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# **The Alkaloids**

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# The Alkaloids

Volume 3

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A Review of the Literature Published between  
July 1971 and June 1972

Senior Reporter

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## Foreword

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This third volume in the series of Specialist Periodical Reports on Alkaloids comprises reviews of progress in the whole field of alkaloid chemistry for the period July 1971 to June 1972. For the first time we include a summary of recent developments in the chemistry of the Steroidal Alkaloids of the *Solanum* and *Veratrum* Groups. In this chapter, contributed by R. B. Herbert, the emphasis has properly been given to the period of review adopted for the volume as a whole, but in order to fill in the gap between existing reviews and July 1971 the salient literature references in this area from the beginning of 1970 have also been included.

Once again it is a pleasure to acknowledge the enthusiastic co-operation of my colleagues in the preparation of this Report, and to record my sincere appreciation of the efforts they have made to produce their respective reviews by the agreed date. That there was a short delay before the final manuscript arrived was solely due to factors that could neither have been anticipated nor circumvented—the inevitable hazard of attempting to compile a comprehensive, critical summary of the literature within three months of the end of the period under review. In this connection it is obvious that the accessibility of material in the major international journals presents no problem; but all contributors to these volumes would greatly appreciate reprints of papers published in minor and/or regional journals that are not found in every library. In case of a change of author it would be most convenient if such reprints were mailed to the Senior Reporter, who will then forward them to the appropriate contributor.

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

J. E. Saxton



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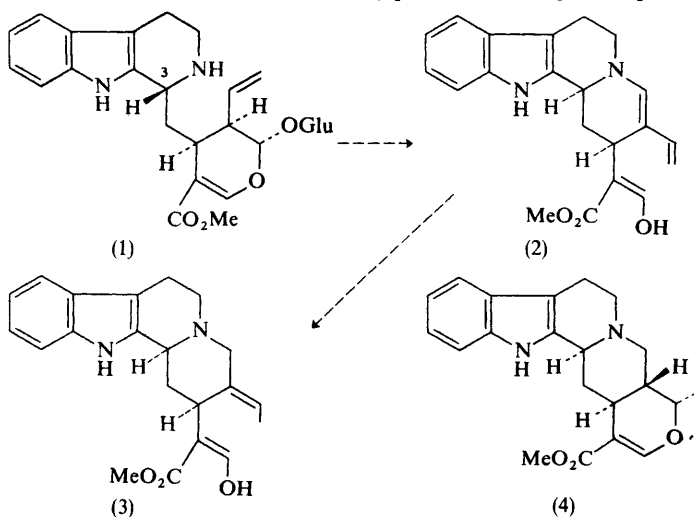
# 1

## Biosynthesis

BY R. B. HERBERT

**Terpenoid Indole Alkaloids.**—Monoterpenes have been the subject of a comprehensive review which includes these alkaloids.<sup>1</sup> Indole alkaloids have been classified according to their biogenesis<sup>2</sup> and another review<sup>3</sup> discusses the application of tritium labelling in biosynthetic studies on these alkaloids as well as several others.

An interesting new technique has been applied to the study of indole alkaloid biosynthesis: the alkaloids in *Vinca rosea* seedlings were examined after the administration of DL-[2'-<sup>14</sup>C]tryptophan (ca. 30% incorporation) and the appearance and disappearance of radioactivity noted as a function of time.<sup>4</sup> The technique is thus similar to the widely used method of <sup>14</sup>CO<sub>2</sub> feeding. The results were in accord with those obtained earlier by precursor feeding.<sup>5,6</sup> In particular,



<sup>1</sup> D. V. Banthorpe, B. V. Charlwood, and M. J. O. Francis, *Chem. Rev.*, 1972, 72, 115.

<sup>2</sup> I. Kompis, M. Hesse, and H. Schmid, *Lloydia*, 1971, 34, 269.

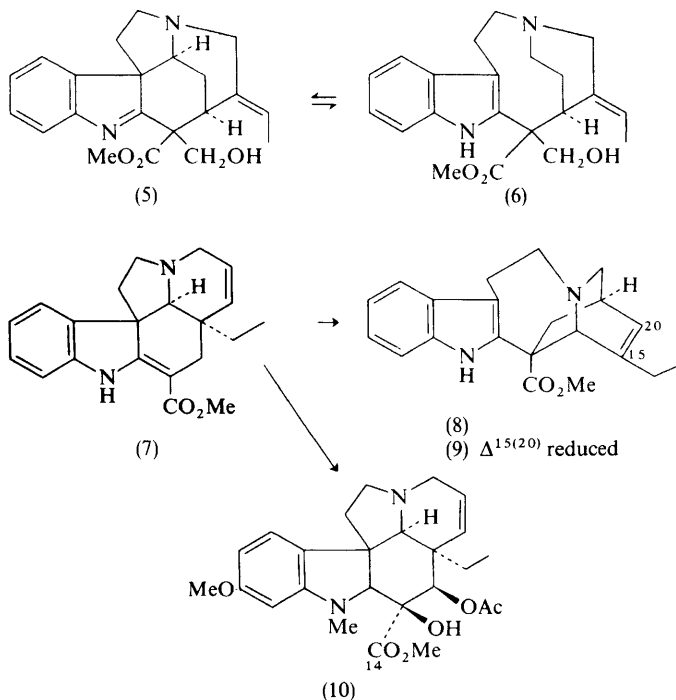
<sup>3</sup> A. R. Battersby, *Accounts Chem. Res.*, 1972, 5, 148.

<sup>4</sup> A. I. Scott, P. B. Reichardt, M. B. Slaytor, and J. G. Sweeny, *Bioorganic Chem.*, 1971, 1, 157.

<sup>5</sup> A. R. Battersby, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1971, vol. 1, p. 31.

<sup>6</sup> A. I. Scott, *Accounts Chem. Res.*, 1970, 3, 151.

geissoschizine (3), preakuammicine (5), and tabersonine (7) were confirmed as important ('dynamic') intermediates in the biosynthesis of other alkaloids, whereas ajmalicine (4), catharanthine (8), coronaridine (9), and vindoline (10) appeared as end-products of biosynthesis. An unknown alkaloid was the first to be labelled in the experiment. It showed rapid turnover and is thus an important precursor for other alkaloids. It appeared that it could be (2), lying between vincoside (1)<sup>7,8</sup> and geissoschizine (3).



The precursor role of tabersonine (7) for the *Aspidosperma* and *Ipoga* alkaloids was further strengthened by feeding radioactive tabersonine to *V. rosea* and examining the products as for tryptophan. It was suggested, in view of the large differences of incorporation observed for the two classes of alkaloid, that tabersonine might be formed as the racemate, one enantiomer of which [the (–)-form] would give vindoline (10) and the other [the unknown (+)-form] catharanthine (8) and coronaridine (9).

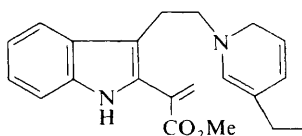
<sup>7</sup> The Stereochemistry at C-3 of vincoside has been established as that shown: K. T. D. De Silva, G. N. Smith, and K. E. H. Warren, *Chem. Comm.*, 1971, 905; W. P. Blackstock, R. T. Brown, and G. K. Lee, *ibid.*, p. 910.

<sup>8</sup> J. Staunton, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1972, vol. 2, p. 1.

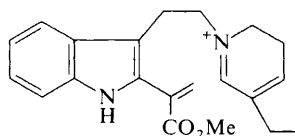
<sup>9</sup> G. A. Cordell, G. F. Smith, and G. N. Smith, *Chem. Comm.*, 1970, 189, 191; R. T. Brown, G. F. Smith, K. S. J. Stapleford, and D. A. Taylor, *ibid.*, p. 190; A. R. Battersby and A. K. Bhatnagar, *ibid.*, p. 193.

Stemmadenine (6) did not show the characteristics, in these experiments, of a dynamic intermediate. This could be explained, however, as the consequence of an equilibration with preakuammicine (5) which is enzyme bound, or if stemmadenine is a stabilized form of preakuammicine (5), and is involved in biosynthesis *via* (5).

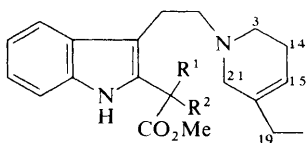
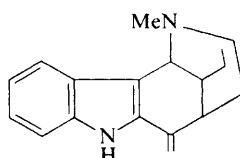
The secodine group of alkaloids<sup>9</sup> are interesting biosynthetically as derivatives of (11)<sup>5,10</sup> or (12),<sup>11,12</sup> which are regarded as likely intermediates in the biosynthesis of indole alkaloids with rearranged monoterpene units. Accordingly,



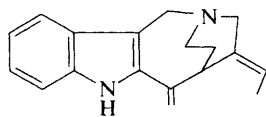
(11)



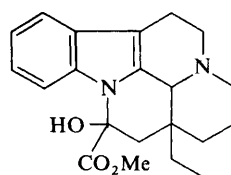
(12)

(13)  $R^1 = \text{CH}_2\text{OH}$ ,  $R^2 = \text{H}$ (14)  $R^1 = R^2 = \text{CH}_2$ 

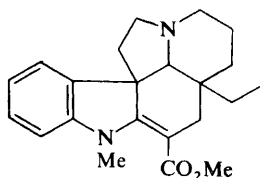
(15)



(16)



(17)



(18)

16,17-dihydrosecodin-17-ol (13) and secodine (14) have been tested<sup>11,12</sup> as precursors for uleine (15), apparicine (16), vincamine (17), minovine (18), vindoline (10), and catharanthine (8), as well as ajmalicine (4), which has an unrearranged unit. All incorporations were similarly low except for those for secodine

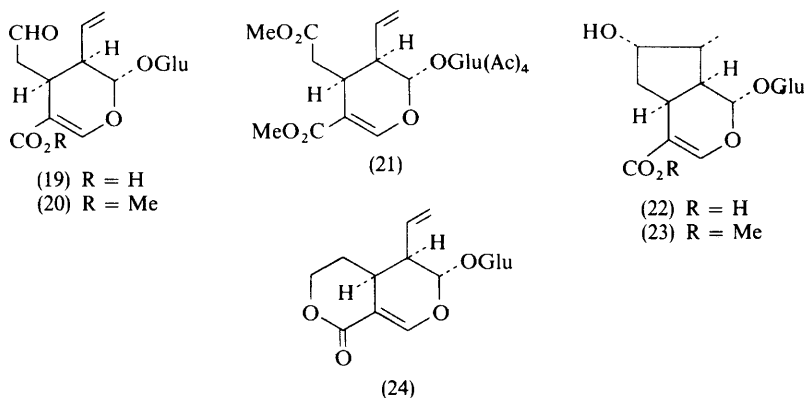
<sup>10</sup> A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 945.

<sup>11</sup> J. P. Kutney, J. F. Beck, N. J. Eggers, H. W. Hanssen, R. S. Sood, and N. D. Westcott, *J. Amer. Chem. Soc.*, 1971, **93**, 7322.

<sup>12</sup> J. P. Kutney, J. F. Beck, C. Ehret, G. Poulton, R. S. Sood, and N. D. Westcott, *Bioorganic Chem.*, 1971, **1**, 194.

into vindoline (10) in *Vinca rosea* and apparicine (16) in *Aspidosperma pyricollum*, which were significantly higher. When [*carboxy*- $^{14}\text{C}$ ; *ar*- $^3\text{H}$ ]secodine was used, both of these alkaloids were formed without change in isotope ratio, indicating intact incorporations of the precursor. Degradation of the vindoline showed that the  $^{14}\text{C}$  label was located at C-14 and thus, reasonably, the methoxycarbonyl group of secodine (14) was transferred as such into vindoline (10).<sup>11</sup> [*carboxy*- $^{14}\text{C}$ ; 19- $^3\text{H}$ ]Secodine was incorporated without change in isotope ratio. On the other hand, [*carboxy*- $^{14}\text{C}$ ; 3,14,15,21- $^3\text{H}_4$ ]secodine was converted into vindoline with loss of 60% of the tritium label,<sup>11,12</sup> consistent with its involvement in vindoline biosynthesis *via* the more highly oxidized (11) or (12). The same precursor was incorporated into apparicine (16) and although the results are regarded as preliminary, the methoxycarbonyl carbon appears to be retained;<sup>12</sup> tritium was lost (48%) from the piperidine ring, again consistent with involvement of an intermediate similar to that which yields vindoline.

Two new acidic terpenes have been isolated from *V. rosea* and rigorously characterized<sup>13</sup> as secologanic acid (19) and secologanoside, which was studied



as its methylation-acetylation product (21). [ $^{14}\text{C}$ ]Loganic acid (22) was efficiently incorporated into secologanic acid in *V. rosea* as well as secologanin (20) and loganin (23). A similar efficient conversion of loganin into secologanic acid was recorded. Taking into account the purification of a methyltransferase from *V. rosea* capable of methylating loganic and secologanic acids, these results suggest a role for these acids in indole alkaloid biosynthesis, and the incorporation of sweroside (24)<sup>14</sup> into the alkaloids may be *via* secologanic acid (19). Sweroside also serves as a precursor for reserpine and quinine.<sup>14a</sup>

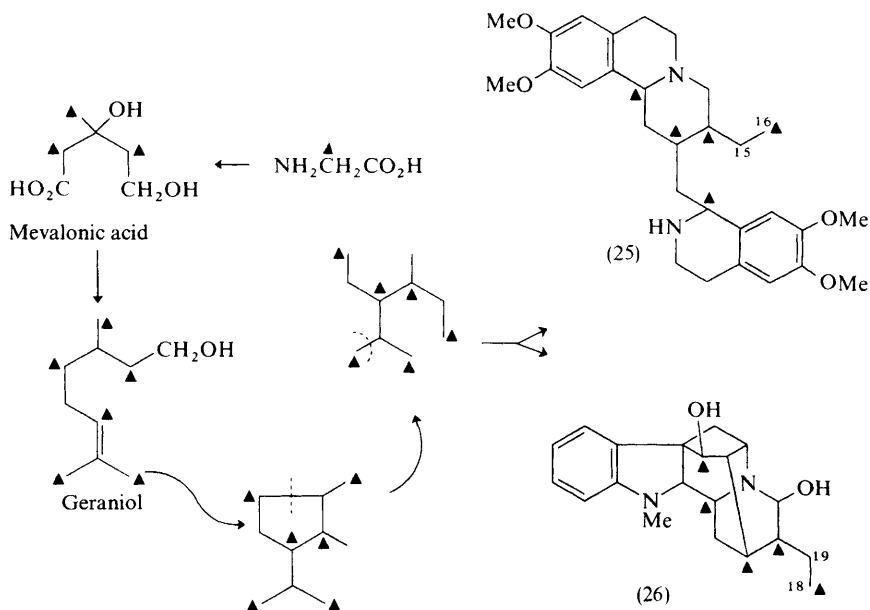
The terpenoid moieties of indole alkaloids have been proved to arise from mevalonate.<sup>5</sup> Although labelled acetate can be specifically incorporated into many terpenoid compounds *via* mevalonate<sup>1,15</sup> it is not a specific precursor for

<sup>13</sup> R. Guarnaccia and C. J. Coscia, *J. Amer. Chem. Soc.*, 1971, **93**, 6320.

<sup>14</sup> H. Inouye, S. Ueda, and Y. Takeda, (a) *Chem. Pharm. Bull.*, 1971, **19**, 587; (b) *Tetrahedron Letters*, 1969, 407; 1968, 3453.

<sup>15</sup> J. W. Cornforth, *Chem. in Britain*, 1968, **4**, 102.

the indole alkaloids.<sup>16</sup> This has prompted a search for a source other than acetate. When intermediates of glycolysis and the Krebs cycle, leucine, and glycollic acid were tested as precursors for cephaeline (25) in *Cephaelis acuminata*, randomization of the labels was observed.<sup>17</sup> [2-<sup>14</sup>C]Glycine, however, was incorporated with specificity; cephaeline (25) was labelled at C-16 but not C-15. In *Rauwolfia serpentina*, ajmaline (26) was labelled at C-18 but not C-19 and reserpine predominantly in the reserpic acid moiety. The labelled positions showed 15–18% of the total activity compared with 20% calculated for utilization of glycine as a C<sub>2</sub> unit *via* mevalonate (Scheme 1). The results for cephaeline were obtained in the summer with four–five-year-old plants. Winter feeding to two-year-old plants, however, gave non-specific incorporation into the terpenoid portions of cephaeline and ipecoside. Similar non-specific incorporation of glycine has been observed for vindoline,<sup>18</sup> ajmalicine,<sup>19</sup> and the *Strychnos* alkaloids.<sup>18,20</sup> On the other hand, specific incorporation of [2-<sup>14</sup>C]glycine into



Scheme 1

<sup>16</sup> A. R. Battersby, *Pure Appl. Chem.* 1967, **14**, 117; E. Leete, *Adv. Enzymol.*, 1969, **32**, 373.

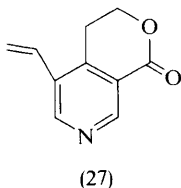
<sup>17</sup> A. K. Garg and J. R. Gear, *Phytochemistry*, 1972, **11**, 689; *Chem. Comm.*, 1969, 1447; *Tetrahedron Letters*, 1969, 4377; 1968, 141.

<sup>18</sup> D. Gröger, W. Maier, and P. Simchen, *Experientia*, 1970, **26**, 820.

<sup>19</sup> J. P. Kutney, J. F. Beck, V. R. Nelson, K. L. Stuart, and A. K. Bose, *J. Amer. Chem. Soc.*, 1970, **92**, 2174.

<sup>20</sup> W. Maier and D. Gröger, *Arch. Pharm.*, 1971, **304**, 351.

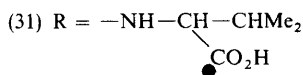
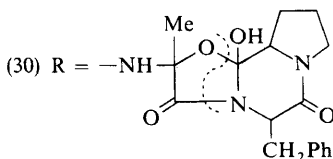
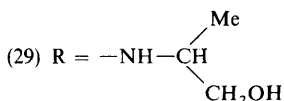
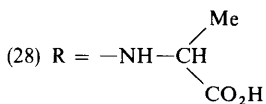
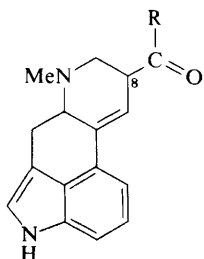
gentianine (27) has been recorded.<sup>21</sup> L-Leucine has been found to be incorporated into vindoline and catharanthine as inefficiently as acetate.<sup>22</sup> Inhibition of protein



synthesis in the plant by puromycin caused a measurable but not dramatic increase in leucine incorporation into the alkaloids.

**Ergot.**—Experiments directed towards solving the outstanding problem of the biosynthesis of the peptide lysergic acid derivatives from lysergic acid have not yet proved definitive, and the recent results for ergotamine and ergometrine represent little advance on those reviewed previously.<sup>23</sup>

[<sup>14</sup>C]Lysergylalanine (28), ergometrine (29), and its stereoisomer ergometrinine,\* were poorly incorporated into the  $\alpha$ -hydroxyalanine portion of ergotamine (30) in *Claviceps paspali*, and with considerable randomization of the



<sup>21</sup> N. Marekov, M. Arnaudov, and St. Popov, *Doklady Bolg. Akad. Nauk.*, 1970, **23**, 169.

<sup>22</sup> D. C. Wigfield, B. Lem, and V. Srinivasan, *Tetrahedron Letters*, 1972, 2659.

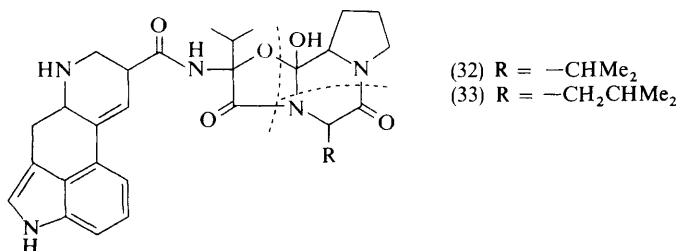
<sup>23</sup> R. B. Herbert, in ref. 5, p. 28.

\* The lysergic acid derivatives used as precursors in the experiments reported here were epimeric at C-8. In each paper both epimers of the appropriate precursors were treated individually, but as the results were similar they are not discussed separately.

labels.<sup>24</sup> Therefore, these compounds were not incorporated intact into ergotamine; a similar result was obtained earlier with ergometrine.<sup>25</sup> L-Alaninol and L-alanine served as precursors for ergotamine.<sup>24,25</sup> Although it appeared that alaninol was a better precursor for ergotamine than alanine this was found<sup>24</sup> to be due to the lower *weight* of alanine administered which could then be more easily metabolized. It was concluded that alanine or a closely related compound was the precursor of the  $\alpha$ -hydroxyalanine portion of ergotamine.

In confirmation of an earlier result<sup>26</sup> lysergylalanine (28) was found<sup>27</sup> to act as a precursor for ergometrine (29), albeit an inefficient one, in *C. paspali*; the D-alanyl derivatives were less efficient precursors than the L-alanyl derivatives. The latter were twice as efficient as L-[1-<sup>14</sup>C]alanine, suggesting some intact conversion into ergometrine. Taking the low incorporation, however, together with the failure to detect lysergylalanine in *C. paspali* cultures by radioisotope dilution, it seems unlikely that lysergylalanine is a normal intermediate in ergometrine biosynthesis.

DL-[1-<sup>14</sup>C]Valine, D-, L-, and DL-[1-<sup>14</sup>C]alanine, and lysergylvaline (31; <sup>14</sup>C label as shown) have been studied as precursors for ergocornine (32) and ergocryptine (33), examined mostly as the 3 : 1 mixture ergotoxine.<sup>28</sup> L-Alanine and



lysergyl-L-valine were more efficiently utilized than the corresponding D-isomers, but lysergyl-L-valine and DL-valine were incorporated, and the labels randomized to a similar extent, indicating the non-intact incorporation of lysergylvaline. Degradation of the ergotoxine obtained in all the above experiments showed significantly that the hydroxyvaline portion of the ergocornine (32) had a higher specific activity than the valine portion, suggesting that the latter is built into a molecule which leads to ergocornine earlier than hydroxyvaline, and is subject to dilution by more non-labelled pools, *i.e.* valine-containing peptide intermediates. A preliminary competition experiment between inactive L-valyl-L-proline and L-[1-<sup>14</sup>C]valine was unsuccessful, however. It is nonetheless an attractive

<sup>24</sup> H. G. Floss, G. P. Basmadjian, M. Tchong, C. Spalla, and A. Minghetti, *Lloydia*, 1971, **34**, 442.

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

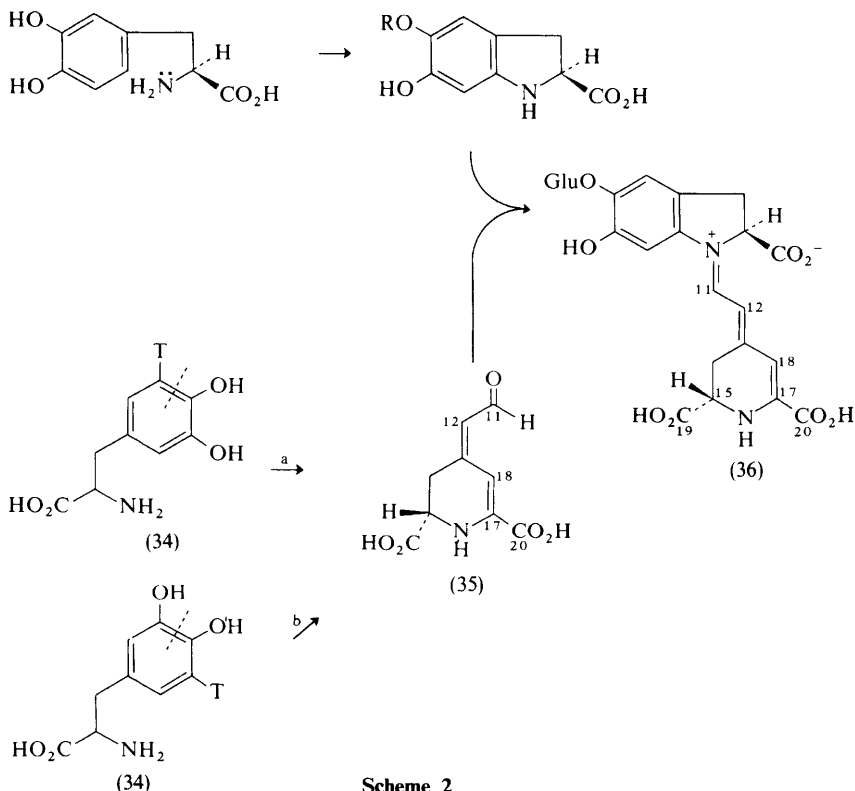
<sup>26</sup> G. Basmadjian, H. G. Floss, D. Gröger, and D. Erge, *Chem. Comm.*, 1969, 418.

<sup>27</sup> H. G. Floss, G. P. Basmadjian, D. Gröger, and D. Erge, *Lloydia*, 1971, **34**, 449.

<sup>28</sup> H. G. Floss, G. P. Basmadjian, M. Tchong, D. Gröger, and D. Erge, *Lloydia*, 1971, **34**, 446.

corollary of this idea that the peptide fragments of ergocornine (32), ergocryptine (33), and indeed ergotamine (30) *etc.* are added on to lysergic acid as *complete* units; this would explain the failure of attempts to demonstrate the stepwise addition of amino-acids to lysergic acid.

**Betalaines.**—The *Centrospermeae* pigments, the betalaines,<sup>29</sup> are derived in a unique pathway from dopa [Scheme 2; shown for betanine (36)].<sup>30,31</sup> DL-[1'-<sup>14</sup>C]-Dopa was incorporated into betanine with almost all of the activity located in



Scheme 2

the three carboxy-groups.<sup>31</sup> Further, as much as 90% of this activity was found in the derived betalanic acid (35). Experiments have now been carried out to

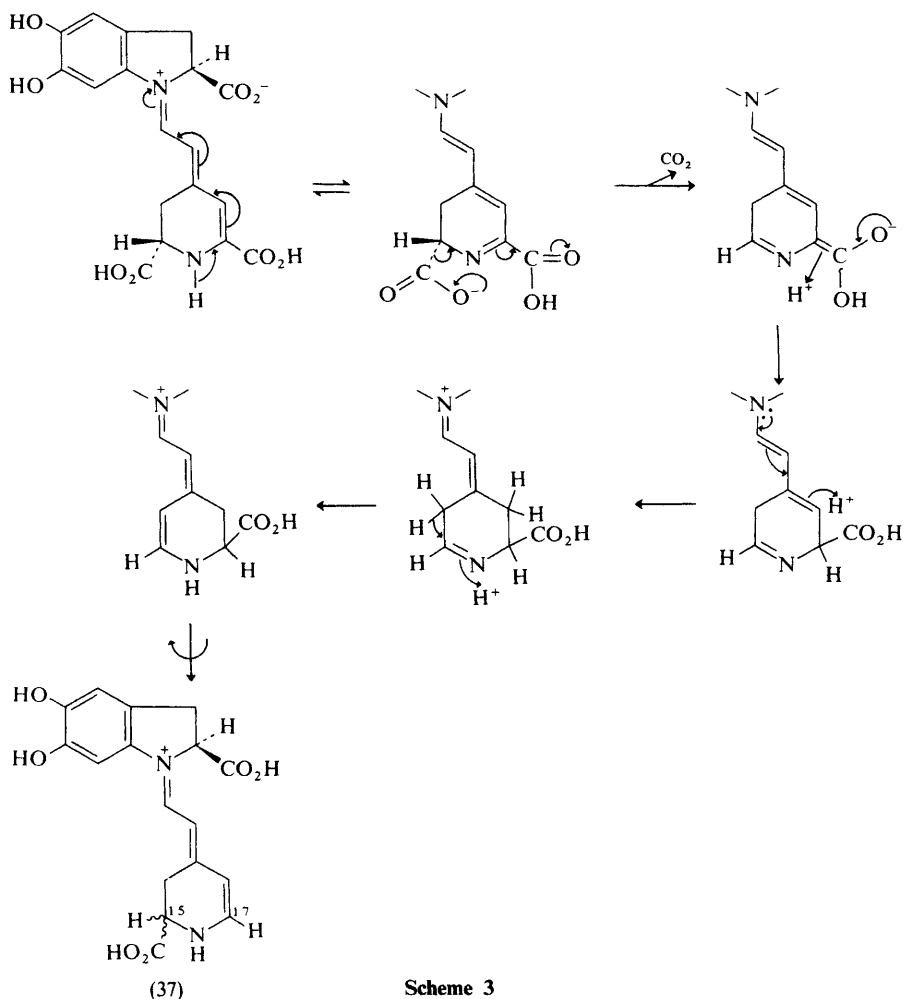
<sup>29</sup> T. J. Mabry, in 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand Reinhold Company, New York, 1970, p. 367.

<sup>30</sup> H. Wyler, T. J. Mabry, and A. S. Dreiding, *Helv. Chim. Acta*, 1963, **46**, 1745; L. Hörhammer, H. Wagner, and W. Fritzsche, *Biochem. Z.*, 1964, **339**, 398; L. Minale, M. Piatelli, and R. A. Nicolaus, *Phytochemistry*, 1965, **4**, 593; A. S. Garay and H. N. Towers, *Canad. J. Botany*, 1966, **44**, 231; K. H. Köhler, *Naturwiss.*, 1965, **52**, 561; H. W. Liebisch, B. Matschiner, and H. R. Schütte, *Z. Pflanzenphysiol.*, 1969, **61**, 269.

<sup>31</sup> H. E. Miller, H. Rösler, A. Wohlpart, H. Wyler, M. E. Wilcox, H. Frohofer, T. J. Mabry, and A. S. Dreiding, *Helv. Chim. Acta*, 1968, **51**, 1470.



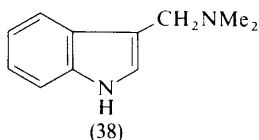
locate the label in the betalainic acid moiety of betanidine.<sup>32</sup> Decarboxylation of betanidine (the aglycone of betanine) in ethanol gave (37). Unexpectedly, decarboxylation of the betanidine from the dopa feed resulted in loss of 86% of the activity, suggesting C-20 rather than C-19 as the labelling site. Decarboxylation in EtOD, however, gave a product in which the C-15 proton was absent but the one at C-17 remained. This is inconsistent with a mechanism for loss of the C-20 carboxy-group, but may be rationalized with loss of the C-19 carboxy-function (Scheme 3), where C-15 and C-17 of betanidine have become C-17 and C-15, respectively, in (37).



<sup>32</sup> E. Dunkelblum, H. E. Miller, and A. S. Dreiding, *Helv. Chim. Acta*, 1972, **55**, 642.

Biological formation of betalnic acid involves ring cleavage of dopa (34) in one of two ways; path a or path b of Scheme 2. Enzymes from sources other than the *Centrospermeae* will catalyse either of these cleavages in several phenols.<sup>33</sup> The reaction to form betalnic acid was examined by incubating L-[3,5-<sup>3</sup>H<sub>2</sub>]-tyrosine with the pulp taken from the soft centre of young cactus fruits (*Opuntia decumbens*).<sup>34</sup> A satisfactory incorporation into betanin (36) was recorded (0.03—0.08%, or 0.06—0.16% allowing for the expected loss of half the tritium on hydroxylation to dopa, compared with 0.53% for L-[1'-<sup>14</sup>C]tyrosine) and the majority of the label was confined to the betalnic acid portion. No NIH shift<sup>35</sup> was expected on formation of dopa. Otherwise C-12 (path b) or C-18 (path a) of betanine would have been labelled, resulting from the presence of tritium at C-2 of dopa. The absence of such a shift was proved when exchange of these positions with trifluoroacetic acid caused no tritium loss from betanidine. The dopa was thus labelled as shown in (34), and as cleavage by path a would give betalnic acid (35) with retention of the tritium label (at C-11) whereas path b would result in its loss (from C-17), the former mode of cleavage is indicated. However, as the tritiated tyrosine was incorporated less well than [1'-<sup>14</sup>C]tyrosine, the operation of path b in addition to path a cannot be excluded at this stage.

**Gramine.**—The mechanism by which gramine (38) arises from tryptophan is still unknown, although it is established that the amino-group,<sup>36</sup> indole nucleus, and



$\beta$ -carbon atom,<sup>37</sup> but not the  $\alpha$ -carbon,<sup>38</sup> of tryptophan are incorporated. An earlier experiment with [2'-<sup>14</sup>C; 2'-<sup>3</sup>H]tryptophan<sup>39</sup> has been repeated<sup>40</sup> and the finding confirmed that the tritium at this position is retained. A small loss of tritium was observed, suggesting possible modification of the  $\beta$ -carbon atom and tritium retention by a primary isotope effect, but this was excluded when [2'-<sup>14</sup>C; 2'-<sup>2</sup>H<sub>2</sub>]tryptophan was incorporated without deuterium loss.

**Indolmycin.**—It has been shown<sup>41</sup> that indolmycin (39; corrected <sup>42</sup> stereochemistry) is derived from its co-metabolite in *Streptomyces griseus*, indolmycenic acid (45; corrected<sup>42</sup> stereochemistry).

<sup>33</sup> O. Hayaishi and M. Nozaki, *Science*, 1969, **164**, 389; O. Hayaishi, in 'Biological Oxidations', ed. T. Singer, Interscience, New York, 1968, p. 581.

<sup>34</sup> N. Fischer and A. S. Dreiding, *Helv. Chim. Acta*, 1972, **55**, 649.

<sup>35</sup> R. B. Herbert, in ref. 5, p. 26, and references cited therein.

<sup>36</sup> D. Gross, A. Nemeckova, and H. R. Schütte, *Z. Pflanzenphysiol.*, 1967, **57**, 60.

