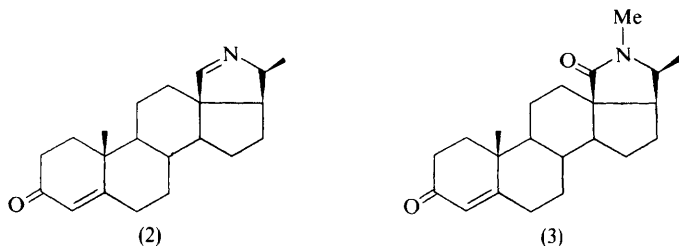
<sup>3</sup> M. Leboeuf, G. P. Wannigama, A. Cavé, and R. Goutarel, *Ann. pharm. franç.*, 1972, **30**, 837.

<sup>4</sup> H. Dadoun, A. Cavé, and R. Goutarel, *Ann. pharm. franç.*, 1973, **31**, 237.

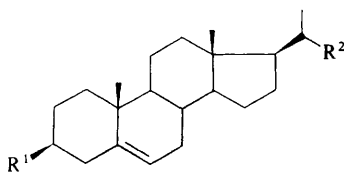
<sup>5</sup> F. Khuong-Huu, M. J. Magdeleine, J. Santamaria, and R. Goutarel, *Phytochemistry*, 1973, **12**, 1813.

<sup>6</sup> M.-M. Janot, F. Lainé, and R. Goutarel, *Ann. pharm. franç.*, 1960, **18**, 673.

product), latifoline, *N*-acetylconamine, malouetafrine (2), and malouetamide (3), have been isolated from *Malouetia heudelotii*, an African species from Congo-Brazzaville which does not contain any alkaloid with a quaternary ammonium function.<sup>5</sup> This makes *M. heudelotii* chemically a neighbour of *M. arborea*, a South American species, studied by Šorm *et al.*<sup>7</sup>



*Synthesis, Reactions, and Transformations of Steroidal Amines.* The synthesis of irehdiamines A—I (4) has been described. Physical constants and i.r., n.m.r., and m.s. data are given.<sup>8</sup>



- (4) Irehdiamine
- A;  $R^1 = R^2 = \text{NH}_2$
  - B;  $R^1 = \text{NHMe}, R^2 = \text{NH}_2$
  - C;  $R^1 = \text{NH}_2, R^2 = \text{NHMe}$
  - D;  $R^1 = R^2 = \text{NHMe}$
  - E;  $R^1 = \text{NMe}_2, R^2 = \text{NH}_2$
  - F;  $R^1 = \text{NH}_2, R^2 = \text{NMe}_2$
  - G;  $R^1 = \text{NMe}_2, R^2 = \text{NHMe}$
  - H;  $R^1 = \text{NHMe}, R^2 = \text{NMe}_2$
  - I;  $R^1 = R^2 = \text{NMe}_2$

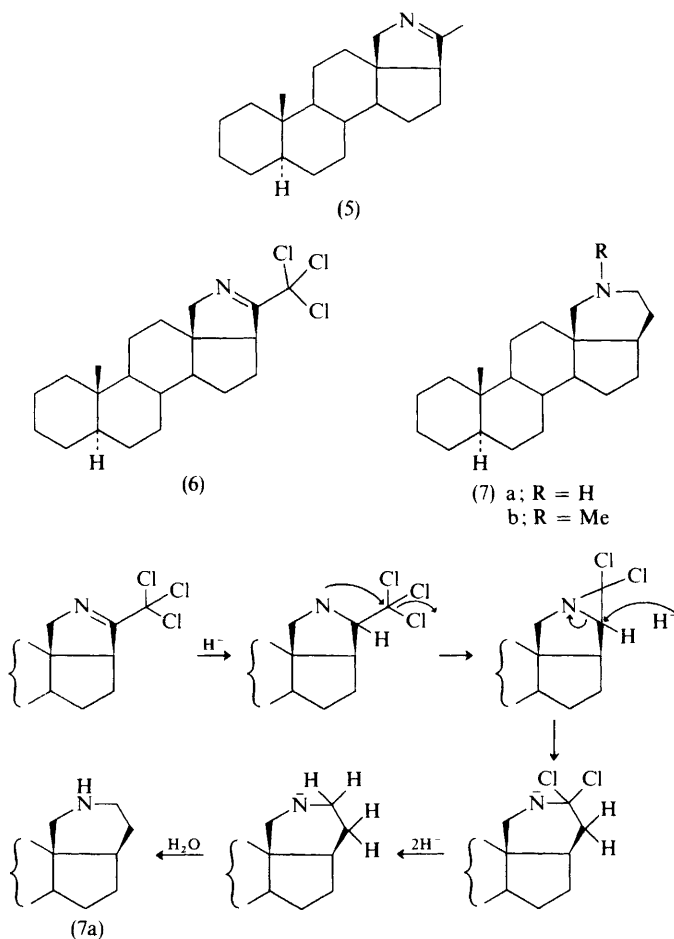
The trichloro-imine (6), obtained from (5) with sodium hypochlorite, when reduced with lithium aluminium hydride gave *N*-demethyl-21-nor-*E*-homo-5 $\alpha$ -conanine (7a) by ring enlargement. Hydrogenolysis of the C—Cl bond by LAH, followed by an intramolecular substitution giving an aziridine ring, was proposed (Scheme 1).<sup>9</sup> Intermediate formation of an aziridinium ring, leading to an eventual ring enlargement, was also involved during solvolysis of  $\beta$ -halogeno tertiary amines.<sup>10</sup> Methylation of (7a) led to (7b).<sup>9</sup>

<sup>7</sup> F. Soti, V. Cerny, and F. Šorm, *Tetrahedron Letters*, 1967, 1437.

<sup>8</sup> A. Cavé, C. Conreur, G. P. Wannigama, G. Charles, and H. J. Hentchoya, *Chim. Ther.*, 1973, **8**, 626.

<sup>9</sup> A. Picot and X. Lusinchi, *Tetrahedron Letters*, 1974, 679.

<sup>10</sup> N. J. Leonard, *Rec. Chem. Progr.*, 1965, **26**, 211; C. F. Hammer, S. R. Heller, and J. H. Craig, *Tetrahedron*, 1972, **28**, 239; C. F. Hammer, M. McC. Ali, and J. D. Weber, *Tetrahedron*, 1973, **29**, 1767.



Scheme 1

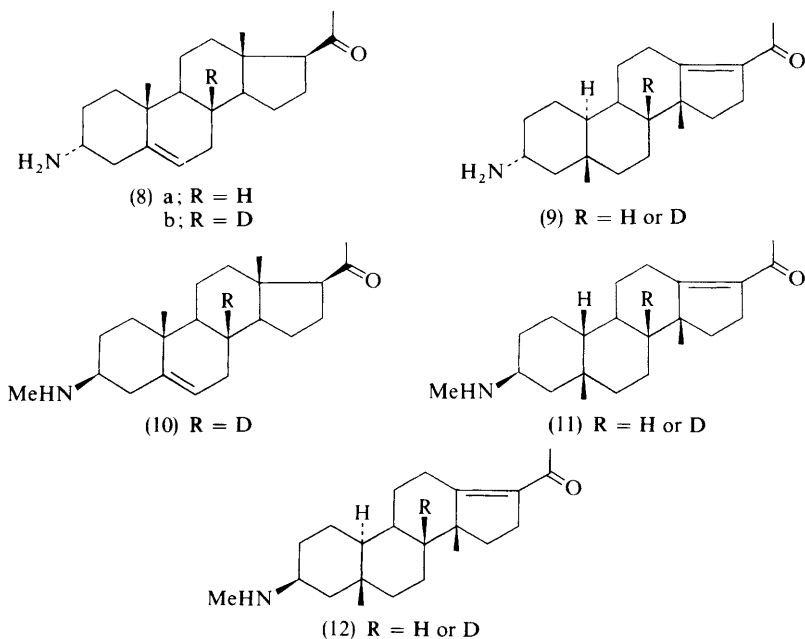
Two possible mechanisms have been invoked to explain backbone rearrangements in the steroid and triterpene series:<sup>11</sup>

- (a) ionization followed by a set of sequential 1,2-shifts proceeding *via* discrete carbonium ion intermediates;
- (b) ionization followed by deprotonation and reprotonation with the formation of tetrasubstituted olefins as intermediates.

The backbone rearrangement of holamine (8a) with  $D_2SO_4$  leads to poly-deuteriated isoholamine (9) with introduction of a deuterium atom on at least one spinal carbon atom (C-8, -9, or -10), a result that can only be explained by

<sup>11</sup> D. N. Kirk, in 'Terpenoids and Steroids', ed. K. H. Overton (Specialist Periodical Reports), The Chemical Society, London, 1972, Vol. 2, p. 300; 1973, Vol. 3, p. 378.

assuming the formation of a tetrasubstituted olefin as intermediate.<sup>12</sup> Hence,  $8\beta$ -[ $^2\text{H}_1$ ]holamine (8b) and  $8\beta$ -[ $^2\text{H}_1$ ]methylholaphylline (10) were synthesized (Scheme 2) and the deuterium extent of their spinally rearranged products with  $\text{H}_2\text{SO}_4$ , (9), (11), and (12), was estimated.<sup>13</sup>



With  $\text{H}_2\text{SO}_4$ ,  $8\beta$ -[ $^2\text{H}_1$ ]-holamine (8b) gave isoholamine (9) with high loss of deuterium (26% deuterium retention); in the same conditions,  $8\beta$ -[ $^2\text{H}_1$ ]methylholaphylline (10) led to  $10\beta$ -isomethylholaphylline (11) as main product (96%), with high loss of deuterium (8.5% deuterium retention), and  $10\alpha$ -isomethylholaphylline (12) (4%), with retention of deuterium (80% deuterium retention). Thus, with  $\text{H}_2\text{SO}_4$ , at the C-8 and C-9 positions, the deprotonation-reprotonation pathway (b) prevails. A 1,3-diaxial interaction between the  $3\beta$ -amino-group and the  $5\beta$ -methyl, disfavoring the formation of a  $\Delta^{8,9}$ -olefin, was invoked to explain the formation of derivative (12) by an 8,9 hydrogen shift.

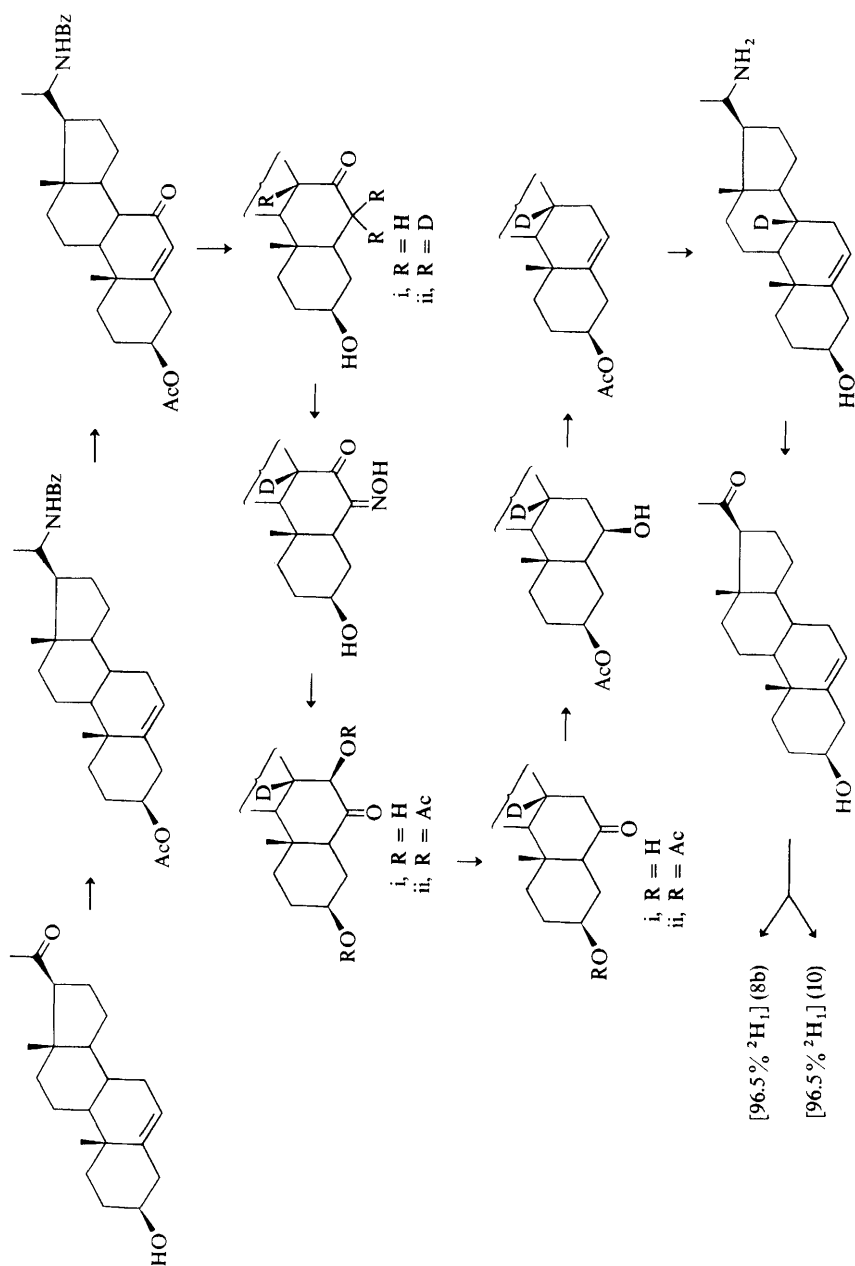
**Photochemistry.** Photo-oxidation reactions, sensitized by dyes, of various tertiary amines and alkaloids have been investigated.<sup>14,15</sup> The formation of

<sup>12</sup> M.-M. Janot, F. Frappier, J. Thierry, G. Lukacs, F. X. Jarreau, and R. Goutarel, *Tetrahedron Letters*, 1972, 3499; see F. Khuong-Huu and R. Goutarel, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4, p. 356.

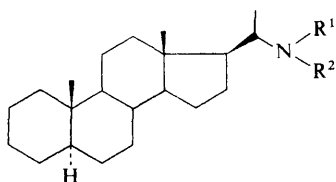
<sup>13</sup> J. Thierry, F. Frappier, M. Païs, and F. X. Jarreau, *Tetrahedron Letters*, 1974, 2149.

<sup>14</sup> D. Herlem, Y. Hubert-Brierre, F. Khuong-Huu, and R. Goutarel, *Tetrahedron*, 1973, **29**, 2195.

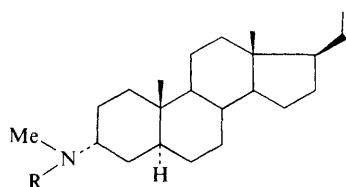
<sup>15</sup> D. Herlem, Y. Hubert-Brierre, and F. Khuong-Huu, *Tetrahedron Letters*, 1973, 4173.



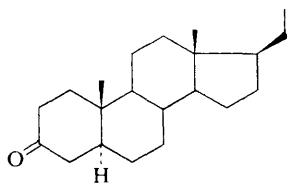
either secondary amines and/or amides was observed, according to the conditions used. Thus, in methanolic solution, in the presence of methylene blue and oxygen, the photolyses of 20 $\alpha$ -dimethylamino-5 $\alpha$ -pregnane (13a), 3 $\alpha$ -dimethylamino-5 $\alpha$ -pregnane (14a), 5 $\alpha$ -conanine (16a), 3 $\beta$ -dimethylaminocyclolaudane (18a), and compound (19) (obtained from cyclomicrophylline B, a *Buxus* alkaloid) led respectively to compounds (13b), (14b) and (15), (17), (18b) and (18c), and the oxazines (20a) and (20b). It was noted that the secondary amines (13b) and (18b) were not available starting from (13a) and (18a) by a Von Braun reaction.



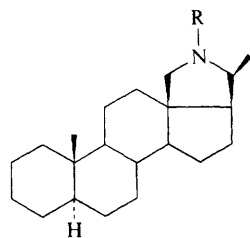
- (13) a; R<sup>1</sup> = R<sup>2</sup> = Me  
 b; R<sup>1</sup> = H, R<sup>2</sup> = Me  
 c; R<sup>1</sup> = CHO, R<sup>2</sup> = Me  
 d; R<sup>1</sup> = CHO, R<sup>2</sup> = H  
 e; R<sup>1</sup> = CH<sub>2</sub>CN, R<sup>2</sup> = Me  
 f; R<sup>1</sup> = CH<sub>2</sub>CO<sub>2</sub>Et, R<sup>2</sup> = Me  
 g; R<sup>1</sup> = CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, R<sup>2</sup> = Me



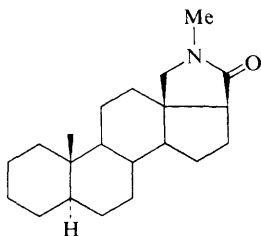
- (14) a; R = Me  
 b; R = H  
 c; R = CHO



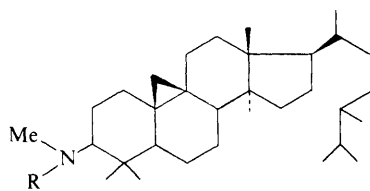
(15)



- (16) a; R = Me  
 b; R = H  
 c; R = CH<sub>2</sub>CN



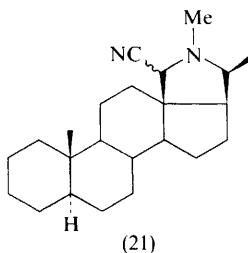
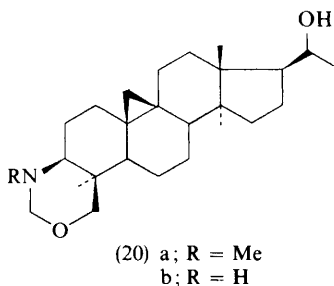
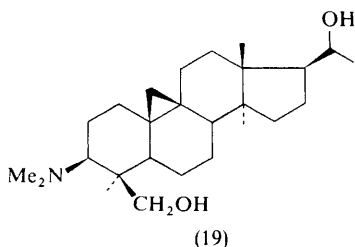
(17)



- (18) a; R = Me  
 b; R = H  
 c; R = CHO

In DMF solution, in the presence of methylene blue and oxygen, photolysis of (13a) led to a mixture of (13b), (13c), and (13d).