<sup>37</sup> E. Leete and L. Marion, *Canad. J. Chem.*, 1953, **31**, 1195.

<sup>38</sup> D. Gross, H. Lehmann, and H. R. Schütte, *Biochem. Physiol. Pflanzen.*, in the press.

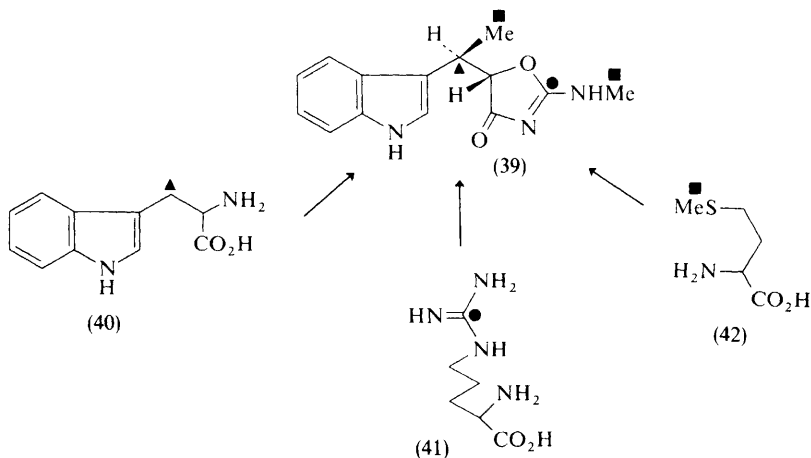
<sup>39</sup> D. O'Donovan and E. Leete, *J. Amer. Chem. Soc.*, 1963, **85**, 461.

<sup>40</sup> D. Gross, H. Lehmann, and H. R. Schütte, *Tetrahedron Letters*, 1971, 4047.

<sup>41</sup> U. Hornemann, L. H. Hurley, M. K. Speedie, and H. G. Floss, *Tetrahedron Letters*, 1970, 2255.

<sup>42</sup> U. Hornemann, M. K. Speedie, L. H. Hurley, and H. G. Floss, *Biochem. Biophys. Res. Comm.*, 1970, **39**, 594.

The origin of the carbon skeleton of indolmycin has been established recently.<sup>43</sup> Specific incorporations were found for  $^{14}\text{C}$  labelled (*R,S*)-tryptophan (40), (*S*)-arginine (41), and (*S*)-methionine (42), as illustrated in Scheme 4. In addition,

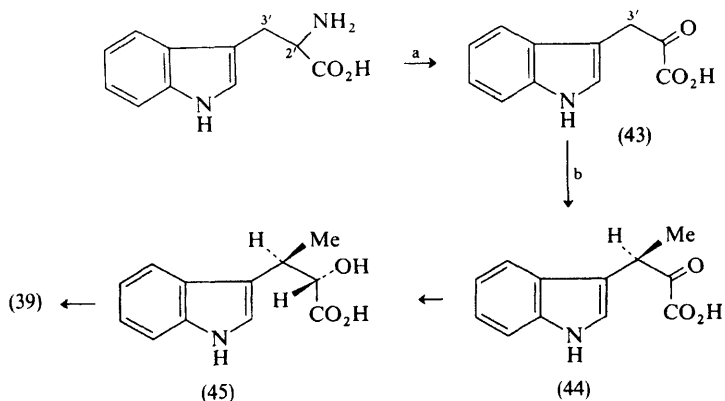


Scheme 4

[1'- $^{14}\text{C}$ ]- and [2'- $^{14}\text{C}$ ]-(*R,S*)-tryptophan and the tryptophan precursors anthranilic acid (as  $G\text{-}^3\text{H}$ ) and indole (as 2- $^{14}\text{C}$ ) were efficiently utilized. [ $\text{Me-}^{14}\text{C}$ ,  $\text{Me-}^3\text{H}$ ]Methionine gave indolmycin without change in isotope ratio, indicating incorporation of all three hydrogen atoms of the methyl group but only if no primary isotope effect was operating. (*R,S*)-[3'- $^{14}\text{C}$ ; 2'- $^3\text{H}$ ]Tryptophan was incorporated with complete tritium loss whereas (*R,S*)-[3'- $^{14}\text{C}$ ; 3'- $^3\text{H}$ ]tryptophan gave indolmycin with 52% retention of tritium. A stereospecific loss of hydrogen from C-3' is thus indicated, which may occur in an enolization step prior to methylation of indolepyruvic acid (43), whose formation from tryptophan would result in loss of the tritium from C-2'. Similar results were obtained for indolmycenic acid. The pathway illustrated (Scheme 5) is consistent with the above results and, further, the steps a and b have been carried out using cell-free extracts of *S. griseus* and tryptophan cannot substitute for indolepyruvic acid in step b.<sup>42,44</sup> The *in vitro* reaction b yielded (*R*)-3'-methylindolepyruvic acid (44), which could be transformed into indolmycin *in vivo*; the (*S*)-isomer was not utilized.<sup>43</sup> Finally, and incidentally, (2'*R*,3'*S* + 2'*S*,3'*R*)-3'-methyltryptophan, but not the (2'*R*,3'*R* + 2'*S*,3'*S*)-racemate, could act as a precursor for indolmycin. Presumably only (2'*S*,3'*R*)-methyltryptophan was incorporated, by way of transamination into (*R*)-3'-methylindolepyruvic acid.

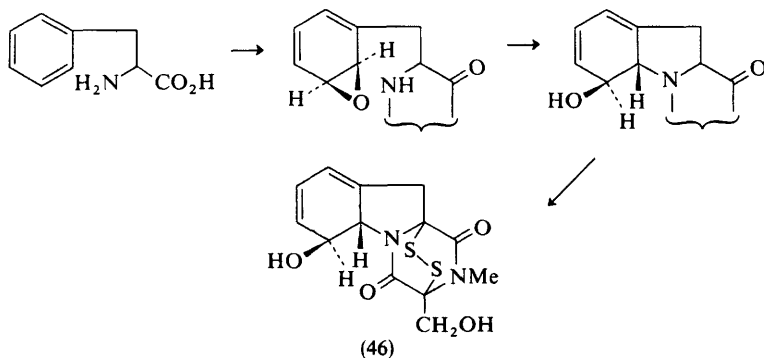
<sup>43</sup> U. Hornemann, L. H. Hurley, M. K. Speedie, and H. G. Floss, *J. Amer. Chem. Soc.*, 1971, **93**, 3028.

<sup>44</sup> U. Hornemann, M. K. Speedie, and H. G. Floss, unpublished results.



Scheme 5

**Gliotoxin.**—Gliotoxin (46) is a metabolite of *Trichoderma viride* and *Penicillium terlikowskii*. Recently, phenylalanine but not *m*-tyrosine (in contrast to earlier work<sup>45</sup>) or *o*-tyrosine or 2,3-dihydroxyphenylalanine has been shown to be incorporated.<sup>46</sup> The incorporation was sufficiently high to allow the use of



Scheme 6

deuterium-labelled precursors and it could then be shown that all five aromatic hydrogens of phenylalanine are retained in gliotoxin formation. The phenol (49) has been reported<sup>47</sup> as a precursor for gliotoxin, but in view of the above cannot be an obligatory intermediate.

Similar results have been found for bisdethiodi(methylthio)acetylarnotin (47) in *Arachniotus aureus*.<sup>48</sup> It was rigorously demonstrated that phenylalanine,

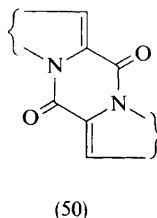
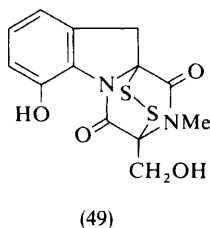
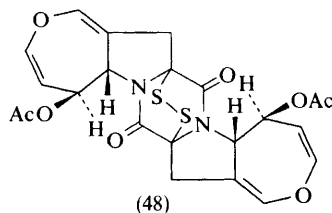
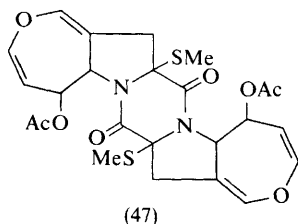
<sup>45</sup> J. A. Winstead and R. J. Suhadolnik, *J. Amer. Chem. Soc.*, 1960, **82**, 1644.

<sup>46</sup> J. D. Bu'Lock and A. P. Ryles, *Chem. Comm.*, 1970, 1404.

<sup>47</sup> M. S. Ali, R. Rahman, and A. Taylor, 5th International Symposium on the Chemistry of Natural Products, IUPAC, London, 1968, Abstracts, p. 94.

<sup>48</sup> D. R. Brannon, J. A. Mabe, B. B. Molloy, and W. A. Day, *Biochem. Biophys. Res. Comm.*, 1971, **43**, 588.

but not *m*-tyrosine, was a precursor. Further, DL-[3'-<sup>14</sup>C; 2,6-<sup>3</sup>H<sub>2</sub>]phenylalanine was incorporated with retention of 80% of the tritium label and L-[<sup>2</sup>H<sub>8</sub>]phenylalanine was incorporated into acetylaranotin (48) in *Aspergillus terreus* with retention of the aromatic and C-3' deuterium atoms. Retention of the latter excludes from acetylaranotin biosynthesis an intermediate of partial structure (50).



Incorporation of phenylalanine into these metabolites would reasonably proceed by a pathway involving 2,3-epoxidation of the aromatic ring, shown in Scheme 6 for gliotoxin (46);<sup>49</sup> additionally, rearrangement of the appropriate 2,3-epoxide would give the oxepin rings found in the aranotins.

It has been found when phenylalanine is administered to *T. viride* that, in competition with incorporation into gliotoxin which proceeds with retention of both hydrogens at C-3', stereospecific exchange of the pro-3'-(S)-hydrogen occurs.<sup>50</sup>

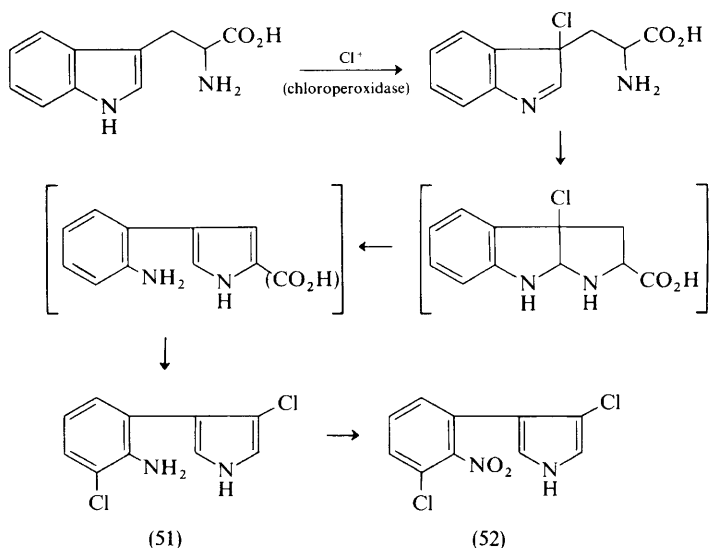
**Pyrrolnitrin.**—Pyrrolnitrin (52), a metabolite of *Pseudomonas aureofaciens*, is known to derive from tryptophan and the D-isomer is a more effective precursor than L-tryptophan.<sup>51</sup> The amino-compound (51) has been isolated from *Ps. aureofaciens* and is efficiently incorporated into pyrrolnitrin.<sup>52</sup> A biosynthetic pathway (Scheme 7) has been proposed.

<sup>49</sup> N. Neuss, L. D. Boeck, D. R. Brannon, J. C. Cline, D. C. De Long, M. Gorman, L. L. Huckstep, D. H. Lively, J. A. Mabe, M. M. Marsh, B. B. Molloy, R. Nagarajan, J. D. Nelson, and W. M. Stark, *Antimicrobial Agents Chemotherapy*, 1968, 213; N. Neuss, R. Nagarajan, B. B. Molloy, and L. L. Huckstep, *Tetrahedron Letters*, 1968, 4467.

<sup>50</sup> J. D. Bu'Lock, A. P. Ryles, N. Johns, and G. W. Kirby, *J.C.S. Chem. Comm.*, 1972, 100.

<sup>51</sup> D. H. Lively, M. Gorman, M. E. Haney, and J. A. Mabe, *Antimicrobial Agents Chemotherapy*, 1966, 462.

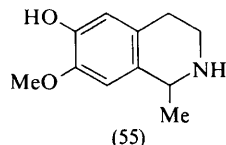
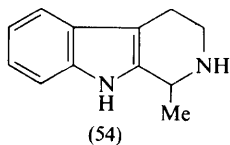
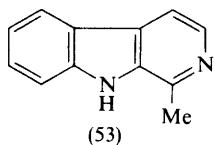
<sup>52</sup> R. Hamill, R. Elander, J. A. Mabe, and M. Gorman, *Antimicrobial Agents Chemotherapy*, 1967, 388.



Scheme 7

Experiments with  $^{14}\text{C}$ -,  $^{15}\text{N}$ -labelled tryptophan<sup>53</sup> have shown, in support of this pathway, intact incorporation of the indole nitrogen (and C-2 of the indole ring) but appreciable loss of the side-chain nitrogen by transamination; this label was, however, confined to the pyrrolic nitrogen. Although D-[3'- $^{14}\text{C}$ ; 2'- $^3\text{H}$ ]-tryptophan was incorporated with almost complete loss of tritium, the corresponding L-isomer inexplicably gave a high tritium retention.

**$\beta$ -Carboline, Simple Isoquinoline, and Phenylethylamine Alkaloids.**—Following upon the efficient and specific incorporation of [2-acetyl- $^{14}\text{C}$ ]-N-acetyltryptamine into harman (53) in *Passiflora edulis*,<sup>54</sup> the acetamides [1-acetyl- $^{14}\text{C}$ ]-N-acetyltryptamine, [1-acetyl- $^{14}\text{C}$ ]-N-acetyl-3-hydroxy-4-methoxyphenylethylamine, and [1-acetyl- $^{14}\text{C}$ ]-N-acetyl-3,4-dimethoxy-5-hydroxyphenylethylamine, were tested as precursors for, respectively, eleagnine (54) in *Eleagnus angustifolia*, salsoline (55) in *Echinocereus merkei*, and anhalonidine (56) in *Lophophora*

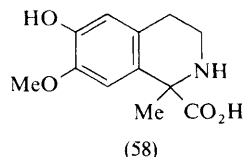
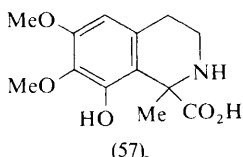
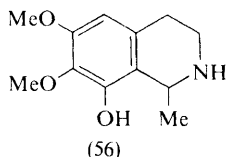


<sup>53</sup> H. G. Floss, P. E. Manni, R. L. Hamill, and J. A. Mabe, *Biochem. Biophys. Res. Comm.*, 1971, **45**, 781.

<sup>54</sup> M. Slaytor and I. J. McFarlane, *Phytochemistry*, 1968, **7**, 605.

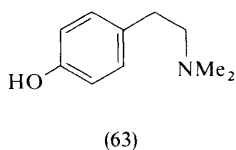
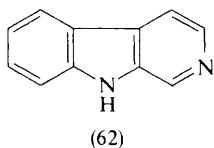
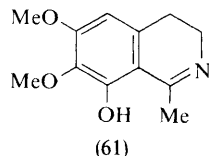
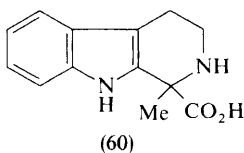
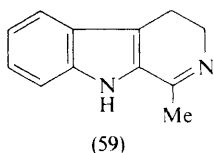
<sup>55</sup> I. J. McFarlane and M. Slaytor, *Phytochemistry*, 1972, **11**, 229.

*williamsii*.<sup>55</sup> None of these compounds was incorporated under conditions when other, known, precursors were. These results are in accord with those found independently for anhalonidine.<sup>56</sup>



It is known that anhalonidine is derived *via* peyoruvic acid (57),<sup>56</sup> but this was not noted in the above study. However, the related amino-acid (58), which is found in *L. williamsii*,<sup>57</sup> was shown later to be incorporated into salsoline (55) in *E. merkei*.<sup>58</sup>

The failure of *N*-acetyltryptamine to act as a precursor for the tetrahydro- $\beta$ -carboline alkaloid eleagnine (54),<sup>55</sup> in contrast to its successful incorporation into the  $\beta$ -carboline harman (53),<sup>54</sup> has led to the suggestion that they may arise by different routes.<sup>55</sup> This is supported by the successful isolation by radioisotope dilution of *N*-acetyltryptamine from *P. edulis*,<sup>54</sup> but failure under similar conditions to detect it in *E. angustifolia*.<sup>55</sup> In contrast, however, eleagnine (54) and harmalan (59) are efficiently and specifically incorporated into harman in *P.*



*edulis*.<sup>54</sup> Clearly, in order to resolve the problem the amino-acid (60) needs to be examined as a possible intermediate in the biosynthesis of  $\beta$ -carboline and tetrahydro- $\beta$ -carboline alkaloids; significantly, harmalan (59) has its analogue in the imine (61), which arises by biological decarboxylation of (57).<sup>56</sup>

A culture from the roots of *Phaseolus vulgaris* has been found to produce harman (53) and norharmian (62) when grown on a tryptophan-rich diet, although the intact plant does not produce  $\beta$ -carbolines.<sup>59</sup>

<sup>56</sup> G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Favez, Y. N. Vaishnav, and H. M. Fales, *J. Amer. Chem. Soc.*, 1970, **92**, 6943; J. Staunton, ref. 8, p. 11.

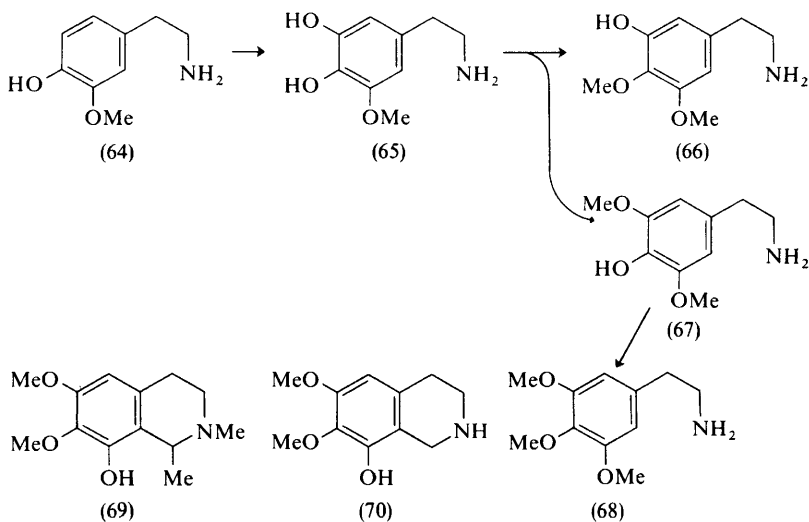
<sup>57</sup> K. J. Kapadia, M. B. E. Favez, Y. S. Vaishnav, H. M. Fales, and G. Subba Rao, *Lloydia*, 1969, **32**, 525.

<sup>58</sup> I. J. McFarlane and M. Slaytor, *Phytochemistry*, 1972, **11**, 235.

<sup>59</sup> I. A. Veliky, *Phytochemistry*, 1972, **11**, 1405.

The difficulties which may be encountered in establishing well-known pathways in a new plant are illustrated by feeding experiments with  $[2\text{'-}^{14}\text{C}]$ tyrosine,  $[1',2\text{'-}^3\text{H}_2]$ dopamine, and 3-hydroxy-4-methoxy[*ar*- $^3\text{H}$ ]phenylethylamine in *E. merkei*.<sup>58</sup> The conversion of tyrosine into hordenine (63), established in barley,<sup>60</sup> could not be demonstrated. Nor were tyrosine and dopamine incorporated into salsoline (55), but all three of the labelled compounds were converted into 3,4-dimethoxyphenylethylamine. These results were rationalized as indicating a pathway that diverged after dopamine with appropriate methylation, giving either salsoline (55) or 3,4-dimethoxyphenylethylamine (a similar branch point is observed in *L. williamsii* for the biosynthesis of mescaline and tetrahydroisoquinolines).<sup>61</sup> Further, at the time of the experiments the required methyltransferases for salsoline and hordenine biosynthesis were apparently blocked. In any event the pathway to 3,4-dimethoxyphenylethylamine is manifestly the dominant one, as this alkaloid and its *N*-methyl derivatives are major constituent bases of this plant.<sup>62</sup>

An *O*-methyltransferase has been isolated from *L. williamsii*, which in conjunction with *S*-adenosyl-L-methionine will effect methylation of various hydroxylated phenylethylamines.<sup>63</sup> Methylation of dopamine gave a single monomethyl compound, the mescaline precursor 4-hydroxy-3-methoxyphenylethylamine (64)<sup>61</sup> which, satisfyingly, was methylated twice as fast as 3-hydroxy-4-methoxyphenylethylamine to give the naturally occurring 3,4-dimethoxyphenylethylamine.



The next step for the *in vivo* formation of mescaline (68), however, is hydroxylation of (64) to give 3,4-dihydroxy-5-methoxyphenylethylamine (65).<sup>61</sup> This

<sup>60</sup> E. Leete and L. Marion, *Canad. J. Chem.*, 1953, **31**, 126.

<sup>61</sup> R. B. Herbert, in ref. 5, p. 16.

<sup>62</sup> S. Agurell, J. Lundström, and A. Masoud, *J. Pharm. Sci.*, 1969, **58**, 1413.

<sup>63</sup> G. P. Basmadjian and A. G. Paul, *Lloydia*, 1971, **34**, 91.

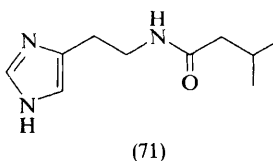


base was methylated enzymically and gave, significantly, a mixture of equal amounts of (66) and (67). The latter compound is known to be the immediate precursor *in vivo* for mescaline (68), whereas the former is used preferentially for the biosynthesis of tetrahydroisoquinolines.<sup>61,64</sup> Accordingly, whereas conversion of (67) into mescaline was catalysed by the *O*-methyltransferase, the methylation of (66) was not. Further, 3,4,5-trihydroxyphenylethylamine, although an efficient mescaline precursor in *Trichocereus pachanoi*, was not methylated by this enzyme system, in accord with its low incorporation into mescaline in *L. williamsii*.<sup>61</sup> 3,5-Dihydroxy-4-methoxyphenylethylamine was also inert to methylation.

*N*-Methyl-3-hydroxy-4,5-dimethoxyphenylethylamine and *NN*-dimethyl-3-hydroxy-4,5-dimethoxyphenylethylamine have been identified in *L. williamsii*.<sup>65</sup> The former base was incorporated with high efficiency into pellotine (69), but not into (56) or (70). Results obtained previously,<sup>66</sup> where pyruvate was shown to be a more specific precursor than acetate for anhalonidine (56), were confirmed. Alanine, and to a lesser extent glycine, could serve as C-2 units for (56). No significant results were obtained for (56) or (70) with formate or methionine. Although *N*-formyl- and *N*-acetyl-3-hydroxy-4,5-dimethoxyphenylethylamine are found in *L. williamsii* they were not incorporated intact into the isoquinoline alkaloids in the cactus, in accord with the discussion above. The mescaline precursors dopamine, 4-hydroxy-3-methoxyphenylethylamine, and 3,4-dihydroxy-5-methoxyphenylethylamine have been isolated from *L. williamsii* by radioisotope dilution.<sup>67</sup> The presence of dopamine and 3,4,5-trihydroxyphenylethylamine was uncertain.

The biosynthesis of the cactus alkaloids has been reviewed.<sup>68</sup>

**Dolichotheline.**—The published scheme<sup>69</sup> for the biosynthesis of dolichotheline (71) has received confirmation by other workers,<sup>70</sup> who have shown in addition



that histamine is a more efficient precursor for the alkaloid than histidine. Further, L-valine may be utilized for the isovaleryl moiety, being incorporated *via* leucine and not by direct reduction to isovalerate.

**Benzylisoquinoline Alkaloids.**—The investigation of the biosynthesis of morphine in *Papaver somniferum*, the Opium poppy, is one of the classics of alkaloid bio-

<sup>64</sup> J. Lundström and S. Agurell, *Acta Pharm. Suecica*, 1971, **8**, 261.

<sup>65</sup> J. Lundström, *Acta Pharm. Suecica*, 1971, **8**, 485.

<sup>66</sup> E. Leete and J. D. Braunstein, *Tetrahedron Letters*, 1969, 451.

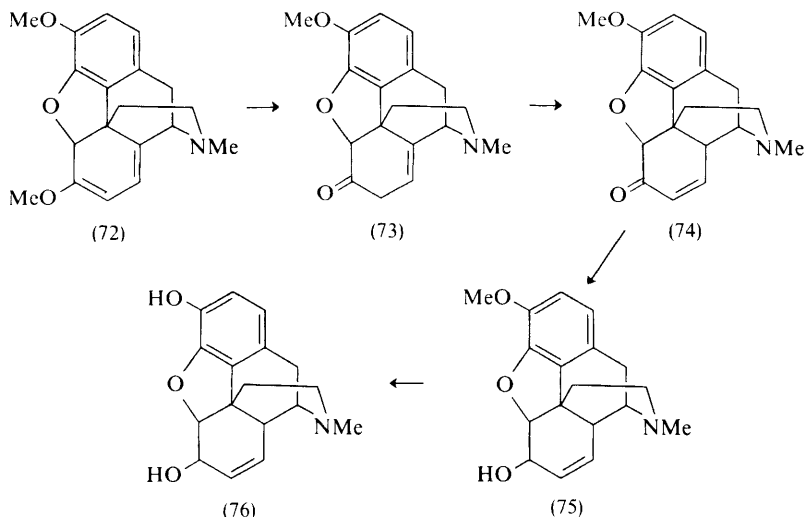
<sup>67</sup> J. Lundström, *Acta Chem. Scand.*, 1971, **25**, 3489.

<sup>68</sup> J. Lundström, *Acta Pharm. Suecica*, 1971, **8**, 275.

<sup>69</sup> H. Horan and D. G. O'Donovan, *J. Chem. Soc. (C)*, 1971, 2083; J. Staunton, ref. 8, p. 32.

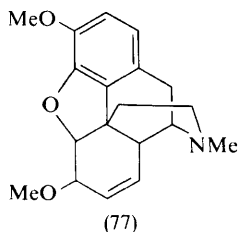
<sup>70</sup> H. Rosenberg and A. G. Paul, *Lloydia*, 1972, **34**, 372.

synthesis and it is interesting to see new work in the field. The last steps of the biosynthesis of morphine are thebaine (72)  $\rightarrow$  codeine (75)  $\rightarrow$  morphine (76).<sup>71</sup>



**Scheme 8**

Both codeinone (74) and codeine methyl ether (77) are incorporated into morphine,<sup>72</sup> suggesting the possibility of two paths for the conversion of thebaine into codeine. The recent experiments<sup>73</sup> have confirmed the previous findings



and allowed firm delineation of the pathway between thebaine and codeine using precursor feeding, in particular  $^{14}\text{CO}_2$ . The method used was for short-term exposure and it was refined so that  $^{14}\text{CO}_2$  concentration was kept constant; this is important if the sequence in which the alkaloids appear in the

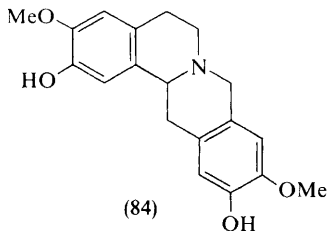
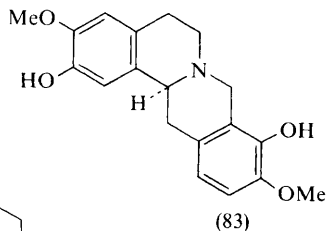
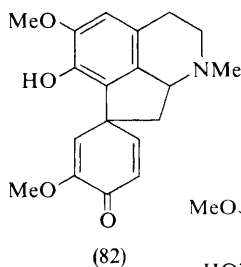
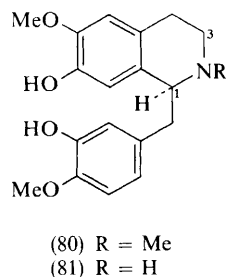
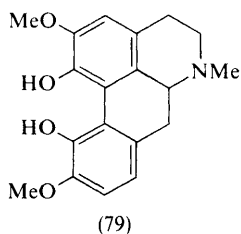
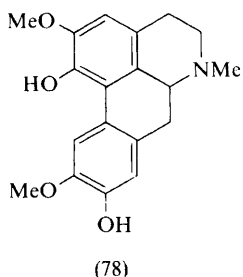
<sup>71</sup> H. Rapoport, F. R. Stermitz, and D. R. Baker, *J. Amer. Chem. Soc.*, 1960, **82**, 2765; F. R. Stermitz and H. Rapoport, *J. Amer. Chem. Soc.*, 1961, **83**, 4045; A. R. Battersby and B. J. T. Harper, *Tetrahedron Letters*, 1960, no. 27, 21.

<sup>72</sup> G. Blaschke, H. Parker, and H. Rapoport, *J. Amer. Chem. Soc.*, 1967, **89**, 1540; A. R. Battersby, E. Brochmann-Hanssen, and J. A. Martin, *Chem. Comm.*, 1967, 483; A. R. Battersby, J. A. Martin, and E. Brochmann-Hanssen, *J. Chem. Soc. (C)*, 1967, 1785; E. Brochmann-Hanssen, B. Nielsen, and G. Aadahl, *J. Pharm. Sci.*, 1967, **56**, 1207.

<sup>73</sup> H. I. Parker, G. Blaschke, and H. Rapoport, *J. Amer. Chem. Soc.*, 1972, **94**, 1276.

pathway is to be reliably related to their activity. The results are (a) whereas both neopinone (73) and codeinone are natural constituents of *P. somniferum*, codeine methyl ether is not ( $< 0.02\%$ ); (b) codeinone (74) and neopinone (73) are converted into codeine (and morphine); and (c) after exposure to  $^{14}\text{CO}_2$  the order of specific activities was thebaine  $>$  codeinone  $>$  codeine, as required for the intermediacy of codeinone in the transformation of thebaine into codeine. Codeinone was not converted into thebaine, and therefore this reaction, like the overall conversion of thebaine into codeine, is irreversible. The pathway, Scheme 8, is thus a most likely one. The incorporation of codeine methyl ether is apparently by an aberrant pathway resulting from demethylation by a non-specific demethylating enzyme.

Isoboldine (78) and magniflorine (79) are minor alkaloids of *P. somniferum* and superficially at least the products of *ortho-para* and *ortho-ortho* oxidative coupling of reticuline, respectively.  $[3\text{-}^{14}\text{C}]$ - or  $[N\text{-Me-}^{14}\text{C}]$ -(+)-reticuline

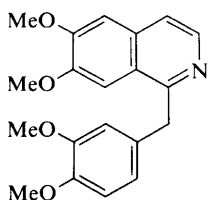


(as 80) gave radioactive isoboldine, and with the latter precursor, activity was confined to the *N*-methyl group.<sup>74</sup> Reticuline was, however, not incorporated into magniflorine (79). The isoboldine may of course arise either by direct coupling or *via* the dienone orientalinone (82).

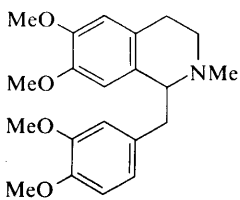
<sup>74</sup> E. Brochmann-Hanssen, C.-C. Fu, and L. Y. Misconi, *J. Pharm. Sci.*, 1971, **11**, 1880.

(-)-Scoulerine (83), which is derived<sup>75</sup> from (+)-reticuline (80), is found in *P. somniferum*.<sup>76</sup> Coreximine (84), with the alternative oxygenation pattern to scoulerine, has not been previously isolated from this plant. Dilution of *P. somniferum* with inactive ( $\pm$ )-coreximine after administration of [3-<sup>14</sup>C]- or [N-Me-<sup>14</sup>C]-( $\pm$ )-reticuline gave radioactive coreximine, which after the former feed was degraded and shown to be specifically labelled. Thus coreximine (of necessarily uncertain stereochemistry) is shown to be present in this plant and derivable from reticuline.

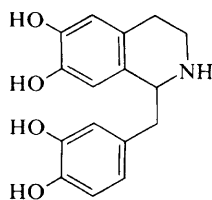
The biosynthesis of papaverine (85) and laudanosine (86) in *P. somniferum*, has received attention.<sup>77</sup> ( $\pm$ )-[3-<sup>14</sup>C]Nor-reticuline (as 80) was specifically and efficiently incorporated into papaverine, and so was [6-O-Me-<sup>14</sup>C]nor-reticuline, this latter result indicating that incorporation was not *via* norlaudanosoline (87). Reticuline itself was poorly utilized and 1,2-dehydronor-reticuline, perhaps surprisingly, not at all. Therefore, 1,2-dehydronor-reticuline was not reduced to nor-reticuline, and its incorporation<sup>78</sup> into morphine must be by *N*-methylation



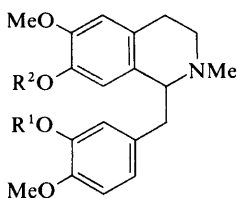
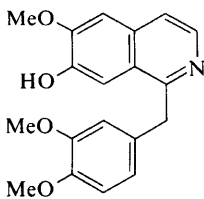
(85)



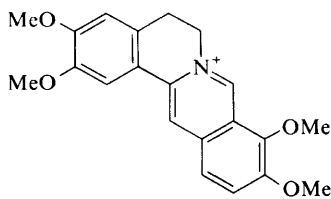
(86)



(87)

(88) R<sup>1</sup> = H, R<sup>2</sup> = Me(89) R<sup>1</sup> = Me, R<sup>2</sup> = H

(90)



(91)

and then reduction. ( $\pm$ )-[N-Me-<sup>14</sup>C]Laudanidine (88) was a specific precursor of laudanosone (86), whereas codamine (89) was but poorly incorporated. The presence of tetrahydropapaverine and pacodine (90) in *P. somniferum* was shown by radioisotope dilution after feeding labelled norlaudanosoline (87) and nor-reticuline, respectively, which also establishes a pathway between each pair.

<sup>75</sup> A. R. Battersby, R. J. Francis, E. Ruveda, and J. Staunton, *Chem. Comm.*, 1965, 89.

<sup>76</sup> E. Brochmann-Hanssen and B. Nielsen, *Tetrahedron Letters*, 1966, 2261.

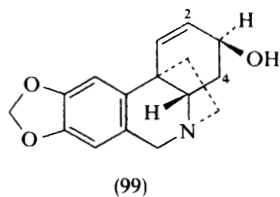
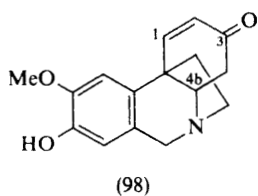
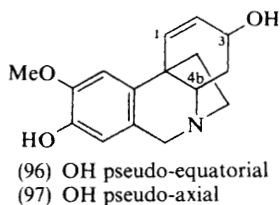
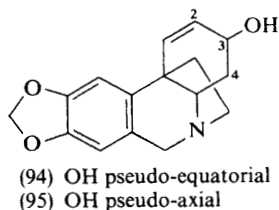
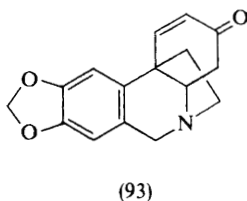
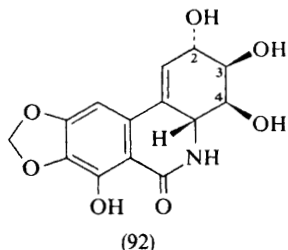
<sup>77</sup> E. Brochmann-Hanssen, C.-C. Fu, A. Y. Leung, and G. Zanati, *J. Pharm. Sci.*, 1971, **60**, 1672.

<sup>78</sup> A. R. Battersby, D. M. Foulkes, M. Hirst, G. V. Parry, and J. Staunton, *J. Chem. Soc. (C)*, 1968, 210.

The sequence of methylation and dehydrogenation which leads from norreticoline to papaverine and pacodine is still obscure.

The 'berberine-bridge' carbon of palmatine (91) has been shown to be derivable from formate,<sup>79</sup> in accord with earlier work on berberine.<sup>80</sup>

**Amaryllidaceae Alkaloids.**—Narciclasine (92) has been found to incorporate *O*-methylnorbelladine (101) and oxocrine (93), and thus arises by a pathway similar to that of haemanthamine (105).<sup>81</sup> In the late stages to narciclasine the two-carbon bridge is lost from the oxocrine skeleton, and preliminary experiments to determine the nature of the late intermediates have been reported.<sup>82,83</sup>



Whereas  $(\pm)$ -[3-<sup>3</sup>H]epicrine (94) and  $(\pm)$ -[1,3,4b-<sup>3</sup>H<sub>3</sub>]epinormaritidine (96) gave no significant incorporation into narciclasine and haemanthamine in daffodils,  $(\pm)$ -[3-<sup>3</sup>H]crinine (95),  $(\pm)$ -[1,3,4b-<sup>3</sup>H<sub>3</sub>]normaritidine (97), and  $(\pm)$ -[1,4b-<sup>3</sup>H<sub>2</sub>]noroxomaritidine (98) were efficiently utilized.<sup>82</sup> Degradation showed

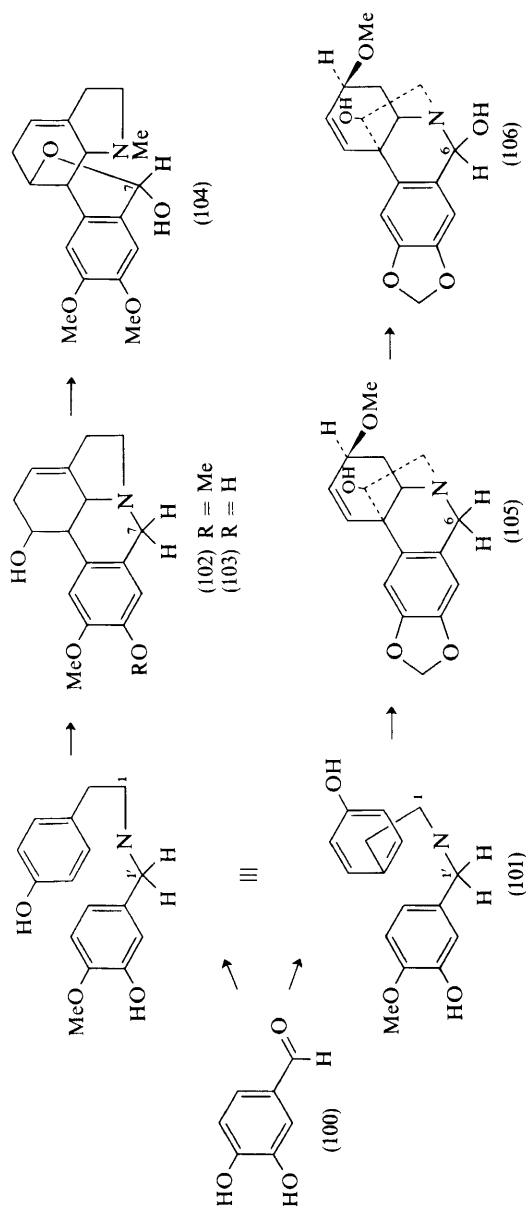
<sup>79</sup> A. R. Skerl and E. G. Gros, *Phytochemistry*, 1971, **10**, 2719.

<sup>80</sup> R. N. Gupta and I. D. Spenser, *Canad. J. Chem.*, 1965, **43**, 133.

<sup>81</sup> C. Fuganti, J. Staunton, and A. R. Battersby, *Chem. Comm.*, 1971, 1154; J. Staunton, ref. 8, p. 16.

<sup>82</sup> C. Fuganti and M. Mazza, *Chem. Comm.*, 1971, 1388.

<sup>83</sup> C. Fuganti and M. Mazza, *J.C.S. Chem. Comm.*, 1972, 239.



Scheme 9

that the tritium atoms were incorporated into the related positions of narciclasine. It is concluded that the biosynthesis of narciclasine passes through intermediates bearing a pseudoaxial hydroxy-group at C-3 and that hydrogen removal from this position does not occur. Further, formation of the methylenedioxy-group does not depend on a particular oxidation level at C-3.

Although racemic crinine was well incorporated into narciclasine it was likely that only one enantiomer was involved in the biosynthesis, either crinine or vittatine (99). Accordingly, whereas narciclasine (92) and haemanthidine (106) were both labelled by  $[2,4\text{-}^3\text{H}_2]$ vittatine in *Pancratium maritimum*,  $[2,4\text{-}^3\text{H}_2]$ crinine was not incorporated into narciclasine in daffodils.<sup>83</sup> The relative activities for positions 2 and 4 of narciclasine (92) after the vittatine feed were 2 : 1, confirming the finding<sup>81</sup> that half the expected activity at C-4 is lost, presumably on hydroxylation. These results, when considered together with those from an X-ray study,<sup>84</sup> allowed assignment of the stereostructure (92) to narciclasine (with revised relative stereochemistry).

Protocatechualdehyde (100) is incorporated into the C<sub>6</sub>-C<sub>1</sub> unit of lycorenine (104) and haemanthidine (106)<sup>85,86</sup> as shown in Scheme 9. It will be seen that each pathway involves the formal addition of hydrogen to the aldehyde carbon and subsequent removal on hydroxylation. The stereochemistry of these two processes has been investigated.<sup>86</sup>

O-Methyl $[1\text{-}^{14}\text{C}; 1'\text{-}^3\text{H}]$ norbelladine (101) was incorporated into haemanthamine (105), haemanthidine (106), pluviine (102), and lycorenine (104). The results show that no tritium is lost into (102) and (105) but that subsequent hydroxylation, as might be expected, leads to loss of half the tritium in the formation of (104) and (106), respectively. The reaction is therefore stereospecific.

$[\text{Formyl-}^3\text{H}]$ protocatechualdehyde gave  $[6\text{-}^3\text{H}]$ haemanthamine (as 105) and  $[7\text{-}^3\text{H}]$ norpluviine (as 103), which after isolation were each mixed with similar  $^{14}\text{C}$ -labelled material and incorporated into haemanthidine (106) and lycorenine (104), respectively, with almost complete tritium retention at the expected positions. Both addition and removal of hydrogen is therefore stereospecific. Moreover, it is the hydrogen initially introduced which is later removed.

Detailed evidence has been published<sup>87</sup> following the preliminary report<sup>88</sup> implicating tyrosine as the progenitor of the C<sub>6</sub>-C<sub>2</sub> unit of mesembrine (107) in *Sceletium strictum* on the one hand, and phenylalanine as the source of the unusual, if not unique, C<sub>6</sub> unit on the other. The results<sup>87,88</sup> showed that (a) methionine served as the specific precursor of the N- and O-methyl groups; (b) whereas DL-[2'- $^{14}\text{C}$ ]- and DL-[3'- $^{14}\text{C}$ ]-phenylalanine gave inactive alkaloid, DL-[*ar*-U- $^{14}\text{C}$ ]phenylalanine specifically labelled the aromatic ring of mesembrine; and (c) DL-[3'- $^{14}\text{C}$ ]- and DL-[2'- $^{14}\text{C}$ ]-tyrosine were incorporated. Degradation of the mesembrine after administration of the former tyrosine precursor

<sup>84</sup> A. Immirzi and C. Fuganti, *J.C.S. Chem. Comm.*, 1972, 240.

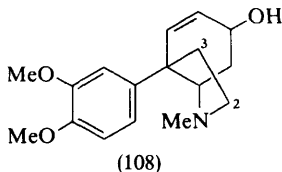
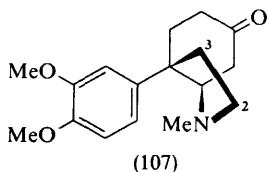
<sup>85</sup> R. J. Suhadolnik, A. G. Fischer, and J. Zulaian, *Proc. Chem. Soc.*, 1963, 132.

<sup>86</sup> C. Fuganti and M. Mazza, *Chem. Comm.*, 1971, 1196.

<sup>87</sup> P. W. Jeffs, W. C. Archie, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, 1971, **93**, 3752.

<sup>88</sup> P. W. Jeffs, W. C. Archie, and D. S. Farrier, *J. Amer. Chem. Soc.*, 1967, **89**, 2509.

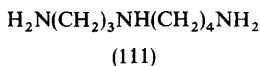
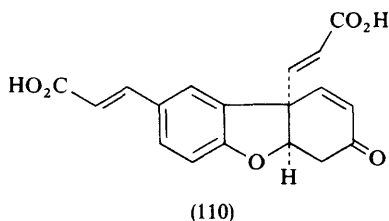
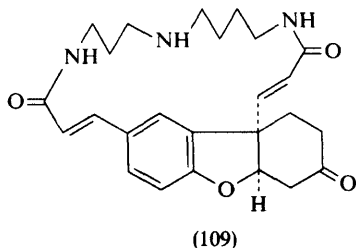
showed that the activity was located at C-2 and/or C-3 (expected at C-3). Mesembrenol (108) is also found in *S. strictum*. Degradation of this alkaloid after administration of  $[2\text{'-}^{14}\text{C}]$ tyrosine revealed the site of labelling as expected at



C-2. Thus tyrosine is incorporated intact and serves as the source of the octahydroindole portion of these alkaloids, whereas phenylalanine provides the aromatic ring only.

Attention is drawn to results<sup>89</sup> which suggest an unusual pathway for the elaboration of mesembrine from these amino-acids, reviewed last year.<sup>90</sup>

**Lunarine.**—The biosynthesis of lunarine (109) has been studied in *Lunaria biennis*.<sup>91</sup> Although  $[3\text{'-}^{14}\text{C}]$ phenylalanine was incorporated,  $[3\text{'-}^{14}\text{C}]$ tyrosine was not. Consequently, phenylalanine is converted first into cinnamic acid, which is then hydroxylated. Oxidative coupling of *p*-hydroxycinnamic acid and cyclization would give (110), the analogue of Pummerer's ketone, and thence to



lunarine.  $[3\text{'-}^{14}\text{C}; 4\text{'-}^3\text{H}]$ Phenylalanine gave lunarine with 32% tritium retention, whereas on the expectation of an NIH shift on hydroxylation of cinnamic acid,<sup>92</sup> 75% of the label should have been retained. Nonetheless, an NIH shift clearly occurs and further loss of tritium presumably occurs by enolization.

Spermidine (111) was shown to give the remaining atoms of lunarine.

<sup>89</sup> P. W. Jeffs, H. F. Campbell, D. S. Farrier, and G. Molina, *Chem. Comm.*, 1971, 228.

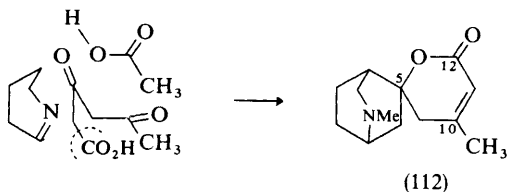
<sup>90</sup> J. Staunton, ref. 8, p. 18.

<sup>91</sup> C. Poupat and G. Kunesch, *Compt. rend.*, 1971, 273, C, 433.

<sup>92</sup> W. R. Bowman, I. T. Bruce, and G. W. Kirby, *Chem. Comm.*, 1969, 1075; R. B. Herbert, in ref. 5, p. 26.



**Piperidine Alkaloids.**—The hypothesis<sup>93</sup> that dioscorine (112) was derived from six acetate units has been tested by administration of sodium [1-<sup>14</sup>C]acetate to *Dioscorea hispida*.<sup>94</sup> Degradation of the dioscorine isolated showed, significantly, that of the carbons of the isoquinuclidine ring only C-5 was heavily labelled (30% of total). The remaining activity was located equally at C-10 and C-12. Thus dioscorine is built of only four acetate units, the remaining carbons of the skeleton being derived probably from lysine *via* a piperidine moiety such as  $\Delta^1$ -piperidine (Scheme 10).



Scheme 10

Although amino-acids have been administered to plants on occasions legion in number, rarely has attention been paid to the question of whether there is any selectivity for the D- or L-amino-acid in alkaloid biosynthesis. An exception appears in work on the *Amaryllidaceae* alkaloids where it was shown that D- and L-tyrosine were equally well utilized in lycorine biosynthesis.<sup>95</sup> The question has now been answered in *Nicotiana glauca* for the biosynthesis of anabasine (118) and pipecolic acid (113) from lysine.<sup>96</sup> Pipecolic acid was found to be derived preferentially from the D-isomer (~48 times better), in accord with a similar preference in intact rats<sup>97</sup> and corn seedlings,<sup>98</sup> whereas L-lysine was the more effective precursor (~30 times) for anabasine.

These results tie in neatly with others obtained for the biosynthesis of sedamine (117), anabasine (118), and N-methylpelletierine (119) where, it was shown, the pathway differs from that which leads to pipecolic acid. In essence the results<sup>99-101</sup> show that (117), (118), and (119) derive from lysine without loss of the hydrogens from C-2 and C-6, whereas the genesis of pipecolic acid (113) is with retention of the hydrogens from C-6 and loss of the one from C-2. Further, all these piperidine derivatives arise from lysine without the intermediacy of a symmetrical intermediate. The results may be summarized in terms of the

<sup>93</sup> E. Leete, in 'Biogenesis of Natural Compounds', ed. P. Bernfeld, Pergamon, Oxford, 2nd edn., 1967, p. 968.

<sup>94</sup> E. Leete and A. R. Pinder, *Chem. Comm.*, 1971, 1499.

<sup>95</sup> I. T. Bruce and G. W. Kirby, *Chem. Comm.*, 1968, 207.

<sup>96</sup> T. J. Gilbertson, *Phytochemistry*, 1972, **11**, 1737.

<sup>97</sup> J. A. Grove, T. J. Gilbertson, R. H. Hammerstedt, and L. M. Henderson, *Biochim. Biophys. Acta*, 1969, **184**, 329.

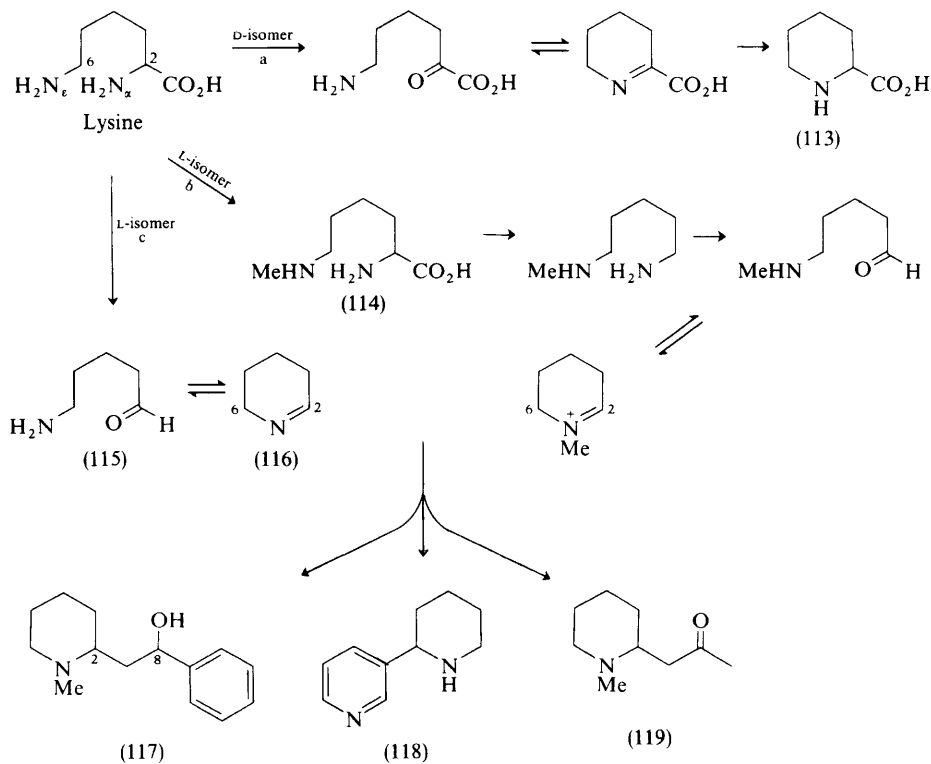
<sup>98</sup> R. H. Aldag and J. L. Young, *Planta*, 1970, **95**, 187.

<sup>99</sup> (a) R. N. Gupta and I. D. Spenser, *Phytochemistry*, 1970, **9**, 2329; (b) references cited therein.

<sup>100</sup> E. Leete, *Accounts Chem. Res.*, 1971, **4**, 100.

<sup>101</sup> J. Staunton, ref. 8, p. 20; R. B. Herbert, in ref. 5, p. 3.

following pathways: for pipecolic acid (113), path a, Scheme 11; for the others, two have been suggested. The first invokes  $\epsilon$ -N-methyl-lysine (114), path b;<sup>99a</sup> its analogue  $\delta$ -N-methylornithine is implicated in a similar scheme for the biosynthesis of pyrrolidine alkaloids.<sup>102</sup> The other suggestion implicates 5-amino-pentanal (115), formed by concerted decarboxylation and deamination of



Scheme 11

lysine.<sup>100</sup> If path b is followed, and feeding experiments with  $\epsilon$ -N-methyl-lysine are surely in hand, then the biosynthesis of anabasine involves a demethylation at some point. It is notable that pelletierine,<sup>103</sup> the demethyl derivative of (119), as well as *e.g.* cernuine (127)<sup>103,104</sup> and decodine,<sup>105</sup> arise from lysine by way of a symmetrical intermediate, reasonably cadaverine (see also ref. 116).

<sup>102</sup> R. B. Herbert, in ref. 5, p. 9.

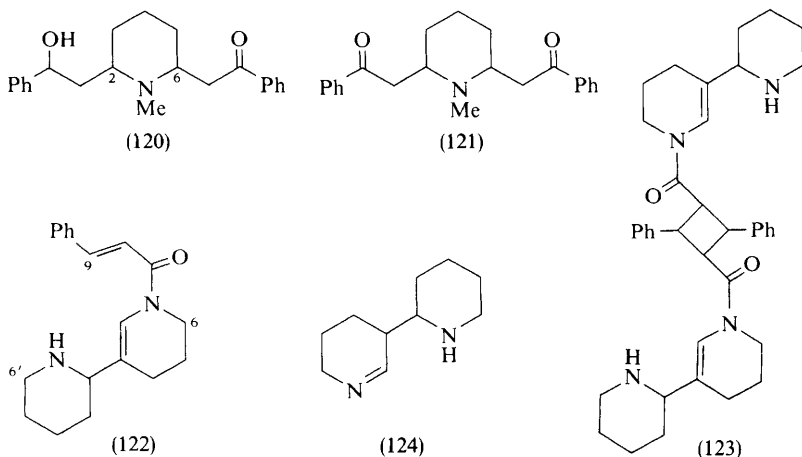
<sup>103</sup> R. B. Herbert, in ref. 5, p. 5.

<sup>104</sup> R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *Chem. Comm.*, 1970, 409.

<sup>105</sup> S. H. Koo, R. N. Gupta, I. D. Spenser, and J. T. Wrobel, *Chem. Comm.*, 1970, 396; R. B. Herbert in ref. 5, p. 6.

8-Phenyl-lobelol-I, which differs from sedamine (117) only in the configuration at C-8,<sup>106</sup> occurs together with lobeline (120) in *Lobelia inflata*.<sup>107</sup> The derivation of sedamine from lysine by way of unsymmetrical intermediates was discussed above, and it may seem surprising therefore that [2-<sup>14</sup>C]lysine (reported as the D-isomer) was incorporated into lobeline with equal labelling of C-2 and C-6.<sup>108</sup> Examination of the structure of lobeline (120), however, immediately suggests that symmetrization of the lysine label could occur at a late stage of biosynthesis and that lobelanine (121) may be an intermediate. Accordingly [N-Me-<sup>14</sup>C]lobelanine was incorporated into lobeline, with high efficiency and specificity, establishing it as an immediate precursor.<sup>109</sup> This indicates that lobelanine is biosynthesized along a similar pathway to sedamine and its congeners, and it seems unlikely, though not disproven, that an early symmetrical intermediate (cadaverine) is implicated.

The tetrahydroanabasine skeleton is found in the *Adenocarpus* alkaloids adenocarpine (122) and santiaguine (123). Adenocarpine is known to incorporate the  $\Delta^1$ -piperidine dimer (124) with efficiency<sup>110</sup> lending credence to the view<sup>111</sup> that the tetrahydroanabasine alkaloids may arise from two molecules of lysine rather than one, as is found for anabasine in *Nicotiana*.<sup>112</sup>



The origin of the truxillic acid moiety of santiaguine has been examined recently. Unexceptionally, specific incorporations were recorded for DL-[2-<sup>14</sup>C]phenylalanine and [2-<sup>14</sup>C]cinnamic acid as progenitors for the truxillic

<sup>106</sup> C. Schöpf, G. Dummer, W. Wust, and R. Rausch, *Annalen*, 1959, **626**, 134.

<sup>107</sup> L. Marion, in 'The Alkaloids', ed. R. H. F. Manske and H. L. Holmes, Academic Press, New York, 1950, vol. 1, p. 189; C. Schöpf and T. Kauffmann, *Annalen*, 1957, **608**, 88.

<sup>108</sup> M. F. Keogh and D. G. O'Donovan, *J. Chem. Soc. (C)*, 1970, 2470.

<sup>109</sup> D. G. O'Donovan and T. Forde, *J. Chem. Soc. (C)*, 1971, 2889.

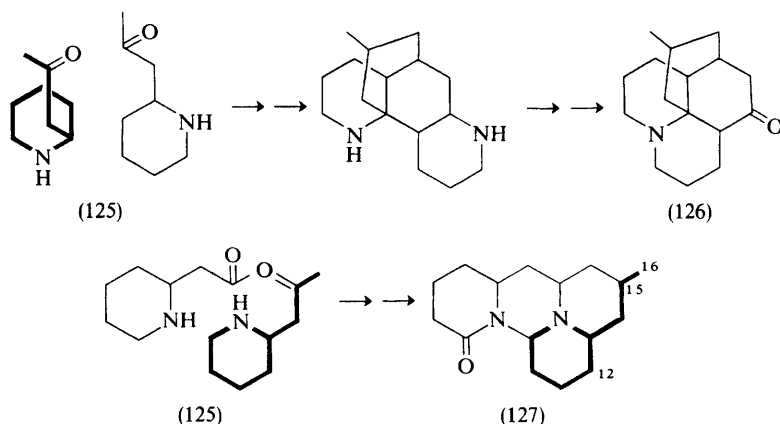
<sup>110</sup> H. R. Schütte, K. L. Kelling, D. Knöfel, and K. Mothes, *Phytochemistry*, 1964, **3**, 249.

<sup>111</sup> C. Schöpf, F. Braun, and A. Komazak, *Chem. Ber.*, 1956, **89**, 1821.

<sup>112</sup> T. Griffith and C. D. Griffith, *Phytochemistry*, 1966, **5**, 1175; E. Leete, *J. Amer. Chem. Soc.*, 1956, **78**, 3520; E. Leete, E. G. Gros, and T. J. Gilbertson, *J. Amer. Chem. Soc.*, 1964, **86**, 3907.

acid portion.<sup>113</sup> [9-<sup>14</sup>C;6,6'-<sup>3</sup>H<sub>2</sub>]Adenocarpine was efficiently built into santiaguine and without change in isotope ratio, demonstrating intact incorporation. It thus appears that santiaguine biosynthesis involves the dimerization of two molecules of adenocarpine (122), rather than initial dimerization of cinnamic acid to give truxillic acid.

Work on the biosynthesis of lycopodine (126)<sup>114</sup> in *Lycopodium tristachyum* and cernuine (127)<sup>104</sup> in *L. cernuum*, previously published in preliminary form and reviewed,<sup>103</sup> has appeared in full: lycopodine<sup>115</sup> and cernuine.<sup>116</sup> It was established that the two alkaloids are derived from two molecules of lysine *via* a symmetrical intermediate which is in all probability cadaverine. The hypothesis that the *Lycopodium* alkaloids were modified dimers of pelletierine (125) (Scheme 12) required reappraisal, as pelletierine gave only one each (shown with heavy bonding) of the two C<sub>8</sub>N units of (126) and (127).



Scheme 12

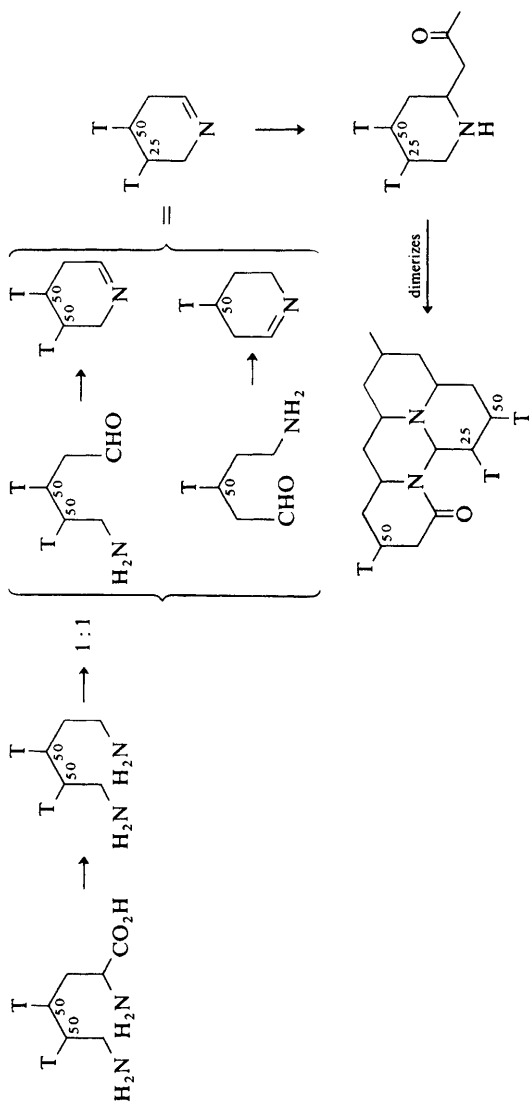
Additional results appear in the full papers: (a) [2-<sup>14</sup>C;4,5-<sup>3</sup>H<sub>2</sub>]lysine was incorporated<sup>116</sup> into cernuine with loss of 39% of the tritium label compared with 37.5% predicted according to Scheme 13, where it was assumed that tritium on carbon atoms adjacent to carbonyl groups would be completely lost by exchange; the close correspondence of the theoretical and observed values further support the outlined pathway to cernuine; (b) <sup>14</sup>C-labelled  $\Delta^1$ -piperidine (128) serves as a specific precursor for cernuine (129)<sup>116</sup> and lycopodine (130)<sup>115</sup> as shown in Scheme 14 ( $\blacktriangle, \blacksquare$  = labelling sites established by degradation;  $\triangle, \square$  = sites

<sup>113</sup> D. G. O'Donovan and P. B. Creedon, *J. Chem. Soc. (C)*, 1971, 1604.

<sup>114</sup> M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *J. Amer. Chem. Soc.*, 1970, **92**, 1074.

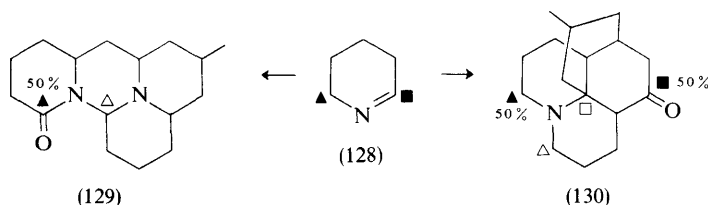
<sup>115</sup> M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1970, **48**, 2911.

<sup>116</sup> Y. K. Ho, R. N. Gupta, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1971, **49**, 3352.



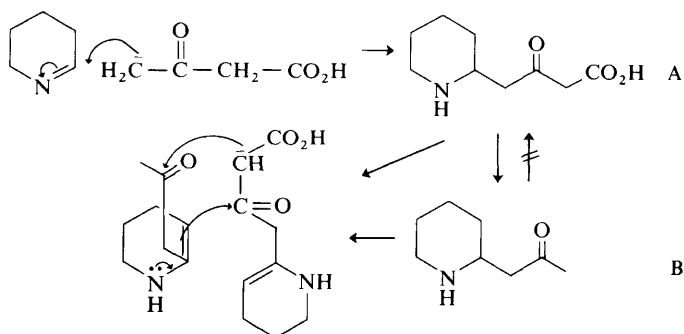
Scheme 13

assumed to be labelled); the results are in accord with the 'pelletierine-dimer' hypothesis.



Scheme 14

It is highly significant that  $\Delta^1$ -piperidine, like other precursors in different experiments, is equally incorporated into both  $C_8N$  units of lycopodine (130).<sup>115</sup> It follows therefore that if lycopodine is formed by the combination of two pelletierine-like units these units must be either identical or, if different, they must be derived from  $\Delta^1$ -piperidine with the same overall dilution by non-labelled pools. A model which implicates pelletierine (Scheme 15) has been suggested

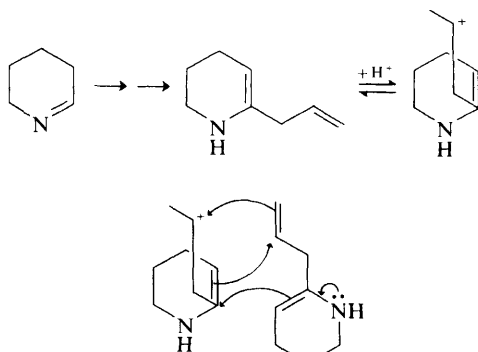


Scheme 15

for the latter alternative;<sup>115</sup> it is a requirement in this scheme that the steady-state concentration of B compared with that of A is low and that B is not convertible into A. The former alternative excludes pelletierine as a normal intermediate, but an ingenious suggestion<sup>115</sup> has been made which allows pelletierine to substitute for one of the two units. This is illustrated in Scheme 16; the protonated species would be replaceable by pelletierine ( $C^+$  roughly equatable with  $C=O$ ), but the other could not be.

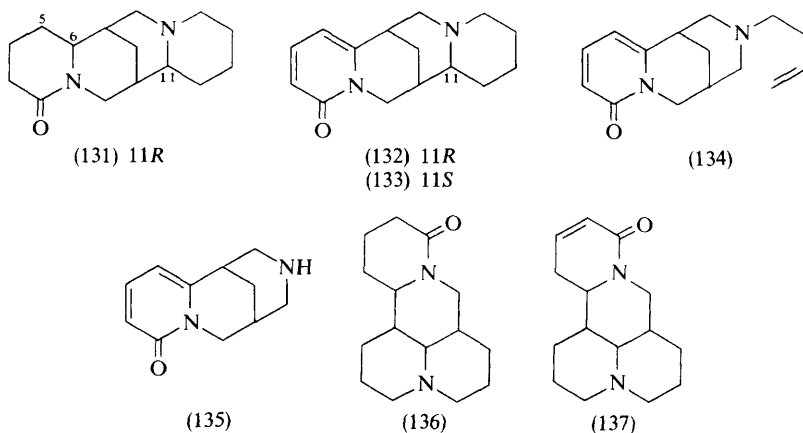
The biosynthesis of lupanine (131), 5,6-dehydrolupanine, anagryne (132), rhombifoline (134), thermopsine (133), cytisine (135), and *N*-methylcytisine has been examined<sup>117</sup> in *Thermopsis rhombifolia* and *T. caroliniana* with  $^{14}CO_2$ . Lupanine was the first alkaloid to be labelled and it was followed by 5,6-dehydrolupanine and anagryne (132). Then the first of the tricyclic bases, rhombifoline

<sup>117</sup> Y. D. Cho and R. O. Martin, *Canad. J. Biochem.*, 1971, **49**, 971.