In the absence of oxygen, but in the presence of an equimolecular amount of dye, irradiation of these tertiary amines under nitrogen gave the secondary



amines only. Thus, (13a) gave (13b) and (16a) led to (16b) quantitatively on photolysis under nitrogen with eosin as sensitizer. A mechanism involving a charge-transfer complex between the triplet state of the dye and the amine in the ground state was proposed to explain this photodemethylation reaction. An immonium ion giving the secondary amines by hydrolysis was postulated as an intermediate. This was confirmed by carrying out the irradiations in an alcoholic solution containing eosin and KCN; thus (13a) gave the amino-nitrile (13e), whilst (16a) led to (16c) as main product and a mixture of the 18-epimeric nitriles (21) as minor products. Treatment of (13e) with sulphuric acid in ethanol yielded the amino-ester (13f), whilst reduction gave the  $\beta$ -diamine (13g).<sup>15</sup>

**Mass Spectra.** A strong scrambling (hydrogen exchange reaction) was observed during fragmentation in the mass spectrometer of deuteriated 1- and 4-dimethylaminocholestanes. Mass spectra of 1 $\alpha$ -dimethylamino-5 $\alpha$ -[2-<sup>2</sup>H<sub>2</sub>]cholestane and 4 $\beta$ -dimethylamino-5 $\alpha$ -[3-<sup>2</sup>H<sub>2</sub>]cholestane showed strong peaks at  $m/e$  84,  $M - 44$ , and  $M - 43$  concomitant with normal peaks at  $m/e$  85 and  $M - 45$ , indicating an H-D exchange between the deuteriated carbon atoms and the other carbon atoms of the molecule. This could be explained by the formation during the fragmentation process of a radical ion of appropriate structure and adequate stability, having a long enough lifetime.<sup>16</sup>

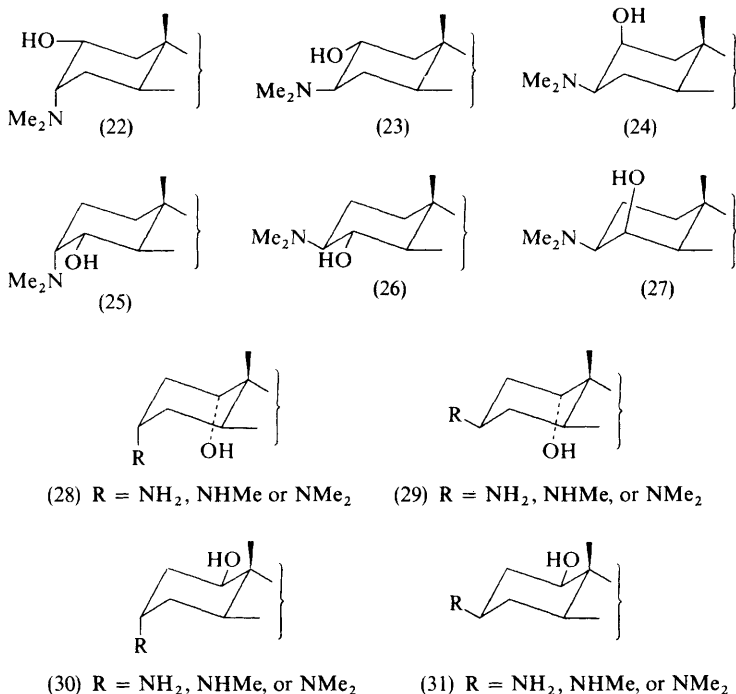
The chemical-ionization mass spectra of several  $\alpha$ -ring 1,2- and 1,3-amino-alcohols have been studied using isobutane as a reagent gas.<sup>17</sup> The loss of water from  $MH^+$  ion protonated at the hydroxy-group occurs only when the distance between the oxygen and the nitrogen is too large to allow the formation of

<sup>16</sup> C. Marazano and P. Longevialle, *Compt. rend.*, 1973, **277**, C, 175.

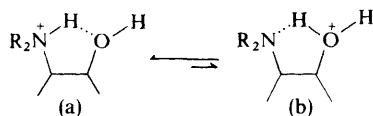
<sup>17</sup> P. Longevialle, G. W. A. Milne, and H. M. Fales, *J. Amer. Chem. Soc.*, 1973, **95**, 6666.



a hydrogen bond. Compounds (22)–(28), having a bonded-OH band in their i.r. spectra, present  $\text{MH}^+$  ion and no  $\text{MH}^+ - \text{H}_2\text{O}$  ion in their chemical-ionization mass spectra, whilst the derivatives (29), (30), and (31), with a free-OH

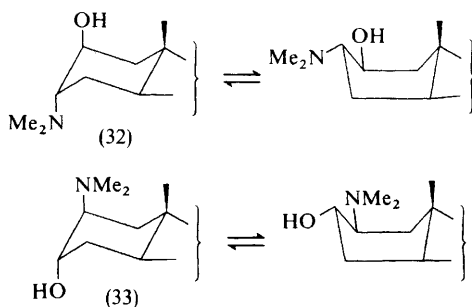


band in their i.r. spectra, exhibit a strong peak due to  $\text{MH}^+ - \text{H}_2\text{O}$ . It was postulated that protonation of an intramolecularly hydrogen-bonded species results in a complex [form (a) in Scheme 3] more stable with respect to dehydration than one that is not so bonded.



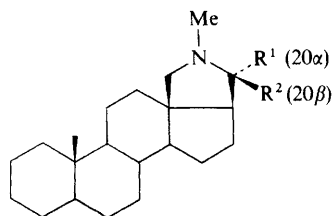
Scheme 3

Derivatives (32) and (33) showed relatively little loss of water in their chemical-ionization mass spectra. This was interpreted by their existence partially in a hydrogen-bonded A-ring boat conformation (Scheme 4). These results are consistent with those derived from i.r. data. Thus, the chemical-ionization mass spectra appear to permit conclusions regarding conformational analysis.

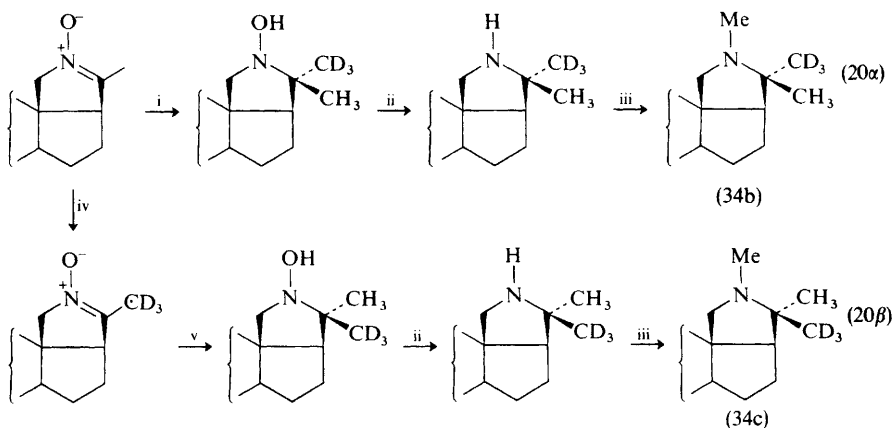


Scheme 4

Deuterium labelling of the 20-methyl group of 20-methylconanine (34) showed the stereoselectivity of  $20\alpha$ -Me loss under the electron impact.<sup>18</sup> The loss of either methyl group from identical (except label) molecules leading to the same



- (34) a;  $R^1 = R^2 = \text{CH}_3$   
 b;  $R^1 = \text{CD}_3, R^2 = \text{CH}_3$   
 c;  $R^1 = \text{CH}_3, R^2 = \text{CD}_3$



Reagents: i,  $\text{IMgCD}_3$ ; ii,  $\text{H}_2$ ; iii,  $\text{HCHO-HCO}_2\text{H}$ ; iv,  $\text{CH}_3\text{OD-CH}_3\text{O}^-$ ; v,  $\text{IMgCH}_3$

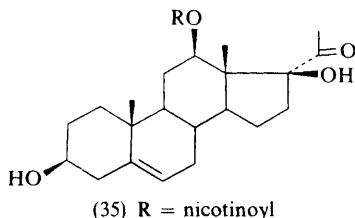
Scheme 5

<sup>18</sup> P. Longevialle, J. P. Alazard, and X. Lusinch, *Org. Mass Spectrometry*, 1974, 9, 480.

fragment, this stereoselectivity was rationalized in terms of energy content of the transition state for the fragmentation. 20-Methyl[20 $\alpha$ -<sup>2</sup>H<sub>3</sub>]conanine (34b) and 20-methyl[20 $\beta$ -<sup>2</sup>H<sub>3</sub>]conanine (34c) were synthesized as shown in Scheme 5.

## 2 Alkaloids of the Asclepiadaceae

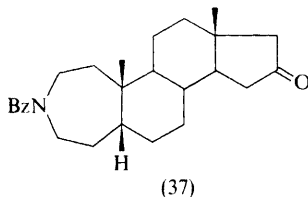
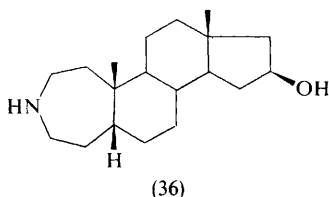
A new alkaloid, rostratamine (35), hydrolysed to nicotinic acid and deacetyl-metaplexigenin, has been isolated from *Marsdenia rostrata*.<sup>19</sup>



## 3 *Salamandra* Alkaloids

The synthesis of 3-benzoyl-A-homo-3-aza-5 $\beta$ -androstan-16-one (37), an analogue of the alkaloid samanine (36) from *Salamandra maculosa*, has been reported.<sup>20</sup> Sodium borohydride reduction of the known compound (38)<sup>21</sup> followed by tosylation afforded the tosylate (39); the nitrile group was reduced by diborane and cyclized by benzoic anhydride-pyridine to the derivative (40a); similar cyclization with acetic anhydride-pyridine yielded the related acetamide (40b). This cyclization requires one equivalent of anhydride and the uncyclized amide is not an intermediate in the reaction. Jones oxidation of (40a) was followed by conversion into a benzylidene ketone derivative (41) with benzaldehyde-KOH in methanol. Reduction of (41) with sodium borohydride and acetylation furnished (42). Treatment of compound (42) with ozone followed by mild zinc reduction produced an acetoxy-ketone, which was further reduced by Zn-HBr-CH<sub>2</sub>Cl<sub>2</sub> to the ketone (37).

Synthetic studies in *Salamandra* alkaloids have been reported.<sup>22</sup> In this work, attempted conversion into samandarine of compound (43), prepared from (38), failed.

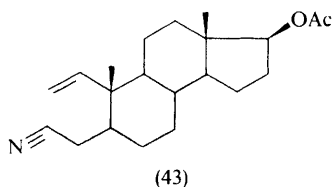
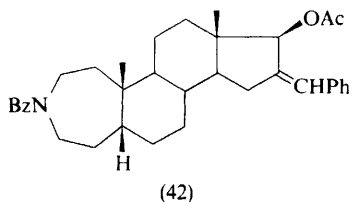
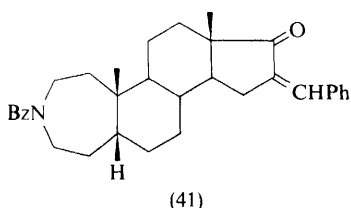
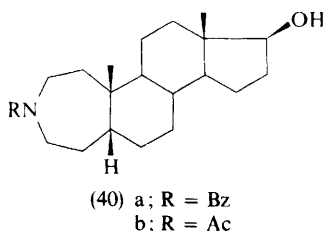
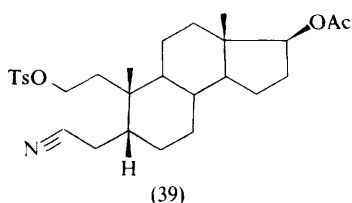
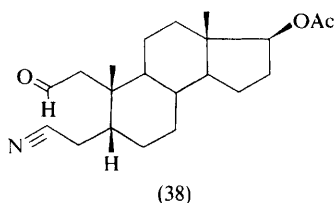


<sup>19</sup> E. Gellert and R. E. Summons, *Austral. J. Chem.*, 1973, **26**, 1835.

<sup>20</sup> R. B. Rao and L. Weiler, *Tetrahedron Letters*, 1973, 4971.

<sup>21</sup> J. K. Paisley and L. Weiler, *Tetrahedron Letters*, 1972, 261.

<sup>22</sup> J. K. Paisley, *Dis. Abs. Internat. (B)*, 1973, **34**, 2529.



#### 4 *Buxus* Alkaloids

The isolation of several alkaloids from *Buxus microphylla* Sub. et Zucc. var. *sinica* Rehd. et Wils. has been described.<sup>23</sup> Buxtauine (major alkaloid), buxaminol E, cyclokoreanine B, cyclovirobuxine D, buxpiine, and buxamine E were identified by comparison with authentic samples. In addition, four new alkaloids, of which structures are not yet determined, were isolated.

Cyclobuxine D, cycloprotobuxines A and D, and cyclovirobuxine D have been extracted from *Buxus sempervirens*.<sup>24</sup>

The isolation from *Buxus sempervirens*, and their structural assignment by physical and chemical methods, of *N*-benzoylbuxodienine E (44a), *N*-benzoyl-*O*-acetylbuxodienine E (44b),<sup>25</sup> and *N*-benzoylcyclovirobuxenine E (45)<sup>26</sup> have been reported.

16-Deoxybuxodienine C and three new alkaloids, cyclobuxupaline C (46), cyclopapilosine D (47), and buxamine C (48) were extracted from *Buxus papillosa*,

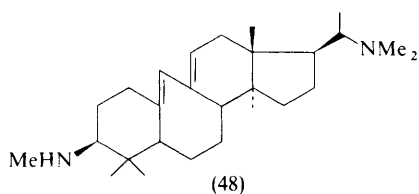
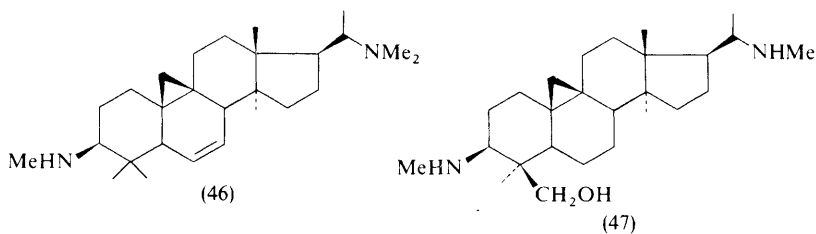
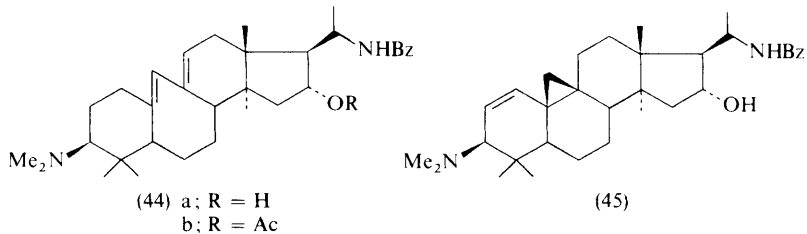
<sup>23</sup> O. Banerova and Z. Voticky, *Pharmazie*, 1973, **28**, 212.

<sup>24</sup> B. U. Khodzhaev, R. Sharikov, S. Yu. Yunusov, A. Zunnunzhanov, S. Iskandarov, and A. Nabiev, *Khim. prirod. Soedinenii*, 1974, 114.

<sup>25</sup> W. Doepke and R. Hartmund, *Z. Chem.*, 1973, **13**, 135.

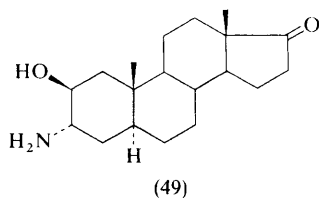
<sup>26</sup> W. Doepke and R. Hartmund, *Z. Chem.*, 1973, **13**, 178.

a species from Pakistan.<sup>27</sup> I.r., u.v., n.m.r., and m.s. data and chemical correlations led to the structural assignments.



## 5 Biological Notes

3-Amino-3-deoxy-compounds of uzarigenin, oleandrigenin, gitoxigenin, and digoxigenin have been prepared for pharmacological investigations.<sup>28</sup> The cardiotonic activity of mitiphylline, an aminodeoxy-glycocardenolide from

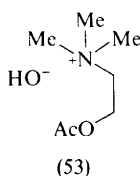
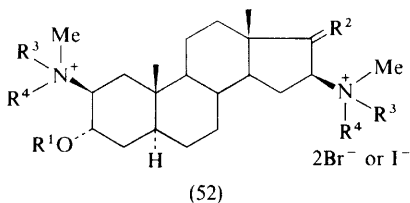
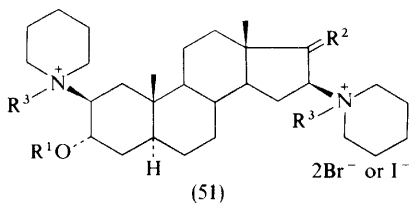
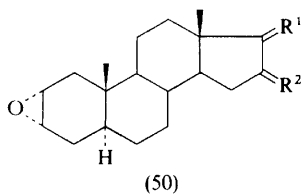


<sup>27</sup> M. Shamma, V. St. Georgiev, G. A. Miana, and F. Sultana Khan, *Phytochemistry*, 1973, **12**, 2051.

<sup>28</sup> E. Hauser, U. Boffo, L. Meister, L. Sawlewicz, H. H. A. Linde, and K. Meyer, *Helv. Chim. Acta*, 1973, **56**, 2782.

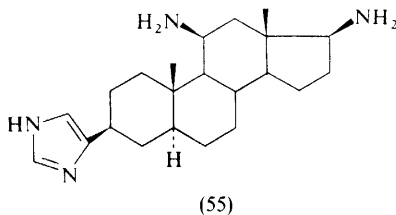
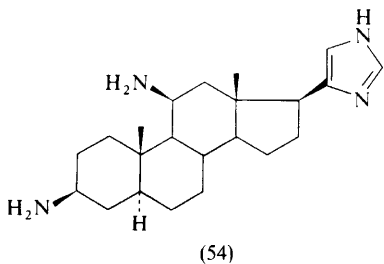
*Holarrhena mitis*, has been studied.<sup>29</sup> Compound (49) and derivatives, useful as antiarrhythmic drugs, have been prepared.<sup>30</sup>

The synthesis and activity of sixty-six 5 $\alpha$ -androstane derivatives of the forms (50), (51), and (52), with acetylcholine-like fragments (53) incorporated into rings A and D, have been reported.<sup>31</sup> These compounds were tested for neuromuscular blocking potency and one of them [francuronium bromide (50; R<sup>1</sup> = Ac, R<sup>2</sup> = H, OAc, R<sup>3</sup> = Me)] has proved to be a clinically useful neuromuscular blocking agent of medium duration of action. Structure-activity relationships were also discussed.



(22R)- and (22S)-22-aminocholesterol were stereospecifically synthesized in order to study their action on the biogenesis of C<sub>21</sub> steroids from cholesterol.<sup>32</sup>

Water-soluble steroids with catalytic substituents were prepared. The synthesis of amino-steroids bearing an imidazolyl nucleus, (54)<sup>33</sup> and (55),<sup>34</sup> has



<sup>29</sup> O. Foussard-Blanpin, F. Hubert, P. Choay, and M. Lebocuf, *Ann. pharm. franc.*, 1973, **31**, 593.

<sup>30</sup> C. L. Colin and D. S. Savage, *Ger. Offen.* 2 335 827/1974.

<sup>31</sup> W. R. Buckett, C. L. Hewett, and D. S. Savage, *J. Medicin. Chem.*, 1973, **16**, 1116.

<sup>32</sup> Q. Khuong-Huu, Y. Letourneux, M. Gut, and R. Goutarel, *J. Org. Chem.*, 1974, **39**, 1065.

<sup>33</sup> J. P. Guthrie, *Canad. J. Chem.*, 1972, **50**, 3993.

<sup>34</sup> J. P. Guthrie and Y. Ueda, *Canad. J. Chem.*, 1973, **51**, 3936.

been described. The catalytic activity of (54) for the hydrolysis of aryl esters of acids with hydrophobic substituents was studied and the rate enhancement observed was attributed to hydrophobic binding between substrate and catalyst.<sup>35</sup> Compound (55) was found to be a better catalyst than (54).<sup>34</sup> The results were discussed in terms of the stereochemistry of the steroidal catalysts. The hydrolysis of various aryl acetates by (54) was also investigated.<sup>36</sup>

2,4,5-Trimethylpyrrole-3-carboxylic acid esters of various alkaloids were synthesized with regard to potentiation or modification of the activity of the parent alkaloids, 2,4,5-trimethylpyrrole-3-carboxylic acid being the acid portion of batrachotoxin on which the activity of batrachotoxin is dependent.<sup>37</sup>

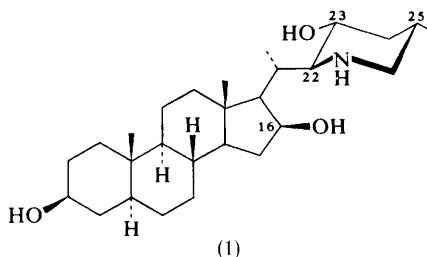
<sup>35</sup> J. P. Guthrie and Y. Ueda, *Fed. Proc.*, 1973, **32**, 628.

<sup>36</sup> J. P. Guthrie and Y. Ueda, *J.C.S. Chem. Comm.*, 1974, 111.

<sup>37</sup> J. A. Waters, C. R. Creveling, and B. Witkop, *J. Medicin. Chem.*, 1974, **17**, 488.

## 1 Solanum Alkaloids

Discrepancies<sup>1</sup> in the n.m.r. assignments of 23-hydroxylated 22,26-epiminocholestanes<sup>2,3</sup> have led investigators to undertake an X-ray analysis of one of them.<sup>1</sup> This compound is now thought to have the structure (1), a correction of the assigned stereochemistry at C-23 having been required by the results. This leads to a change in the stereochemistry at C-23 for the base previously designated 22S:23R:25S.



The hydroxy-group absorption in the i.r. spectra of 16-hydroxylated 22,26-epiminocholestanes has been examined.<sup>4</sup> Absorption maxima consistent with seven-membered-ring hydrogen bonding between the amino-function and hydroxy-group at C-16 was observed for both the 16 $\alpha$ - and 16 $\beta$ -series. The i.r. absorptions of several acetylated derivatives were also studied.

Following upon closely related earlier work,<sup>5</sup> it has been found<sup>6</sup> that photolysis of the *N*-chloroamine (3) leads to loss of the piperidine ring as 5-methyl- $\Delta^1$ -piperidine and formation of the C-20 diastereoisomeric derivatives (4).

<sup>1</sup> E. Höhne, I. Seidel, G. Reck, H. Ripperger, and K. Schreiber, *Tetrahedron*, 1973, **29**, 3065.

<sup>2</sup> H. Ripperger and K. Schreiber, *Chem. Ber.*, 1969, **102**, 4080.

<sup>3</sup> R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3, p. 287.

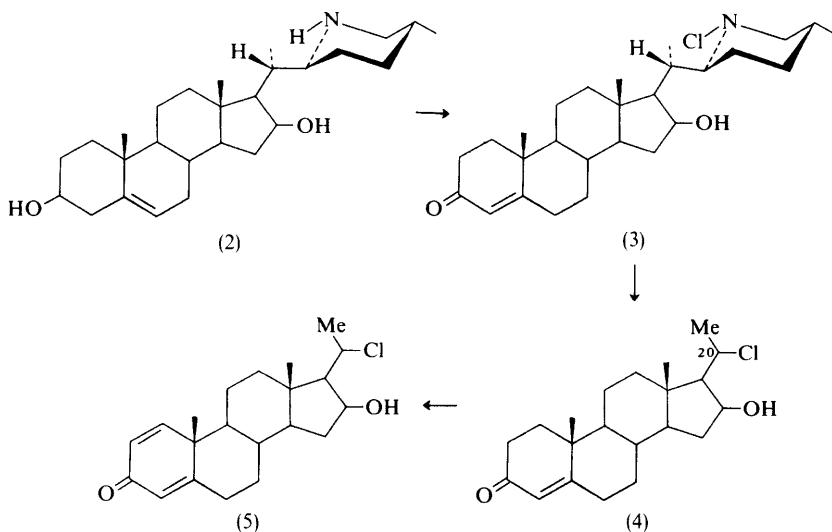
<sup>4</sup> G. Adam, D. Voigt, and K. Schreiber, *Z. Chem.*, 1974, **14**, 96.

<sup>5</sup> G. Adam and K. Schreiber, *Tetrahedron*, 1966, **22**, 3581; G. Adam, *Chem. Ber.*, 1968, **101**, 1.

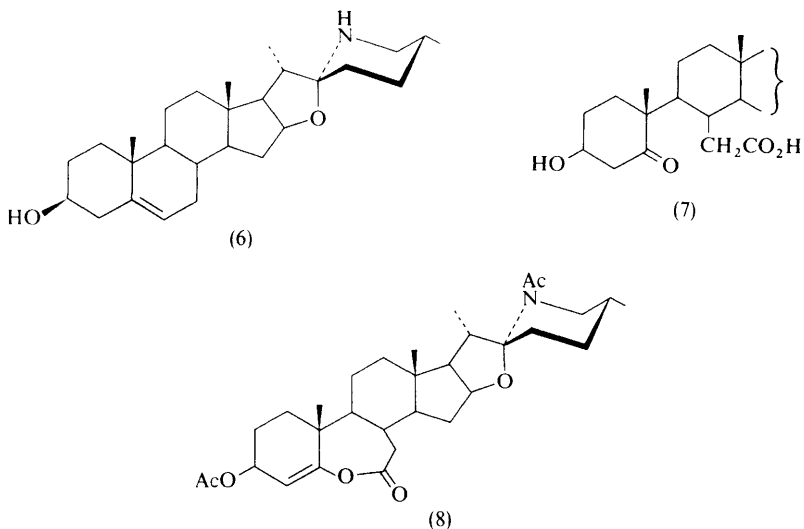
<sup>6</sup> G. Adam and K. Schreiber, *Annalen*, 1973, 2048.



Dehydrogenation of (4) with DDQ afforded (5). The starting *N*-chloroamine (3) was readily obtained from (2) by partial Oppenauer oxidation and subsequent *N*-chlorination.

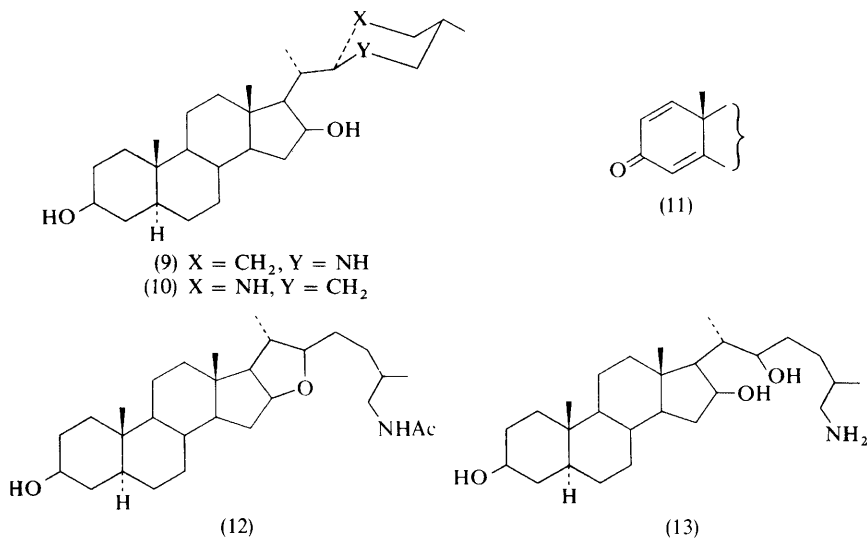


Oxidation of solasodine (6) with oxygen has given the keto-acid (7), which was lactonized by heating in acetyl chloride-acetic anhydride, to yield (8).<sup>7</sup>

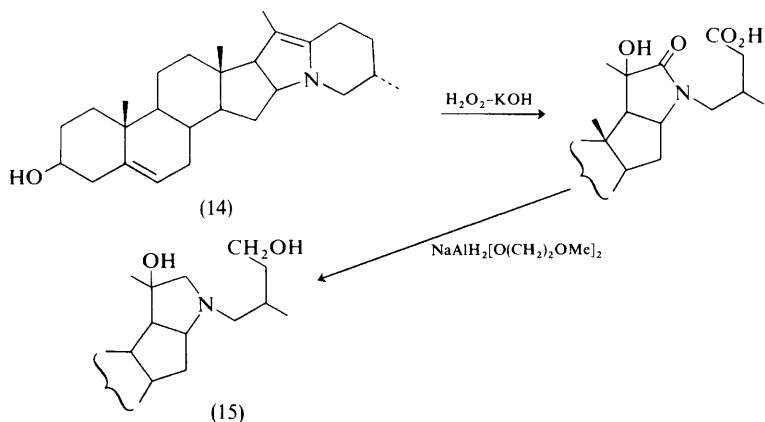


<sup>7</sup> G. N. Romachenko, M. P. Irismetov, and M. I. Goryaev, *Izvest. Akad. Nauk. Kazakh. S.S.R., Ser. khim.*, 1973, **23**, 76 (*Chem. Abs.*, 1974, **82**, 3708).

The bases (9) and (10) have been found to be dehydrogenated in ring A by the micro-organism *Nocardia restrictus* to give (11).<sup>8</sup> A similar dienone was obtained from (12) but only in low yield. No further degradation of any of the dienones was observed. Instead of dienone derivatives, (13) yielded the simple *N*-acetyl derivative.



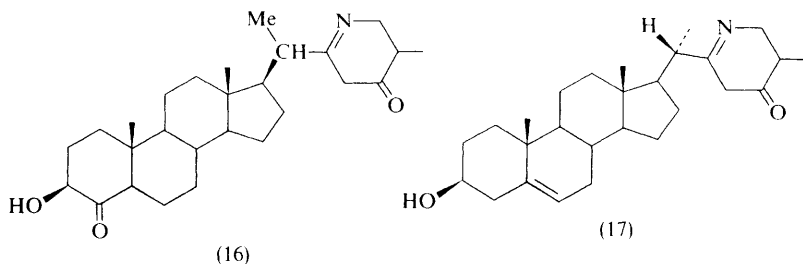
Treatment of (14) with alkaline hydrogen peroxide and subsequent reduction of the acidic product gave (15).<sup>9</sup> The 5,6-dihydro-derivative of (14) afforded an analogous product.



<sup>8</sup> I. Belič, V. Kramer, and H. Sočič, *J. Steroid Biochem.*, 1973, **4**, 363 (*Chem. Abs.*, 1973, **79**, 144 832).

<sup>9</sup> Oesterreichische Stickstoffwerke A.-G., B.P., 1973, 1 311 307 (*Chem. Abs.*, 1973, **79**, 18 954).

Solamaladine, which was isolated from the green fruits of *Solanum hypomalacophyllum*, has been assigned<sup>10</sup> the structure (16) by analysis of its mass, n.m.r., and i.r. spectra and the i.r. and u.v. spectra of its mono- and di-acetyl derivatives. Comparison of the mass spectral data of solamaladine with those of tomatillidine (17) and the n.m.r. spectrum with that of dihydrotomatillidine provided confirmation of the assigned structure.



Three solanaceous plants that grow in the Cuyo region of Argentina have been found to contain *Solanum* alkaloids: solasodine was isolated from *S. euacanthum* and the fruits of *S. juvenale*, and solasodiene from *S. euacanthum* and *S. pyretrofolium*.<sup>11</sup> Solasodine has been found in *S. eleagnifolium*<sup>12</sup> and isolated<sup>13</sup> from the acid-hydrolysed extracts of mature fruits of *S. platanifolium* in a yield of nearly 2%. This alkaloid and other nonglycosidic alkaloids, which were not identified, have been found in *S. nigrum* berries.<sup>14</sup> A colorimetric method has been developed for the determination of solasodine and total glyco-alkaloids in *S. laciniatum*.<sup>15</sup>

The glyco-alkaloids solamargine and solasonine have been identified at different stages of growth in *S. laciniatum*, with the synthesis of the former predominating at the early stages of leaf development and synthesis of solasonine during the later stages of growth.<sup>16</sup> Solamargine has been identified chromatographically in extracts of the green fruits of *S. eleagnifolium* and the aerial portions of *S. pyretrofolium*, *S. euacanthum*, and *S. lorentzii*.<sup>17</sup> Solasonine has also been found in *S. lorentzii*,<sup>17</sup> and together with solamargine and solanine in the unripe fruits of *S. arundo*.<sup>18</sup> Solamargine, solasonine, and an alkaloid that gave solasodine on hydrolysis, have been isolated from *S. pseudomeum*.<sup>19</sup>

<sup>10</sup> A. Usubillaga, *Rev. Latinoamer. Quim.*, 1973, **4**, 32 (*Chem. Abs.*, 1973, **79**, 123 632).

<sup>11</sup> O. S. Giordano, J. Kavka, J. C. Gianello, and A. T. D'Arcangelo, *Anales Asoc. quim. argentina*, 1973, **61**, 47 (*Chem. Abs.*, 1973, **79**, 75 849).

<sup>12</sup> B. L. Kaul and U. Zutshi, *Indian J. Pharm.*, 1973, **35**, 94.

<sup>13</sup> J. K. Bhatnagar and R. K. Puri, *Lloydia*, 1974, **37**, 318.

<sup>14</sup> B. Bose, C. Ghosh, and D. Roy, *J. Inst. Chemists (India)*, 1972, **44**, 181 (*Chem. Abs.*, 1973, **79**, 123 608).

<sup>15</sup> K. Drost, M. Drozdzyńska, Z. Kowalewski, B. Ostrowska, and P. Zurawski, *Herba Polonica*, 1973, **19**, 5 (*Chem. Abs.*, 1973, **79**, 102 738).

<sup>16</sup> M. A. Moursi and S. S. Ahmed, *Pharmazie*, 1973, **28**, 62.

<sup>17</sup> J. Kavka, E. Guerreiro, J. C. Gianello, O. S. Giordano, and A. T. D'Arcangelo, *Anales de Quim.*, 1973, **69**, 929 (*Chem. Abs.*, 1974, **80**, 24 793).

<sup>18</sup> M. Saleh, *Planta Med.*, 1973, **23**, 377.

<sup>19</sup> M. Saleh and S. S. Ahmed, *Qual. Plant. Mater. Veg.*, 1973, **22**, 133 (*Chem. Abs.*, 1973, **79**, 39 992).

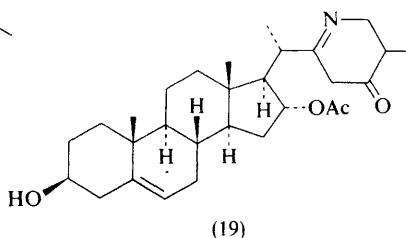
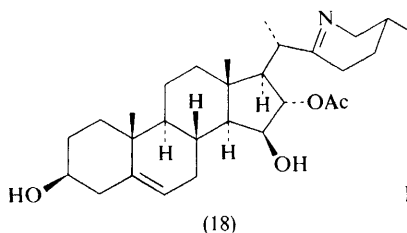
Two tomatidenol glycosides  $\alpha$ - and  $\beta$ -solamarine have been isolated<sup>20</sup> as major glyco-alkaloids from the leaves and aged tuber slices of *S. tuberosum* L. var. Kennebec in addition to the alkaloids  $\alpha$ -solanine and  $\alpha$ -chaconine, usually found as major components of potatoes.<sup>21</sup>

Extraction<sup>22</sup> of *S. ecuadorensis* berries afforded solaphyllidine<sup>23</sup> and a new alkaloid, deacetylsolaphyllidine. Acetylation of each gave an identical tetraacetate. The same tetraol was obtained by lithium aluminium hydride reduction of solaphyllidine and catalytic hydrogenation of deacetylsolaphyllidine.