Scheme 16

(134), was formed, which appeared to play a primary role in the formation of cytisine (135) and *N*-methyleytisine. As the tricyclic bases were labelled after the tetracyclic ones it appeared that the latter were the precursors of the former and the results suggested a role for 5,6-dehydrolupanine in this connection.



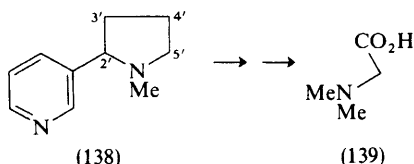
Thermopsine (133) appeared after rhombifoline (134). As in the biosynthesis of the alkaloids of *Lupinus angustifolius*,<sup>118</sup> no evidence could be found for the formation of sparteine. Finally, two unknown alkaloids, it was noted, were labelled early in both *Thermopsis* species.

[1,4-<sup>14</sup>C<sub>2</sub>]Cadaverine has been shown to be a precursor for matrine (136), its *N*-oxide, sophoramine, sophorocarpine (137), and its *N*-oxide in *Goebelia pachycarpa* and, further, matrine serves as a precursor for its *N*-oxide, and sophorocarpine (137) and its *N*-oxide.<sup>119</sup>

<sup>118</sup> Y. D. Cho, R. O. Martin, and J. D. Anderson, *J. Amer. Chem. Soc.*, 1971, **93**, 2087; J. Staunton, ref. 8, p. 26.

<sup>119</sup> B. A. Abdusalamov, A. A. Takanaev, Kh. A. Aslanov, and A. S. Sadykov, *Biochemistry (U.S.S.R.)*, 1971, **36**, 239.

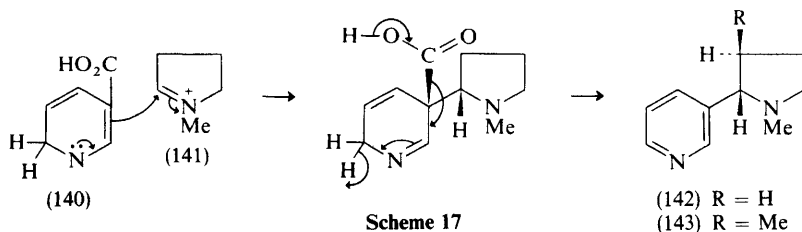
**Pyrrolidine Alkaloids.**— $^{14}\text{CO}_2$  and tracer feeding results are in conflict for the biosynthesis of the pyrrolidine ring of nicotine. On the one hand<sup>120</sup>  $[2\text{-}^{14}\text{C}]$ lysine afforded nicotine (138) with equal labelling of C-2' and C-3', whereas on the other<sup>121</sup> the alkaloid obtained after exposing *Nicotiana glutinosa* plants to  $^{14}\text{CO}_2$  was found to be more heavily labelled at C-4' and C-5' than C-2' and C-3'; other workers<sup>122</sup> have found uniform labelling of the pyrrolidine ring after application of  $^{14}\text{CO}_2$ .



The conflict has been partially resolved<sup>123</sup> by examination of one of the steps of the degradative sequence, *i.e.* lead tetra-acetate oxidation of *NN*-dimethylglycine (139). It could be shown by submitting  $[N\text{-Me-}^{14}\text{C}]$ - and  $[2\text{-}^{14}\text{C}]$ -dimethylglycine to this oxidation that the formaldehyde produced in the reaction, formerly thought to originate from C-2 only, was derived in appreciable amounts from the *N*-methyl groups. Since in the  $^{14}\text{CO}_2$  experiments the activity in the *N*-methyl group of nicotine was appreciably higher than that in the pyrrolidine ring, a high value for C-2' of nicotine would be observed.

A nicotinic acid decarboxylase has been isolated from the roots of *N. rustica*.<sup>124</sup>

The pyrroline (141) is a nicotine precursor<sup>125</sup> and gives nicotine, it has been suggested,<sup>126</sup> by condensation with the dihydronicotinic acid (140), Scheme 17.



Partially in an endeavour to define the stereochemical requirements for enzyme activity in nicotine biosynthesis, *C*-methyl derivatives of (141), namely (144),

<sup>120</sup> E. Leete, *Chem. and Ind.*, 1955, 537; L. J. Dewey, R. U. Byerrum, and C. D. Ball, *Biochim. Biophys. Acta*, 1955, **18**, 141.

<sup>121</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, *J. Amer. Chem. Soc.*, 1965, **87**, 4399; A. A. Liebman, B. P. Mundy, and H. Rapoport, *J. Amer. Chem. Soc.*, 1967, **89**, 664.

<sup>122</sup> H. R. Zielke, R. U. Byerrum, R. M. O'Neal, L. C. Burns, R. E. Koeppe, *J. Biol. Chem.*, 1968, **243**, 4757.

<sup>123</sup> E. Leete, *Chem. Comm.*, 1971, 1524.

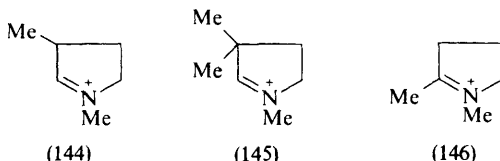
<sup>124</sup> J. L. R. Chandler and R. K. Gholson, *Phytochemistry*, 1972, **11**, 239.

<sup>125</sup> E. Leete, *J. Amer. Chem. Soc.*, 1967, **89**, 7081.

<sup>126</sup> R. F. Dawson, D. R. Christman, A. D'Adamo, M. L. Solt, and A. P. Wolf, *J. Amer. Chem. Soc.*, 1960, **82**, 2628.

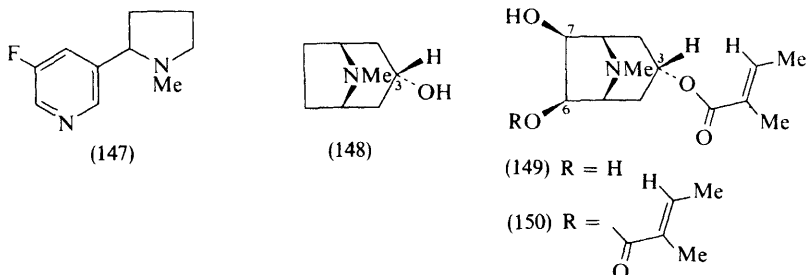


(145), and (146), have been tested as substrates in *Nicotiana glutinosa*.<sup>127</sup> Marked differences in efficiency of conversion into the corresponding methyl derivatives of nicotine were observed [360 (14%) : 20 : 1, respectively], which is in accord

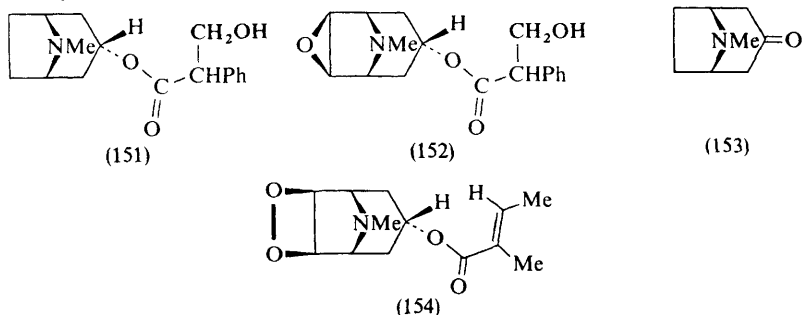


with the amount of steric hindrance expected on condensation of the pyrrolines with (140). It is interesting to note that of the optical isomers of 3'-methylnicotine, only (143) was isolated. Finally, it was suggested that the same enzyme system may be involved in the late stages of nicotine and anabasine biosynthesis.

In addition to the 'unnatural' nicotine precursors mentioned above, 5-fluoro-nicotinic acid has been administered, initially with fatal consequences, to *Nicotiana* (*N. tabacum*).<sup>128</sup> The plants were able to adapt to small doses of the substrate, however, and the fluoronicotine (147) was produced.



[*N*-Me-<sup>14</sup>C;3β-<sup>3</sup>H]Tropine (as 148) has been examined as a precursor for the alkaloids of *Datura meteloides*.<sup>129</sup> In particular it was specifically and efficiently built into meteloidine (149). Hyoscyamine (151) showed significantly



<sup>127</sup> M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, **93**, 7021; *ibid.*, 1970, **92**, 5528.

<sup>128</sup> E. Leete, G. B. Bodein, and M. F. Manuel, *Phytochemistry*, 1971, **10**, 2687.

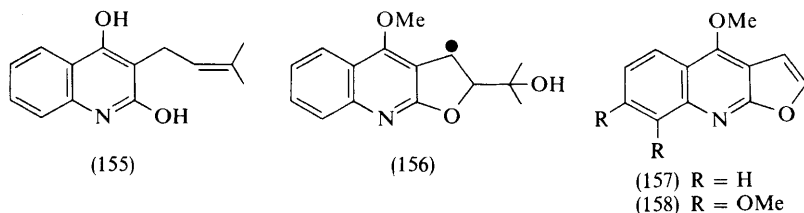
<sup>129</sup> E. Leete, *Phytochemistry*, 1972, **11**, 1713.

greater utilization of labelled tropine than scopolamine (152), consistent with the finding that hyoscyamine is a precursor for scopolamine.<sup>130</sup> Likewise, meteloidine showed higher radioactivity than 7 $\beta$ -hydroxy-3 $\alpha$ ,6 $\beta$ -ditigloyloxytropene (150) and is therefore its precursor. A similar conclusion was reached following work with the tigloyl moieties.<sup>131</sup> As the isotope ratio of the tropine showed essentially no change in the derived alkaloids or reisolated tropine, no oxidation to the precursor (153) occurred.

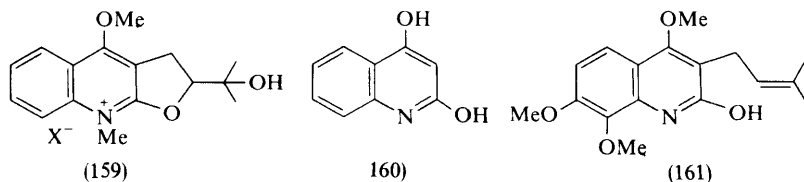
The intriguing problem of the mechanism of hydroxylation of the tropine nucleus to give meteloidine (149) remains. The stereochemistry of the hydroxy-groups in (149) precludes an epoxide intermediate like scopolamine, and suggests the involvement of the dioxetan (154).

Tritiated atropine was rapidly metabolized but not incorporated into hyoscyamine or other alkaloids in mature *Datura innoxia*.<sup>132</sup>

**Quinoline Alkaloids.**—An efficient and specific conversion of (+)-platydesmine (156), <sup>14</sup>C-labelled as shown, into dictamnine (157) has been demonstrated in *Skimmia japonica*, as has its presence in this plant.<sup>133</sup> Its role as an intermediate between the dimethylallylquinoline (155) and the furanoquinoline dictamnine is thus established. Platydesmine was also incorporated into platydesminium metho-salt (159) and skimmianine (158), but into the latter with low efficiency. The metho-salt (159) was poorly incorporated into dictamnine.



The incorporation of platydesmine (156) into skimmianine (158) suggests that dictamnine (157) is a precursor for (158). The low level of this incorporation and that with 2,4-dihydroxyquinoline (160) also in *S. japonica*,<sup>134</sup> however, is more



<sup>130</sup> H. W. Liebisch, in 'Biosynthese der Alkaloide', ed. K. Mothes and H. R. Schütte, VEB Deutscher Verlag der Wissenschaften, Berlin, 1969, p. 185.

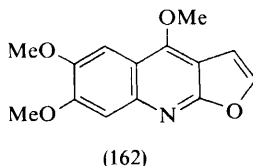
<sup>131</sup> W. C. Evans and J. G. Woolley, *J. Pharm. Pharmacol.*, 1965, 17, 37S; J. G. Woolley, *Abhandl. Deut. Akad. Wiss. Berlin Kl. Chem. Geol. Biol.*, 1966, 531.

<sup>132</sup> N. W. Hamon and H. W. Youngken, jun., *Lloydia*, 1971, 34, 199.

<sup>133</sup> M. F. Grundon and K. J. James, *Chem. Comm.*, 1971, 1311.

<sup>134</sup> J. F. Collins and M. F. Grundon, *Chem. Comm.*, 1969, 621; R. B. Herbert, in ref. 5, p. 12.

easily rationalized in terms of a minor pathway, where the major pathway involves the hydroxylated analogues of (155) and (156). This is strongly supported by the isolation of preskimmianine (161) from *Dictamnus albus*.<sup>135</sup> It is interesting to note that the incorporation of 2,4-dihydroxyquinoline into skimmianine in *Ruta*



*graveolens* was perhaps on the low side although specific, but more significantly the kokusaginine (162) isolated in this experiment showed randomization of the label.<sup>136</sup>

**Quinazoline Alkaloids.**—The biosynthesis of vasicine ( $\equiv$  peganine) (163) has been investigated in *Adhatoda vasica* (Acanthaceae) and *Peganum harmala* (Zygophyllaceae). In both plants the anthranoyl portion is known<sup>137</sup> to derive from anthranilic acid [the reported<sup>138</sup> incorporation of tryptophan (0.017%) suggested as *via* anthranilic acid seems of questionable significance]. The remaining atoms of vasicine, however, appear to arise by different pathways in the two plants.

In *P. harmala*, ornithine and related compounds have been incorporated<sup>138</sup> and the necessary degradations carried out.<sup>139</sup> Both [2-<sup>14</sup>C]- and [5-<sup>14</sup>C]-ornithine yield vasicine (163) with equal labelling of C-1 and C-10 (65% and 84.5%, respectively, of the total), indicating the involvement of a symmetrical intermediate in vasicine biosynthesis, possibly putrescine. In accord with this, [1,4-<sup>14</sup>C<sub>2</sub>]putrescine was found to be incorporated with slightly greater efficiency than ornithine. Curiously, however, C-1 and C-10 were clearly unequally labelled (27.7% and 41.2%, respectively). Incorporation of DL-[5-<sup>14</sup>C]glutamic acid and DL-[5-<sup>14</sup>C]proline was more random, but C-1 and C-10 were marginally more heavily labelled. The pathway to vasicine in *P. harmala* may be summarized as path a, Scheme 18.

In contrast, the biosynthesis of vasicine (163) in *A. vasica* does not involve ornithine and its congeners.<sup>140,141</sup> However, [3-<sup>14</sup>C]aspartic acid (as 164) was incorporated with heavy labelling of C-2 of vasicine; [4-<sup>14</sup>C]aspartic acid was only randomly incorporated.<sup>141</sup> Aspartic acid appears then to provide a C<sub>2</sub> unit (for C-1 and C-2). The origin of the other C<sub>2</sub> unit (C-3 and C-10) has been tested using [1-<sup>14</sup>C]- and [2-<sup>14</sup>C]-acetate, [3-<sup>14</sup>C]pyruvate, and [2-<sup>14</sup>C]glycine.<sup>142</sup> In

<sup>135</sup> R. Storer and D. W. Young, *Tetrahedron Letters*, 1972, 2199.

<sup>136</sup> M. Cobet and M. Luckner, *Phytochemistry*, 1971, 10, 1031.

<sup>137</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>138</sup> D. R. Liljegren, *Phytochemistry*, 1968, 7, 1299.

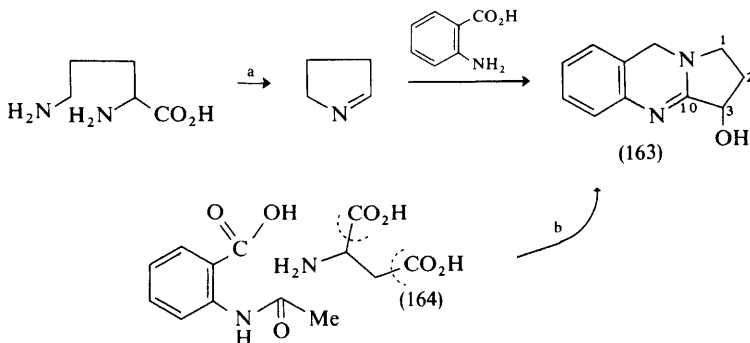
<sup>139</sup> D. R. Liljegren, *Phytochemistry*, 1971, 10, 2661.

<sup>140</sup> D. Gröger, S. Johne, and K. Mothes, *Abhandl. Deut. Akad. Wiss. Berlin Kl. Chem. Geol. Biol.*, 1966, 581; S. Johne and D. Gröger, *Z. Pflanzenphysiol.*, 1969, 61, 353.

<sup>141</sup> S. Johne and D. Gröger, *Phytochemistry*, 1968, 7, 429.

<sup>142</sup> K. Waiblinger, S. Johne, and D. Gröger, *Phytochemistry*, 1972, 11, 2263.

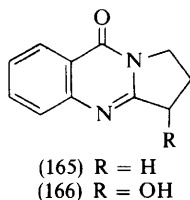
each case scrambling of the label was observed. Pyruvate, however, did give vasicine (163) with 84 % of the label at the expected site, C-3, whereas  $[2-^{14}\text{C}]$ acetate labelled C-3 to the extent of 44 %, with nothing at C-10. None of these substrates



Scheme 18

gave vasicine with labelling of C-1 or C-2. Further,  $[\text{acetyl-2-}^{14}\text{C}; ^{15}\text{N}]N$ -acetyl-anthranilic acid was incorporated into vasicine specifically and without change in isotope ratio, indicating intact incorporation. The biosynthesis of vasicine in *A. vasica* may be summarized then as path b, Scheme 18.

4-Amino-2-hydroxy[4- $^{14}\text{C}$ ]butyric acid<sup>142</sup> (the corresponding aldehyde has been condensed with *o*-aminobenzaldehyde to give vasicine<sup>143</sup>), 4-hydroxy-[2- $^{14}\text{C}$ ]glutamic acid<sup>141</sup> (found with vasicine in *Linaria vulgaris*<sup>144</sup>), *N*-methyl-anthranilic acid,<sup>141</sup> and *N*-formylanthranilic acid<sup>141</sup> have been tested as vasicine precursors in *A. vasica*, without success.



In addition to vasicine (163), *P. harmala* produces vasicinone (165) and deoxyvasicinone (166). Attempts to observe either the interconversion or order of biosynthesis of these three alkaloids have been unsuccessful.<sup>139</sup>

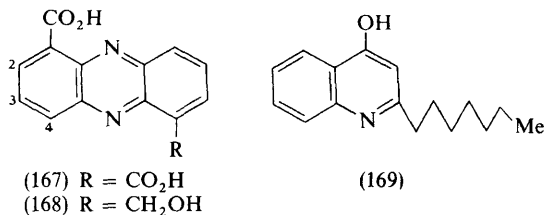
**Phenazines.**—The phenazine ring system is common to some thirty microbial metabolites,<sup>145</sup> some of which bear carbon substituents at C-1 and C-6, e.g. phenazine-1,6-dicarboxylic acid (167).<sup>145a</sup> This skeletal arrangement suggests a derivation from two molecules of anthranilic acid and this idea is made more

<sup>143</sup> N. J. Leonard and M. J. Martell, jun., *Tetrahedron Letters*, 1960, no. 25, 44.

<sup>144</sup> S.-I. Hatanaka, *Acta Chem. Scand.*, 1962, **16**, 513.

<sup>145</sup> (a) N. N. Gerber, *J. Heterocyclic Chem.*, 1969, **6**, 297; (b) references cited therein; C. D. Tipton and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1970, **92**, 1425.

plausible by the proven involvement of this amino-acid in the biosynthesis of a number of secondary metabolites in plants and micro-organisms.<sup>146,147</sup> In particular, the pseudans, e.g. (169), produced, like many naturally occurring



phenazines, by a *Pseudomonas* species, have been shown to incorporate labelled anthranilic acid with high efficiency.<sup>148</sup> There is, however, only sparse experimental evidence<sup>149</sup> to support a role for this amino-acid in phenazine biosynthesis. On the other hand, two shikimic acid molecules are implicated in the biosynthetic pathway.<sup>150</sup> As yet the nature of the shikimic acid derivatives involved in coupling is unknown, except that chorismic acid, like anthranilic acid, is an unlikely intermediate.<sup>151</sup>

Pyocyanin (173) is produced by *Ps. aeruginosa*,<sup>152</sup> alternative strains of which produce the aeruginosins, A (174)<sup>153</sup> and B (175).<sup>154</sup> It seemed reasonable that these three metabolites might arise by similar biosynthetic pathways and, in particular, the betaine (171) might be a common intermediate.<sup>155</sup> This idea has been validated recently. The conversion of (171) into aeruginosin A (174) has been demonstrated using *Ps. aeruginosa* cultures conveniently at a stage of growth when no (174) was being produced.<sup>156</sup>

Both 1-carboxy-5-methyl[6,7,8,9-<sup>2</sup>H<sub>4</sub>]phenazinium betaine (as 171) and 1-carboxy[6,7,8,9-<sup>2</sup>H<sub>4</sub>]phenazine (as 170) were incorporated efficiently into pyocyanin (173) without loss of deuterium.<sup>157</sup> Hydroxylation of (171) thus occurs, as a specific decarboxylative reaction. This specificity, together with the high level of incorporation of these two compounds, strongly suggested that they are normal intermediates in pyocyanin biosynthesis and since 1-hydroxy-

<sup>146</sup> D. Gröger, *Lloydia*, 1969, **32**, 221.

<sup>147</sup> K. Mothes and H. R. Schütte, 'Biosynthese der Alkaloide', VEB Deutscher Verlag der Wissenschaften, Berlin, 1969.

<sup>148</sup> C. Ritler and M. Luckner, *European J. Biochem.*, 1971, **18**, 391; J. Staunton, ref. 8, p. 28.

<sup>149</sup> R. E. Carter and J. H. Richards, *J. Amer. Chem. Soc.*, 1961, **83**, 495.

<sup>150</sup> (a) M. Podojil and N. N. Gerber, *Biochemistry*, 1970, **9**, 4616; (b) references cited therein.

<sup>151</sup> W. M. Ingledew and J. J. R. Campbell, *Canad. J. Microbiol.* 1969, **15**, 535.

<sup>152</sup> F. Wrede and E. Strack, *Z. physiol. Chem.*, 1929, **181**, 58.

<sup>153</sup> F. G. Holliman, *J. Chem. Soc. (C)*, 1969, 2514.

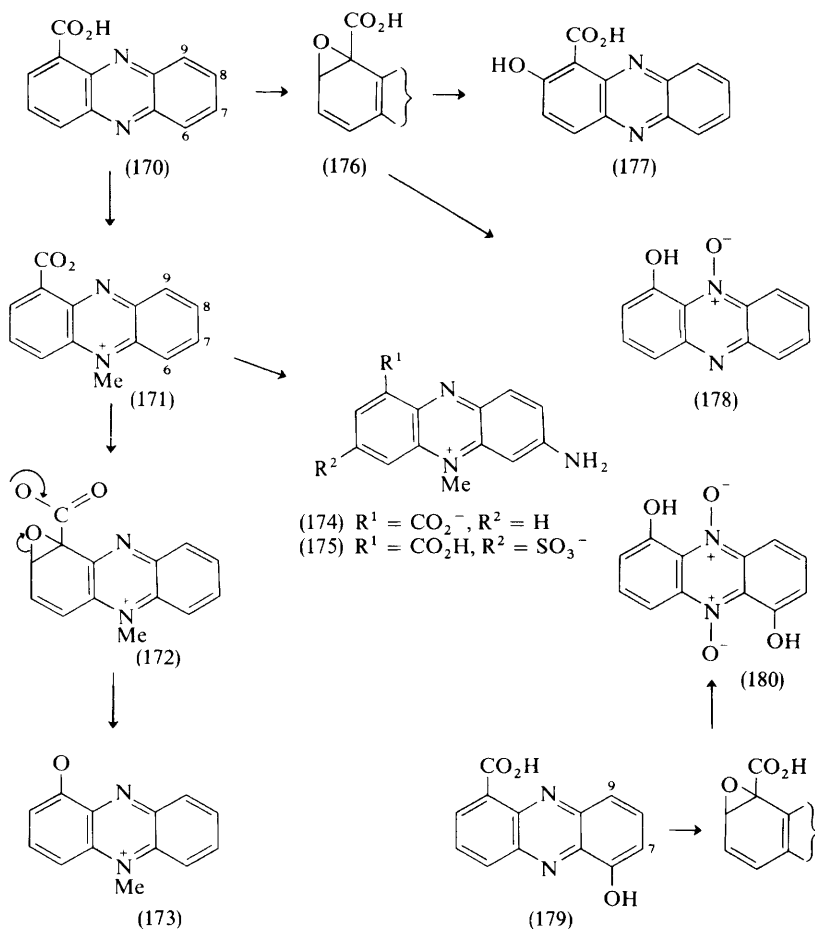
<sup>154</sup> R. B. Herbert and F. G. Holliman, *J. Chem. Soc. (C)*, 1969, 2517.

<sup>155</sup> F. G. Holliman, *S. African Ind. Chem.*, 1961, **15**, 233.

<sup>156</sup> G. S. Hansford, F. G. Holliman, and R. B. Herbert, *J. C. S. Perkin I*, 1972, 103.

<sup>157</sup> (a) M. E. Flood, R. B. Herbert, and F. G. Holliman, *J. C. S. Perkin I*, 1972, 622; (b) *Chem. Comm.*, 1970, 1514.

phenazine was not incorporated, in confirmation of an earlier finding,<sup>158</sup> the sequence is (170) → (171) → (172) → (173); the proposed intermediate (172) seems a likely one on biochemical grounds<sup>159</sup> and on chemical grounds by analogy with the mechanism of the Darzens glycidic ester condensation.



Scheme 19

It was shown, in addition, that phenazine methosulphate could serve as a pyocyanin precursor but, in the light of the specificity of the hydroxylative decarboxylation of (171) and a lower incorporation than (170) or (171), is probably not a normal intermediate.

<sup>158</sup> L. H. Frank and R. D. De Moss, *J. Bacteriol.*, 1959, **77**, 776.

<sup>159</sup> D. M. Jerina, J. W. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, 1968, **90**, 6523, and references cited therein; D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltman-Nirenberg, and S. Udenfriend, *ibid.*, p. 6525.

It was of interest to see whether the betaine (171) would serve as a precursor for 2-hydroxyphenazine-1-carboxylic acid (177) and 2-hydroxyphenazine, which are produced by *Ps. aureofaciens* along with 1-carboxyphenazine (170).<sup>160</sup> 2-Hydroxyphenazine-1-carboxylic acid could, it was thought, arise by opening of the epoxide ring of (172) in an alternative manner to the one which would give pyocyanin. In the event, however, only 1-carboxyphenazine served as a precursor for (177) and 2-hydroxyphenazine; the respective levels of incorporation are in accord with the sequence (170)  $\rightarrow$  (177)  $\rightarrow$  2-hydroxyphenazine.<sup>157a</sup> As 1-carboxyphenazine is produced in much greater abundance than the other two metabolites by this organism, the hydroxylation reaction, which may include the intermediate (176), is inefficient in contrast to the analogous step in pyocyanin biosynthesis. The higher chemical reactivity towards nucleophiles and radicals of phenazinium salts when compared with phenazines is perhaps of significance in considering mechanisms of hydroxylation.

Phenazine-1,6-dicarboxylic acid (167) might appear to be the phenazine formed initially by the coupling of two shikimic acid derivatives, but [2,4-<sup>2</sup>H<sub>2</sub>]-phenazine-1,6-dicarboxylic acid (as 167) was not incorporated into pyocyanin (173) in *Ps. aeruginosa*,<sup>157a</sup> or iodinin (180) in *Brevibacterium iodinum* (*Ps. iodina*).<sup>161</sup>

Iodinin also showed no incorporation of deuteriated (168), (170), (171), or 1-hydroxyphenazine.<sup>161</sup> On the other hand, the *N*-oxide (178), which was isolated from *B. iodinum*, showed efficient incorporation of deuteriated 1-hydroxyphenazine and 1-carboxy[6,7,8,9-<sup>2</sup>H<sub>4</sub>]phenazine (as 170). Further, the latter was incorporated without deuterium loss and thus its conversion into (178) is analogous to its conversion into pyocyanin (173).

It follows from the above evidence that one of the hydroxy-groups in iodinin (180) is present before formation of the phenazine ring system. Accordingly, a highly efficient incorporation of 6-hydroxy-[7,9-<sup>2</sup>H<sub>2</sub>]phenazine-1-carboxylic acid (as 179) into iodinin (180) was found. It thus appears probable that *B. iodinum* converts (170) and (179) by the same or similar enzyme systems into (178) and iodinin (180), respectively, *N*-oxide formation occurring either before or after hydroxylative decarboxylation. The two acids, (170) and (179), may well arise from the same (non-aromatic) precursor, by alternative aromatization reactions.

1,6-Dihydroxyphenazine<sup>161,162</sup> and its 5-oxide<sup>162</sup> have been found to serve as iodinin precursors. The former compound is unlikely to be a normal intermediate as it was significantly less efficiently utilized than (179).<sup>161</sup>

Mention was made above that the nature of the shikimic acid derivatives involved in phenazine ring formation was unknown. In addition, little is known of which atoms of shikimic acid correspond to particular atoms in the phenazine nuclei of the various metabolites: a degradation of iodinin after incorporation of [1,6-<sup>14</sup>C<sub>2</sub>]shikimic acid<sup>150a</sup> was open to at least two interpretations.<sup>150a,161</sup>

<sup>160</sup> R. B. Herbert, F. G. Holliman, and J. D. Kynnersley, *Tetrahedron Letters*, 1968, 1907, and references cited therein; M. E. Levitch and P. Rietz, *Biochemistry*, 1966, **5**, 689.

<sup>161</sup> R. B. Herbert, F. G. Holliman, and P. N. Ibberson, *J.C.S. Chem. Comm.*, 1972, 355.

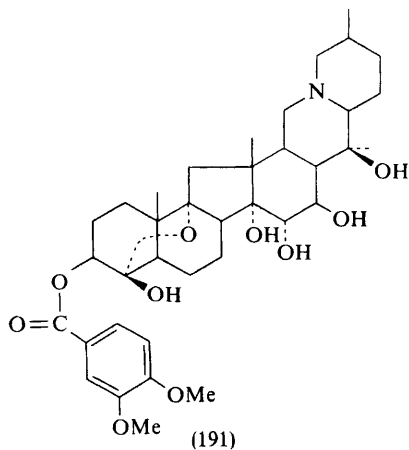
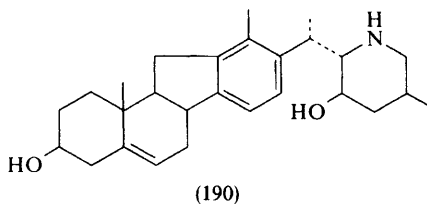
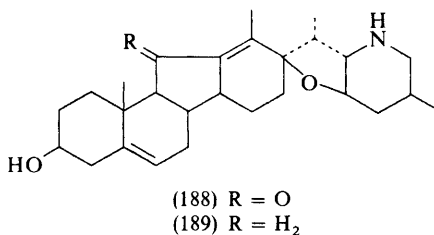
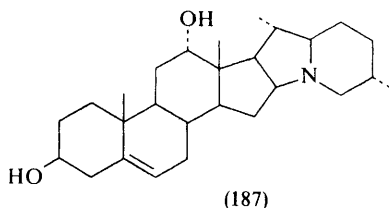
<sup>162</sup> M. Podojil and N. N. Gerber, *Biochemistry*, 1967, **6**, 2701.





*S. pseudocapsicum*.<sup>166</sup> Low incorporations were found into each alkaloid. Cycloartanol was the better precursor of the two. In the case of tomatidine (185) the radioactivity was shown to be confined to ring F, indicating intact incorporation of the C<sub>27</sub> precursor. Similar low incorporations had been recorded with cholesterol into tomatidine,<sup>167</sup> although other workers had found good incorporation into tomatidine<sup>168</sup> and solanidine.<sup>169</sup>

Cholesterol and acetic acid have been examined as precursors for rubijervine (187), jervine (188), veratramine (190), and veratroylzygadenine (191) in *Veratrum*



<sup>166</sup> H. Ripperger, W. Moritz, and K. Schreiber, *Phytochemistry*, 1971, **10**, 2699.

<sup>167</sup> E. Heftmann, E. R. Lieber, and R. D. Bennett, *Phytochemistry*, 1967, **6**, 225.

<sup>168</sup> R. Tschesche and H. Hulpke, *Z. Naturforsch.*, 1966, **21b**, 893.

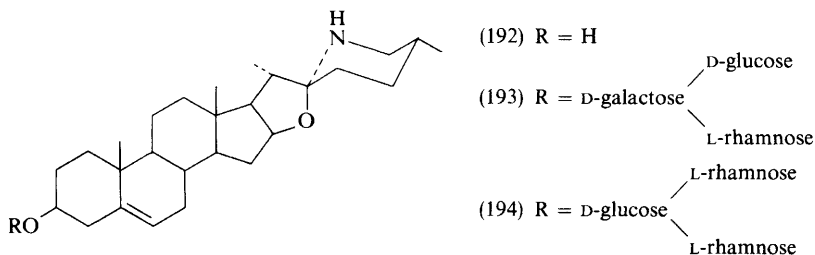
<sup>169</sup> R. Tschesche and H. Hulpke, *Z. Naturforsch.*, 1967, **22b**, 791.

*grandiflorum*.<sup>170</sup> The last three alkaloids are of interest as C-nor-D-homo-steroidal alkaloids.