The glyco-alkaloid  $\alpha$ -tomatine has been the subject of a detailed review, which covers chemical, biochemical, and biological aspects.<sup>24</sup> The synthesis and biogenesis of steroidal *Solanum* alkaloids has also been reviewed.<sup>25</sup>

## 2 *Veratrum* Alkaloids

The alkaloid constituents of *Veratrum lobelianum* have been the subject of continuing close scrutiny.<sup>26-29</sup> Veralosidinine and veralodisine have recently been isolated from this plant and have been assigned the structures (18)<sup>28</sup> and (19),<sup>29</sup> respectively.



Zygacine and zygadenine have been identified as the most abundant alkaloids of *Zygadenus gramineus*.<sup>30</sup>

Further confirmation for the structures assigned to germerine (20) and germitrine (21)<sup>31</sup> has been adduced from the observation that sodium

<sup>20</sup> M.-J. Shih and J. Kuć, *Phytochemistry*, 1974, **13**, 997.

<sup>21</sup> R. Kuhn and I. Löw, *Angew. Chem.*, 1954, **66**, 639; R. Kuhn, I. Löw, and H. Trischmann, *Chem. Ber.*, 1955, **88**, 1492.

<sup>22</sup> A. Usabillaga, A. Paredes, P. Martinod, and J. Hidalgo, *Planta Med.*, 1973, **23**, 286.

<sup>23</sup> A. Usabillaga, C. Seelkopf, I. L. Karle, J. W. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, 1970, **92**, 700; R. B. Herbert, in ref. 3, pp. 287, 288.

<sup>24</sup> J. G. Roddick, *Phytochemistry*, 1974, **13**, 9.

<sup>25</sup> K. Schreiber, *Biochem. Soc. Trans.*, 1974, **2**, 1.

<sup>26</sup> R. B. Herbert, in ref. 3, p. 294; and references cited therein.

<sup>27</sup> R. B. Herbert, in 'The Alkaloids' ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4, p. 391; and references cited therein.

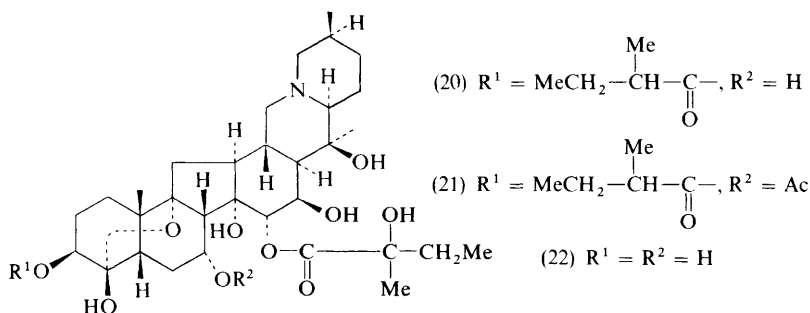
<sup>28</sup> R. Shakirov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 501 (*Chem. Abs.*, 1974, **80**, 60 078).

<sup>29</sup> R. Shakirov, A. M. Kashimov, K. Samikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, 44 (*Chem. Abs.*, 1974, **80**, 121 205).

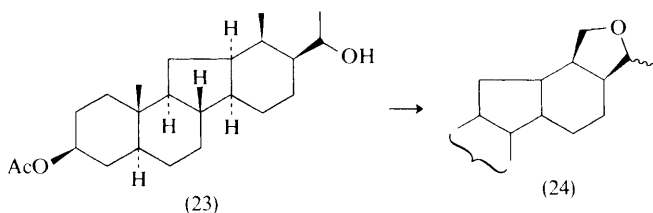
<sup>30</sup> T. J. Gilbertson, *Phytochemistry*, 1973, **12**, 2079.

<sup>31</sup> S. M. Kupchan and A. W. By, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1968, Vol. 10, p. 193.

borohydride reduction of both germerine and germitrine gave germine 15-[(-)-2-methylbutyrate] (22).<sup>32</sup>



In earlier work it has been found that the C-18 methyl group of the c-nor-D-homo-steroid (23) could be functionalized by photolysis in the presence of iodine, lead tetra-acetate, and sodium carbonate, when (24) was produced.<sup>33</sup> The usefulness of the hypiodite reaction<sup>34</sup> for the derivatization of c-nor-D-homo-steroids



has been explored<sup>35</sup> with the base (26), which was obtained by catalytic reduction of (25).

Photolysis of (26) in the presence of iodine and mercuric oxide gave a large amount of the expected aldehyde (27)<sup>36</sup> and a low yield of the product (28) obtained by hydrogen abstraction from C-17.<sup>35</sup> The structure of this product was established from its <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra. Direct comparison with (31), prepared by catalytic reduction of *O,N*-diacetyljervine (29), showed that (28) and (31) were not identical, and so the oxygen at C-17 of (28) has the  $\alpha$ -orientation. This configurational difference between (28) and (31) affects their reaction towards base, for whilst (31) suffers inversion of configuration at C-12, under basic conditions (28) does not.

c-Nor-D-homo-steroids with a 3-hydroxy- $\Delta^5$  system undergo the hypiodite reaction with the formation of modified ring A products. Thus photolysis of

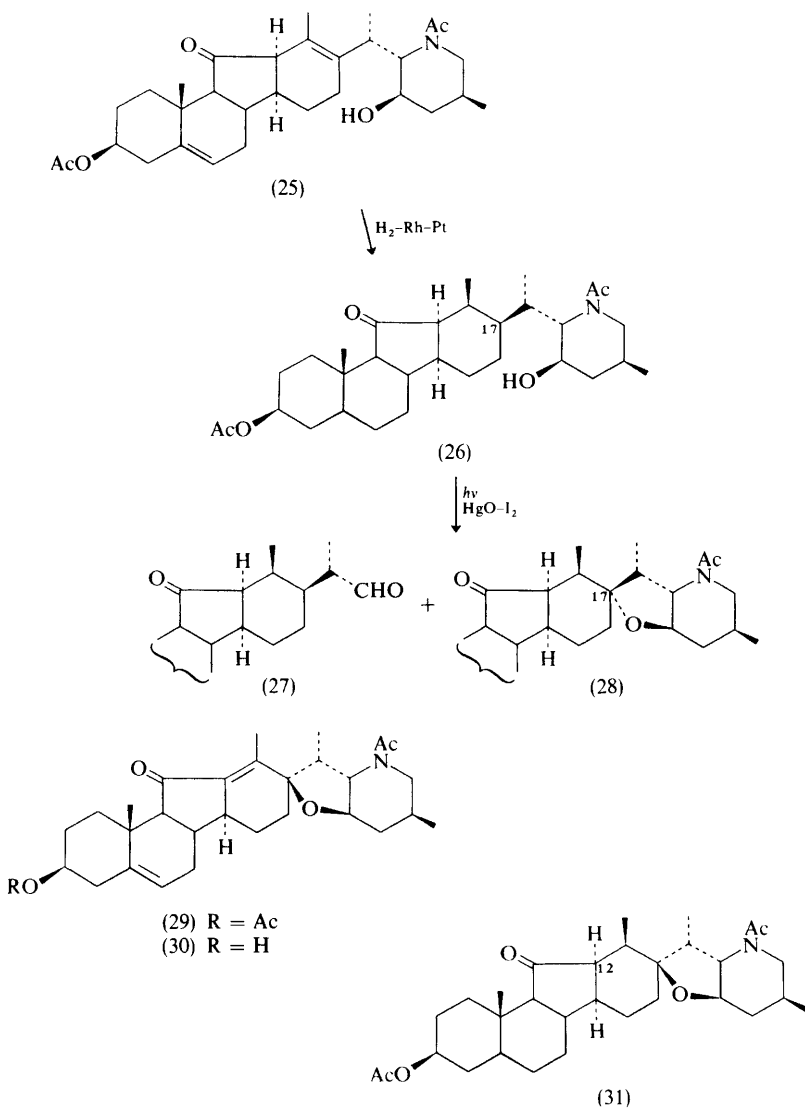
<sup>32</sup> N. V. Bondarenko, *Khim. prirod. Soedinenii*, 1973, 54 (*Chem. Abs.*, 1973, **79**, 5 477).

<sup>33</sup> H. Sugimoto, N. Sato, and T. Masamune, *Tetrahedron Letters*, 1969, 2671.

<sup>34</sup> For a review see: J. Kalvoda and K. Heusler, *Synthesis*, 1971, 501.

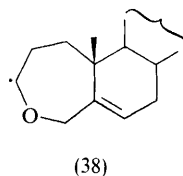
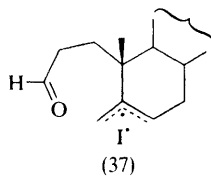
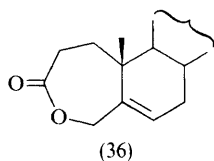
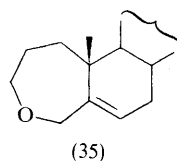
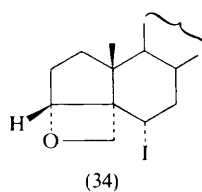
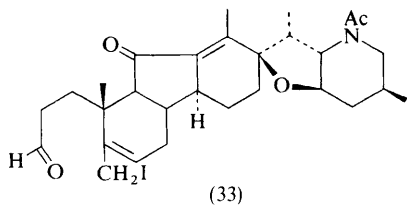
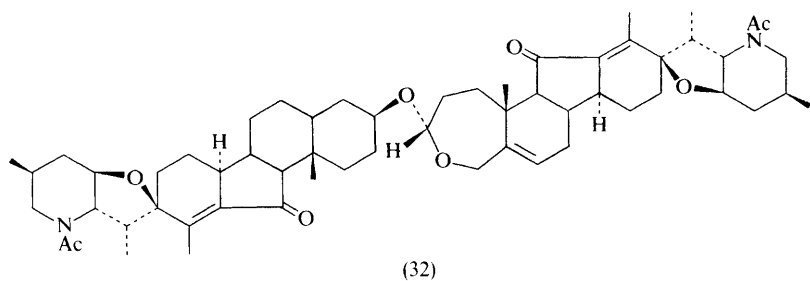
<sup>35</sup> H. Sugimoto, H. Ono, M. Kuramoto, and T. Masamune, *Tetrahedron Letters*, 1973, 4147.

<sup>36</sup> H. Sugimoto, H. Umeda, and T. Masamune, *Tetrahedron Letters*, 1970, 4571; R. B. Herbert in ref. 3, p. 297.

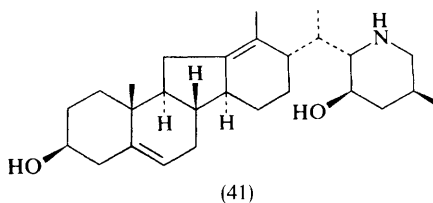
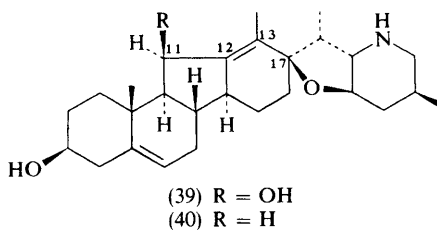


*N*-acetyljervine (30) in the presence of iodine and mercuric oxide gives five compounds: (32), (33), (34), (35), and (36), of which (32) is the major component.<sup>37</sup> The products can all be accounted for in terms of the intermediacy of (37), which could give (33) directly. For the other products (38) seems a likely further intermediate.

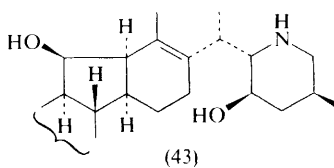
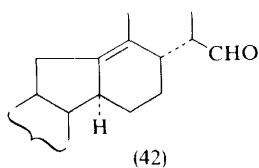
<sup>37</sup> H. Suginome, K. Kato, and T. Masamune, *Tetrahedron Letters*, 1974, 1161; *ibid.*, p. 1165.



In contrast to the formation here of oxepan derivatives, compounds with the normal steroid nucleus afford only compounds of the type (33) and (34).<sup>38</sup> In part, at least, the formation of oxepans from (30) must be attributed to conformational differences imposed on the intermediates by a five-membered ring C.<sup>37</sup>



<sup>38</sup> H. Suginome and K. Kato, *Tetrahedron Letters*, 1973, 4139.



Lithium-amine reduction of the jervine derivatives (39) and (40) gives (41) as the major product in each case.<sup>39</sup> Uncertainty about the configuration at C-17 has been resolved following degradation *via* the aldehyde (42) to compounds of known configuration.<sup>40</sup> Re-examination of the reduction products of (39) has led to the isolation of several compounds in addition to the previously reported pair, (41) and (43).<sup>40</sup> They arise formally by combinations of the following: cleavage of the C-17-oxygen bond, double-bond migration ( $\Delta^{13(17)}$  or  $\Delta^{11}$ ) or saturation, and hydrogenolysis of the C-11 hydroxy-group. It appears that the pattern of reduction of both (39) and (40) is that (*a*) introduction of hydrogen at C-17 is on the  $\beta$ -face of the molecule, and (*b*) hydrogen at C-12 has the  $\alpha$ -configuration in  $\Delta^{13,17}$  products and the  $\beta$ -orientation when the double bond is saturated.

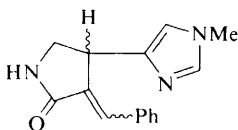
<sup>39</sup> T. Masamune, K. Kobayashi, M. Takasugi, Y. Mori, and A. Murai, *Tetrahedron*, 1968, **24**, 3461.

<sup>40</sup> A. Murai, K. Arita, and T. Masamune, *Bull. Chem. Soc. Japan*, 1973, **46**, 3536.

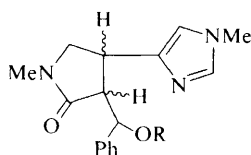




The leaves of *Cynometra anata* have yielded the structurally interesting new alkaloids anatanine (5), cynometriner (6; R = H), and cynodine (6; R = COPh), whose structures were deduced on the basis of spectral and chemical evidence.<sup>3</sup> The stereochemistry embodied in the 2-pyrrolidone ring, and the geometry about the double bond in (5), remain to be elucidated.



(5)



(6)

An earlier report by Bernauer<sup>4</sup> regarding the interesting synthesis of ( $\pm$ )-pilosinine [( $\pm$ )-(10)] (Scheme 2) and the determination of the absolute configuration of the alkaloids (+)-pilosinine (10) and (+)-isopilosinine was inadvertently overlooked by this Reporter. The readily available ester (7) was converted in two steps into the aldehyde (8), which upon Stobbe condensation with succinic ester gave the expected half-ester acid salt (9). Lithium borohydride reduction followed by prolonged acid treatment gave ( $\pm$ )-pilosinine [( $\pm$ )-(10)] together with 2,3-dehydropilosinine. Resolution with (–)-di-O, O'-*p*-toluoyl-L-tartaric acid provided (+)-pilosinine (10), which condensed with ethyl acetate in the presence of base to give the 2-acetyl derivative (11), whose thermodynamically more stable 2,3-*trans* stereochemistry was confirmed by n.m.r. spectroscopy. Successive catalytic reduction and acetylation at elevated temperature led to (12) as a mixture of geometrical isomers, which upon further catalytic reduction produced (+)-pilocarpine (13a) and (+)-isopilocarpine (13b) in a ratio of 93 : 7 (g.c. analysis). Since the absolute stereochemistry of (+)-pilocarpine is known as being that depicted in (13a), the above sequence established the (3*R*) absolute configuration of the alkaloid (+)-pilosinine, as shown in (10). Furthermore, (+)-pilosinine was converted into the alkaloid (+)-isopilosine (14a) and (–)-epi-isopilosine (14b). Since (+)-pilosinine (10) can be obtained by retroaldolization of (+)-isopilosine (14a), the latter alkaloid must also possess the (3*R*) absolute configuration. Confirmation of this fact as well as assignment of the (2*S*, 3*R*, 6*R*) absolute configuration of (+)-isopilosine (14a) was achieved by X-ray analysis.<sup>5</sup> It follows that (–)-epi-isopilosine (14b) possesses the (2*S*, 3*R*, 6*S*) absolute configuration. Recently, it has been shown that (–)-epi-isopilosine is, in fact, an alkaloid elaborated by *Pilocarpus microphyllus*.<sup>6</sup>

The correctness of the absolute stereoformulae for (+)-isopilosine (14a), (–)-epi-isopilosine (14b), and (+)-pilosine (15) [a further *Pilocarpus* alkaloid, whose (2*R*, 3*R*, 6*R*) absolute configuration also rests on the above work<sup>4</sup>] has

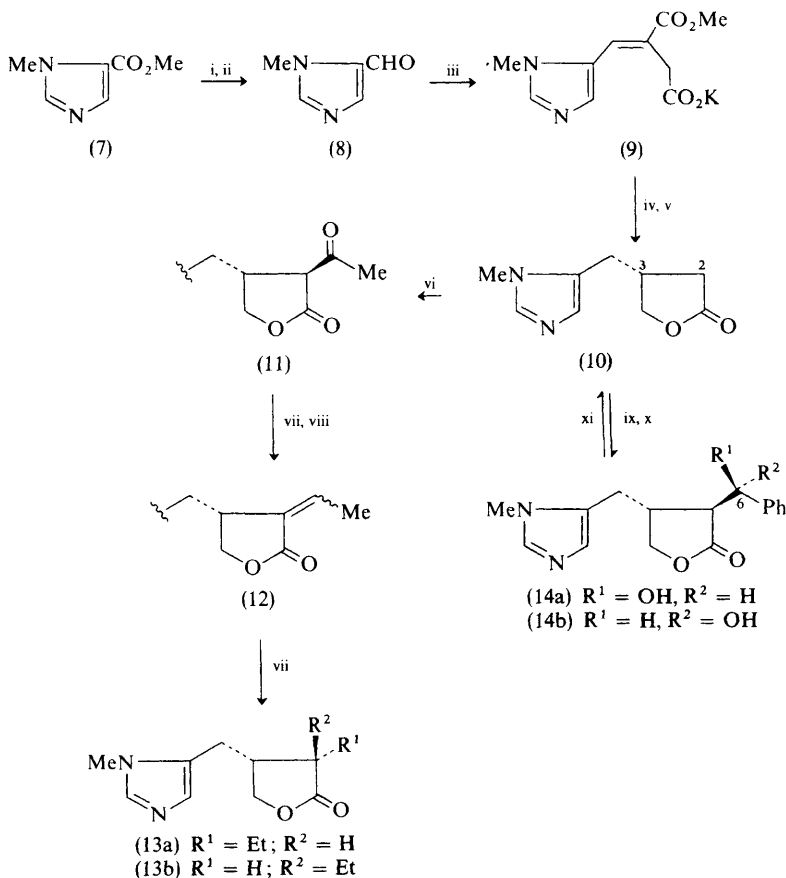
<sup>3</sup> F. Khuong Huu, H. Monseur, G. Ratle, G. Lukacs, and R. Goutarel, *Tetrahedron Letters*, 1973, 1757.