[1-<sup>14</sup>C]Acetate served as a similarly effective precursor for each of these alkaloids, which is consistent with the derivation of the C-nor-D-homo-steroidal bases from a precursor with a normal steroidal skeleton. Evidence for a common intermediate for veratramine (190) and jervine (188) was obtained when it was shown that the incorporation of labelled acetate into veratramine could be increased by simultaneous administration of inactive jervine to *V. grandiflorum*.

Cholesterol (4-<sup>14</sup>C- and 26-<sup>14</sup>C-labelled) was incorporated into the alkaloids of this plant with low efficiency. Nonetheless, it is regrettable that the alkaloids obtained after the cholesterol or acetate feeding were not degraded. Further experiments<sup>171</sup> showed that (a) 11-deoxy-[<sup>14</sup>C]jervine gave radioactive jervine, and (b) incorporation of labelled acetate into jervine was inhibited by exogenous 11-deoxyjervine. Thus 11-deoxyjervine (189) is probably a normal precursor for jervine (188). It did not, however, serve as a precursor for veratramine (190).

Solasodine (192) has been shown to be an equally efficient precursor for the glycoalkaloids solasonine (193) and solamargine (194).<sup>172</sup> In addition, an



enzyme has been isolated from *S. nigrum* which will carry out a stepwise removal of the sugar residues of these glycoalkaloids.<sup>173</sup> In consideration of these results it is likely that glycoside formation is a late biosynthetic step and a stepwise addition of sugar units occurs.

<sup>170</sup> K. Kaneko, H. Mitsuhashi, K. Hirayama, and N. Yoshida, *Phytochemistry*, 1970, **9**, 2489.

<sup>171</sup> K. Kaneko, H. Mitsuhashi, K. Hirayama, and S. Ohmori, *Phytochemistry*, 1970, **9**, 2497.

<sup>172</sup> D. R. Liljegren, *Phytochemistry*, 1971, **10**, 3061.

<sup>173</sup> D. R. Liljegren, unpublished results.

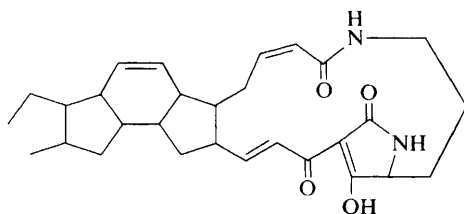
# 2

## Pyrrolidine, Piperidine, and Pyridine Alkaloids

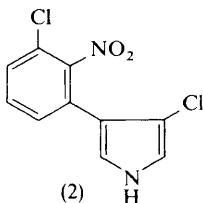
BY V. A. SNIECKUS

### 1 Pyrrolidine Alkaloids

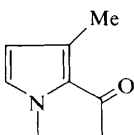
As in previous Reports, pyrrolidine compounds of other than plant origin will not be discussed. However, attention is drawn to the structural elucidation of ikarugamycin (1) from *Streptomyces phaeochromogenes* var. *ikaruganensis*,<sup>1</sup> to new synthetic work on pyrrolnitrin (2) from *Pseudomonas pyrocinia*,<sup>2</sup> and to structural analogues of the male butterfly sex pheromone (3).<sup>3</sup>



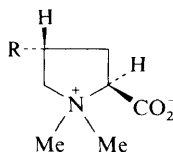
(1)



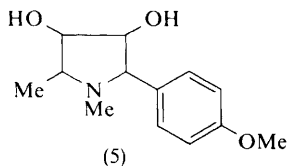
(2)



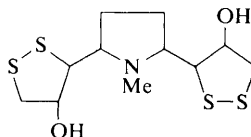
(3)



(4)



(5)



(6)

Few structural surprises have emerged from new isolation studies: stachydrine (4; R = H) was obtained from *Asphodelus microcarpus*<sup>4</sup> while combretine

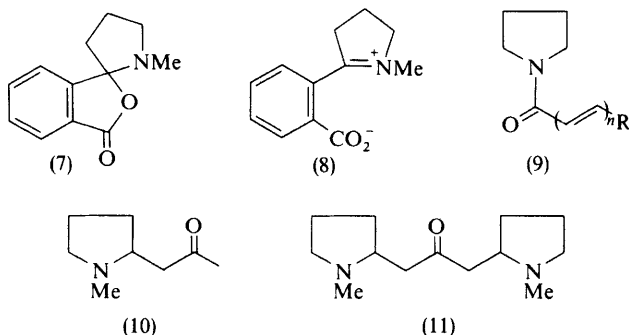
<sup>1</sup> S. Ito and Y. Hirata, *Tetrahedron Letters*, 1972, 1181, 1185.

<sup>2</sup> J. Gosteli, *Helv. Chim. Acta*, 1972, **55**, 451.

<sup>3</sup> H. C. J. Ottenheym and J. Meinwald, *Tetrahedron*, 1971, **27**, 3307.

<sup>4</sup> F. M. Hammouda, A. M. Rizk, and M. M. Abdel-Gawad, *Current Sci.*, 1971, **40**, 631 (*Chem. Abs.*, 1972, **76**, 56 576d).

( $C_7H_{13}NO_3$ ) was found in *Combretum micranthum*.<sup>5</sup> Combretine appears to be a stereoisomer of betonicine (4;  $R = OH$ ) and had not been reported previously. The previous structural assignment<sup>6</sup> for codonopsinine (5)\* has been strengthened by further chemical and spectral evidence.<sup>7</sup> The structure of gerrardine (6) from *Cassipourea gerrardii* has been determined solely by X-ray crystallographic analysis.<sup>8</sup> This represents the second alkaloid containing two 1,2-dithiolan rings bridged in novel ways to the pyrrolidine ring which has been isolated from *Cassipourea* species. Shihunine (7), an alkaloid previously obtained from *Dendrobium lohohense*, has now been isolated from *D. pierardii* (*D. aphyllum*).<sup>9</sup> The n.m.r. spectrum of shihunine in nonpolar solvents fully supports the structural assignment (7); however, the spectrum in methanol or water indicates that it exists fully as the betaine form (8) and it is likely that this form also obtains in the plant. *Piper trichostachyon* leaves have yielded trichonine [9;  $n = 2$ ,  $R = (CH_2)_{14}Me$ ];<sup>10</sup> *Salpichroa origanifolia* root has produced hygrine (10) and cuscohygrine (11);<sup>11</sup> and five of the twelve known species of the genus *Solandra* were shown to contain cuscohygrine (11).<sup>12</sup> Incidentally, the *meso* stereochemical assignment for cuscohygrine may require re-examination in light of recent work with homologous piperidine alkaloids (Section 2).



In the realm of synthesis, the preparation of peepuloidine (9;  $n = 1$ ,  $R = 2,3$ -dimethoxy-3,4-methylenedioxyphenyl) has been facilitated by a new source of highly oxygenated benzaldehyde derivatives.<sup>13</sup> Careful experimental execution

<sup>5</sup> A. U. Ogan, *Planta Med.*, 1972, **21**, 210.

<sup>6</sup> V. A. Snieckus, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1972, vol. 2, p. 33.

<sup>7</sup> S. F. Matkhalikova, V. M. Malikov, M. R. Yagudaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 210 (*Chem. Abs.* 1971, **75**, 36 409c).

<sup>8</sup> G. Gafner and L. J. Admiraal, *Acta Cryst.*, 1971, **B27**, 565.

<sup>9</sup> M. Elander, L. Gawell, and K. Lander, *Acta Chem. Scand.*, 1971, **25**, 721.

<sup>10</sup> J. Singh, K. L. Dhar, and C. K. Atal, *Tetrahedron Letters*, 1971, 2119.

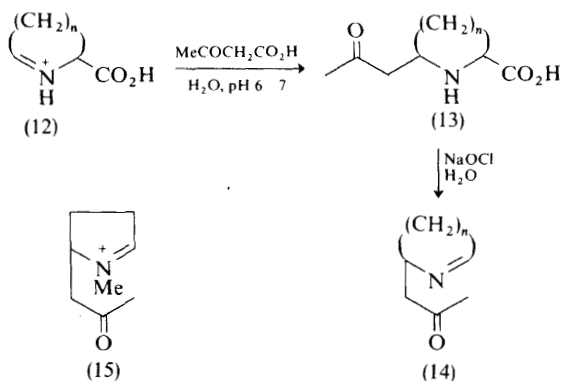
<sup>11</sup> W. C. Evans, A. Ghani, and V. A. Woolley, *Phytochemistry*, 1972, **11**, 469.

<sup>12</sup> W. C. Evans, A. Ghani, and V. A. Woolley, *Phytochemistry*, 1972, **11**, 470.

<sup>13</sup> F. Dallacker and J. Schubert, *Chem. Ber.*, 1971, **104**, 1706.

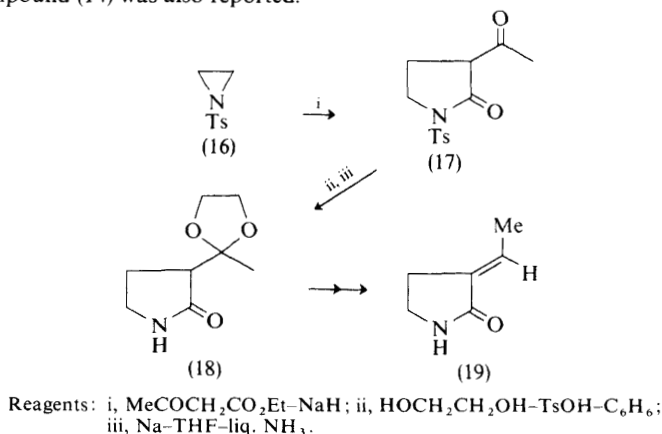
\* The position of the OMe substituent in (5) is in doubt to this Reporter owing to unavailability of original literature source; cf. also ref. 6.

is the keynote of a report which describes the preparation of 1,5-didehydronorhygrine (14;  $n = 2$ ) and 1,5-didehydrohygrine (15), biogenetic intermediates leading to pyrrolidine and tropane alkaloids (Scheme 1).<sup>14, 15</sup> Treatment of diethyl acetamidomalonate with acrolein in ethanolic HCl solution gave a low



Scheme 1

yield of the unconjugated imino-ester (12;  $n = 2$ ), which was converted by reaction with acetoacetic acid under neutral conditions into (13;  $n = 2$ ). The latter was oxidized to the somewhat unstable compound (14;  $n = 2$ ) in unreported yield.<sup>14</sup> In a related report,<sup>15</sup> a one-pot synthesis of 1,5-didehydrohygrine (15) was achieved by reaction of succinic dialdehyde and methylamine hydrochloride in the presence of citric acid followed by treatment of the resulting intermediate with acetoacetic acid. A lengthier route to (15) using terminal steps described for the preparation of compound (14) was also reported.



Scheme 2

<sup>14</sup> K. Hasse, J. Hess, and H. W. Hörnig, *Chem. Ber.*, 1971, **104**, 2420.

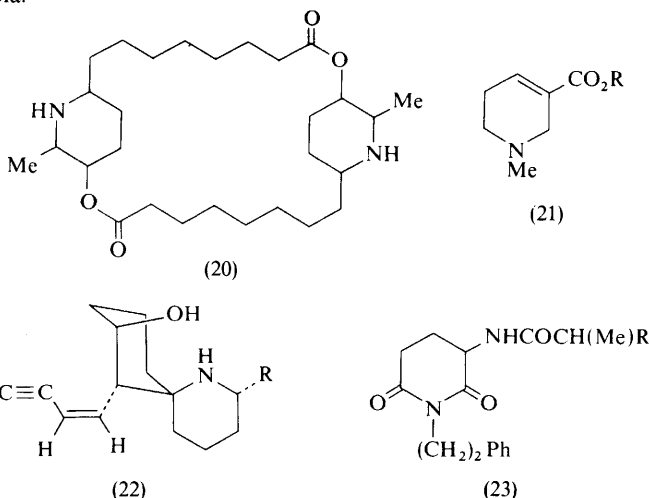
<sup>15</sup> J. Hess, *Chem. Ber.*, 1972, **105**, 441.

A new synthesis of corydolactam (19) ('alkaloid P') has been reported (Scheme 2).<sup>16</sup> Advantage was taken of a known reaction of 1-toluene-*p*-sulfonylaziridine (16) with  $\beta$ -dicarbonyl compounds to prepare the pyrrolidone (17), which upon ketalization and desotylation yielded (18), a compound previously transformed<sup>17</sup> in two steps into corydolactam (19).

Synthetic methods for pyrrolidines as well as  $\Delta^1$ - and  $\Delta^2$ -pyrrolines have been surveyed.<sup>18</sup> Some un-natural <sup>14</sup>C-labelled pyrrolinium salts have been prepared in connection with biosynthetic work in *Nicotiana glutinosa* (see Section 3).

## 2 Piperidine Alkaloids

A brief review on carpaine (20), the major alkaloid from *Carica papaya*, stresses the need to reinvestigate the pharmacological properties of this alkaloid in pure form (see below).<sup>19</sup> A review on the chemistry and pharmacology of tetrahydropyridine derivatives includes a discussion of arecoline (21).<sup>20</sup> Undoubtedly the most intriguing naturally occurring piperidine derivatives isolated this year, histrionicotoxin (22; R = CH<sub>2</sub>CH=CHC $\equiv$ CH) and dihydroisohistrionicotoxin (22; R = CH<sub>2</sub>CH<sub>2</sub>CH=C=CH<sub>2</sub>), fall out of the scope of this Report in that they were isolated from *Denrobates histrionicus*, a frog species native to Columbia.<sup>21</sup>



New isolation work has not uncovered unusual structural types. The Nigerian variety of *Carica papaya* has been shown to yield a much smaller amount

<sup>16</sup> T. Kametani and M. Ihara, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2256.

<sup>17</sup> Ref. 6, p. 34.

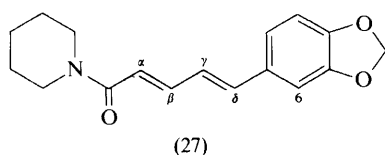
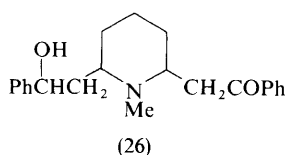
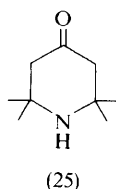
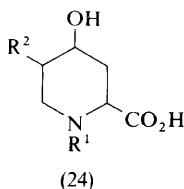
<sup>18</sup> S. Ohki, *Yuki Gosei Kagaku Shi*, 1972, **30**, 1 (*Chem. Abs.*, 1972, **76**, 153 441p).

<sup>19</sup> E. M. Burdick, *Econ. Botany*, 1971, **25**, 363.

<sup>20</sup> R. T. Coutts and J. R. Scott, *Canad. J. Pharm. Sci.*, 1971, **6**, 78.

<sup>21</sup> J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters, and B. Witkop, *Proc. Nat. Acad. Sci. U.S.A.*, 1971, **68**, 1870.

(0.0115% of dry wt.) of carpaine (20) than the American or Asian varieties (up to 0.2%).<sup>22</sup> On the other hand, a larger amount of choline was found, but apparently its presence does not explain the medicinal properties of *C. papaya*. Two glutarimide peptides, (23; R = Me) and (23; R = Et), have been isolated from *Croton humilis*.<sup>23</sup> The alkaloids were obtained as a 1 : 1 crystalline mixture which resisted all separation attempts. Their structures were thus determined by extensive application of double-resonance n.m.r. and INDOR experiments, and were further supported by acidic hydrolysis to give 2-phenylethylamine, glutamic acid, and, significantly, 2-methylpropionic and 2-methylbutanoic acids. A report has appeared<sup>24</sup> on the isolation and separation of alkaloids from *Lythrum anceps* whose structural elucidation has been previously described.<sup>25</sup> A reinvestigation of pegaline, an alkaloid isolated from *Peganum harmala* and previously thought to contain a pyrrolidine ring, has shown that in fact it is identical to L-( - )-4-hydroxypipelicolic acid (24; R<sup>1</sup> = R<sup>2</sup> = H) by direct comparison with an authentic sample.<sup>26</sup> The common Indian tree, *Pongamia glabra*, has yielded the pipelicolic acid derivative (24; R<sup>1</sup> = Me, R<sup>2</sup> = OH), whose structure was established by classical chemical and spectroscopic methods.<sup>27</sup> The mass spectrum of compound (24; R<sup>1</sup> = Me, R<sup>2</sup> = OH) showed expected sequential fragmentation of CO<sub>2</sub>H and two H<sub>2</sub>O units cascading down to the *N*-methylpyridinium ion. Triacetoneamine (25) has been isolated from *Salsola tetrandra*; two other nitrogen-containing compounds were obtained but their structures could not be established owing to lack of material.<sup>28</sup>



Environmental and developmental effects of certain piperidine alkaloids have been studied. *Conium maculatum* tissue cultures cultivated *in vitro* have shown a decrease in the level of alkaloids (*N*-methylconicine and coniine) compared with

<sup>22</sup> A. U. Ogan, *Phytochemistry*, 1971, **10**, 2544.

<sup>23</sup> J. P. Kutney, F. K. Klein, G. Eigendorf, D. McNeill, and K. L. Stuart, *Tetrahedron Letters*, 1971, 4973.

<sup>24</sup> E. Fujita, K. Bessho, Y. Saeki, M. Ochiai, and K. Fuji, *Lloydia*, 1971, **34**, 306.

<sup>25</sup> Ref. 6, pp. 36—41.

<sup>26</sup> V. U. Ahmad and M. A. Khan, *Phytochemistry*, 1971, **10**, 3339.

<sup>27</sup> P. S. S. Kumar, V. V. S. Murti, and T. R. Seshadri, *Tetrahedron Letters*, 1971, 4451.

<sup>28</sup> M. S. Karawya, G. M. Wassel, G. Ruecker, H. H. Baghdadi, and Z. F. Ahmed, *Phytochemistry*, 1971, **10**, 3303.

fresh plant extracts.<sup>29</sup> The distribution of lobeline (26) in the leaves, stems, and flowers of *Lobelia inflata* and the influence of age, soil pH, and other factors on growth has been investigated.<sup>30</sup> Liquid carbon dioxide extracts of *Piper nigrum*, which contains piperine (27), have been shown to be efficient and to preserve the pepper flavour.<sup>31</sup>

<sup>13</sup>C N.m.r. spectroscopy is the latest important general technique in natural product structural elucidation work and is on the verge of becoming routinely used. As part of broad and systematic studies, Wenkert and his students have examined the <sup>13</sup>C n.m.r. spectrum of piperine (27) and found that differentiation between the chemical shifts of the aromatic C-6 and olefinic  $\alpha$  and  $\gamma$  carbons as well as olefinic  $\beta$  and  $\delta$  carbons was still not possible.<sup>32</sup> However, it was found that the Eu(dpm)<sub>3</sub> shift reagent is as useful in <sup>13</sup>C n.m.r. as in <sup>1</sup>H n.m.r. spectroscopy in that in its presence, all seventeen carbons in piperine (27) could be assigned. The comparable <sup>1</sup>H n.m.r. study with Eu(dpm)<sub>3</sub> was also reported.

Details of the absolute configuration assignments of (+)-sedridine (28) and (–)-allosedridine (29) have appeared.<sup>33</sup> von Braun degradation of *ON*-dibenzoylsedridine with phosphorus pentabromide gave a 50% yield of the (+)-4,8-dibromo-2-octyl benzoate, which upon successive catalytic hydrogenolysis and basic hydrolysis provided (S)-(+)-octan-2-ol. Since an (S) configuration at C-2 of the piperidine ring had been previously established, the (2*S*,2'*S*) absolute configuration of (+)-sedridine (28) could be assigned. On the other hand, the absolute configuration of (–)-allosedridine (29) was determined to be (2*S*,2'*R*) by examination of its piperido-oxazine derivative (30). Examination of the n.m.r. spectra of both racemic piperido-oxazines (30) indicated a *trans* ringjunction and an equatorial orientation of the substituents. These observations were confirmed and the absolute configuration was deduced from the X-ray crystal structure of natural (30). Complementary evidence from o.r.d. and c.d. studies of (27), (28), and related alkaloids was found to be in full agreement with these results.<sup>33</sup> Work summarized previously<sup>34</sup> had assigned the *meso* structure (31; R = H) to the alkaloid anaferine. The fact that *meso* and racemic forms of synthetic 1,3-bis-(2-piperidyl)propan-2-one, represented by gross structure (31; R = H) are easily interconverted under mild basic conditions (isomerization and racemization) suggested that the original stereochemical assignment of anaferine may be open to question.<sup>35</sup> Resolution of synthetic racemic (32; R = H) with 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acids and o.r.d. measurements of the optically active compounds, as well as their corresponding acetals, in acidic and

<sup>29</sup> G. Netien and J. Combet, *Compt. rend. Soc. Biol.*, 1971, **165**, 103 (*Chem. Abs.*, 1972, **76**, 70 080u).

<sup>30</sup> A. Krochmal, I. Wilken, and M. Chien, *U.S. Dep. Agric., Forest Serv., Res. Paper*, NE. 1970, NE-178, 13 pp (*Chem. Abs.*, 1971, **75**, 106 182z).

<sup>31</sup> A. N. Katyzhanskaya and N. F. Dyuban'kova, *Priklad. Biokhim. i Microbiol.*, 1971, **7**, 717 (*Chem. Abs.*, 1972, **76**, 70 063r).

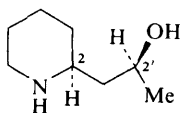
<sup>32</sup> E. Wenkert, D. W. Cochran, E. W. Hagaman, R. B. Lewis, and F. M. Schell, *J. Amer. Chem. Soc.*, 1971, **93**, 6271.

<sup>33</sup> D. Butruille, G. Fodor, S. C. Huber, and F. Letourneau, *Tetrahedron*, 1971, **27**, 2055.  
<sup>34</sup> Ref. 6, p. 36.

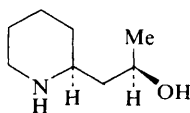
<sup>35</sup> H. C. Beyerman, L. Maat, and C. A. Moerman, *Rec. Trav. chim.*, 1971, **90**, 1326.



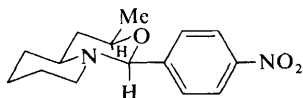
alkaline media has now provided evidence for the (*R,R*) absolute configuration of anaferine (32; *R* = H). Mandelic acid has been found to be a superior reagent to tartaric acid for the resolution of coniine and simpler piperidine derivatives.<sup>36</sup>



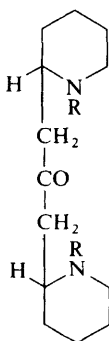
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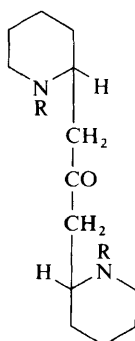
(29)



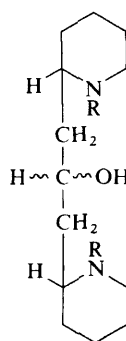
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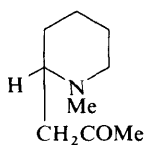
(31)



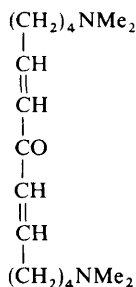
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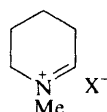
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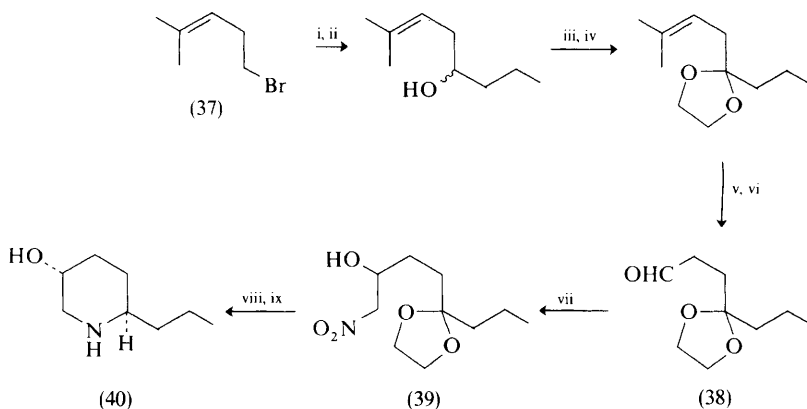
The instability of the racemic form of compound (32; *R* = H) with respect to (31; *R* = H) (see above) has been further investigated by co-workers in the late Professor Schöpf's laboratories.<sup>37</sup> Treatment of (31; *R* = H) with formic acid and formaldehyde gave the *meso* *N*-methyl derivative (31; *R* = Me), whereas (32; *R* = H) was decomposed under these conditions. However, when the carbonyl function in (32; *R* = H) was first reduced and the resulting mixture of stereoisomeric alcohols (33; *R* = H) was successively methylated under the

<sup>36</sup> C. J. Cymerman and A. R. Pinder, *J. Org. Chem.*, 1971, **36**, 3648.

<sup>37</sup> C. Schöpf, G. Benz, S. Kluessendorf, G. Krueger, H. Remy, and R. Rokohl, *Annalen*, 1971, **753**, 8.

same conditions and reoxidized [ $\text{CrO}_3$ -pyridine (?)], the same *meso* compound (31; R = Me) was obtained. The configuration of (31; R = Me) was proved by its back-reduction to the two stereoisomeric alcohols (33; R = Me), which could be also obtained by the methylation of the two alcohols (33; R = H) whose configuration had been previously determined. Thus the isomerization step in the transformation of (32; R = H) to (33; R = Me) must be occurring in the chromium trioxide oxidation step. Several interesting reactions were also reported in this study.<sup>37</sup> Exposure of (31; R = Me) to strongly alkaline conditions gave methylisopelletierine (34; 29%) and recovered starting material (32%). No equilibration [(31; R = Me)  $\rightleftharpoons$  (32; R = Me)] was observed, in contrast to the corresponding secondary amines (31; R = H) and (32; R = H), either of which equilibrated with the other under similar conditions. A satisfactory explanation for these observations is not available. The bismethiodide of (31; R = Me) upon treatment with base was converted into the de-base (35) which could not be purified but was catalytically reduced to 1,13-bisdimethylamino-tridecan-7-one. The transformation (31; R = Me)  $\rightarrow$  (35) was readily reversible by acidic treatment. A short synthesis of (31; R = Me) starting with acetone-dicarboxylic acid and the tetrahydropyridinium salt (36) was also reported.<sup>37</sup>

A general method<sup>38</sup> for the preparation of piperid-3-ols has been adapted to the biogenetic-type synthesis of pseudoconhydrine (40) (Scheme 3).<sup>39</sup> Of the two



Reagents: i,  $\text{Mg-Et}_2\text{O}$ ; ii,  $\text{n-C}_3\text{H}_7\text{CHO}$ ; iii, Jones oxidation; iv,  $\text{HOCH}_2\text{CH}_2\text{OH-TsOH}$  (?); v,  $\text{O}_3\text{-MeOH-C}_3\text{H}_5\text{N}$ ; vi,  $\text{Na}_2\text{SO}_3$ ; vii,  $\text{MeNO}_2\text{-NaOEt-Et}_2\text{O}$ ; viii, conc.  $\text{HCl-MeCOMe}$ ,  $0^\circ\text{C}$ ; ix,  $\text{H}_2\text{-Pd/C-HCl-EtOH}$ .

Scheme 3

schemes for the preparation of the key intermediate (38) which were successfully executed, the one shown starting from (37) was the more economical. Treatment of (38) with nitromethane gave the nitro-alcohol (39), which was successively

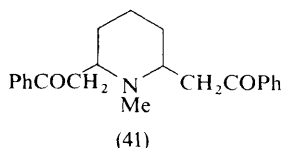
<sup>38</sup> E. Brown, R. Dhal, and J. Lavoue, *Tetrahedron Letters*, 1971, 1055.

<sup>39</sup> E. Brown, R. Dhal, and J. Lavoue, *Tetrahedron Letters*, 1971, 2767.

deketalized and hydrogenated to yield pseudoconhydrine (40). A scheme analogous to the one (Scheme 1) used for the preparation of 1,5-didehydronorhygrine (14;  $n = 2$ ) has been used for the preparation of 1,6-didehydroisopelletierine (14;  $n = 3$ ).<sup>14</sup>

[<sup>15</sup>N]Coniine was prepared from 5-oxo-octanal by the new reductive amination method using  $\text{NaBH}_3\text{CN}$  and [<sup>15</sup>N]ammonium bromide.<sup>40</sup>

A colorimetric method applicable to the estimation of lobelanine (41) and related alkaloids in pharmaceutical preparations has been reported.<sup>41</sup>



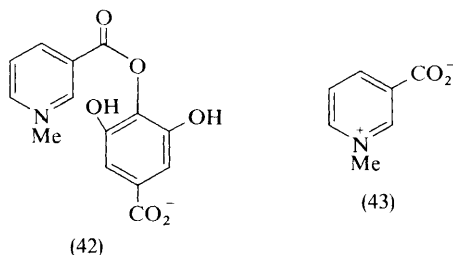
Two investigations concerned with metabolism and pharmacology of arecoline (21;  $\text{R} = \text{Me}$ ) may be of interdisciplinary interest.<sup>42</sup>

The mention of arecaine (21;  $\text{R} = \text{H}$ ) in a short review<sup>43</sup> dealing with a sigmatropic rearrangement in a 2-dehydroquinuclidine system is of incidental interest (see also Section 4).

### 3 Pyridine Alkaloids

An excellent overview of pyridine compounds both of plant and fungal origin has been published.<sup>44</sup> A comprehensive volume describing the chemistry of tobacco has appeared.<sup>45</sup>

New reports concerning alkaloid isolation have been few in number. The leaves, stems, roots, and seeds of *Abrus precatorius*, a plant long used in Indian medicine, have yielded<sup>46</sup> two new alkaloids, precatorine (42) and the methyl



<sup>40</sup> E. Leete, H. V. Isaacson, and H. D. Durst, *J. Labelled Compounds*, 1971, **7**, 313.

<sup>41</sup> M. S. Karawya, S. M. Abdel-Wahab, and A. Y. Zaki, *J. Assoc. Offic. Analyt. Chemists*, 1971, **54**, 1423 (*Chem. Abs.*, 1972, **76**, 27 965z).

<sup>42</sup> M. K. Krstic, *Arch. Internat. Pharmacodyn. Therap.*, 1971, **194**, 238 (*Chem. Abs.*, 1972, **76**, 121 639t); R. Nery, *Biochem. J.*, 1971, **122**, 503.

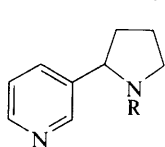
<sup>43</sup> J. Dolby, *Acta Pharm. Suecica*, 1971, **8**, 523 (*Chem. Abs.*, 1972, **76**, 25 444e).

<sup>44</sup> D. Gross, *Fortschr. Chem. org. Naturstoffe*, 1970, **28**, 109.

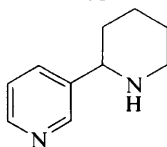
<sup>45</sup> J. Schormueller, 'Handbook of Food Chemistry, Vol. 6: Alkaloid-Containing Food Substances, Spices, Salt', Springer-Verlag, Berlin, 1970.

<sup>46</sup> S. Ghosal and S. K. Dutta, *Phytochemistry*, 1971, **10**, 195.

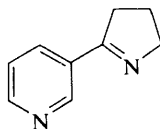
ester of *NN*-dimethyltryptophan metho cation, as well as abrine, hypaphorine, choline, and traces of trigonelline (43). Trigonelline has also been isolated, together with several tryptophan and tryptamine derivatives, from the leaves of



(44)



(45)



(46)

*Desmodium triflorum*.<sup>47</sup> Nicotine (44; R = Me), nornicotine (44; R = H), anabasine (45), and two unidentified alkaloids have been isolated from *Nicotiana noctiflora*.<sup>48</sup> Confirmation that myosmine (46) is true alkaloid in various *Nicotiana* species and not a decomposition product of nicotine has been obtained.<sup>49</sup> Anabasine (45) has also been found in *Verbascum songaricum*.<sup>50</sup>

The determination of the alkaloid composition of different parts of tobacco varieties is becoming an increasingly active field of study. Fluctuation in chemical composition for different varieties of tobacco leaves has been determined over a four-year period.<sup>51</sup> Nicotine, nornicotine, nicotine *N*-oxide, anabasine, and anatabine content was determined during ontogenesis of several *Nicotiana* species.<sup>52</sup> Changes in alkaloid composition have been studied during germination of *Nicotiana* seeds<sup>53</sup> and curing of tobacco leaves.<sup>54</sup> The influence of soil moisture on alkaloid content<sup>55</sup> and the composition of alkaloids in hybrid and wild *Nicotiana* species<sup>56</sup> have received attention. One of the interesting findings in a series of papers dealing with alkaloid physiology<sup>57</sup> was the fact that synthesis of alkaloids in tobacco-stem callus cultures did not take place until the onset of root development either spontaneously or by chemical stimulation.<sup>57c</sup> Preliminary evidence for growth inhibition being related to increased alkaloid

<sup>47</sup> S. Ghosal, R. S. Srivastava, P. K. Banerjee, and S. K. Dutta, *Phytochemistry*, 1971, **10**, 3312.

<sup>48</sup> D. M. Paez and G. B. Americo, *Rev. Asoc. bioquím. argentina*, 1971, **36**, 86 (*Chem. Abs.*, 1971, **75**, 115 989v).

<sup>49</sup> O. Fejer-Kossey, *Phytochemistry*, 1972, **11**, 415.

<sup>50</sup> R. Ziyaev, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 853 (*Chem. Abs.*, 1972, **76**, 124 154s).

<sup>51</sup> M. Yamazaki, M. Uehara, M. Shigematsu, K. Aso, T. Odaka, and Y. Kuwahara, *Nippon Senbai Koshu Chuo Kenkyusho Kenkyu Hokoku*, 1970, no. 112, 35 (*Chem. Abs.*, 1971, **75**, 72 703c).

<sup>52</sup> M. Ya. Lovkova, G. S. Il'in, N. S. Minozhedinova, and Sh. U. Usmanov, *Izvest. Akad. Nauk S.S.S.R., Ser. biol.*, 1971, 839 (*Chem. Abs.*, 1972, **76**, 70 332c); M. Ya. Lovkova, G. S. Il'in, and N. S. Minozhedinova, *ibid.*, 1972, 255 (*Chem. Abs.*, 1972, **77**, 2900g).

<sup>53</sup> M. Ya. Lovkova, G. S. Il'in, and N. S. Minozhedinova, *Priklad. Biokhim. i Mikrobiol.*, 1972, **8**, 121 (*Chem. Abs.*, 1972, **76**, 110 271r).

<sup>54</sup> B. I. Townes and S. J. Sheen, *Beitr. Tobakforsch.*, 1970, **5**, 279 (*Chem. Abs.*, 1971, **75**, 60 017u); D. R. Bowman, *Tobacco Sci.*, 1972, **16**, 6 (*Chem. Abs.*, 1972, **76**, 110 459h).

<sup>55</sup> N. Honda and N. Arakawa, *Okayama Tab. Shikensho Hokoku*, 1971, 25 (*Chem. Abs.*, 1972, **76**, 58 221h).

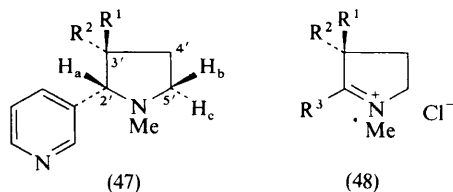
<sup>56</sup> V. S. Vasinev, *Stud. Nauch. Rab., Univ. Druzhby Nar.*, 1970, 108 (*Chem. Abs.*, 1971, **75**, 72 704d).

<sup>57</sup> (a) E. Mueller, A. Nelles, and D. Neumann, *Biochem. Physiol. Pflanz.*, 1971, **162**, 272 (*Chem. Abs.*, 1971, **75**, 45 676q); (b) A. Nelles and E. Mueller, *ibid.*, p. 495 (*Chem. Abs.*, 1971, **75**, 44 010b); (c) D. Neumann and E. Mueller, *ibid.*, p. 503 (*Chem. Abs.*, 1972, **76**, 56 784v).

synthesis was also obtained in this study.<sup>57c</sup> Anabasine has been found to increase the fungal pathogenicity of *Verticillium dahliae*.<sup>58</sup> A 'hereditary aptitude' for *Nicotiana* alkaloid synthesis has been determined.<sup>59</sup>

Most of the synthetic work has dealt with modification of known alkaloid structures. Dehydrogenation of anabasine (45) with pyridine *N*-oxide<sup>60</sup> and *N*-aminopyridinium chloride<sup>61</sup> yielded 2,3'-bipyridyl in varying amounts. The same conversion was also effected by a longer procedure.<sup>62</sup> The bromination of anabasine has been studied<sup>63</sup> and a series of *N*-substituted derivatives of this alkaloid have been prepared.<sup>64</sup>

A paper dealing with the biosynthesis of nicotine analogues from un-natural precursors [e.g. (47; R<sup>1</sup> = Me, R<sup>2</sup> = H) from (48; R<sup>1</sup> = Me, R<sup>2</sup> = R<sup>3</sup> = H)] in *Nicotiana glutinosa* has nevertheless important implications for all natural



product chemists.<sup>65</sup> In connection with this study, synthetic work was required in order to establish rigorously the structure and stereochemistry of the un-natural analogues.<sup>65,66</sup> As one example, adaptation of a known route for nicotine (44; R = Me) was used to prepare a mixture of *cis*-3'-methylnicotine (47; R<sup>1</sup> = H, R<sup>2</sup> = Me) and *trans*-3'-methylnicotine (47; R<sup>1</sup> = Me, R<sup>2</sup> = H).<sup>65</sup> Alternatively, the same *trans*-isomer was obtained starting from the Schiff base (49) (Scheme 4).<sup>66</sup> Treatment of (49) with succinic anhydride gave the pyrrolidone (50), which by a series of more conventional steps was converted into compound (47; R<sup>1</sup> = Me, R<sup>2</sup> = H). Examination of the n.m.r. spectra of the *cis*- and *trans*-isomers of (47) and related deuteriated derivatives provided the necessary stereochemical and structural evidence.<sup>65,66</sup> Compound (47; R<sup>1</sup> = H, R<sup>2</sup> = Me) showed a doublet

<sup>58</sup> B. S. Salikhova and V. I. Runov, *Fiziol. Mikroorganizmov*, 1970, 13 (*Chem. Abs.*, 1972, 76, 124 269h).

<sup>59</sup> P. Schiltz and J. C. Coussirat, *Compt. rend.*, 1971, 272, D, 2900.

<sup>60</sup> Yu. V. Kurbatov, A. S. Kurbatova, O. S. Otroshchenko, and A. S. Sadykov, *Trudy Samarkand. Gos. Univ.*, 1969, 71 (*Chem. Abs.*, 1971, 75, 139 950b); A. S. Kurbatova, S. V. Zalyalieva, O. S. Otroshchenko, and A. S. Sadykov, *ibid.*, p. 9 (*Chem. Abs.*, 1971, 75, 35 646r).

<sup>61</sup> Yu. V. Kurbatov, S. V. Zalyalieva, O. S. Otroshchenko, and A. S. Sadykov, *Trudy Samarkand. Gos. Univ.*, 1969, 185 (*Chem. Abs.*, 1971, 75, 48 837d).

<sup>62</sup> Yu. V. Kurbatov, A. S. Kurbatova, G. Ya. Markeeva, O. S. Otroshchenko, and A. S. Sadykov, *Trudy Samarkand. Gos. Univ.*, 1969, 3 (*Chem. Abs.*, 1971, 75, 48 835b).

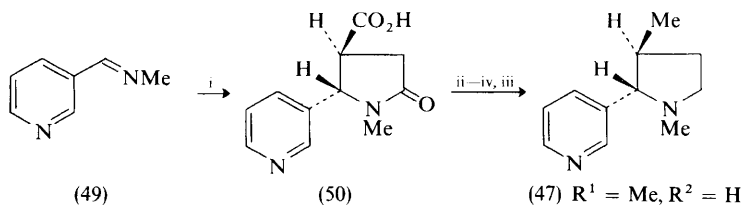
<sup>63</sup> M. Goshayev, O. S. Otroshchenko, V. B. Leont'ev, and A. S. Sadykov, *Izvest. Akad. Nauk Turkm. S.S.R., Ser. Fiz.-Tekh., Khim. Geol.*, 1971, 109 (*Chem. Abs.*, 1972, 76, 85 981n).

<sup>64</sup> L. S. Aryanunyan, A. S. Tsatinyan, O. M. Abakyan, S. G. Karagezyan, V. G. Sarafyan, and V. A. Mnatsakanyan, *Armenian. khim. Zhur.*, 1972, 25, 78 (*Chem. Abs.*, 1972, 77, 5646q).

<sup>65</sup> M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, 93, 7021.

<sup>66</sup> M. Cushman and N. Castagnoli, jun., *J. Org. Chem.*, 1972, 37, 1268.

at  $\delta$  0.55, consistent with the *cis* stereochemistry in which the C-3' methyl group is strongly shielded by the pyridine ring. On the other hand, the *trans*-isomer (47;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) showed a normal chemical shift for the C-3' methyl



Reagents: i, succinic anhydride–xylene, reflux; ii, MeOH–H<sub>2</sub>SO<sub>4</sub>–molecular sieves; iii, LiAlH<sub>4</sub>–Et<sub>2</sub>O; iv, TsCl–C<sub>5</sub>H<sub>5</sub>N.

**Scheme 4**

doublet signal ( $\delta$  0.97). Furthermore, a multiplet at  $\delta$  3.2 (1H) in the spectrum of the *trans*-isomer was assigned to H<sub>c</sub> on the basis of comparison with the spectra of nicotine (47;  $R^1 = R^2 = \text{H}$ ) and 5',5'-dideuterionnicotine.<sup>66</sup> Nicotine also shows an absorption at  $\delta$  3.2 but corresponding to two hydrogens, whereas 5',5'-dideuterionnicotine exhibits a triplet at  $\delta$  3.04 (1H,  $J$  8 Hz) which can be unambiguously assigned to H<sub>a</sub>. Clearly one of the low-field signals in nicotine must be due to one of the C-5' protons, probably H<sub>c</sub> on the basis of the deshielding effect of the pyrrolidine nitrogen lone-pair. These observations require that the  $\delta$  3.2 multiplet in (47;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) also be assigned to H<sub>c</sub> and therefore that a broad doublet at  $\delta$  2.55 ( $J$  8 Hz) be assigned to H<sub>a</sub>. Not only were these assignments fully confirmed but the complete assignment of all protons was achieved by using the Eu(dpm)<sub>3</sub> shift reagent.<sup>66</sup> Significantly, the  $\delta$  2.55 signal due to H<sub>a</sub> showed the greatest downfield shift ( $\Delta\delta$  1.9) as expected from the previously established fact that nicotine undergoes co-ordination with europium at the pyridine rather than at the pyrrolidine nitrogen. Chemical and spectral information on several related compounds was concurrently obtained.<sup>65, 66</sup>

The preparation of several <sup>14</sup>C-labelled precursors (48;  $R^1 = {}^{14}\text{CH}_3$ ,  $R^2 = R^3 = \text{H}$ ;  $R^1 = R^2 = \text{H}$ ,  $R^3 = {}^{14}\text{CH}_3$ ;  $R^1 = R^2 = {}^{14}\text{CH}_3$ ,  $R^3 = \text{H}$ ) for the above aberrant biosynthesis investigation may be noted.<sup>65</sup> [1'-<sup>15</sup>N]Nornnicotine (44;  $R = \text{H}$ ) has been synthesized by reductive amination (NaBH<sub>3</sub>CN–<sup>15</sup>NH<sub>4</sub>Br) of 4-oxo-4-(3'-pyridyl)butanal.<sup>40</sup> Methylation of <sup>15</sup>N-labelled nornnicotine with formic acid–formaldehyde provides [1'-<sup>15</sup>N]nicotine (44;  $R = \text{Me}$ ).

Among new reports dealing with analytical methods, those concerned with g.l.c.,<sup>67</sup> g.c.,<sup>68</sup> and t.l.c.<sup>69, 70</sup> of nicotine and related alkaloids may be of general interest. In one of these,<sup>70</sup> it is noted that cigarettes contain a higher proportion

<sup>67</sup> D. J. Jenden, M. Roch, and R. Booth, *J. Chromatog. Sci.*, 1972, **10**, 151.

<sup>68</sup> I. R. Lange and M. I. Goryaev, *Zdravookhr. Kaz.*, 1971, **30**, 78 (*Chem. Abs.*, 1972, **76**, 49 865u).

<sup>69</sup> T. Constantinescu, M. Patrascu, and N. Anita, *Ind. Aliment. (Bucharest)*, 1971, **22**, 466 (*Chem. Abs.*, 1972, **76**, 1928q).

<sup>70</sup> T. Constantinescu, *Ind. Aliment. (Bucharest)*, 1971, **22**, 701 (*Chem. Abs.*, 1972, **76**, 138 323h).

of secondary alkaloids (nornicotine, cotinine, oxynicotine) which are less toxic than nicotine. Rapid extraction of *Anabasis* alkaloids by vibration<sup>68</sup> and a simple extraction and photometric determination of nicotine<sup>71</sup> have been reported.

The relationship between  $pK_a$  and lipid solubility of nicotine alkaloids given orally to man and the amounts excreted in the urine has been studied.<sup>72</sup> A report on the effect of nicotine on ATPase activity has appeared.<sup>73</sup>

#### 4 Mono- and Sesqui-terpenoid Alkaloids

A brief but extensively referenced review of the monoterpene group has been published.<sup>44</sup>

As may be surmized from the Table, interest in isolation and structural elucidation has been maintained at a high level and a significant number of new

**Table** *Mono- and sesqui-terpenoid alkaloids*

| Species   | Alkaloid (Structure)                                 | Ref.   |
|---|--|--------|
| <i>Monoterpenoid Alkaloids</i>  |  |        |
| <i>Dipsacus azurcus</i>   | Gentianine (51)                                      | 74     |
| <i>Erythraea centaurium</i> *   | Gentianine (51)                                      | 75     |
| <i>Olea paniculata</i>  | Jasminine† (52)                                      | 76     |
| <i>Pedicularis olgae</i>  | Pediculidine (53, R = O, $\alpha\beta$ -double bond) | 77     |
|   | Pediculine (53; R = H, OH)                           | 78     |
| <i>Tecoma stans</i>   | Alkaloid C (54) }                                    | 79     |
| ( <i>Stenolobium stans</i> )  | Tecomanine (55)                                      |        |
| <i>Valeriana stolonifera</i>  | Alkaloids‡ VP-2 and VP-3                             | 80     |
| <i>Verbascum nobile</i>   | Pedicularine   | 81     |
| <i>V. songaricum</i>  | Plantagonine (56)                                    | 50     |
| <i>Sesquiterpenoid Alkaloids</i>  |  |        |
| <i>Dendrobium crepidatum</i>  | Crepidine (57)                                       | 82, 83 |
| <sup>71</sup> M. Bangarayya, Y. Gh. Narasimhamurty, and N. L. Pal, <i>Tobacco Sci.</i> , 1971, <b>15</b> , 47 ( <i>Chem. Abs.</i> , 1972, <b>76</b> , 23 153k).<br><sup>72</sup> A. H. Beckett, J. W. Gorrod, and P. Jenner, <i>J. Pharm. Pharmacol.</i> , 1972, <b>24</b> , 115.<br><sup>73</sup> D. H. Meyer, C. E. Cross, A. B. Ibrahim, and M. G. Mustafa, <i>Arch. Environ. Health</i> , 1971, <b>22</b> , 362 ( <i>Chem. Abs.</i> , 1971, <b>75</b> , 61 518v).<br><sup>74</sup> P. K. Alimbaeva, Zh. S. Nuralieva, and M. M. Mukhamedziev, <i>Fiziol. Aktiv. Soedin. Rast. Kirg.</i> , 1970, 88 ( <i>Chem. Abs.</i> , 1971, <b>75</b> , 148 459a).<br><sup>75</sup> F. Rulko and K. Witkiewicz, <i>Diss. Pharm. Pharmacol.</i> , 1972, <b>24</b> , 73 ( <i>Chem. Abs.</i> , 1972, <b>77</b> , 2771r).<br><sup>76</sup> N. K. Hart, S. R. Johns, and J. A. Lamberton, <i>Austral. J. Chem.</i> , 1971, <b>24</b> , 1739.<br><sup>77</sup> A. Abdusamatov, M. U. Rashidov, and S. Yu. Yunusov, <i>Khim. prirod. Soedinenii</i> , 1971, <b>7</b> , 304 ( <i>Chem. Abs.</i> , 1971, <b>75</b> , 110 476r).<br><sup>78</sup> A. Abdusamatov and S. Yu. Yunusov, <i>Khim. prirod. Soedinenii</i> , 1971, <b>7</b> , 306 ( <i>Chem. Abs.</i> , 1971, <b>75</b> , 110 477s).<br><sup>79</sup> G. Jones, G. Ferguson, and W. C. Marsh, <i>Chem. Comm.</i> , 1971, 994.<br><sup>80</sup> Yu. I. Kornievskii, A. G. Nikolaeva, and K. E. Koreschchuk, <i>Farm. Zhur. (Kiev)</i> , 1972, <b>27</b> , 81 ( <i>Chem. Abs.</i> , 1972, <b>77</b> , 2804d).<br><sup>81</sup> P. Ninova, A. Abdusamatov, and S. Yu. Yunusov, <i>Khim. prirod. Soedinenii</i> , 1971, <b>7</b> , 540 ( <i>Chem. Abs.</i> , 1972, <b>76</b> , 1812x).<br><sup>82</sup> (a) P. Kierkegaard, A. M. Pilotti, and K. Leander, <i>Acta Chem. Scand.</i> , 1970, <b>24</b> , 3757;<br>(b) A. M. Pilotti, <i>Acta Cryst.</i> , 1971, <b>B27</b> , 887.<br><sup>83</sup> A. M. Pilotti, <i>Chem. Comm., Univ. Stockholm</i> , 1971, no. 7, 26 pp. ( <i>Chem. Abs.</i> , 1972, <b>76</b> , 19 015z). |  |        |

**Table .Mono- and sesqui-terpenoid alkaloids—contd.**

| <i>Sesquiterpenoid Alkaloids—contd.</i> |  |        |
|---|--|--------|
| <i>D. friedricksianum</i>               | <i>N</i> -Isopentenylidendroxine (58; $R^1 = R^2 = H$ ,<br>$\begin{array}{c} + \\ NCH_2CH=CMc_2 \end{array} Cl^-$ )<br><i>N</i> -Isopentenyl-6-hydroxydendroxine (58;<br>$R^1 = OH, R^2 = H, \begin{array}{c} + \\ NCH_2CH=CMc_2 \end{array} Cl^-$ ) | 84     |
| <i>D. hildebrandii</i>                  | Dendramine [= 6-Hydroxydendrobine (59;<br>$R = OH$ )]<br>6-Hydroxynobilonine§ (60; $R = OH$ )<br><i>N</i> -Isopentenylidendroxine<br><i>N</i> -Isopentenyl-6-hydroxydendroxine }<br>Nobilonine§ (60; $R = H$ )                                       |        |
| <i>D. nobile</i>                        | 4-Hydroxydendroxine (58; $R^1 = H, R^2 = OH$ )   | 85     |
| <i>Euonymus europaeus</i>               | Euroline**   | 84     |
|   | Evopine**  | 85     |
|   | Evovoline**  | 86     |
|   | Evoline**  | 87     |
|   | Evomine**  | 88     |
|   | Evonine (61; $R^1 = R^2 = Ac, R^3 = OH, R^4 = O$ )   | 89—91  |
|   | Evonoline (61; $R^1 = R^2 = Ac, R^3 = H, R^4 = O$ )  | 89     |
|   | Evopine**  | 87     |
|   | Evorine [= Neoevonine (61; $R^1 = Ac, R^2 = H$ ,<br>$R^3 = OH, R^4 = O$ )]   | 90, 91 |
|   | Evozine (61; $R^1 = R^2 = H, R^3 = OH, R^4 = O$ )  | 90, 91 |
|   | Isoevorine†, $C_{34}H_{41}NO_{16}$ , m.p. 185—188 °C,<br>$[\alpha]_D + 20 (CHCl_3)$  | 90     |
| <i>E. sieboldianus</i>                  | Euonymine (61; $R^1 = R^2 = Ac, R^3 = OH$ ,<br>$R^4 = H, OAc$ )  | 92, 93 |
|   | Evonine  | 92—95  |
|   | Neoeuonymine (61; $R^1 = Ac, R^2 = H, R^3 = OH$ ,<br>$R^4 = H, OAc$ )  | 92, 93 |
|   | Neoevonine (= Evorine from <i>E. europaeus</i> )   |        |
| <i>Maytenus ovatus</i>                  | Maytine (62; $R = H$ )   | 96, 97 |
|   | Maytoline (62; $R = OH$ )  |        |
| <i>Nuphar variegatum</i>                | 3-Epinupharamine (63)  | 98     |

\* Five other alkaloids were obtained; two were crystallized and their i.r. and mass spectra were determined.

† Possibly an artifact.

‡ Of undetermined structure; i.r. and u.v. spectra were recorded.

¶ Proposed structure (cf. R. H. F. Manske in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1971, vol. XIII, p. 416) is undoubtedly incorrect.

§ Preferred names to those derived from nobiline since the latter may be confused with a sesquiterpene, nobilin (cf. ref. 84).

\*\* Access to original literature was not possible; alkaloid may be identical to one of those described in refs. 89—95.

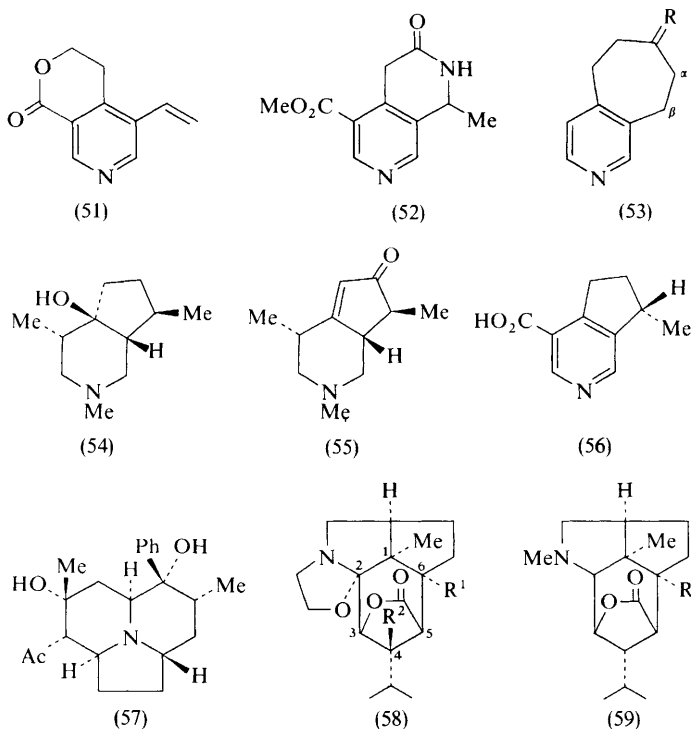
<sup>84</sup> K. Hedman, K. Leander, and B. Luning, *Acta Chem. Scand.*, 1971, **25**, 1142.

<sup>85</sup> M. Elander and K. Leander, *Acta Chem. Scand.*, 1971, **25**, 717.

<sup>86</sup> T. Okamoto, M. Natsume, T. Onaka, F. Uchimaru, and M. Shimizu, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 418.

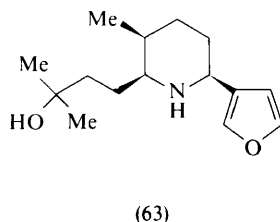
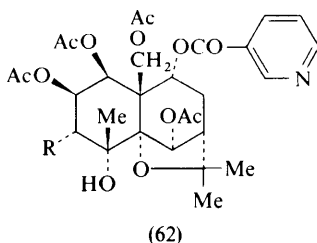
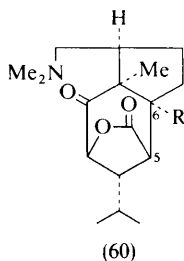
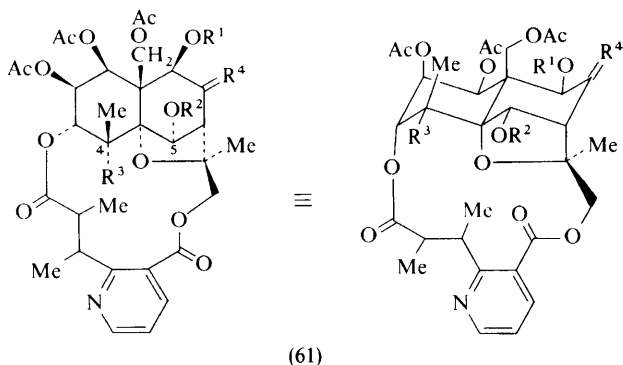


and intriguing alkaloids has been discovered. The structures proposed for pediculidine (53; R = O,  $\alpha\beta$ -double bond) and pediculinine (53; R = H, OH) rest mainly on spectral evidence.<sup>77, 78</sup> Tecomanine and alkaloid C, two alkaloids from *Tecoma stans* whose structures had been advanced previously, have been shown to possess the stereochemistry and absolute configuration expressed by (55) and (54), respectively, by *X*-ray analysis.<sup>79</sup>

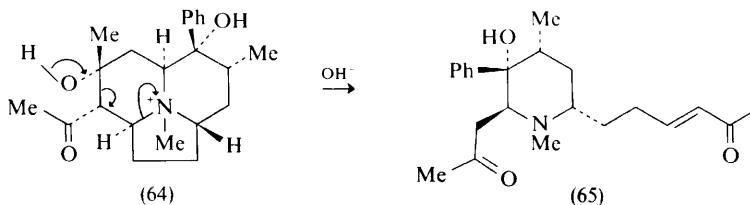


- <sup>87</sup> D. W. Bishay and Z. Kowalewski, *Herba Pol.*, 1971, **17**, 97 (*Chem. Abs.*, 1971, **75**, 115 894k).
- <sup>88</sup> D. W. Bishay and Z. Kowalewski, *Herba Pol.*, 1971, **17**, 233 (*Chem. Abs.*, 1972, **76**, 131 414e).
- <sup>89</sup> M. Pailer, W. Streicher, and J. Leitich, *Monatsh.*, 1971, **102**, 1873.
- <sup>90</sup> A. Klasek, F. Santavy, A. M. Duffield, and T. Reichstein, *Helv. Chim. Acta*, 1971, **54**, 2144.
- <sup>91</sup> A. Klasek, Z. Samek, and F. Santavy, *Tetrahedron Letters*, 1972, 941.
- <sup>92</sup> K. Sugiura, Y. Shizuri, H. Wada, K. Yamada, and Y. Hirata, *Tetrahedron Letters*, 1971, 2733.
- <sup>93</sup> H. Wada, Y. Shizuri, K. Sugiura, K. Yamada, and Y. Hirata, *Tetrahedron Letters*, 1971, 3131.
- <sup>94</sup> H. Wada, Y. Shizuri, K. Yamada, and Y. Hirata, *Tetrahedron Letters*, 1971, 2655.
- <sup>95</sup> Y. Shizuri, H. Wada, K. Sugiura, K. Yamada, and Y. Hirata, *Tetrahedron Letters*, 1971, 2659.
- <sup>96</sup> R. F. Bryan and R. M. Smith, *J. Chem. Soc. (B)*, 1971, 2159.
- <sup>97</sup> S. M. Kupchan, R. M. Smith, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1970, **92**, 6667.
- <sup>98</sup> T. P. Forrest and S. Ray, *Canad. J. Chem.*, 1971, **49**, 1774.

The structure of crepidine (57), a most intriguing alkaloid isolated from *Dendrobium crepidatum*, has been deduced by *X*-ray crystallographic analysis of its methiodide.<sup>82</sup> An unusual but readily explained base-catalyzed fragmentation of crepidine methiodide [(64)  $\rightarrow$  (65)] is given in the same report.<sup>82a</sup> Apparently

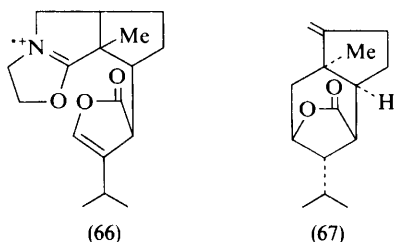


four other structurally similar alkaloids have been isolated from the same species.<sup>82b, 83</sup> An obvious biogenetic relationship between crepidine (57) and known *Dendrobium* alkaloids [(58)—(60)] is not evident and a partial acetogenin origin may be a first hypothesis on which to base biosynthetic experiments.



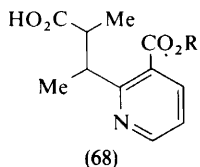
Several alkaloids varying slightly from the dendrobine skeleton (59) have been isolated from *Dendrobium friedricksianum* and *D. hildebrandii*.<sup>84-86</sup> The structure of 6-hydroxynobilonine (60; R = OH) was assigned on the basis of its n.m.r. spectrum, which showed a doublet at  $\delta$  2.87 (1H) assigned to the C-5 hydrogen thus indicating that the extra hydroxy-group is located at C-6.<sup>84</sup>

Confirmation was obtained by conversion of 6-hydroxynobilonine into dendramine (59;  $R = OH$ ) using a von Braun cyanogen bromide induced demethylation as the key step. Since the absolute configuration of dendramine was known, this inter-relationship also established the absolute configuration of 6-hydroxynobilonine as written (60;  $R = OH$ ). The quaternary alkaloids, *N*-isopentenylidendroxine (58;  $R^1 = R^2 = H$ ,  $\overset{+}{N}CH_2CH=CMe_2$   $Cl^-$ ) and *N*-isopentenyl-6-hydroxydendroxine (58;  $R^1 = OH, R^2 = H, \overset{+}{N}CH_2CH=CMe_2$   $Cl^-$ ) were converted into dendroxine (58;  $R^1 = R^2 = H$ ) and 6-hydroxydendroxine (58;  $R^1 = OH, R^2 = H$ ), respectively, by pyrolysis.<sup>84</sup> In addition, *N*-isopentenyl-6-hydroxydendroxine was readily synthesized by alkylation of (58;  $R^1 = OH, R^2 = H$ ) with 1-bromo-3-methylbut-2-ene. Nobilonine (60;  $R = H$ ) and 6-hydroxynobilonine (60;  $R = OH$ ) have also been isolated from *D. friedricksianum*.<sup>84</sup> A particularly rich source of *Dendrobium* alkaloids, *D. nobile*, has yielded a new compound, 4-hydroxydendroxine (58;  $R^1 = H, R^2 = OH$ ).<sup>86</sup> Strong support for this structural assignment was obtained from the n.m.r. spectrum, which showed a singlet at  $\delta$  4.08 (1H) assignable to the C-3 hydrogen, and from the mass spectrum, which exhibited the base peak at  $(M - 17)^+$  attributable to a facile loss of water to give the ion (66). The stereochemical assignment of the C-4 hydroxy-group in (58;  $R^1 = H, R^2 = OH$ ) is

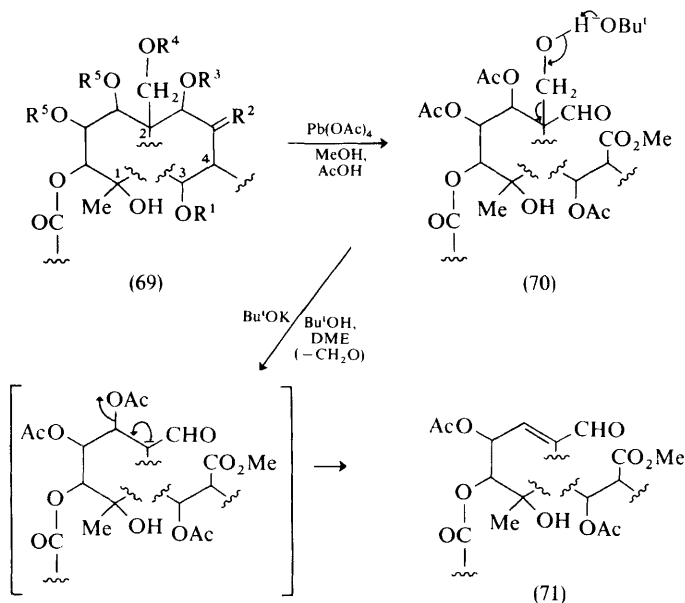


tentative. Nobilomethylene (67) was also obtained from *D. nobile*, but this compound appears to be an artifact arising from nobilonine (60;  $R = H$ ) *N*-oxide. Although (67) could be obtained by pyrolysis of the synthetic *N*-oxide, attempts to isolate the latter from plant material were not successful.