<sup>4</sup> H. Link and K. Bernauer, *Helv. Chim. Acta*, 1972, **55**, 1053.

<sup>5</sup> W. E. Oberhänsli, *Cryst. Struct. Comm.*, 1972, **1**, 203.

<sup>6</sup> W. Loewe and K. H. Pook, *Annalen*, 1973, **9**, 1476.

been questioned by Sarel and co-workers.<sup>7</sup> These workers proposed structures epimeric at C-6 for these alkaloids on the basis of comparison of their c.d. spectra with those of aromatic amino-acids of known absolute configuration. It had been previously shown that the sign of the low-wavelength phenyl transition ( $^1L_a$ ) at *ca.* 220 nm is positive for aromatic amino-acids with (*S*) configuration. Since both (15) and (14a) exhibit positive dichroic bands in the low-wavelength region, Sarel and co-workers *tentatively*, and in the absence of the chemical correlation discussed above (Scheme 2), assigned the (6*S*) configurations to these alkaloids

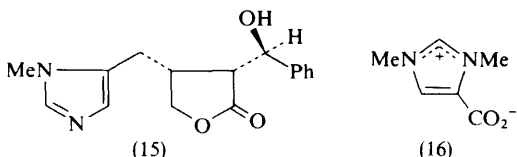


Reagents: i,  $AlBu_2H$ , THF; ii,  $MnO_2$ ; iii,  $KOBu^t$ ,  $(CH_2CO_2Et)_2$ ; iv,  $LiBH_4$ , DME; v, HCl; vi,  $KOBu^t$ ,  $MeCO_2Et$ ; vii,  $H_2$ ,  $PtO_2$ , MeOH; viii,  $Ac_2O$ , HOAc; ix,  $KOBu^t$ ,  $PhCO_2Me$ ; x,  $H_2$ , Pt, EtOH; xi,  $OH^-$

### Scheme 2

<sup>7</sup> E. Tedeschi, J. Kamionsky, D. Zeider, S. Fackler, S. Sarel, V. Usieli, and J. Deutsch, *J. Org. Chem.*, 1974, **39**, 1864.

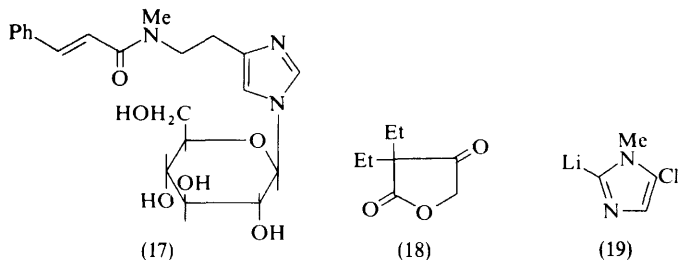
and the (6*R*) configuration to (–)-epi-isopilosine (14b). Bernauer has correctly pointed out (a) the inappropriateness of comparison of the C-6 chiral centre of the alkaloids with the corresponding C-2 centre of aromatic amino-acids (e.g., *S*-2-phenylglycine) with regard to c.d. spectra, and (b) the fact that application of the 'aromatic amino-acid chirality rule' is a treacherous undertaking even in that particular class of compounds.<sup>8</sup> In view of the chemical correlation<sup>4</sup> and X-ray<sup>5</sup> information discussed above, it is clear that the absolute structures (14a), (14b), and (15) assigned to (+)-isopilosine, (–)-epi-isopilosine, and (+)-pilosine, respectively, by Bernauer<sup>4</sup> are correct.



Pilosine, which was originally isolated from *Pilocarpus microphyllus* and *P. jaborandi*, has been shown to be a 1 : 1 molecular compound composed of (+)-pilosine (15) and (+)-isopilosine (14a).<sup>6,7</sup> The mass spectra of (14a), (14b), and (15) have been studied.<sup>7</sup> This report also describes a detailed investigation of the aldol condensation between pilosinine (10) and benzaldehyde and its 2- and 4-fluoro-derivatives.<sup>7</sup>

The betaine norzooanemonin (16) has been isolated from the marine organism *Pseudopterogorgia americana*.<sup>9</sup>

The total synthesis of casimiroedine (17), isolated from *Casimiroa edulis*, has been achieved.<sup>10</sup> The synthesis also establishes the *trans*-cinnamamide stereochemistry, a point which had remained unresolved in the original structural elucidation study. The reaction of the keto-lactone (18) with the imidazolyl-lithium (19) generated *in situ* yields a number of products,<sup>11–14</sup> the major ones being the pilocarpine-related (20)<sup>11</sup> and the ditetrahydrofuran (21).<sup>13</sup> Treatment



<sup>8</sup> H. Link, K. Bernauer, and W. E. Oberhänsli, *Helv. Chim. Acta*, 1974, **57**, 2199.

<sup>9</sup> A. J. Weinheimer, E. K. Metzner, and M. L. Mole, jun., *Tetrahedron*, 1973, **29**, 3125.

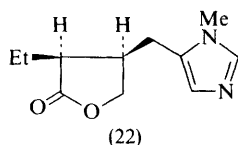
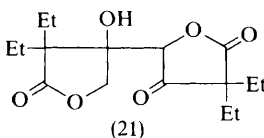
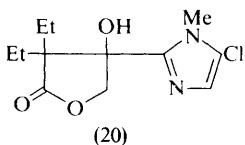
<sup>10</sup> R. P. Panzica and L. B. Townsend, *J. Amer. Chem. Soc.*, 1973, **95**, 8737.

<sup>11</sup> W. Doepke and U. Muecke, *Z. Chem.*, 1973, **13**, 177.

<sup>12</sup> W. Doepke and U. Muecke, *Z. Chem.*, 1973, **13**, 217.

<sup>13</sup> W. Doepke and U. Muecke, *Z. Chem.*, 1973, **13**, 255.

<sup>14</sup> W. Doepke and U. Muecke, *Z. Chem.*, 1973, **13**, 297.



of pilocarpine (22) with a number of primary amines leads to amide alcohols or lactams depending on the conditions of the reaction.<sup>15</sup> The synthesis of new histamine analogues has been described.<sup>16,17</sup>

A number of new methodological developments in the analysis and purification of pilocarpine (22) hydrochloride have been published.<sup>18–21</sup> A microcrystallographic determination of imidazole derivatives using antimony acid complexes has been studied.<sup>22</sup>

Imidazolyethylamines have been shown to inhibit histamine uptake by blood platelets.<sup>23</sup>

### 3 Purine Alkaloids

Reviews concerned with synthesis and reactions of purine derivatives may be of general interest.<sup>24,25</sup>

A new synthesis of *trans*-4-amino-1-hydroxy-2-methylbut-2-ene, an intermediate in the preparation of *trans*-zeatin (see Vol. 4 of these Reports) has been developed.<sup>26</sup> A large number of 7-substituted theophylline derivatives (23a–i) have been synthesized by conventional steps as a result of observed pharmacological activity of this type of compound.<sup>27–33</sup> For example, various 7-amino-

<sup>15</sup> R. T. Koda, F. J. Dea, K. Fung, C. Elison, and J. A. Biles, *J. Pharm. Sci.*, 1973, **62**, 2021.

<sup>16</sup> W. Schunack, *Arch. Pharm. (Weinheim)*, 1973, **306**, 934.

<sup>17</sup> W. Schunack, *Arch. Pharm. (Weinheim)*, 1974, **307**, 517.

<sup>18</sup> L. Jusiak, *Acta Polon. Pharm.*, 1973, **30**, 49 (*Chem. Abs.*, 1973, **79**, 18 905q).

<sup>19</sup> J. Jarzebinski, Z. Zakrzewski, and B. Nowiszewska-Jasinska, *Acta Polon. Pharm.*, 1973, **30**, 485 (*Chem. Abs.*, 1974, **81**, 6291q).

<sup>20</sup> J. Jarzebinski, *Farm. Pol.*, 1973, **29**, 1107 (*Chem. Abs.*, 1974, **81**, 41 383t).

<sup>21</sup> T. Bican-Fister, B. Pavelic, and J. Merkas, *Acta Pharm. Jugoslav.*, 1973, **23**, 17 (*Chem. Abs.*, 1973, **79**, 9946b).

<sup>22</sup> T. P. Churina, *Fiz.-Khim. Probl. Sovrem. Biol. Med. Mater. Konf.*, 1970, 216 (*Chem. Abs.*, 1974, **80**, 7004q).

<sup>23</sup> J. Tuomisto, E. J. Walaszek, and T. L. Pazdernik, *Ann. Med. Exp. Biol. Fenn.*, 1973, **51**, 59.

<sup>24</sup> J. H. Lister and J. Kiburis, *Jerusalem Symp. Quantum Chem. Biochem.*, 1972, **4**, 504.

<sup>25</sup> E. S. Golovchinskaya, *Uspekhi Khim.*, 1973, **42**, 941 (*Chem. Abs.*, 1973, **79**, 53 263a).

<sup>26</sup> M. Ohsugi, S. Takahashi, I. Ichimoto, and H. Ueda, *Nippon Nokei Kagaku Kaishi*, 1973, **47**, 807 (*Chem. Abs.*, 1974, **81**, 3280z).

<sup>27</sup> A. Lespagnol, M. Debaert, A. Blears, M. Devergnies, J. C. Cazin, and M. Cazin, *Ann. pharm. franc.*, 1973, **31**, 751.

<sup>28</sup> K. Harsanyi, R. Szebeni, and D. Korbonits, *Acta Pharm. Hung.*, 1973, **43**, 235 (*Chem. Abs.*, 1974, **80**, 37 074e).

<sup>29</sup> M. Miyata, K. Kondo, and K. Takemoto, *Technol. Reports Osaka Univ.*, 1973, **23**, 339 (*Chem. Abs.*, 1974, **80**, 27 210g).

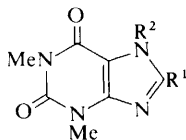
<sup>30</sup> R. Szebeni, K. Harsanyi, and D. Korbonits, *Acta Chim. Acad. Sci. Hung.*, 1973, **77**, 427 (*Chem. Abs.*, 1973, **79**, 137 093h).

<sup>31</sup> I. M. Roushdi, E. A. Ibrahim, S. M. Rida, and F. Ashour, *Pharmazie*, 1973, **28**, 300.

<sup>32</sup> A. Rybar and L. Stibranyi, *Coll. Czech. Chem. Comm.*, 1973, **38**, 1571.

<sup>33</sup> A. Lespagnol, Ch. Lespagnol, A. Lefebvre, A. Martine, J. C. Cazin, and M. Cazin, *Bull. Soc. Pharm. Lille*, 1972, 171 (*Chem. Abs.*, 1973, **79**, 126 442v).

ethyltheophyllines (23a) have been shown to possess spasmolytic activity similar to papaverine,<sup>27</sup> while (23b) has been tested as a potential new antiatherosclerosis agent.<sup>28</sup> Some 8-substituted theophyllines (23g) show sedative action.<sup>33</sup> The 8-aminomethyl-xanthines (23h) produce hypotensive effects in cats.<sup>34</sup> A number of potentially antituberculous caffeine derivatives (23i) have been prepared.<sup>35</sup> Uric acid derivatives have been converted into xanthines by treatment with formic acid and trimethylamine.<sup>36</sup>



23(a)  $R^1 = H$ ;  $R^2 = CH_2CH_2NR_2$  (ref. 27)

(b)  $R^1 = H$ ;  $R^2 = CH_2CH(OH)CH_2NH^+(Me)CH_2CH_2OH$ ;  
 $p-ClC_6H_4OCMe_2CO_2^-$  (ref. 28)

(c)  $R^1 = H$ ;  $R^2 = CH_2CH_2CH(NH_2)CO_2H$  (ref. 29)

(d)  $R^1 = H$ ;  $R^2 = (CH_2)_nNHCH_2CH_2COPh$  (ref. 30)

(e)  $R^1 = H$ ;  $R^2 = CH_2CONHR$  and  $CH(CONHR)_2$  (ref. 31)

(f)  $R^1 = H$  and alkyl;  $R^2 = (CH_2)_3NCS$  (ref. 32)

(g)  $R^1 = N(CH_2CH_2OR)_2$ ;  $R^2 = H$  (ref. 33)

(h)  $R^1 = CH_3NH_2$ ;  $R^2 = Me$  and  $PhCH_2$  (ref. 34)

(i)  $R^1 = CH_2CONHNHSO_2C_6H_4-p-R$ ;  $R^2 = Me$  (ref. 35)

The pyridinium ylide (24) is obtained from the reaction of 8-bromotheophylline with pyridine.<sup>37</sup> Alkylsulphonate salts of caffeine have been synthesized.<sup>38</sup> A new purine-into-pteridine ring transformation has been discovered.<sup>39</sup> For example, the quaternary salt (25) was obtained by direct alkylation of an appropriate xanthine with ethyl bromoacetate. Base-catalysed hydrolysis of (25) gave the pyrimidine (26), which could be cyclized to give the isoxanthopterin derivative (27).

Theobromine has been converted in three steps into 2,6,8-trichloro-7-methylpurine (28).<sup>40</sup> A safe and improved procedure for the preparation of 2-amino-6-chloropurine has been developed.<sup>41</sup> Treatment of 8-nitro-caffeine and -theophylline with liquid HF provides the corresponding 8-fluoro-derivatives.<sup>42</sup> The synthesis of the tritium-labelled kinetin (29) has been accomplished.<sup>43</sup>

<sup>34</sup> P. Nantka-Namirski, B. Jarynowicz, and J. Wojciechowski, *Acta Polon. Pharm.*, 1974, **31**, 5 (*Chem. Abs.*, 1974, **81**, 77 862n).

<sup>35</sup> H. M. Nour El-Din, M. Y. Ebeid, and F. A. El-Sayed Romeih, *Bull. Fac. Pharm., Cairo Univ.*, 1971, **10**, 61 (*Chem. Abs.*, 1973, **79**, 5306v).

<sup>36</sup> S. Takayama, F. Ashizawa, J. Suzuki, and M. Sekiya, *Chem. and Pharm. Bull. (Japan)*, 1974, **22**, 1200.

<sup>37</sup> A. Lespagnol and C. Van Aerde, *Compt. rend.*, 1974, **278**, C, 1145.

<sup>38</sup> I. Zeid, A. Saleh, and I. Ismail, *Chem. and Ind.*, 1973, 1001.

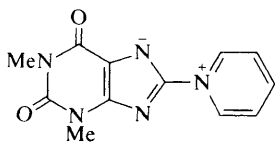
<sup>39</sup> K. Eistetter and W. Pfeiderer, *Chem. Ber.*, 1973, **106**, 1389.

<sup>40</sup> L. A. Gutorov and E. S. Golovchinskaya, *Khim. -Farm. Zhur.*, 1973, **7**, 6 (*Chem. Abs.*, 1973, **79**, 126 453z).

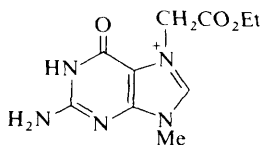
<sup>41</sup> W. A. Nasutavicus and J. Love, *J. Heterocyclic Chem.*, 1974, **11**, 77.

<sup>42</sup> S. R. Naik, J. T. Witkowski, and R. K. Robins, *J. Org. Chem.*, 1973, **38**, 4353.

<sup>43</sup> O. Buchman, D. Milstein, and M. Shimoni, *J. Labelled Compounds*, 1973, **9**, 7309.



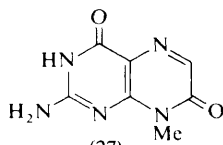
(24)



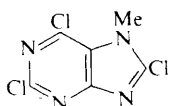
(25)



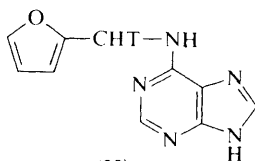
(26)



(27)



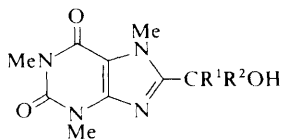
(28)



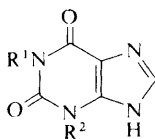
(29)

Continued interest is being expressed in the synthesis<sup>44</sup> and chemical properties<sup>45</sup> of thiopurine derivatives.

Peroxide-initiated photolysis of a variety of purines in the presence of alcohols yields corresponding 8-hydroxyalkyl derivatives, *e.g.* (30), in excellent yield.<sup>46</sup> Irradiation of 1-hydroxyxanthine (31;  $R^1 = OH$ ,  $R^2 = H$ ) with u.v. light gives mainly the photoreduction product, (31;  $R^1 = R^2 = H$ ) together with the rearranged 3-hydroxyxanthine (31;  $R^1 = H$ ,  $R^2 = OH$ ).<sup>47</sup> A mechanism involving oxaziridine intermediates is proposed for the photochemical rearrangement.



(30)



(31)

Specific thin-layer-chromatographic procedures for the separation of caffeine have been published.<sup>48-50</sup> One of these has been developed for the student

<sup>44</sup> R. J. Badger, D. J. Brown, and J. H. Lister, *J.C.S. Perkin I*, 1974, 152; R. J. Badger, D. J. Brown, and J. H. Lister, *ibid.*, 1973, 1906.

<sup>45</sup> U. Reichman, F. Bergmann, and D. Lichtenberg, *J.C.S. Perkin I*, 1973, 2647.

<sup>46</sup> J. Salomon and D. Elad, *J. Org. Chem.*, 1973, **38**, 3420.

<sup>47</sup> F. L. Lam, G. B. Brown, and J. C. Parham, *J. Org. Chem.*, 1974, **39**, 1391.

<sup>48</sup> D. W. Chasar and G. B. Toth, *J. Chem. Educ.*, 1974, **51**, 22.

<sup>49</sup> F. Conine and J. Paul, *Mikrochim. Acta*, 1974, 443.

<sup>50</sup> T. Okumura and T. Kadono, *J. Chromatog.*, 1973, **86**, 57.

laboratory.<sup>48</sup> Assays of caffeine using dialysis<sup>51</sup> and complexometric titration<sup>52</sup> have been studied. This complexometric method<sup>52</sup> as well as a different spectrophotometric method<sup>53</sup> have also been used for the determination of theobromine and theophylline. Theophylline has been analysed using non-aqueous potentiometry.<sup>54</sup> Finally, liquid chromatography of xanthines and coffee using a sulfonated polystyrene cation exchanger as a stationary phase has been reported.<sup>55</sup>

#### 4 *Securinega* Alkaloids

The first X-ray crystal structure determination of a *Securinega* free base has been reported.<sup>56</sup> Direct X-ray analysis of allosecurinine (phyllochrysine) shows that the molecule adopts a conformation in which the nitrogen lone pair is not directed towards the ring C double bond, as was previously suggested by spectral and chemical data.<sup>57</sup> The *cis* A/B ring conformation (32) was also previously shown for allosecurinine methiodide by X-ray analysis.<sup>57</sup>

The yellow colour of allosecurinine in solution [u.v. (max) 342 nm in hexane] as well as in the crystal suggests the presence of the transannular interaction between the nitrogen lone pair and the conjugated diene in both states. Interestingly, available chemical and physical (including X-ray) evidence supports the conformational representation (33) for securinine (diastereomeric with allosecurinine), and this alkaloid also exhibits the transannular interaction [u.v. (max) 328 nm in hexane].<sup>57</sup> On the basis of the results on securinine and allosecurinine, it may be conjectured that this interaction is independent of conformation. Further work is required: in particular, an X-ray structure determination of securinine as the free base would be welcome.

Amination of allosecurinine (32) and securinine (33) with *O*-mesitylenesulphonylhydroxylamine has been shown to give the *N*-amino-salts (34) and (37), respectively (Scheme 3).<sup>58</sup> The stereochemistry of (34) and (37) is assigned on the basis of the observed rearrangements of the corresponding ylides (35) and (38) into compounds (36) and (39), respectively. These reactions may be envisaged to proceed by a [2,3] sigmatropic shift mechanism. The stereochemistry of the amination reaction parallels that of the quaternization of the two alkaloids with methyl iodide.

<sup>51</sup> A. Affonso and D. M. Shingbal, *Canad. J. Pharm. Sci.*, 1973, **8**, 57.

<sup>52</sup> M. Gajewska, *Chem. analit.*, 1973, **18**, 313 (*Chem. Abs.*, 1973, **79**, 97 016b).

<sup>53</sup> F. E. Kagan and L. O. Kirichenko, *Farm. Zhur. (Kiev)*, 1973, **28**, 34 (*Chem. Abs.*, 1974 **80**, 100 245d).

<sup>54</sup> E. Galfalvi and V. Molnar, *Rev. Med. (Tirgu-Mures, Rom.)*, 1973, **19**, 147 (*Chem. Abs.*, 1974, **80**, 52 420h).

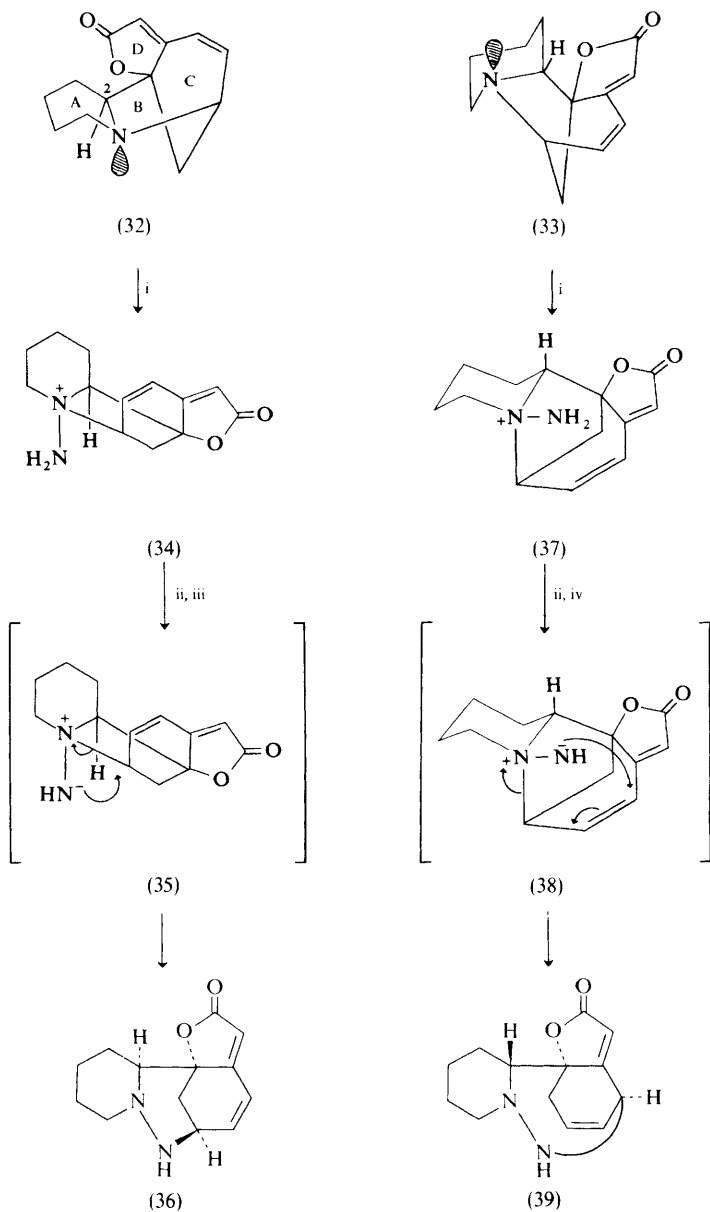
<sup>55</sup> E. Murgia, P. Richards, and H. F. Walton, *J. Chromatog.*, 1973, **87**, 523.

<sup>56</sup> C. Rich, *Acta Cryst.*, 1973, **B29**, 2147.

<sup>57</sup> V. Snieckus, in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1973, Vol. 14, p. 425.

<sup>58</sup> Y. Tamura, J. Minamikawa, Y. Kita, J. H. Kim, and M. Ikeda, *Tetrahedron*, 1973, **29**, 1063.





Reagents: i,  $\text{H}_2\text{NSO}_2\text{C}_6\text{H}_2\text{-2,4,6-Me}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; ii, IRA-410,  $\text{MeOH}$ ; iii,  $125\text{--}130^\circ\text{C}$ ; iv, room temp.

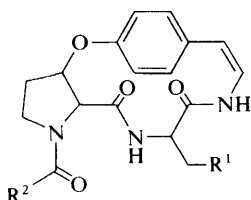
**Scheme 3**

## 5 Peptide Alkaloids

This section will also deal with *Lunaria* and spermidine alkaloids, since these are undoubtedly derived in part from amino-acids.

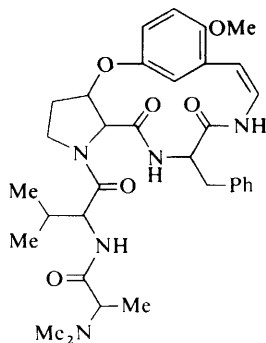
Biochemical reactions of toxic peptides obtained from *Amanita* species have been reviewed.<sup>59</sup>

In continuation of their chemical investigation of peptide alkaloids obtained from *Zizyphus amphibia* (see Vols. 3 and 4 of these Reports), Tschesche and co-workers have elucidated the structures of the new amphibines F (40), G (41), and H (42) by the established spectroscopic and degradative methods.<sup>60</sup> Amphibine I (43), an alkaloid of obvious mixed biogenesis, has been isolated from *Z. amphibia*.<sup>61</sup> Interestingly, the aporphine base (–)-nuciferine was also obtained from this species.

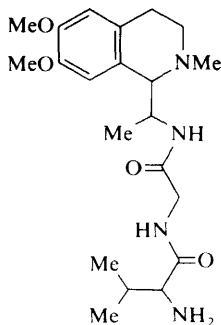


(40)  $R^1 = \text{Ph}$ ;  $R^2 = \text{CH}(\text{CHMeEt})\text{NHMe}$

(41)  $R^1 = \text{CHMe}_2$ ;  $R^2 = \text{CH}(\beta\text{-indolylmethyl})\text{NMe}_2$



(42)



(43)

Zizyphine, the major alkaloid from *Zizyphus oenopia*, for which a structure containing an unusual diketopiperazine unit had been proposed (see Vol. 1 of these Reports), has been shown to possess the more normal structure (44) on the basis of extensive spectral and degradative evidence.<sup>62</sup> The alkaloid has been

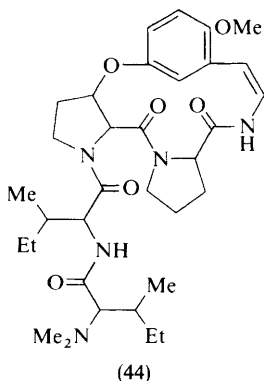
<sup>59</sup> T. Wieland and O. Wieland, in 'Microbial Toxins,' ed. S. Kadis, Academic Press, New York, 1972, Vol. 8, p. 249.

<sup>60</sup> R. Tschesche, C. Spilles, and G. Eckhardt, *Chem. Ber.*, 1974, **107**, 686.

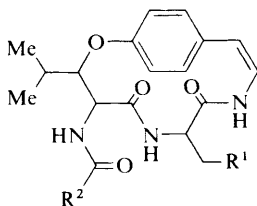
<sup>61</sup> R. Tschesche, C. Spilles, and G. Eckhardt, *Chem. Ber.*, 1974, **107**, 1329.

<sup>62</sup> R. Tschesche, E. U. Kaussmann, and G. Eckhardt, *Tetrahedron Letters*, 1973, 2577.

given the new name zizyphine A. The earlier structural assignment was partially based on the formation of a diketopiperazine derivative from the dry distillation of the alkaloid at 330 °C. This product can now be explained to have arisen from the combination of hydroxyproline with proline under these drastic reaction conditions. The structural reassignment (44) may prove of value to the structural elucidation of ziphinine, a minor alkaloid also isolated from *Z. oenoplia* (see Vol. 1 of these Reports).



*Hovenia dulcis* and *H. tomentella* have been shown to elaborate the new alkaloids hovenine A and hovenine B in addition to the known frangulanine.<sup>63</sup> Hovenine A has been shown to be *N*-desmethylfrangulanine (45) on the basis of chemical correlation with frangulanine. The structure of hovenine B has not been defined. Texensine, isolated from *Colubrina texensis*, has been assigned structure (46),



(45)  $R^1 = \text{CHMe}_2$ ;  $R^2 = \text{CH}(\text{NHMe})\text{CHMeEt}$

(46)  $R^1 = \beta\text{-indolyl}$ ;  $R^2 = \text{CH}(\text{NMe}_2)\text{CH}_2\text{CHMe}_2$

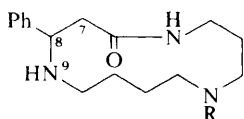
(47)  $R^1 = \beta\text{-indolyl}$ ;  $R^2 = \text{CH}(\text{NHMe})\text{CH}_2\text{CHMe}_2$

almost exclusively on the basis of mass spectral studies.<sup>64</sup> It appears that texensine is the *N*-methylated derivative of homoamericine (47), an alkaloid known only as a contaminant of americine (see Vol. 1 of these Reports) and not yet obtained in pure form.

<sup>63</sup> M. Takai, Y. Ogihara, and S. Shibata, *Phytochemistry*, 1973, **12**, 2985.

<sup>64</sup> M. C. Wani, H. L. Taylor, and M. E. Wall, *Tetrahedron Letters*, 1973, 4675.

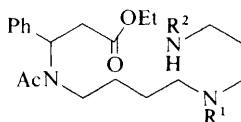
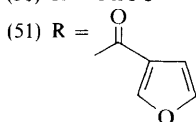
Celacinnine (48), isolated from *Maytenus arbutifolia* and *Tripterygium wilfordii*, is the first representative of a new macrocyclic alkaloid type.<sup>65</sup> Key evidence for the structure of celacinnine was obtained from its n.m.r. spectrum and acid hydrolysis. N.m.r. signals for the C-7 and C-8 protons in celacinnine and its *N*-acetyl derivative compared favourably with those of *N*-methyl- $\beta$ -phenyl- $\beta$ -alanine methyl ester and *N*-acetyl- $\beta$ -phenyl- $\beta$ -alanine methyl ester, respectively, and not with the corresponding  $\beta$ -phenyl- $\alpha$ -alanine derivatives. This comparison strongly suggested the  $\beta$ -amino-acid relationship and also established that N-9 did not carry the cinnamoyl unit. Mild acid hydrolysis of celacinnine followed by successive esterification and acetylation gave compound (52), whose mass spectrum showed characteristic  $\text{—N—(CH}_2\text{)}_3\text{—N—}$  spermidine fragmentation, thus supporting the attachment of the four-carbon end of the spermidine chain to the  $\beta$ -amino-function. The corresponding *cis*-cinnamamide celalocinnine (49) was also isolated from *Maytenus arbutifolia*, and the closely related alkaloids celabenzine (50) and celafurine (51) were obtained from *Tripterygium wilfordii*.<sup>65</sup>



(48) R = *trans*-PhCH=CHCO

(49) R = *cis*-PhCH=CHCO

(50) R = PhCO



(52) R<sup>1</sup>, R<sup>2</sup> = Ac, *trans*-PhCH=CHCO

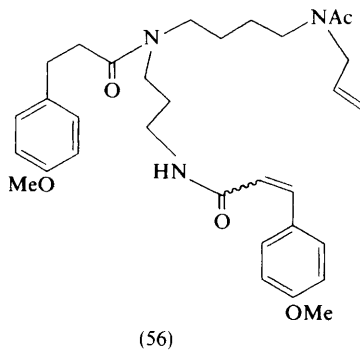
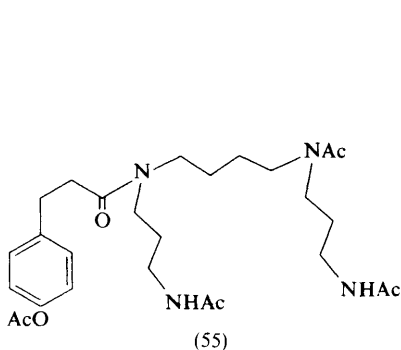
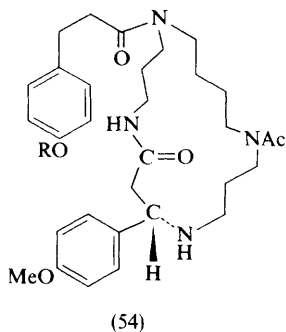
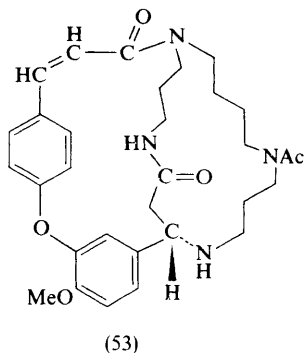
Following an intensive spectral and chemical investigation, the structure originally assigned<sup>66</sup> to chaenorhine, isolated from *Chaenorhinum origanifolium*, has been revised to that depicted by (53).<sup>67</sup> Reaction with sodium in liquid ammonia gave the key degradation product tetrahydro-*seco*-chaenorhine (54; R = H). Hydrolysis of (54; R = H) with ethanolic sodium hydroxide gave

<sup>65</sup> S. M. Kupchan, H. P. J. Hintz, R. M. Smith, A. Karim, M. W. Cass, W. A. Court, and M. Yatagai, *J.C.S. Chem. Comm.*, 1974, 329.

<sup>66</sup> 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.

<sup>67</sup> H. O. Bernhard, I. Kompis, S. John, D. Groeger, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1973, **56**, 1266.

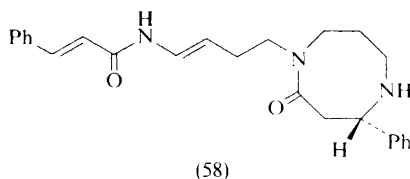
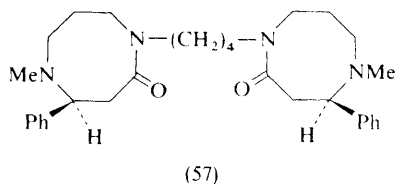
4-hydroxydihydrocinnamic acid and spermine, while treatment with concentrated hydrochloric acid followed by acetylation produced the partially hydrolysed product (55). Methylation of tetrahydro-*seco*-chaenorhine with dimethyl sulphate afforded (54; R = Me), which upon exhaustive Hofmann degradation gave the spermidine derivative (56). Interpretation of high-resolution mass spectra of (55), (56), and of other derivatives allowed the formulation of (53) for chaenorhine. The (*S*) absolute configuration of the chiral benzylic carbon was established by correlation of the c.d. curve of (54; R = H) with that of (*S*)-(-)-ethyl-1-(4-methoxyphenyl)ethylamine.



Details concerning the structural elucidation of homaline (57) and the related alkaloids hopromine, hoprominol, and hopromalinol, isolated from *Homalium pornyense*, have been published.<sup>68</sup> The related spermidine alkaloid periphyllene (58) has been recently isolated from the leaves of *Peripterygia marginata*.<sup>69</sup> Its structure and absolute stereochemistry were determined by spectral and chemical-degradation studies.

<sup>68</sup> M. Pais, R. Sarfati, F. X. Jarreau, and R. Goutarel, *Tetrahedron*, 1973, **29**, 1001.