Concurrent investigations in several parts of the world helped to establish the structures of a series of alkaloids from *Euonymus europaeus* and *E. sieboldianus*.<sup>87-95</sup> Japanese workers deduced the structure of evonine (61;  $R^1 = R^2 = Ac, R^3 = OH, R^4 = O$ ) by extensive spectral analysis and chemical degradation.<sup>94,95</sup> Earlier work had established the structure and stereochemistry of evoninic acid (68;  $R = H$ ), obtained by basic hydrolysis of evonine. More



recently the structural elucidation of sesquiterpenoid alkaloids from *Maytenus ovatus* (*vide infra*) invited the suggestion that a relationship may exist between these and the complex *Euonymus* alkaloids since both species belong to the Celastraceae family. The partial structure (69;  $R^1 = R^3 = R^4 = R^5 = \text{Ac}$ ,  $R^2 = \text{O}$ ) was supported by n.m.r. (including double resonance) data and by a variety of transformations of which the key sequence which brought together several smaller fragment structures is represented by Scheme 5.<sup>94</sup> The triacetate



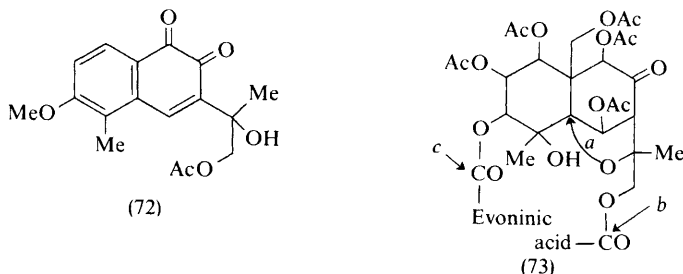
Scheme 5

(69;  $R^1 = R^5 = \text{Ac}$ ,  $R^2 = \text{O}$ ,  $R^3 + R^4 = \text{CMe}_2$ ) was oxidized to the aldehyde-ester (70), which upon base treatment suffered a reverse aldol reaction with expulsion of formaldehyde and acetic acid to yield the  $\alpha\beta$ -unsaturated aldehyde (71). Further degradation of evonine and the triacetate (69;  $R^1 = R^5 = \text{Ac}$ ,  $R^2 = \text{O}$ ,  $R^3 + R^4 = \text{CMe}_2$ ) led to the complete structural elucidation of the alkaloid as represented by structure (61;  $R^1 = R^2 = \text{Ac}$ ,  $R^3 = \text{OH}$ ,  $R^4 = \text{O}$ ).<sup>95</sup> The critical reaction sequence involved the conversion in five steps of evonine into the 1,2-naphthoquinone derivative (72), whose structure was assigned on the basis of characteristic u.v. and mass spectral data as well as a consistent n.m.r.

spectrum. Partial structure (69), together with a further unit  $\text{Me}-\text{C}(\text{Me})_2-\text{CH}_2\text{OAc}$ , originally indicated from a long-range coupling effect between a tertiary methyl and a hydroxymethylene group ( $J \sim 1$  Hz), accounted for 14 carbons of the  $\text{C}_{15}$  sesquiterpenoid component of evonine. The remaining carbon must be

quaternary and bonded to C-1, C-2, and C-3 in (69) and not to C-4 on the basis of the formation of a 1,2-naphthoquinone derivative (72). Therefore the unit

$\text{Me}-\overset{\textstyle |}{\underset{\textstyle |}{\text{C}}}-\text{CH}_2\text{OAc}$  must be bonded to C-4, a conclusion which assures that the assignment of the substitution pattern in (72) is correct. The partial structure (69) was thus expanded to (73) and the final bond (arrow *a*) of the sesquiterpenoid



part was fixed on the basis of the presence of a tertiary hydroxy-group in (72) and deductions concerning the nature of the ten oxygen functions in the alkaloid. The remaining question, that of the manner in which evoninic acid (68;  $\text{R} = \text{H}$ ) is linked into the sesquiterpenoid component, was answered by establishing the correctness of the structure of evoninic acid monomethyl ester (68;  $\text{R} = \text{Me}$ ) obtained during a  $\text{NaOAc}-\text{MeOH}$  degradation step of an intermediate which had the *b* and not *c* carboxylic acid group free in structure (73).<sup>95</sup>

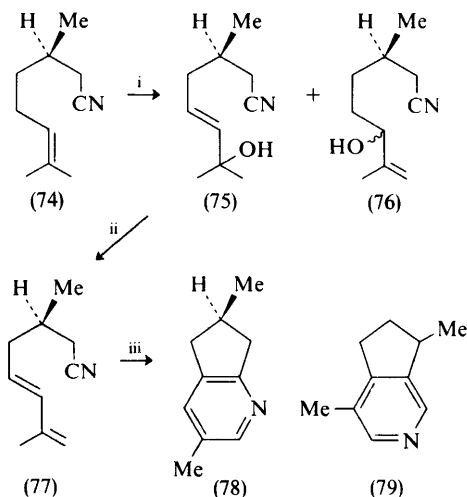
Once the structure of evonine was established as (61;  $\text{R}^1 = \text{R}^2 = \text{Ac}$ ,  $\text{R}^3 = \text{OH}$ ,  $\text{R}^4 = \text{O}$ ), related alkaloids isolated from *Euonymus sieboldianus* (see Table) were readily shown to be slight functional group modifications of this major alkaloid by spectral comparison and simple chemical transformation.<sup>92</sup> Further confirmation of the manner in which evoninic acid (68;  $\text{R} = \text{H}$ ) is attached to the sesquiterpenoid portion was also obtained in this study. The stereochemistry of evonine indicated in structure (61) and thus also of neoevonine, euonymine, and neoeuonymine (see Table) were advanced on the basis of n.m.r. and nuclear Overhauser effect experiments.<sup>93</sup>

Workers in Europe and the United States independently and concurrently arrived at the same structural representation for evonine (61;  $\text{R}^1 = \text{R}^2 = \text{Ac}$ ,  $\text{R}^3 = \text{OH}$ ,  $\text{R}^4 = \text{O}$ ).<sup>89-91</sup> In addition, the new alkaloids evonoline (61;  $\text{R}^1 = \text{R}^2 = \text{Ac}$ ,  $\text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{O}$ )<sup>89</sup> and evozine (61;  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{OH}$ ,  $\text{R}^4 = \text{O}$ )<sup>90,91</sup> were elucidated by these groups. Comparison of spectral and physical constants showed that another alkaloid, evorine,<sup>91</sup> was identical to neoevonine isolated by the Japanese group.<sup>92,93</sup> Interconversion of evonine, evorine, and evozine was effected by partial hydrolysis and acetylation reactions, including a deacetylation of evonine to evorine by an enzymic preparation obtained from *E. europaeus*.<sup>90</sup> One of these transformations yielded an alkaloid, isoevorine, whose structure was not clarified.<sup>90</sup> Criticism of the stereostructure for evonine (61;  $\text{R}^1 = \text{R}^2 = \text{Ac}$ ,  $\text{R}^3 = \text{OH}$ ,  $\text{R}^4 = \text{O}$ ) advanced by the Japanese

workers<sup>93</sup> has been offered<sup>91</sup> specifically with regard to the arrangement of substituents at C-4 and C-5. Extracts from *E. europaeus* appear to have insecticidal properties.<sup>90</sup>

Details of the X-ray crystal structure determination of the methiodide of maytoline (62; R = OH) from *Maytenus ovatus* have been published.<sup>96</sup> The original characterization<sup>97</sup> of this alkaloid and its relative maytine (62; R = H) played a significant role in the structural elucidation of the *Euonymus* alkaloids (see above).

Refreshing synthetic work in the monoterpenoid alkaloid area has appeared during the past year. The pyridine derivative (78), an isomer of the alkaloid actinidine (79) and as yet unknown in nature, has been synthesized (Scheme 6).<sup>99</sup>



Reagents: i,  $h\nu$ -O<sub>2</sub>-Rose Bengal; ii, 1N-H<sub>2</sub>SO<sub>4</sub>-MeCOMe; iii, heat (500 °C).

**Scheme 6**

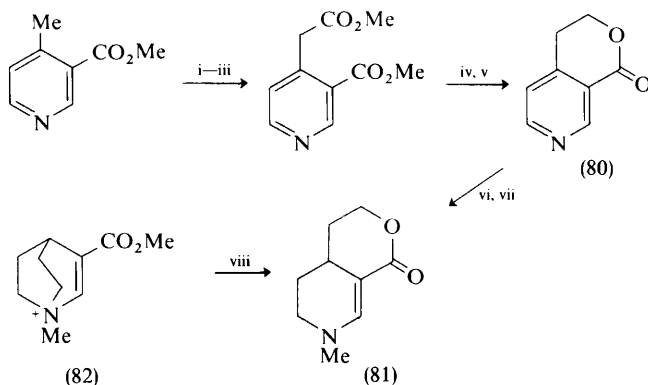
Photo-oxygenation of (-)-citronellonitrile (74) followed by reduction of the intermediate hydroperoxides gave a 1 : 1 mixture of two allylic alcohols, (75) and (76). This mixture upon treatment with acid provided the diene (77) and recovered (76). Pyrolysis of (77) effected an intramolecular Diels-Alder reaction and a dehydrogenation to yield (78).

The discovery of an interesting rearrangement [(82) → (81)] prompted the execution of an independent synthesis of the product (81) (Scheme 7).<sup>100</sup> As a fringe benefit, this work provided the pyridine lactone (80) whose physical data are in good agreement with those of gentianadine, an alkaloid isolated from

<sup>99</sup> Y. Butsugan, S. Yoshida, M. Muto, T. Bito, T. Matsuura, and R. Nakashima, *Tetrahedron Letters*, 1971, 1129; Y. Butsugan, S. Yoshida, M. Muto, T. Bito, T. Matsuura, and R. Nakashima, *Nippon Kagaku Zasshi*, 1971, 92, 548 (*Chem. Abs.*, 1972, 76, 127 165g).

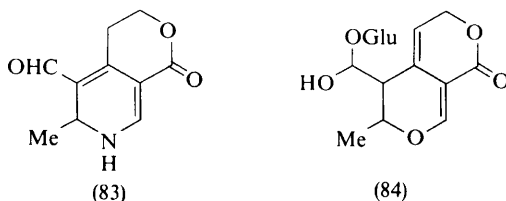
<sup>100</sup> J. Dolby, R. Dahlbom, K. H. Hasselgren, and J. L. G. Nilsson, *Acta Chem. Scand.*, 1971, 25, 735.

*Gentiana turkestanorum*. Gentioflavine (83) has been obtained by treatment of gentioflavoside (84) with aqueous ammonia. The latter is a new sesquiterpenoid



Reagents: i,  $(\text{CO}_2\text{Me})_2\text{-Bu}^+\text{OK-C}_6\text{H}_6$ ; ii,  $\text{KOH-H}_2\text{O}_2$ ; iii,  $\text{MeOH-HCl}$ ; iv,  $\text{LiAlH}_4$ ; v,  $\text{MnO}_2$ ; vi,  $\text{H}_2\text{-Pd/C-MeOH}$ ; vii,  $\text{CH}_2\text{O-HCO}_2\text{H}$ ; viii, heat ( $150^\circ\text{C}$ )- $\text{N}_2$ .

Scheme 7



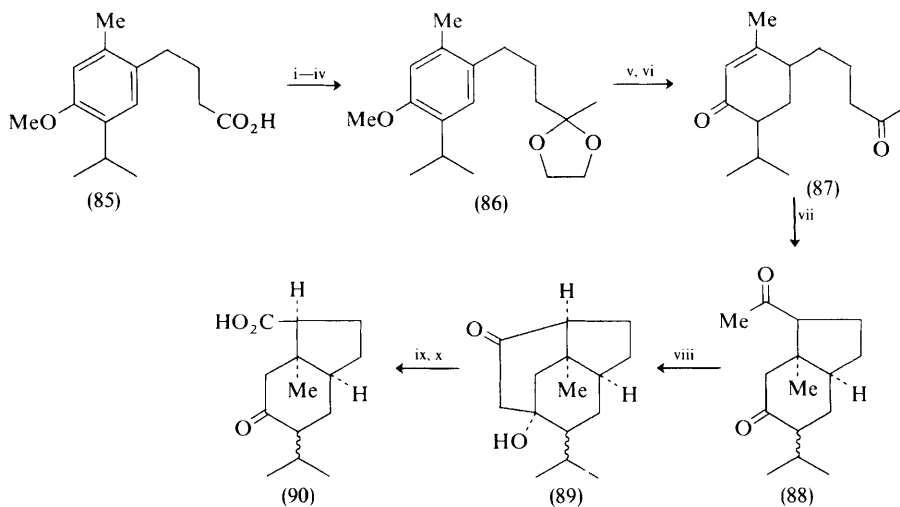
isolated from *G. punctata*.<sup>101</sup> Some new chemistry of gentioflavine has been reported.<sup>102</sup>

New and continuing efforts towards the total synthesis of dendrobine (59; R = H) have been reported.<sup>103,104</sup> In one sequence (Scheme 8),<sup>103</sup> the butyric acid (85) was readily transformed into the ketal (86), which was submitted to a Birch reduction and hydrolysis to yield the cyclohexenone (87) as the single diastereomeric product. Acid treatment of (87) gave a stereoisomeric mixture of products (88) which were not separated but subjected to reaction with base to give compound (89). The same compound was obtained directly by treatment of (87) with strong base (Michael and aldol condensations combined). After some discouraging results, the tricyclic compound (89) was transformed into the desired keto-acid (90) via an abnormal ozonolysis reaction. Compound (90) possesses the correct stereochemistry at three asymmetric centres required for elaboration of dendrobine (59; R = H).

<sup>101</sup> St. Popov and N. L. Marekov, *Chem. and Ind.*, 1971, 655.

<sup>102</sup> St. Popov and N. Marekov, *Doklady Bolg. Akad. Nauk*, 1971, **24**, 883 (*Chem. Abs.*, 1971, **75**, 140 739w).

<sup>103</sup> Y. Hayakawa, H. Nakamura, K. Aoki, M. Suzuki, K. Yamada, and Y. Hirata, *Tetrahedron*, 1971, **27**, 5157.



Reagents: i,  $(\text{COCl})_2\text{-C}_6\text{H}_6$ ; ii,  $\text{CH}_2\text{N}_2\text{-Et}_2\text{O}$ ; iii,  $\text{Zn-HOAc}$ ; iv,  $\text{HOCH}_2\text{CH}_2\text{OH-TsOH-C}_6\text{H}_6$ ; v,  $\text{Li-NH}_3\text{-Bu}^t\text{OH-THF}$ ; vi,  $0.2\text{N-HCl-EtOH}$ ; vii,  $2\text{N-HCl-EtOH-H}_2\text{O}$ ; viii,  $\text{Bu}^t\text{OK-Bu}^t\text{OH}$ ; ix, camphorsulphonic acid- $\text{Ac}_2\text{O-100}^\circ\text{C}$ ; x,  $\text{O}_3\text{-HOAc-EtOAc}$ .

Scheme 8

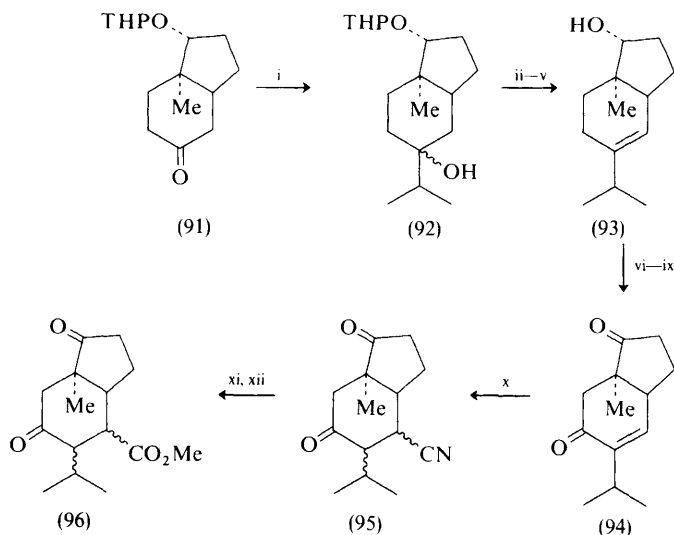
An entirely different approach towards an intermediate (96), potentially useful for the synthesis of dendrobine, is lengthy and lacks regio- and stereo-selectivity (Scheme 9).<sup>104</sup> Treatment of the ketone (91) with isopropyl-lithium gave the alcohol (92) which upon hydrolysis, oxidation, and dehydration produced a mixture of olefins from which the desired isomer (93) was isolated after tedious preparative g.c. work. The unsaturated diketone (94), obtained in overall low yield from (93), was hydrocyanated to give a mixture of three isomeric cyanoketones (95). Hydrolysis and esterification of this mixture provided a diastereomeric mixture of keto-esters (96).

A report on the Polonovski reaction of nupharidine (97;  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{Me}$ ,  $\text{N} \rightarrow \text{O}$ ), a naturally occurring *N*-oxide, has broad synthetic and biogenetic interest.<sup>105</sup> Treatment of nupharidine with an excess of acetic anhydride at  $25^\circ\text{C}$  for 75–120 h gave the  $\Delta^6$ -enamine (98;  $\text{R} = \text{H}$ ) in 82% yield. This compound was shown to undergo *N*-protonation and alkylation and therefore, not unexpectedly, resisted acidic and basic hydrolytic ring-opening. Catalytic reduction of (98;  $\text{R} = \text{H}$ ) gave the alkaloids (–)-deoxynupharidine (97;  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{Me}$ ) and (–)-epideoxynupharidine (97;  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ,  $\text{R}^3 = \text{Me}$ ), whereas osmium tetroxide–paraperiodic acid oxidation followed by Grignard reaction with methylmagnesium iodide produced

<sup>104</sup> K. Yamamoto, T. Sohda, I. Kawasaki, and T. Kaneko, *Bull. Chem. Soc. Japan*, 1971, **44**, 2197.

<sup>105</sup> R. T. LaLonde, E. Auer, C. F. Wong, and V. P. Muralidharan, *J. Amer. Chem. Soc.*, 1971, **93**, 2501.

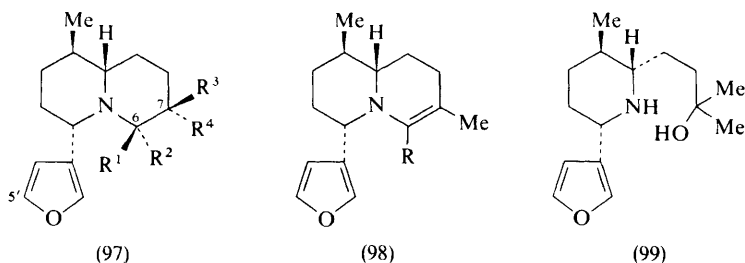




Reagents: i,  $\text{LiPr}^t\text{-pet. ether}$ ; ii,  $2\text{N-HCl-THF}$ ; iii,  $\text{CrO}_3\text{-HOAc-MeCOMe}$ ; iv,  $200^\circ\text{C-KHSO}_4$ ; v,  $\text{LiAlH}_4\text{-Et}_2\text{O}$ ; vi,  $\text{Ac}_2\text{O}$ ; vii,  $\text{SeO}_2\text{-C}_6\text{H}_6$ ; viii,  $2\text{N-KOH-MeOH}$ ; ix, Jones oxidation; x,  $\text{KCN-NH}_4\text{Cl-DMF-H}_2\text{O-}100^\circ\text{C}$ ; xi,  $6\text{N-H}_2\text{SO}_4$ ; xii,  $\text{CH}_2\text{N}_2\text{-Et}_2\text{O}$ .

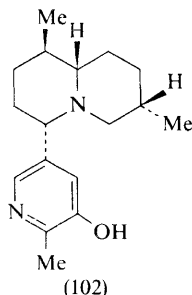
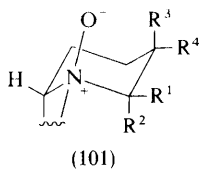
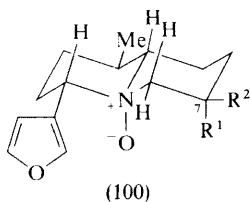
### Scheme 9

(-)-nupharamine (99), also a natural product. Furthermore, the facile formation of the  $\Delta^6$ -enamine (98;  $\text{R} = \text{H}$ ) provided an opportunity for examining the stereochemical outcome of the Polonovski reaction. The dideuterio *N*-oxide (97;  $\text{R}^1 = \text{R}^3 = \text{D}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{R}^4 = \text{Me}$ ,  $\text{N} \rightarrow \text{O}$ ) was prepared by successive



catalytic deuteration and oxidation (hydrogen peroxide) of (98;  $\text{R} = \text{H}$ ) and its stereochemistry was established by comparison of its n.m.r. spectrum with spectra of nuphar alkaloids of known configuration. Polonovski reaction gave the  $\Delta^6$ -enamine (98;  $\text{R} = \text{D}$ ) whose deuterium content and location were determined from n.m.r. and mass spectral data. This result appeared to be consistent with a *cis* elimination mechanism from a *trans*-fused nupharidine system (100;

$R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ). However, oxidation of deoxynupharidine (97;  $R^1 = R^2 = R^3 = \text{H}$ ,  $R^4 = \text{Me}$ ) to nupharidine was found to be faster than oxidation of 7-epideoxynupharidine (97;  $R^1 = R^2 = R^4 = \text{H}$ ,  $R^3 = \text{Me}$ ) to 7-epinupharidine. These observations were difficult to interpret in terms of the oxidation proceeding with retention to yield the *trans*-fused system (100;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$  or  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ). On the basis of this premise it would be expected that oxidation of deoxynupharidine (97;  $R^1 = R^2 = R^3 = \text{H}$ ,  $R^4 = \text{Me}$ ) would proceed more slowly because of the development of unfavourable 1,3-diaxial interaction between the C-7 methyl and the *N*-oxide function [cf. (100;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ )].



On the other hand, the difference in rate may be understood in terms of oxidation of deoxynupharidine with inversion of nitrogen to give the *cis*-fused *N*-oxide (101;  $R^1 = R^2 = R^3 = \text{H}$ ,  $R^4 = \text{Me}$ ). Oxidation would be expected to be faster in this case than in 7-epideoxynupharidine since in the latter 1,3-diaxial interactions in its favoured conformation (101;  $R^1 = R^2 = R^4 = \text{H}$ ,  $R^3 = \text{Me}$ ) would be predicted to have a significant rate-diminishing effect. In order to settle this point unequivocally an *X*-ray diffraction study on nupharidine hydrobromide was carried out. This study showed that the ring system is *cis*-fused as in (101) and, when considered together with the formation of (98;  $R = \text{D}$ ) from (97;  $R^1 = R^3 = \text{D}$ ,  $R^2 = \text{H}$ ,  $R^4 = \text{Me}$ ,  $\text{N} \rightarrow \text{O}$ ) proved that the Polonovski reaction occurred by a *trans* elimination mechanism. This finding seems to be in disagreement with results obtained on lupanine *N*-oxide.

Treatment of deoxynupharidine (97;  $R^1 = R^2 = R^3 = \text{H}$ ,  $R^4 = \text{Me}$ ) with acetyl chloride gave the 5'-acetyl derivative, which upon exposure to aqueous ammonia solution containing ammonium chloride yielded (102).<sup>106</sup> Some related reactions were also reported in this study.

A spectrophotometric method for the quantitative determination of nobilonine (60;  $R = \text{H}$ ) in extracts from *Verbascum nobile* has been devised.<sup>107</sup> An extract from *Nuphar luteum* has been shown to possess antimitotic activity similar to that observed with colchicine.<sup>108</sup>

<sup>106</sup> Y. Arata and K. Yamanouchi, *Yakugaku Zasshi*, 1971, **91**, 476 (*Chem. Abs.*, 1971, **75**, 36 417d).

<sup>107</sup> P. Ninova and I. Buklova, *Farmatsiya (Sofia)*, 1970, **20**, 18 (*Chem. Abs.*, 1971, **75**, 40 505y).

<sup>108</sup> M. Furmanowa and I. Nikogosian, *Acta Pol. Pharm.*, 1971, **28**, 195 (*Chem. Abs.*, 1972, **76**, 562d).

## 3

## Tropane Alkaloids

BY J. E. SAXTON

This group of alkaloids continues to attract some attention, and the contributions published during the period under review range in emphasis from the purely pharmacological to the purely mechanistic aspects of organic chemistry. As well as reports on the isolation of new alkaloids, attempts to find new pharmaceuticals, and improved methods of assay, the recent publications include studies in which tropane derivatives have been used as a convenient vehicle for conformational and mechanistic studies.

The genetic differences, if any, between *Datura stramonium* L. and *D. tatula* L. have been studied, with particular reference to their alkaloid content.<sup>1</sup> There appears to be no difference between these species either in alkaloid content or in the kinds of alkaloids present in the leaves. Variations in alkaloid content were observed, however, in individual plants of interspecific hybrids, which seems to suggest some genetic differences in the parent species in those factors that affect alkaloid production. This confirms the accepted botanical view that *D. stramonium* and *D. tatula* should be regarded as two varieties of a single species.<sup>1</sup>

*Scopolia carniolica*<sup>2,3</sup> and *S. tangutica*<sup>4,5</sup> have been studied yet again. The total alkaloid content of rhizomes of *S. carniolica*, grown in the Ukraine and in Moldavia,<sup>2</sup> is less than that found in Caucasian-grown plants,<sup>6</sup> but the proportion of scopolamine present is higher. In the Ukrainian and Moldavian plants the highest alkaloid content was observed in plants grown at an altitude of 350–650 m. Apparently plants grown in the shade contained a somewhat higher alkaloid content than those grown in conditions of better illumination.<sup>2</sup> As noted earlier, the aerial parts of *S. tangutica* contain hyoscyamine and scopolamine,<sup>4</sup> while the roots contain these two alkaloids, together with cuscohygrine and tropine; two other, unidentified, alkaloids were also detected.<sup>5</sup>

<sup>1</sup> M. Tabata, N. Hiraoka, and M. Konoshima, *Japanese J. Pharmacognosy (Shoyakugaku Zasshi)*, 1970, **24**, 65 (*Chem. Abs.*, 1971, **75**, 16 252).

<sup>2</sup> I. L. Krylova, L. N. Shaknovskii, and S. V. Rusakova, *Rast. Resur.*, 1972, **8**, 54 (*Chem. Abs.*, 1972, **76**, 124 146).

<sup>3</sup> B. Srepeš, *Acta Pharm. Jugoslav.*, 1971, **21**, 84 (*Chem. Abs.*, 1971, **75**, 143 944).

<sup>4</sup> B. A. Samoryadov and S. A. Minina, *Khim. prirod. Soedinenii*, 1971, **7**, 209 (*Chem. Abs.*, 1971, **75**, 31 332).

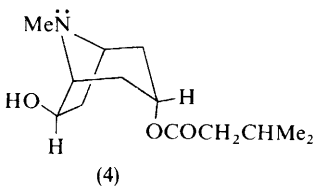
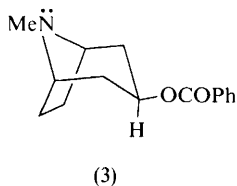
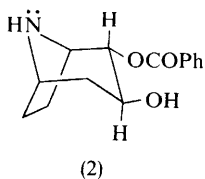
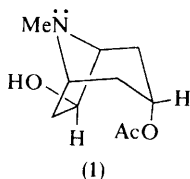
<sup>5</sup> I. Barene and S. A. Minina, *Khim. prirod. Soedinenii*, 1971, **7**, 379 (*Chem. Abs.*, 1971, **75**, 115 920).

<sup>6</sup> I. L. Krylova, L. N. Shaknovskii, S. V. Rusakova, and E. F. Mikhailova, *Rast. Resur.*, 1971, **7**, 9 (*Chem. Abs.*, 1971, **74**, 108 128).

Scopolamine is also the major alkaloid of *Latua pubiflora* (fam. Solanaceae) from S. Chile; the remainder of the alkaloid content is represented by atropine and/or hyoscyamine.<sup>7</sup>

Several other solanaceous plants have been investigated thoroughly for the first time. These include *Salpichroa origanifolia* (Lam.) Baillon [*S. rhomboidea* (Hook.) Miers], the roots of which contain pseudotropine and cuscohygrine, together with trace amounts of tropine, hyoscyamine, and hygrine.<sup>8</sup> Five *Solandra* species investigated proved to constitute a uniform phytochemical group.<sup>9</sup> The roots of *S. grandiflora* Sw. contain hyoscyamine, littorine, hyoscine, tigloidine, 3 $\alpha$ -tigloyloxytropane, 3 $\alpha$ -acetoxytropane, valtropine [(+)-3 $\alpha$ -(2-methylbutyryloxy)tropane], tropine, pseudotropine, and cuscohygrine. The aerial parts of the plant yielded atropine as the major alkaloid, together with noratropine, hyoscine, tigloidine, 3 $\alpha$ -tigloyloxytropane, 3 $\alpha$ -acetoxytropane, valtropine, tropine, pseudotropine, and cuscohygrine. The other species investigated (*S. guttata* D. Don ex Lindley, *S. hartwegii* N. Br., *S. hirsuta* Dun., and *S. macrantha* Dun.) contained a smaller proportion of alkaloids, although the pattern of alkaloid content was in general similar. The only other alkaloid encountered was ( $\pm$ )-norhyoscine, which was isolated from the stems of *S. guttata*.<sup>9</sup>

Three tropane alkaloids, two of which are new, have been isolated from the leaves of a tree belonging to the Queensland species *Peripentadenia mearsii* (C. T. White) L. S. Smith. (fam. Euphorbiaceae).<sup>10</sup> The two new alkaloids are (+)-(3*R*,6*R*)-3 $\alpha$ -acetoxy-6 $\beta$ -hydroxytropane (1) and (+)-2 $\alpha$ -benzoyloxy-3 $\beta$ -hydroxynortropane (2) (relative configuration only is shown here); the known alkaloid is 3 $\beta$ -benzoyloxytropane (3).



The first of these alkaloids was identified by acetylation, which afforded a product enantiomeric with the product of hydrolysis of (–)-valeroidine (4) and

<sup>7</sup> T. Plowman, L. O. Gyllenhaal, and J. E. Lindgren, *Bot. Mus. Leaflet*, Harvard Univ., 1971, **23**, 61 (*Chem. Abs.*, 1972, **76**, 56 598).

<sup>8</sup> W. C. Evans, A. Ghani, and V. A. Woolley, *Phytochemistry*, 1972, **11**, 469.

<sup>9</sup> W. C. Evans, A. Ghani, and V. A. Woolley, *Phytochemistry*, 1972, **11**, 470.

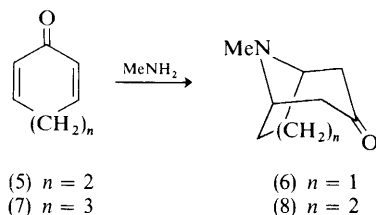
<sup>10</sup> S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1971, **24**, 2399.

subsequent acetylation. The second alkaloid is a benzoyl ester, which forms an *NO*-diacetyl derivative; its structure was deduced from an analysis of its n.m.r. spectrum, together with the n.m.r. spectra of the tropane-2 $\alpha$ ,3 $\beta$ -diol obtained by reductive methylation with formaldehyde-sodium borohydride, and its diacetyl derivative.

Subsequent attempts to repeat the isolation of these alkaloids from plants collected from the same area in Queensland have so far met with failure; markedly lower yields of alkaloids were obtained, and these appear not to be tropane alkaloids. Since the leaves originally shown to contain the three tropane alkaloids were carefully identified it appears that *P. mearsii* must be very variable in alkaloid content, or possibly that the tropane alkaloids, if present, are normally lost during the drying of the leaves.<sup>10</sup>

Recent contributions to the analytical chemistry of this group include an improved determination of total belladonna alkaloids, expressed as hyoscyamine content, based on a simple extraction and titration procedure.<sup>11</sup> A method for the estimation of hyoscyamine and hyoscyamine utilizes u.v. spectrophotometric determination of the alkaloids following t.l.c. separation.<sup>12</sup> Another method involves the spectrophotometric determination of cobalt thiocyanate complexes, e.g. of *n*-butylscopolammonium bromide.<sup>13</sup> Further procedures based on column,<sup>14</sup> t.l.c.,<sup>15,16</sup> g.l.c.,<sup>17</sup> or paper chromatographic separation,<sup>18</sup> have been reported.

A new synthesis<sup>19</sup> affords a 64% yield of tropinone (6) by the direct addition of methylamine to cyclohepta-2,6-dienone (5), a reaction whose feasibility was first noted by Robinson<sup>20</sup> in his celebrated paper published in 1917. Similarly, cyclo-octa-2,7-dienone (7) affords pseudopelletierine (8).



<sup>11</sup> M. Dorer and M. Luby, *Arch. Pharm.*, 1972, **305**, 273.

<sup>12</sup> C. D. Padha, M. C. Nigam, and P. R. Rao, *J. Inst. Chem. (Calcutta)*, 1971, **43**, 5 (*Chem. Abs.*, 1971, **75**, 59 560).

<sup>13</sup> T. Minamikawa, K. Matsumura, A. Kamei, and M. Yamakawa, *Japan Analyst*, 1971, **20**, 1011 (*Chem. Abs.*, 1971, **75**, 148 365).

<sup>14</sup> S. Gill, *Gdansk. Tow. Nauk. Rozpr. Wydz.*, 1970, 175 (*Chem. Abs.*, 1971, **75**, 64 040).

<sup>15</sup> B. Pekic, K. Petrovic, and M. Gorunovic, *Arhiv Farm.*, 1971, **21**, 209 (*Chem. Abs.*, 1972, **76**, 96 502).

<sup>16</sup> J. Polesuk and T. S. Ma, *J. Chromatography*, 1971, **57**, 315.

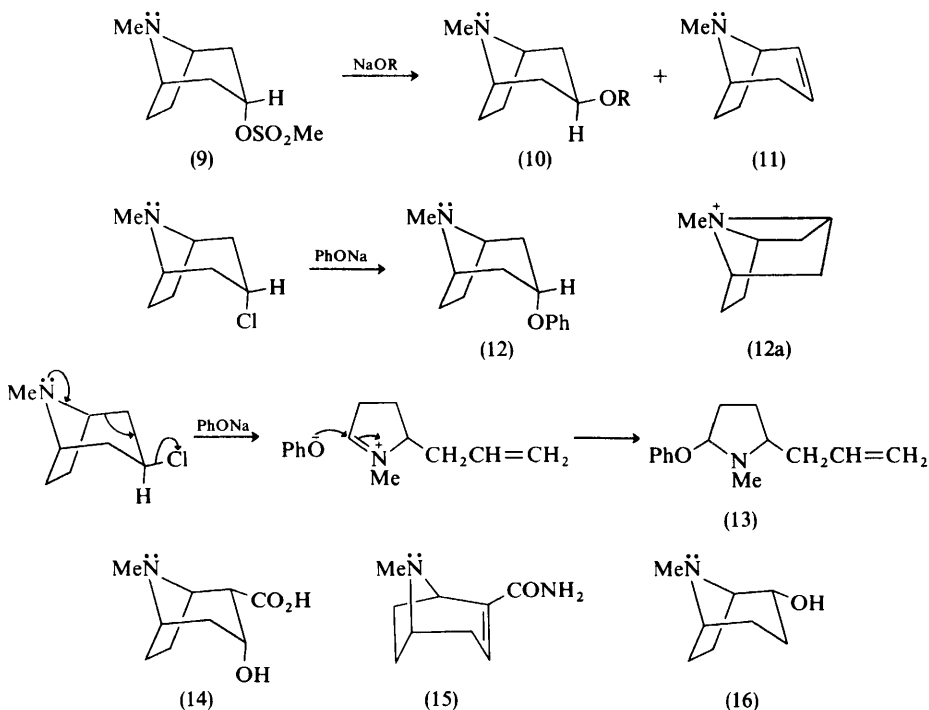
<sup>17</sup> R. Achari and F. Newcombe, *Planta Med.*, 1971, **19**, 241 (*Chem. Abs.*, 1971, **75**, 1062).

<sup>18</sup> A. Puech and M. Jacob, *Ann. pharm. franç.*, 1971, **29**, 437.

<sup>19</sup> A. T. Bottini and J. Gal, *J. Org. Chem.*, 1971, **36**, 1718.