<sup>69</sup> R. Hocquemiller, M. Leboeuf, B. C. Das, H. P. Husson, P. Potier, and A. Cavé, *Compt. rend.*, 1974, **278**, C, 525.



*Equisetum palustre* and *E. ramosissimum*, of Turkish origin, have been shown to elaborate palustrine.<sup>70</sup> (See Vol. 4, p. 419, of these Reports). Optimum conditions for counter-current extraction of alkaloids from *Secalis cornuta* have been developed.<sup>71</sup>

Maytenine, a pharmacologically active spermidine alkaloid from *Maytenus chuchuhuasha* (see Vol. 4 of these Reports), has been synthesized by two different routes.<sup>72,73</sup> Details of the previously reviewed synthesis of ( $\pm$ )-tetrahydrolunaridine (see Vol. 3 of these Reports) have been published.<sup>74</sup>

## 6 Unclassified Alkaloids and Alkaloid-containing Plants

The continuation of alkaloid screening studies on a large number of plants has been summarized.<sup>75,76</sup> The results of an extensive survey of alkaloid-containing plants growing in New Guinea and Papua have become available.<sup>2</sup>

A review on the occurrence, chemistry, and pharmacology of *Erythrophleum* alkaloids has appeared.<sup>77</sup> The *Euphorbia* alkaloids have also been reviewed.<sup>78</sup>

<sup>70</sup> T. Baytop and E. Gurkan, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1972, **8**, 63 (*Chem. Abs.*, 1973, **79**, 15817b).

<sup>71</sup> V. Mascov and L. Rosca, *Farmacia (Bucharest)*, 1973, **21**, 281 (*Chem. Abs.*, 1974, **80**, 24 799v); V. Mascov, E. Nichiforescu, L. Rosca, C. Rizescu, and I. Velea, *ibid.*, p. 557 (*Chem. Abs.*, 1974, **80**, 124 656q).

<sup>72</sup> E. Schlitter, U. Spitaler, and N. Weber, *Helv. Chim. Acta*, 1973, **56**, 1097.

<sup>73</sup> H. P. Husson, C. Poupat, and P. Potier, *Compt. rend.*, 1973, **276**, C, 1039.

<sup>74</sup> H. P. Husson, C. Poupat, B. Rodriguez, and P. Potier, *Tetrahedron*, 1973, **29**, 1405.

<sup>75</sup> S. J. Smolenski, H. Silinis, and N. R. Farnsworth, *Lloydia*, 1973, **36**, 359.

<sup>76</sup> S. J. Smolenski, H. Silinis, and N. R. Farnsworth, *Lloydia*, 1974, **37**, 30.

<sup>77</sup> H. Hauth, *Planta Med.*, 1974, **25**, 201.

<sup>78</sup> J. K. Bhatnagar and O. Parkash, *Pharmacos*, 1973, **18**, 28 (*Chem. Abs.*, 1974, **81**, 74 841u).

Single species in which alkaloids have been detected but not characterized are listed in the Table.<sup>79-91</sup>

**Table** Alkaloid-containing plants

Species	Comment	Ref.
<i>Amaranthus blitorides</i>	Alkaloids in stems, leaves, and flowers	79
<i>Anaphalis racemiberae</i>	Low alkaloid content	79
<i>Astragalus khlopunets</i>	Highest alkaloid content in fruit	80
<i>Catha edulis</i>	D-norpseudoephedrine and at least six unidentified nitrogenous compounds	81
<i>Cerbera thevetia</i>	One unidentified alkaloid	82
<i>Cortinarius</i> and <i>Lactarius</i> genera	Several species of these fungi showed positive tests for alkaloids	83
<i>Costus speciosus</i>	Crude extract showed a spectrum of pharmacological effects	84
<i>Dasiphora fruticosa</i>	Low concentration of alkaloids	85
<i>Cynoglossum divaricatum</i> and <i>C. officinale</i>	Crude extracts showed diuretic and hypotensive effects	86
<i>Dimorphandra mollis</i>	Alkaloids in bark (0.58 %) and leaves (0.70 %)	87
<i>Duranta repens</i>	Preliminary characterization of a new alkaloid described	88
<i>Euphrasia officinalis</i>	Tertiary alkaloids detected	89
<i>Pithecellobium foliolosum</i> , <i>P. multiflorum</i> , <i>P. polycephalum</i> , and <i>P. saman</i>	Inhibitory action on muscle correlates with alkaloid content	90
<i>Rhodiola pinnatifida</i>	Alkaloids detected	91

### *Cannabis sativa*

Choline has been isolated from the roots of a Mexican variant of this species.<sup>92</sup>

<sup>79</sup> Z. I. Saina, *Tr. Inst. Fiziol., Akad. Nauk Kazakh. S.S.R.*, 1973, **18**, 44 (*Chem. Abs.*, 1974, **80**, 130 469x).

<sup>80</sup> I. V. Griga, V. M. Kochergan, and G. V. Nalegatskaya, *Farm. Zhur. (Kiev)*, 1973, **28**, 83 (*Chem. Abs.*, 1973, **79**, 134 325z).

<sup>81</sup> G. Ruecker, H. Kroeger, M. Schikarski, and S. Qedan, *Planta Med.*, 1973, **24**, 61.

<sup>82</sup> S. N. Tewari, S. P. Harpalani, and N. Bhatt, *Proc. Nat. Acad. Sci. India. Sect. A*, 1972, **52**, 131 (*Chem. Abs.*, 1974, **80**, 57 446f).

<sup>83</sup> O. M. Efimenko, *Mikol. Fitopatol.*, 1973, **7**, 200 (*Chem. Abs.*, 1974, **80**, 24 781h).

<sup>84</sup> S. K. Bhattacharya, A. K. Parikh, P. K. Debnath, V. B. Pandey, and N. C. Neogy, *J. Res. Indian Med.*, 1973, **8**, 10 (*Chem. Abs.*, 1974, **81**, 45 259e).

<sup>85</sup> V. V. Telyat'ev and T. V. Tyunina, *Nauch. Tr., Irkutsk. Gosud. Med. Inst.*, 1971, **113**, 25 (*Chem. Abs.*, 1974, **81**, 74 895q).

<sup>86</sup> K. V. Rakshain and M. N. Mats, *Rast. Resur.*, 1973, **9**, 418 (*Chem. Abs.*, 1974, **80**, 22 615h).

<sup>87</sup> J. E. Murad and N. C. Gazinelli, *Rev. Farm. Bioquim.*, 1971, **2**, 49 (*Chem. Abs.*, 1973, **79**, 113 234d).

<sup>88</sup> F. Yousef, S. K. Khalil, and P. S. P. Wahba, *Planta Med.*, 1973, **23**, 173.

<sup>89</sup> K. J. Harkiss and P. Timmins, *Planta Med.*, 1973, **23**, 342.

<sup>90</sup> G. S. Barros Viana, M. P. Sousa, M. C. Medeiros, and F. J. A. Matos, *Rev. Brasil. Pesqui. Med. Biol.*, 1973, **6**, 71 (*Chem. Abs.*, 1973, **79**, 113 215y).

<sup>91</sup> Yu P. Surov, E. A. Krasnov, P. S. Sol'yarik, and S. N. Vydrina, *Izvest. sibirsk. Otdel. Akad. Nauk S.S.S.R., Ser. biol. Nauk*, 1973, **64** (*Chem. Abs.*, 1974, **80**, 68 364d).

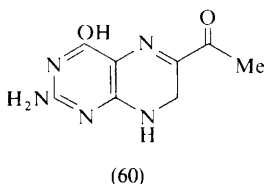
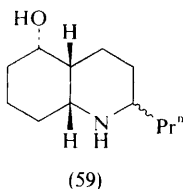
<sup>92</sup> M. L. Mole, jun. and C. E. Turner, *Acta Pharm. Jugoslav.*, 1973, **23**, 203 (*Chem. Abs.*, 1974, **80**, 57 455h).

Coccinellidae Alkaloids (Vol. 4, pp. 114, 418).

The activity of these ladybug alkaloids as defensive agents against ants and quail has been investigated.<sup>93</sup>

*Dendrobates pumilio*

The perhydroquinoline derivative (59), which was encountered in connection with studies of the toxic principle of this Panamanian frog, has been synthesized in three steps, starting with cyclohexane-1,3-dione.<sup>94</sup>

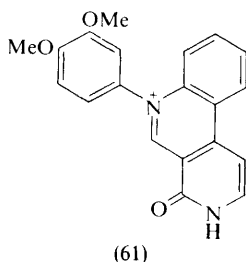


*Drosophila melanogaster*

Sepiapterin (60) has been isolated from the sepia mutant of this species.<sup>95</sup>

*Festuca* and *Lolium* spp.

*Festuca elatior* and *Lolium multiflorum* contain the highest and lowest amounts of perloine (61), an unusual diazaphenanthrene alkaloid which may inhibit digestion in ruminants.<sup>96</sup> It is speculated that *Lolium-Festuca* hybrids can be developed which show high or low perloine concentrations.



*Helminthosporium dematioideum* and *Rosellinia necatrix*

Cytochalasin E has been shown to possess the revised structure (62) on the basis of detailed examination of its <sup>13</sup>C n.m.r. spectrum.<sup>97</sup> The previously proposed structure (63) possesses fifteen *sp*<sup>2</sup> carbon atoms whereas the <sup>13</sup>C n.m.r. spectrum showed signals due to only thirteen such atoms. On the other hand,

<sup>93</sup> J. M. Pasteels, C. Deroe, B. Tursch, J. C. Braekman, D. Daloze, and C. Hootele, *J. Insect Physiol.*, 1973, **19**, 1771.

<sup>94</sup> G. Habermehl and W. Kissing, *Chem. Ber.*, 1974, **107**, 2326.

<sup>95</sup> K. Sugiura, S. Takikawa, M. Tsusue, and M. Goto, *Bull. Chem. Soc. Japan*, 1973, **46**, 3312.

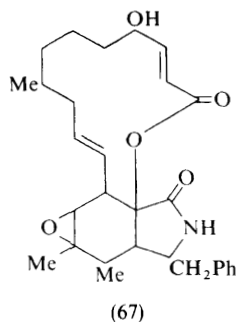
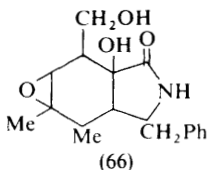
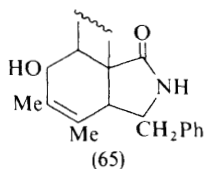
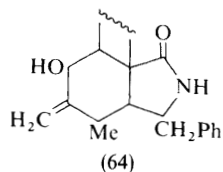
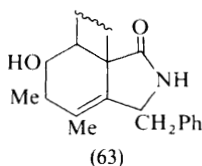
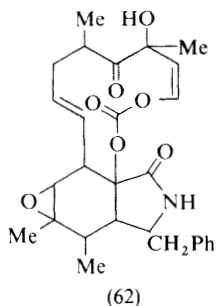
<sup>96</sup> R. C. Buckner, L. P. Bush, and P. B. Burrus, jun., *Crop Sci.*, 1973, **13**, 666.

<sup>97</sup> D. C. Aldridge, D. Greatbanks, and W. B. Turner, *J.C.S. Chem. Comm.*, 1973, 551.



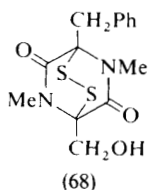
the spectra of the products of acid-catalysed hydrolysis, (64) and (65), of cytochalasin E showed the expected fifteen  $sp^2$  carbon atoms. Therefore, a new ring must be formed in the hydrolysis, and cytochalasin E must have one more ring than the structure (63). Ozonolysis of cytochalasin E followed by sodium borohydride reduction gave (66), whose  $^1\text{H}$  n.m.r. spectrum clearly defined the nature of the additional ring in the natural product.

The revised structure (67) of cytochalasin F follows from its similar  $^1\text{H}$  n.m.r. spectrum to that of cytochalasin E, its similar behaviour to acid hydrolysis, and the fact that it forms a monoacetate.



#### *Hyalodendron* sp.

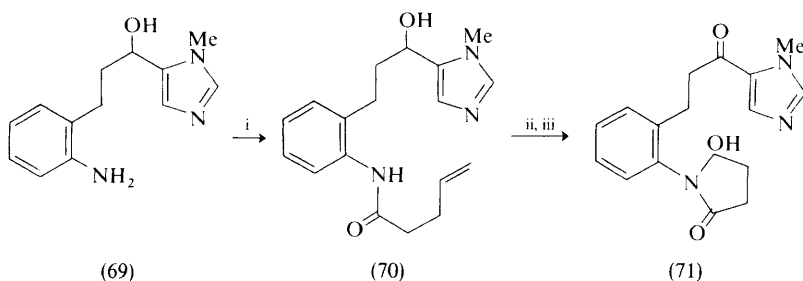
Hyalodendrin (68) has been isolated from a culture medium which supports the growth of a *Hyalodendron* species.<sup>98</sup>



<sup>98</sup> G. M. Strunz, M. Kakushima, M. A. Stillwell, and C. J. Heissner, *J.C.S. Perkin I*, 1973, 2600.

*Macrorungia longistrobus* (Vol. 4, p. 422)

The previously suggested structure (71) for isolongistrobine has been confirmed by synthesis (Scheme 4).<sup>99</sup> The amino-alcohol (69) available from related synthetic work (see Vol. 4 of these Reports), was acylated with 4-pentenoyl chloride to give (70), which upon successive oxidation with Cornforth's reagent and oxidative double-bond cleavage with sodium periodate-osmium tetroxide gave isolongistrobine (71).

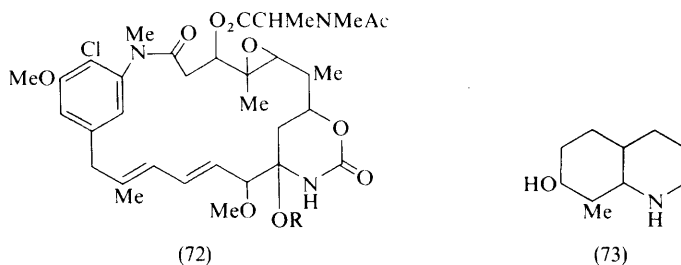


Reagents: i,  $\text{ClOC}(\text{CH}_2)_2\text{CH}=\text{CH}_2$ ,  $\text{C}_5\text{H}_5\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; ii,  $\text{CrO}_3$ ,  $\text{C}_5\text{H}_5\text{N}$ ,  $\text{H}_2\text{O}$ ; iii,  $\text{NaIO}_4$ ,  $\text{OsO}_4$ , dioxan,  $\text{H}_2\text{O}$

Scheme 4

*Maytenus ovatus* (Vol. 4, p. 423)

The structure and absolute configuration of maytansine (72;  $\text{R} = \text{H}$ ) has been established by X-ray crystallographic analysis of its 3-bromopropyl ether [72;  $\text{R} = (\text{CH}_2)_3\text{Br}$ ].<sup>100</sup> Maytansine represents the first ansa macrolide-type compound that shows *in vivo* tumour inhibitory properties.<sup>101</sup>

*Nitraria schoberi*

Structure (73) has been proposed for nitramine on the basis of spectral data and its dehydrogenation to 8-methylquinoline.<sup>102</sup>

<sup>99</sup> M. A. Wuonola and R. B. Woodward, *J. Amer. Chem. Soc.*, 1973, **95**, 5098.

<sup>100</sup> R. F. Bryan, C. J. Gilmore, and R. C. Haltiwanger, *J.C.S. Perkin II*, 1973, 897.

<sup>101</sup> *Chem. and Eng. News*, June 4, 1974, p. 15.

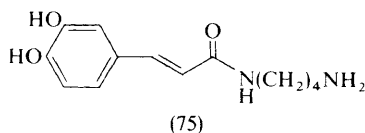
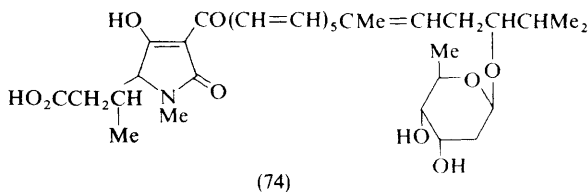
<sup>102</sup> N. Yu. Novgorodova, S. Kh. Maekh, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, 196 (*Chem. Abs.*, 1973, **79**, 32 150w).

*Oldenlandia affinis*

Tetramethylputrescine (tetramethyl-1,4-diaminobutane) has been isolated.<sup>103</sup> This species was known to be in use as an oral oxytocic agent in African folk medicine.

*Penicillium islandicum*

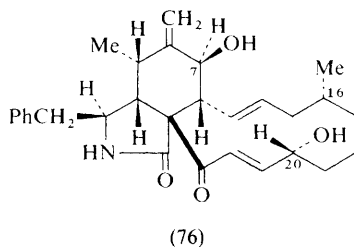
Structure (74) has been shown for olefinin, a new polyenic antibiotic agent possessing antibacterial activity.<sup>104</sup> Particularly helpful for the structural elucidation was the comparison of spectral data of olefinin and the related pigment erythroskyrine, isolated from the same source.

*Pentaclethra macrophylla*

Caffeoyleputrescine (75) has been isolated as its hydrochloride dihydrate.<sup>105</sup>

*Phoma* sp.

The cultures of this species (strain S 298) (Fungi Imperfecti) have yielded the macrocyclic metabolite deoxaphomin (76).<sup>106</sup> The structure and absolute



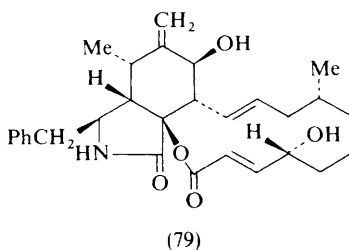
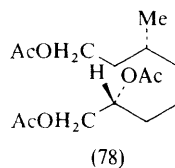
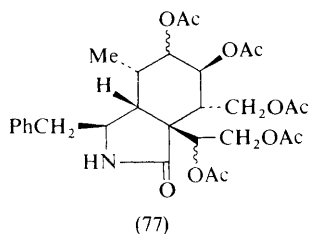
configuration (7*S*, 16*R*, 20*R*) are based on extensive spectral analysis and chemical degradation. Ozonolysis followed by reductive cleavage of the resulting ozonide with sodium borohydride gave a pentahydroxy-2-lactam, isolated as its penta-acetyl derivative (77), and 3-methyloctane-1,7,8-triol, isolated as its triacetate (78),

<sup>103</sup> L. Gran, *Lloydia*, 1973, **36**, 209.

<sup>104</sup> Gy. Horvath, J. Gyimesi, and Zs. Mehesfalvi-Vajna, *Tetrahedron Letters*, 1973, 3643.

<sup>105</sup> E. I. Mbadiwe, *Phytochemistry*, 1973, **12**, 2546.

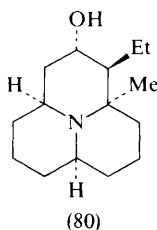
<sup>106</sup> M. Binder and C. Tamm, *Helv. Chim. Acta*, 1973, **56**, 966.



both of which are known degradation products of phomin (79), a metabolite obtained from the same species whose structure and absolute configuration had been established. A biogenetic relationship between phomin (79) and deoxaphomin (76), formally *via* a Baeyer–Villiger oxidation, is evident. An attempt to correlate the two compounds by treatment of (76) with peracetic acid has not been successful. Deoxaphomin and phomin are also obviously related to the cytochalasins E and F (see *Helminthosporium dematioideum* and *Rosellinia necatrix*).

*Poranthera corymbosa* (Vol. 3, p. 322)

Details of the X-ray crystallographic studies which established the molecular structures and absolute configurations of the interesting alkaloids porantherine,<sup>107</sup> porantheridine,<sup>108</sup> and poranthericine (80)<sup>109</sup> have been published.



*Rhizoctonia leguminicola* (Vol. 4, p. 425)

Slaframine (87), an alkaloid which stimulates excess salivation in livestock foraging on fungus-infected red clover, has been synthesized (Scheme 5).<sup>110</sup> The

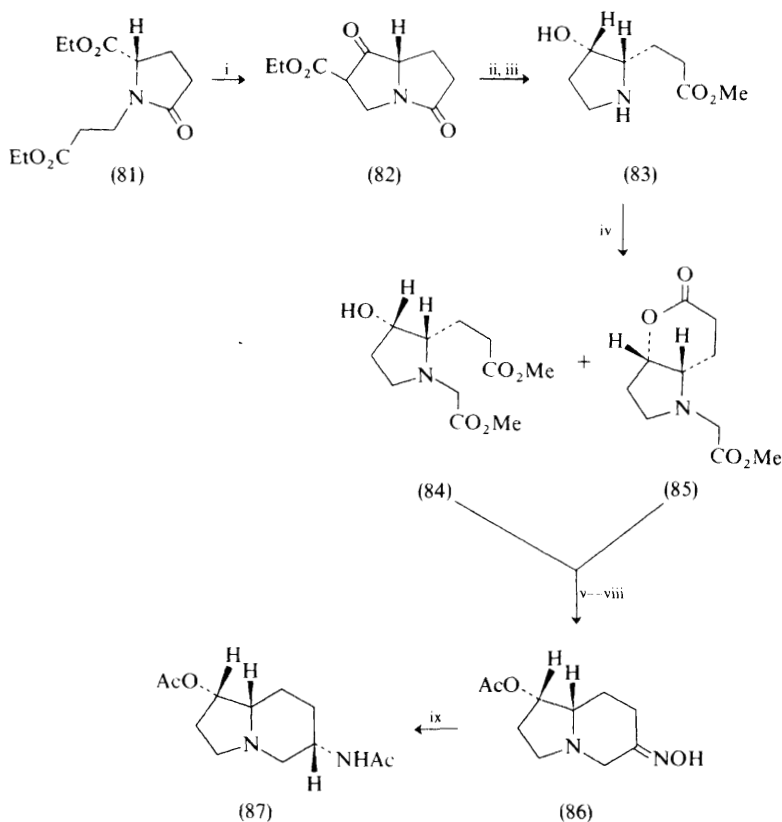
<sup>107</sup> W. A. Denne and A. McL. Mathieson, *J. Cryst. Mol. Structure*, 1973, 3, 79.

<sup>108</sup> W. A. Denne and A. McL. Mathieson, *J. Cryst. Mol. Structure*, 1973, 3, 87.

<sup>109</sup> W. A. Denne and A. McL. Mathieson, *J. Cryst. Mol. Structure*, 1973, 3, 139.

<sup>110</sup> W. J. Gensler and M. W. Hu, *J. Org. Chem.*, 1973, 38, 3848.

pyrrolidone (81), readily obtained from (+)-glutamic acid and acrylonitrile, was subjected to Dieckmann cyclization to give racemic (82), which upon acid hydrolysis and catalytic hydrogenation in methanol solution afforded the alcohol ester (83). Alkylation of (83) with methyl bromoacetate gave a mixture of the diester (84) (40%) and the lactone (85) (23%). This mixture was subjected to Dieckmann cyclization and the resulting product was hydrolysed and decarboxylated, acetylated, and oximated to give compound (86) as a mixture of separable *syn*- and *anti*-isomers. Hydrogenation of (86) gave ( $\pm$ )-slaframine (87). The two catalytic hydrogenation steps (iii and ix in Scheme 5) determine the stereochemical outcome of the synthesis. That these would proceed in the desired stereoselective sense could be predicted on the basis of inspection of models.

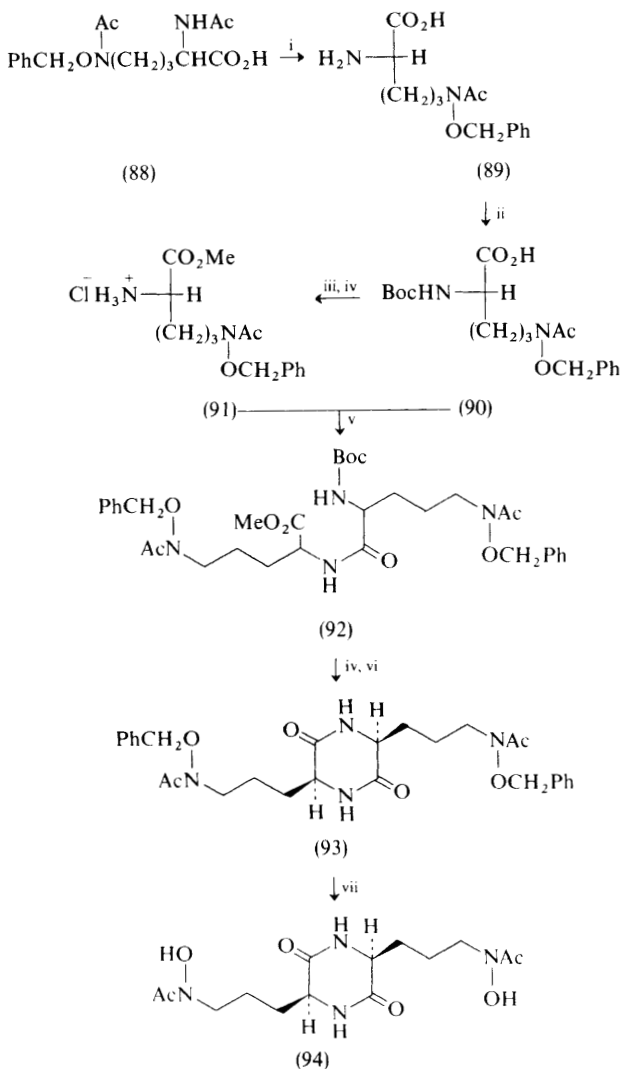


Reagents: i, NaOEt, EtOH; ii, 15% HCl, 75 °C; iii, H<sub>2</sub>, Pt, HCl, MeOH; iv, BrCH<sub>2</sub>CO<sub>2</sub>Me, MeOH, 60 °C; v, NaH, PhH; vi, conc. HCl, 85 °C; vii, Ac<sub>2</sub>O, C<sub>5</sub>H<sub>5</sub>N; viii, NH<sub>2</sub>OH-HCl, C<sub>5</sub>H<sub>5</sub>N, EtOH; ix, H<sub>2</sub>, PtO<sub>2</sub>, HCl, EtOH

Scheme 5

*Rhodotorula pilimanae*

The second synthesis of rhodotorulic acid (94) has been achieved (Scheme 6).<sup>111</sup> The readily available carboxylic acid (88) was selectively and asymmetrically



Reagents: i, Taka-diestase, pH 6.9, 37 °C; ii, Triton B, Bu'OCO<sub>2</sub>C<sub>6</sub>H<sub>2</sub>-2,4,5-Cl<sub>3</sub>, MeOH; iii, CH<sub>2</sub>N<sub>2</sub>; iv, HCl, EtOAc; v, DCC, NH<sub>3</sub>, Et<sub>2</sub>O; vi, NH<sub>3</sub>, room temp.; vii, H<sub>2</sub>, Pd/C, EtOH

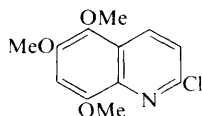
**Scheme 6**

<sup>111</sup> T. Fujii and Y. Hatanaka, *Tetrahedron*, 1973, **29**, 3825.

deacetylated with Taka-diaxase to give the L-amino-acid (89), which was converted into the L-amino-ester (91) *via* the N-protected L-amino-acid (90) by conventional peptide-synthesis steps. Combination of (90) and (91) provided the LL-dipeptide (92), which upon N-deprotection and cyclization gave the LL-benzyl hydroxamate (93). Selective catalytic benzyl-*O*-hydrogenolysis, a reaction first shown with model compounds, gave rhodotorulic acid (94).

#### *Streptomyces flocculus*

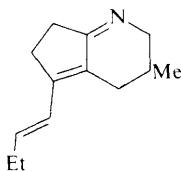
The chloroquinoline (95), a potentially useful intermediate for the synthesis of the streptonigrin skeleton, has been prepared.<sup>112</sup>



(95)

#### *Streptomyces griseoflavus* var. *pyrindicus*

Pyrindicin (96), a compound possessing weak antimicrobial activity, has been isolated from the culture broth of this variant of *Streptomyces griseoflavus*.<sup>113,114</sup> The structure was established on the basis of spectral data and Hofmann and other degradation reactions.



(96)

#### *Streptomyces hyalinus*

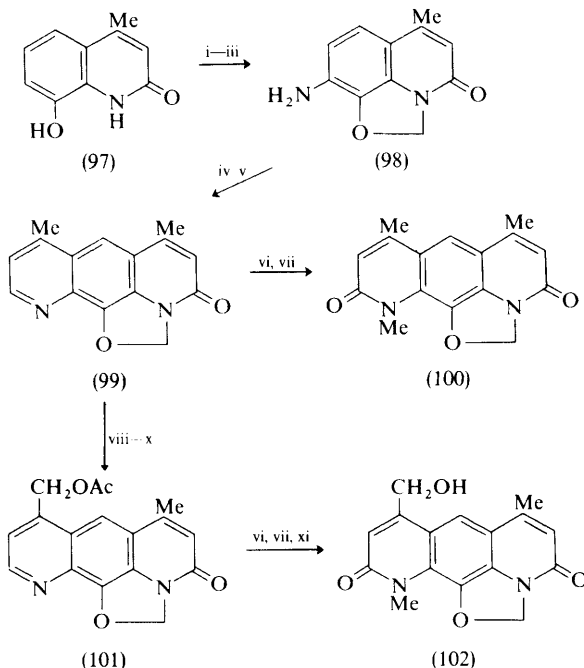
Syntheses of the antibiotic compounds deoxynybomycin (100) and nybomycin (102) as well as related heterocyclic compounds have been described (Scheme 7).<sup>115</sup> The 8-hydroxy-2-quinolone (97), readily prepared from *o*-anisidine in three steps, was converted into the fused oxazoline-quinoline derivative (98) by successive nitration, reaction with dibromomethane, and hydrogenation. Adaptation of the Doebner-von Miller quinoline synthesis to (98) provided the tetracyclic product (99), which upon methylation and oxidation gave deoxynybomycin (100) in 0.83% overall yield from *o*-anisidine. The key intermediate

<sup>112</sup> T. Kametani, A. Kozuka, and T. Terui, *Yakugaku Zasshi*, 1973, **93**, 406 (*Chem. Abs.*, 1973, **79**, 31 817g).

<sup>113</sup> S. Omura, H. Tanaka, J. Awaya, Y. Narimatsu, Y. Konda, and T. Hata, *Agric. and Biol. Chem. (Japan)*, 1974, **38**, 899.

<sup>114</sup> M. Onda, Y. Konda, Y. Narimatsu, S. Omura, and T. Hata, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2048.

<sup>115</sup> R. M. Forbis and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1973, **95**, 5003.



Reagents: i,  $\text{HNO}_3$ ,  $\text{Ac}_2\text{O}$ ; ii,  $\text{CH}_2\text{Br}_2$ ,  $\text{K}_2\text{CO}_3$ , DMF; iii,  $\text{H}_2$ ,  $\text{PtO}_2$ ,  $\text{HOAc}$ ; iv,  $\text{MeCO-CH=CH}_2$ ,  $\text{ZnCl}_2$ ,  $\text{FeCl}_3$ ; v, PPA; vi,  $\text{Me}_2\text{SO}_4$ ; vii,  $\text{K}_3\text{Fe(CN)}_6$ ,  $\text{KOH}$ ; viii,  $\text{SeO}_2$ , dioxan- $\text{H}_2\text{O}$ ; ix,  $\text{NaBH}_4$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{EtOH}$ ; x,  $\text{HOAc}$ ,  $\text{H}_2\text{SO}_4$ ,  $100^\circ\text{C}$ ; xi,  $\text{KOH}$ ,  $\text{EtOH}$ , reflux

**Scheme 7**

(99) also served for the synthesis of nybomycin (102). Successive selenium dioxide oxidation, hydride reduction, and acetylation afforded the acetate (101), which was readily transformed into nybomycin (102) in three steps.

#### *Vaccinium oxycoccus* (Vol. 3, p. 323)

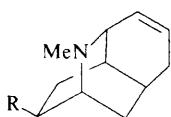
In addition to the previously reported alkaloid, cannivonine (103;  $\text{R} = \text{H}$ ) (see Vol. 3), three related bases, named cannivonines 1, 2, and 3, have been isolated from the leaves of this species (cranberry).<sup>116</sup> High-resolution mass spectrometry shows the molecular formulae  $\text{C}_{13}\text{H}_{21}\text{N}$ ,  $\text{C}_{16}\text{H}_{25}\text{NO}$ , and  $\text{C}_{14}\text{H}_{21}\text{N}$  for cannivonines 1, 2, and 3, respectively. Structure and stereochemistry depicted by (104) have been proposed for cannivonine 2 (also called cannivonine b) solely on the basis of an analysis of its 100 or 220 MHz n.m.r. spectrum, using the shift-reagent technique.<sup>116,117</sup> Aside from the high-resolution mass spectra yielding the molecular ions, no spectral or chemical information is presented for

<sup>116</sup> K. Jankowski, *Experientia*, 1973, **29**, 1334.

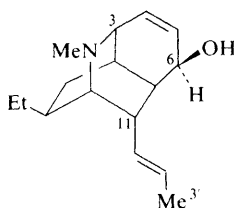
<sup>117</sup> K. Jankowski, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1973, **21**, 741 (*Chem. Abs.*, 1974, **80**, 37 341q).



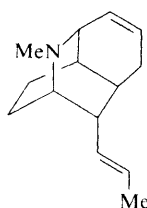
cannivonines 1 and 3, although stereostructures (103;  $R = Et$ ) and (105), respectively, have been proposed for these alkaloids.<sup>116</sup> Although the reported data for cannivonine 2 appear consistent with the proposed structure (104), several disturbing general points exist concerning the structure of the cannivonines, among which are: (i) the indication\* that a total of three alkaloids only have been isolated, yet four have been reported in the literature; (ii) the surprising result that deuteration of cannivonine 2 occurs at C-3, C-6, C-11, and C-3' hydrogens using 'Djerassi's classic method' (sodium methoxide, [*hydroxy*-<sup>2</sup>H]methanol, and heavy water at reflux); and (iii) the proposal that an oxidative degradation of cannivonine (103;  $R = H$ ) (see Vol. 3 of these Reports) proceeds *via* the Bredt-rule-violating diene (106) [u.v. (max) 273 nm; *cf.* normal dienamine u.v. (max) 281 nm<sup>118</sup>]. Thus complete spectral and degradative information on these alkaloids would be welcome. In view of the small amounts of alkaloids isolated, confirmation or reassignment of the proposed structures may well require a careful reappraisal of the data, coupled with total synthesis.



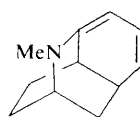
(103)



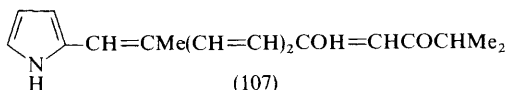
(104)



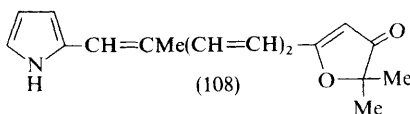
(105)



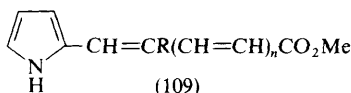
(106)



(107)



(108)



(109)

### *Wallemia sebi*

This fungus yields walleimia A and walleimia C, whose structures (107) and (108), respectively, were established by comparison of spectral data with the model

<sup>118</sup> S. K. Malhotra in 'Enamines: Synthesis, Structure, and Reactions,' ed. A. G. Cook, Dekker, New York, 1969, p. 43.

\* Personal communication from Dr. K. Jankowski.

compounds (109;  $n = 0-2$ ,  $R = H$  or  $Me$ ) and (109;  $n = 3$ ,  $R = Me$ ), prepared by Wittig synthesis from 2-formylpyrrole.<sup>119</sup> Chloro-derivatives of (107) and (108) were also isolated from this species.

<sup>119</sup> Y. Badar, W. J. S. Lockley, T. P. Toubé, B. C. L. Weedon, and L. R. G. Valadon, *J.C.S. Perkin I*, 1973, 1416.

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