<sup>20</sup> R. Robinson, *J. Chem. Soc.*, 1917, **111**, 762.

The hitherto elusive tropan-3 $\beta$ -yl ethers (10) have now been prepared<sup>21</sup> by the S<sub>N</sub>2 displacement reaction of tropan-3 $\alpha$ -yl methanesulphonate (9) with sodium alkoxides. Some elimination to give trop-2-ene (11) was observed, but the displacement reaction proved to be highly stereoselective, only small amounts



of the 3 $\alpha$ -ether being formed. When 3 $\alpha$ -chlorotropane was treated with sodium methoxide under vigorous conditions, only elimination occurred; however, with sodium phenoxide tropan-3 $\alpha$ -yl phenyl ether (12) was obtained, the reaction being somewhat less stereoselective than the ether synthesis with the methanesulphonate. Reaction of 3 $\beta$ -chlorotropane with sodium phenoxide resulted in fragmentation with formation of 2-allyl-1-methyl-5-phenoxy pyrrolidine (13). The conformations of the 3 $\alpha$ - and 3 $\beta$ -phenyl ethers were determined by consideration of i.r. and n.m.r. spectra, dipole moments, and Kerr constant data.<sup>22</sup>

The mechanisms of these displacement reactions are of some interest. With powerful nucleophiles (PhO<sup>-</sup>, PhS<sup>-</sup>) the reactions of tropan-3 $\alpha$ -yl methanesulphonate are rapid, and the 3 $\beta$ -ethers are formed almost exclusively.<sup>23</sup> With weak nucleophiles (e.g. PhCH<sub>2</sub>NH<sub>2</sub>) the reaction is comparatively slow, and the 3 $\alpha$ -ethers are formed, presumably by a mechanism involving neighbouring group

<sup>21</sup> G. Kraiss, P. Scheiber, and K. Nádor, *J. Chem. Soc. (B)*, 1971, 2145.

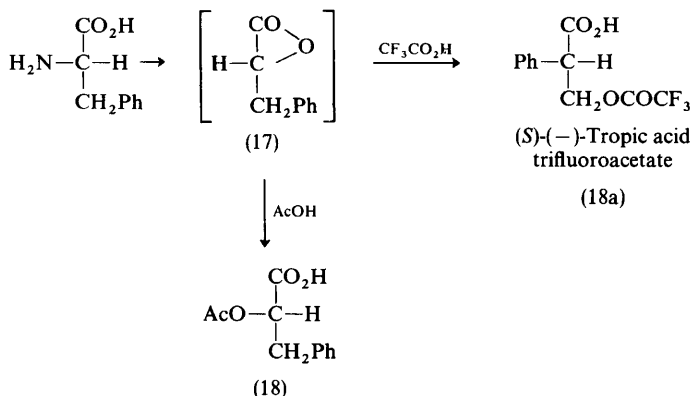
<sup>22</sup> P. Scheiber, G. Kraiss, K. Nádor, and A. Neszmélyi, *J. Chem. Soc. (B)*, 1971, 2149.

<sup>23</sup> P. Scheiber, G. Kraiss, and K. Nádor, *J. Chem. Soc. (B)*, 1971, 2154.

participation by the nitrogen atom, *i.e. via* (12a). Presumably the nucleophilic displacement reactions of tropan-3 $\alpha$ -yl derivatives containing a poor leaving group (*e.g.* chlorine) proceed by a similar mechanism.<sup>24</sup>

A total synthesis of the four isomeric tropan-2-ols has been reported.<sup>25</sup> The route adopted starts with 2-methoxycarbonyltropan-3-one, prepared by a Robinson synthesis, and proceeds *via* the previously described ( $\pm$ )-allopseudo-ecgonine (14). A Hofmann reaction on the related unsaturated amide (15) afforded ( $\pm$ )-2-tropanone, which was hydrogenated in the presence of Adams' catalyst to ( $\pm$ )-2 $\alpha$ -tropanol (16). Resolution by means of tartaric acid then gave D-( $-$ )-2 $\alpha$ -tropanol (not previously prepared) and L-( $+$ )-2 $\alpha$ -tropanol; these were separately epimerized by heating with sodium pentoxide and fluorenone in pentanol-toluene, which gave the novel D-( $+$ )-2 $\beta$ -tropanol and the known L-( $-$ )-2 $\beta$ -tropanol.<sup>25</sup>

The conversion of L-phenylalanine *in vivo* into (*S*)-( $-$ )-tropic acid may be contrasted with the nitrous acid deamination of L-phenylalanine ester in acetic acid, which affords (*R*)-( $+$ )-tropic acid ester acetate, among other products;<sup>26</sup> in this latter reaction preferential migration of the aryl group occurs.<sup>27</sup> The nitrous acid deamination of L-phenylalanine itself also gives a number of products, the ratio depending partly on the nucleophilicity of the solvent employed. In solvents of low nucleophilicity, *e.g.* trifluoroacetic acid, a considerable yield of the trifluoroacetate (18a) of tropic acid, mainly (*S*)-( $-$ )-tropic acid, may be obtained. This reaction involves predominantly retention of configuration, and is explained as proceeding *via* the  $\alpha$ -lactone (17), which suffers aryl migration before attack by nucleophilic solvent.<sup>28</sup> Attack on (17) by a stronger nucleophile, *e.g.* acetate ion, leads to the overall replacement of the amino-group by the acetoxy-group, with overall retention of configuration, and the product is the acid (18).<sup>28</sup>



<sup>24</sup> A. T. Bottini, C. A. Grob, E. Schumacher, and J. Zergenyi, *Helv. Chim. Acta*, 1966, **49**, 2516.

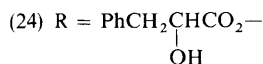
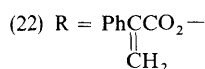
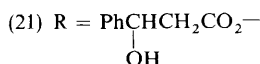
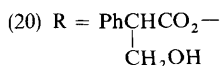
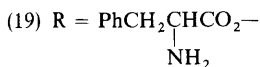
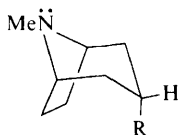
<sup>25</sup> E. R. Atkinson and D. D. McRitchie, *J. Org. Chem.*, 1971, **36**, 3240.

<sup>26</sup> S. Yamada, T. Kitagawa, and K. Achiwa, *Tetrahedron Letters*, 1967, 3007.

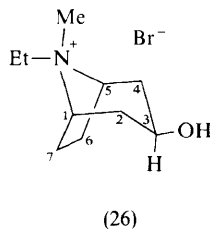
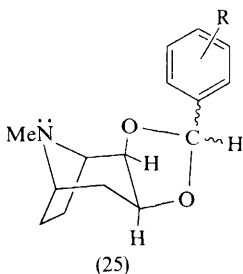
<sup>27</sup> E. Leete, *Tetrahedron Letters*, 1968, 5793.

<sup>28</sup> K. Koga, C. C. Wu, and S. Yamada, *Tetrahedron Letters*, 1971, 2287.

The established migration of the aryl group in the deamination reaction of phenylalanine ester has been ingeniously utilized in a synthesis of some tropane alkaloids.<sup>29</sup> Thus, treatment of the 3 $\alpha$ -tropanyl ester (19) of ( $\pm$ )-phenylalanine with nitrous acid affords a separable mixture of atropine (20), the 3 $\alpha$ -tropanyl ester (21) of ( $\pm$ )-3-hydroxy-3-phenylpropionate, apo-atropine (22), and 3 $\alpha$ -tropanyl *trans*-cinnamate (23). Although not obtained in a pure state the *cis*-isomer of (23), and littorine (24), were also shown to be present in the product mixture.<sup>29</sup>



A series of acetals (25) have been synthesized from tropan-2 $\beta$ ,3 $\beta$ -diol and variously substituted benzaldehydes for pharmacological evaluation as central nervous system stimulants.<sup>30</sup> The configurations of the isomers obtained were elucidated by consideration of the n.m.r. spectra of the related methiodides; in the  $\beta$ -isomers one *N*-methyl group is shielded by the aromatic ring and this results in a significant separation of the two *N*-methyl singlets. In the  $\alpha$ -isomer there is little difference in the chemical shifts of these two signals.



<sup>29</sup> Y. Takeuchi, K. Koga, T. Shioira, and S. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2603.

<sup>30</sup> S. J. Daum, A. J. Gambino, M. D. Aceto, and R. L. Clarke, *J. Medicin. Chem.*, 1972, **15**, 509.



The demethylation of tropine derivatives by means of ethyl chloroformate has been extended to tropinone, which was allowed to react as its ethylene ketal.<sup>31</sup> A series of *N*-ethoxycarbonylnortropine derivatives have been prepared from the intermediate *N*-ethoxycarbonylnortropinone by reaction with appropriate Grignard reagents.<sup>32</sup>

Further evidence has been provided<sup>33</sup> in support of Fodor's conclusion that equatorial attack is preferred in the quaternization reactions of tropine derivatives. Thus, the major product (26) from pseudotropine and ethyl bromide has been shown by *X*-ray crystal structure analysis to contain an equatorial ethyl group. Ruthenium dioxide oxidation of the mixture of *N*-ethylpseudotropinium bromides obtained in this reaction and of the mixture of *N*-ethyltropinium bromides obtained in the analogous reaction of tropine afforded mixtures of *N*-ethyltropinonium bromides, in which the major diastereoisomer was the same as the major isomer produced in the quaternization of tropinone with ethyl bromide. Hence, tropine, pseudotropine, and tropinone all quaternize by preferential equatorial attack. A similar result was obtained in quaternization reactions with deuteriomethyl benzenesulphonate and ethyl bromoacetate. Further experiments showed the same preference for equatorial attack when other leaving groups were involved, and when different solvents were employed.

In the quaternization reactions of tropinone it was observed that the product ratios varied as the reaction proceeded, and they were also affected by the addition of either tropinone or pyridine after completion of the reaction. Presumably the *N*-alkyltropinonium ion, being the quaternary derivative of a Mannich base, can equilibrate with its diastereoisomer *via* the product of reverse Mannich fission, which is a 6-dialkylaminocyclohept-2-enone analogous to the intermediate in the same workers' synthesis<sup>19</sup> of tropinone from methylamine and cycloheptadienone. This conclusion is supported by the observation that equilibration with pyridine of the 87 : 13 and 37 : 63 mixtures of salts obtained, respectively, from quaternizations of tropinone with benzyl brosylate and *N*-benzylnortropinone with methyl brosylate gave the same 72 : 28 mixture in which the predominant isomer was identical with the major benzylation product. Essentially the same product ratio was obtained in the synthesis of *N*-benzyltropinonium salts by the addition of *N*-methylbenzylamine to cycloheptadienone, a reaction which would be expected to lead predominantly to the isomer carrying an equatorial benzyl group.<sup>33</sup>

Some facets of this work overlap that of Kashman and Cherkez,<sup>34</sup> whose attention was focused primarily on the c.d. spectra of 4-substituted piperidones and analogous compounds in which an asymmetric substituent is situated in

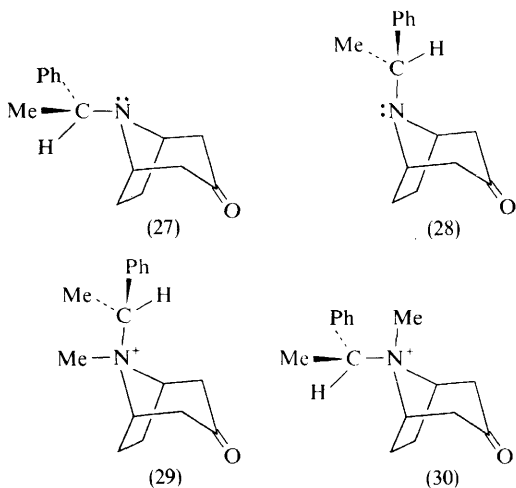
<sup>31</sup> J. Fischer and G. Mikite, *Acta Chim. Acad. Sci. Hung.*, 1971, **68**, 261 (*Chem. Abs.*, 1971, **75**, 20 718).

<sup>32</sup> J. Fischer and G. Mikite, *Acta Chim. Acad. Sci. Hung.*, 1971, **68**, 253 (*Chem. Abs.*, 1971, **75**, 20 720).

<sup>33</sup> U. O. de la Camp, A. T. Bottini, C. C. Thut, J. Gal, and A. G. Bellettini, *J. Org. Chem.*, 1972, **37**, 324.

<sup>34</sup> Y. Kashman and S. Cherkez, *Tetrahedron*, 1972, **28**, 1211.

the symmetry plane of the molecule. During the course of this work *N*-[(*S*)- $\alpha$ -phenylethyl]nortropinone (27) was synthesized, also by the Robinson-Schöpf reaction, from cycloheptadienone (5) and (*S*)-(-)- $\alpha$ -phenethylamine. Although the carbonyl group is situated four  $\sigma$ -bonds distant from the asymmetric substituent, it was nevertheless sufficiently strongly perturbed to exhibit an  $n \rightarrow \pi^*$  Cotton effect in the 290 nm region. Application of the octant rule to the preferred rotamers of (27) and its axial isomer (28) leads to the prediction that both conformers should exhibit a positive Cotton effect, as is found experimentally. The axial and equatorial conformer populations were independently assessed from their n.m.r. spectra in acidic solution, and thus the approximate magnitudes of their respective contributions to the total rotational strength were estimated. As expected from the proximity of its chiral *N*-substituent to the carbonyl group, the axial isomer (28) is responsible for a stronger Cotton effect than (27). Support for this view was obtained from the c.d. spectra of the methiodides (29) and (30);

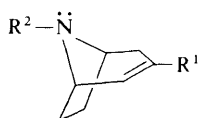


of these, the former was the major product formed on quaternization of (27) with methyl iodide, but on recrystallization from water it gave rise to an equilibrium mixture of (29) and (30), from which the more soluble isomer (30) could be obtained pure by fractional recrystallization from ethanol. The axial epimer (29) exhibited a stronger positive Cotton effect than the equatorial epimer (30), a phenomenon which, if proved to be general, may well supplement the existing methods for the assignment of nitrogen stereochemistry in systems of this kind.<sup>34</sup>

Two explanations have been advanced to account for the preferred equatorial attack in the quaternization reactions of tropane derivatives.<sup>35</sup> One obvious possibility is that 1,3-diaxial interactions with hydrogen at positions 2 and 4 may well discourage axial attack on the nitrogen atom, but it is also possible that

<sup>35</sup> G. Fodor, R. V. Chastain, D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Amer. Chem. Soc.*, 1971, **93**, 403.

compression of a group already attached to nitrogen against the axial hydrogen atoms at C-2 and C-4 (equatorial attack) is energetically less demanding than compression of this same group against the  $\beta$ -hydrogen atoms attached to C-6 and C-7 (axial attack). If the first suggestion is correct the nature of the incoming alkyl group will be decisive, but if the second possibility is correct, the group already attached to nitrogen will be the determining factor. In this connection the behaviour of tropidine (31) and its derivatives [(32)—(34)] should clearly be informative, since if non-bonded interactions experienced by the incoming group are decisive these compounds [(31)—(34)] should exhibit a much greater preference for axial quaternization than tropine and its derivatives. In fact, all four tropidines [(31)—(34)] quaternized predominantly by equatorial approach by the incoming group to give, respectively, the quaternary salts [(35)—(38)]. It thus appears that in the tropidine series, and presumably also in the tropine series, in the transition state for quaternization the interactions of an equatorial substituent on nitrogen with two of the hydrogen atoms of the ethane bridge must be greater than the interactions the substituent experiences when being fixed in the axial position.<sup>36</sup>

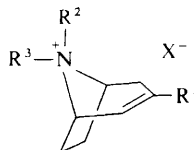


(31)  $R^1 = H, R^2 = Me$

(32)  $R^1 = Ph, R^2 = Me$

(33)  $R^1 = H, R^2 = CH_2Ph$

(34)  $R^1 = Ph, R^2 = CH_2Ph$

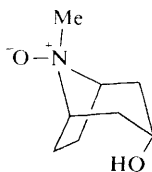


(35)  $R^1 = H, R^2 = Me, R^3 = CH_2Ph, X = Br$

(36)  $R^1 = Ph, R^2 = Me, R^3 = CH_2Ph, X = Br$

(37)  $R^1 = H, R^2 = CH_2Ph, R^3 = Me, X = I$

(38)  $R^1 = Ph, R^2 = CH_2Ph, R^3 = Me, X = I$



(39)

In consonance with this conclusion, and in contrast to the conclusion reached earlier,<sup>37</sup> it has now been demonstrated,<sup>38</sup> on the basis of a detailed analysis of 220 MHz n.m.r. spectra, that the predominant isomer, m.p. 252 °C, obtained in the oxidation of tropine by means of hydrogen peroxide, is the equatorial N-oxide (39).

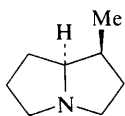
<sup>36</sup> J. H. Supple and E. Eklum, *J. Amer. Chem. Soc.*, 1971, **93**, 6684.

<sup>37</sup> G. Werner and R. Schickfluss, *Annalen*, 1971, **746**, 65.

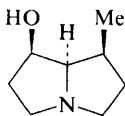
<sup>38</sup> K. Bachmann and W. von Philipsborn, *Helv. Chim. Acta*, 1972, **55**, 637.

## 1 General

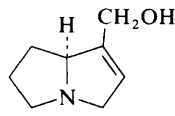
The c.d. spectra of seventeen pyrrolizidine alkaloids have been measured, together with the spectra of some simple pyrrolizidine bases, and the necic acids.<sup>1</sup> The simple pyrrolizidine bases exhibit a c.d. maximum at about 204–206 nm in methanol, and may be divided into four groups. The saturated pyrrolizidines containing  $8\alpha$ -hydrogen, with a substituent at C-1 but not at C-7 [*e.g.* heliotridane (1)], give negative Cotton effects. In contrast retronecanol (2), which has an extra  $7\beta$ -hydroxy-group, gives a positive Cotton effect. The unsaturated pyrrolizidines containing  $8\alpha$ -hydrogen and a 1,2-double bond all give positive Cotton effects. This appears to be true for bases lacking a substituent at C-7 [*e.g.* supinidine (3)], as well as those containing a  $7\alpha$ -substituent [heliotridine (4)] or a  $7\beta$ -substituent [retronecine (5)]; however, it should be noted that the unsaturated bases containing a C-7 substituent show Cotton effects of considerably greater magnitude than the other bases in this group. The open pyrrolizidine ester alkaloids, *e.g.* esters of supinidine or heliotridine, fall into the same categories as the parent bases; the stereochemistry of the esterifying acid appears to have little effect on the c.d. spectra.



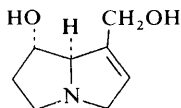
Heliotridane (1)



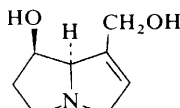
Retronecanol (2)



Supinidine (3)



Heliotridine (4)



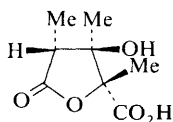
Retronecine (5)

For the saturated bases the c.d. maxima correspond approximately in wavelength to the maxima in the unpolarized u.v. spectra of the tertiary amine chromophore. The unsaturated bases, however, contain an additional olefinic

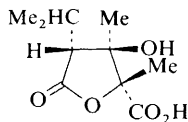
<sup>1</sup> C. C. J. Culvenor, D. H. G. Crout, W. Klyne, W. P. Mose, J. D. Renwick, and P. M. Scopes, *J. Chem. Soc. (C)*, 1971, 3653.

bond which absorbs in the same region, and so the observed Cotton effects may be the result of superposition of two independent Cotton effects; alternatively, they may be due to effectively a single chromophore, produced by interaction of the tertiary nitrogen and the double bond across the five-membered ring. The former seems the more probable explanation, since in acidic solution the c.d. maxima of the saturated bases [*e.g.* (1)] disappear. In contrast, the broad c.d. maximum exhibited by the unsaturated bases in methanol is replaced in acidic solution by a much sharper peak over a narrower wavelength range.

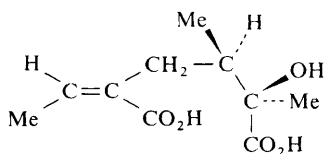
Correlation of absolute configuration of the necic acids with their c.d. spectra is rendered difficult by the number of chromophores within each relatively small molecule. However, some useful deductions emerge from a comparison of the spectra of closely related molecules. Thus, monocrotalic acid (6) is known to have the (2*R*,3*R*,4*R*)-configuration, and the closely similar c.d. spectrum of trichodesmic acid, which is known by stereospecific synthesis to have either the (2*R*,3*R*,4*R*)-, or (2*S*,3*S*,4*S*)-configuration, proves that the (2*R*,3*R*,4*R*)-configuration (7) is correct. Similarly, comparison of the c.d. spectra of senecic acid (8) and its geometrical isomer, integerrinecic acid, both of established absolute configuration, with the spectrum of isatinecic acid, of unknown configuration at C-2, establishes the absolute stereochemistry (9) for isatinecic acid. Finally in this group, the absolute configuration of retronecic acid lactone (10) follows from comparison of its c.d. spectrum with that of integerrinecic acid lactone (11).



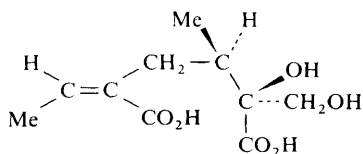
Monocrotalic  
acid (6)



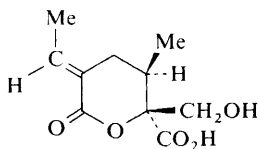
Trichodesmic  
acid (7)



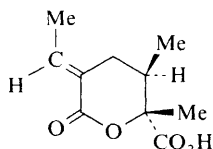
Senecic acid (8)



Isatinecic acid (9)

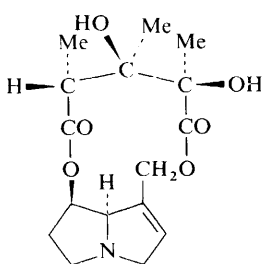


Retronecic acid  
lactone (10)

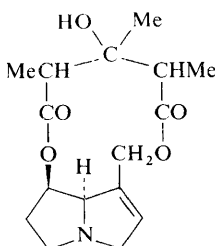


Integerrinecic acid  
lactone (11)

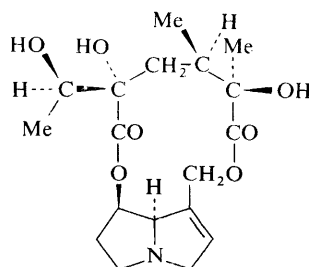
The macrocyclic diester alkaloids are formed by esterification of retronecine (5) with a substituted glutaric or adipic acid, and their c.d. spectra pose a considerable problem in interpretation, owing to the number of chromophores absorbing in the same spectral region, the number of chiral centres, and the number of conformations each molecule may adopt. The alkaloids containing an eleven-membered ring, *e.g.* monocrotaline (12), show strong positive Cotton effects, and in methanol solution the  $\Delta\epsilon$  values are much greater than those observed for the open-chain esters, probably owing to the greater rigidity of the cyclic structure. This is consistent with the observation that the c.d. spectrum of fulvine (13) shows no significant variation in the range 0 to  $-180^\circ\text{C}$ , suggesting very little conformational freedom in the macrocyclic ester molecule. The alkaloids containing a twelve-membered ring but no additional unsaturation, *e.g.* jacoline (14), exhibit smaller  $\Delta\epsilon$  values than their eleven-membered counterparts, which suggests a greater conformational freedom in the larger ring. The exception here is jacobine (15), in which the epoxide ring is presumably responsible for some conformational restraint. When additional unsaturation is present, *e.g.* senecionine (16), two Cotton effects are observed, and the close similarity of the curves in this series suggests that all the molecules have similar preferred conformations, in agreement with conclusions reached from other physical evidence. The small change observed in the c.d. curves in acidified methanol indicates that the tertiary amine chromophore makes only a minor contribution to the c.d. spectra.



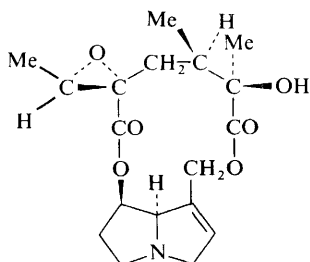
Monocrotaline (12)



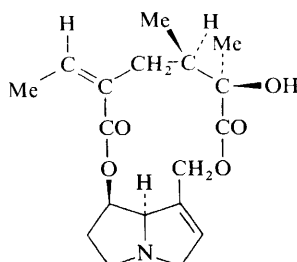
Fulvine (13)



Jacoline (14)

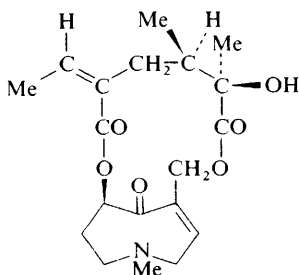


Jacobine (15)

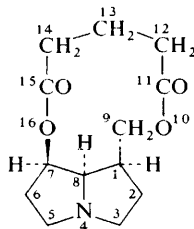


Senecionine (16)

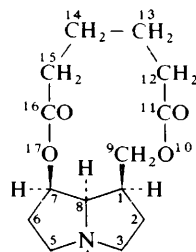
The otonecine bases, *e.g.* senkirkine (17), may be regarded as 4,8-*seco*-derivatives of bases of the senecionine group; it is therefore not surprising that their c.d. spectra resemble those of senecionine and other bases containing an exocyclic ethylidene group.<sup>1</sup>



Senkirkine (17)



Crotalanine (18)

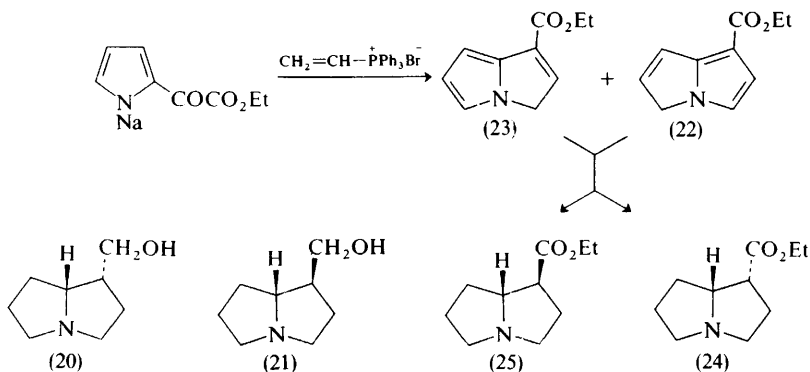


Senecanine (19)

The same group of workers have proposed<sup>1</sup> the use of the stem-names crotalanine and senecanine, respectively, for the fundamental structures (18) and (19), these names implying also the absolute configurations shown. The opposite configuration at C-1 or C-7 is indicated by a prefix giving the position of the relevant *hydrogen* atom(s), *e.g.* 1 $\beta$ -H, or 1 $\beta$ ,7 $\beta$ -H. Compounds containing  $\beta$ -hydrogen at C-8 are denoted by the prefix *ent*, which implies inversion at *all* centres in the name which it governs. This proposal will obviously facilitate the systematic naming of the macrocyclic ester alkaloids, for which the trivial names, for reasons of convenience, have hitherto been the only ones in common use.

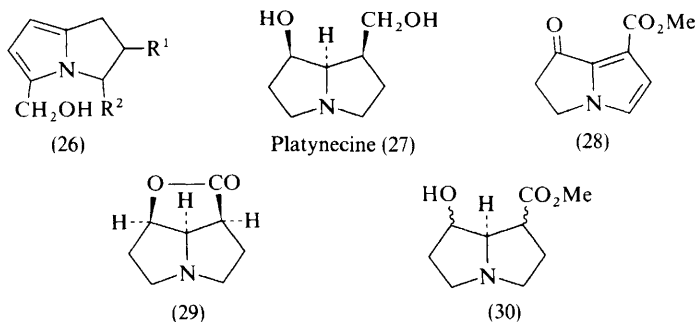
## 2 The Necine Bases and Simple Related Alkaloids

New syntheses of *endo*- and *exo*-1-hydroxymethylpyrrolizidine [(20) and (21)], all four stereoisomers of which occur naturally, have been reported. The sodium derivative of ethyl 2-pyrrolyl-glyoxylate was allowed to react with vinyltriphenylphosphonium bromide, which afforded mainly the dehydropyrrolizidine derivative



(22), presumably *via* the initially formed ester (23). The mixture of pyrrolizines [(22) and (23)] was hydrogenated at atmospheric pressure in the presence of a rhodium–alumina catalyst to give a mixture of 1-ethoxycarbonylpyrrolizidines [(24) and (25)], in which the thermodynamically less stable *endo*-isomer (24) predominated.<sup>2</sup> The structure of the corresponding acid has been verified by X-ray crystal structure analysis.<sup>3</sup> The related *endo*-methyl ester (chysine) was converted into the more stable *exo*-isomer by equilibration with sodium methoxide in methanol; the purity of the isomerization product was estimated to be greater than 99%. Reduction of the *exo*- and *endo*-esters then yields the required 1-hydroxymethylpyrrolizidines [(20) and (21)].

A series of 5-hydroxymethyl-1,2-dihydropyrrolizines (26) have been prepared<sup>4</sup> by reaction of the parent dihydropyrrolizine derivative with formaldehyde and potassium carbonate. Analysis of the n.m.r. spectra of the products shows conclusively that the substituent enters position 5 in all cases examined, and that the saturated five-membered ring adopts the envelope conformation.



Viscontini's synthetic route to the pyrrolizidine bases<sup>5</sup> has now been modified<sup>6</sup> to afford a total synthesis of ( $\pm$ )-platynecine (27). The keto-ester (28), an intermediate in the earlier synthesis<sup>5</sup> of dehydroheliotridine, affords on hydrogenation ( $\text{PtO}_2\text{--H}_2\text{--AcOH}$ ) the lactone (29) as major product, together with a mixture of stereoisomeric hydroxyesters of structure (30). Reduction of the lactone (29) with an excess of lithium aluminium hydride then affords ( $\pm$ )-platynecine (27).<sup>6</sup>

The shielding of the  $\gamma$ -hydrogen atom in pyrrolizidine derivatives by the C-1 to C-8 bond, originally postulated by Skvortsov and Elvidge,<sup>7</sup> has now been confirmed by Australian workers,<sup>8</sup> following an analysis of the n.m.r. spectra of the pyrrolizidine derivatives (31), (32), and (33). All three compounds contain a shielded  $\beta$ -proton at position 7, owing to the fact that the ring system is folded,

<sup>2</sup> S. Brandänge and C. Lundin, *Acta Chem. Scand.*, 1971, **25**, 2447.

<sup>3</sup> E. Soderberg, *Acta Chem. Scand.*, 1971, **25**, 615.

<sup>4</sup> S. A. Kolesnikov, I. M. Skvortsov, and Y. Y. Samitov, *J. Org. Chem. (U.S.S.R.)*, 1971, **7**, 1589 (*Zhur. org. Khim.*, 1971, **7**, 1533).

<sup>5</sup> M. Viscontini and H. Gillhof-Schaufelberger, *Helv. Chim. Acta*, 1971, **54**, 449.

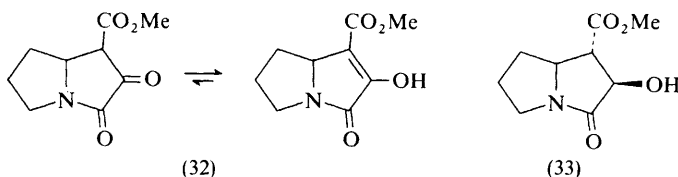
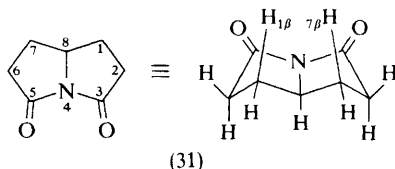
<sup>6</sup> M. Viscontini and H. Buzek, *Helv. Chim. Acta*, 1972, **55**, 670.

<sup>7</sup> I. M. Skvortsov and J. A. Elvidge, *J. Chem. Soc. (B)*, 1968, 1589.

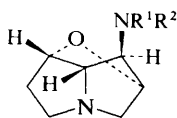
<sup>8</sup> A. J. Aasen, C. C. J. Culvenor, and R. I. Willing, *Austral. J. Chem.*, 1971, **24**, 2575.



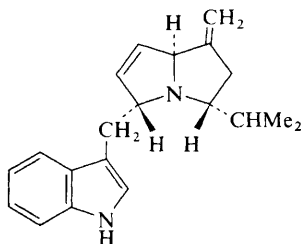
and the rings are puckered so that H-7 $\beta$  is brought forward into the fold of the rings, and into the shielding zone of the C-1 to C-8 bond. This conformation necessarily brings the 7 $\beta$  hydrogen close also to the shielding zone of the amide system, but it is now regarded as unlikely that the amide function can be responsible for shielding of the 7 $\beta$  hydrogen. In any event this can not be the explanation for the shielding of this proton in pyrrolizidine itself,<sup>7</sup> and for this phenomenon shielding by the 1,8-bond must be accepted.<sup>8</sup>



Loline ( $\equiv$  festucine; 34), norloline (35), loline (36), and decorticasine (37) form a quartet of closely related alkaloids whose structures and relative configurations have been established by interconversions,<sup>9</sup> particularly with loline, for which the relative configuration expressed in (34) has been established by *X*-ray crystal structure determination of its dihydrochloride.<sup>10</sup> The absolute configurations for these bases implied in the structures [(34)–(37)] have now been established<sup>11</sup> by the *X*-ray technique of anomalous dispersion, using the dihydrochloride of loline.



Loline (34;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ )  
 Norloline (35;  $R^1 = R^2 = \text{H}$ )  
 Loline (36;  $R^1 = \text{Me}$ ,  $R^2 = \text{Ac}$ )  
 Decorticasine (37;  $R^1 = \text{H}$ ,  $R^2 = \text{COEt}$ )



Peduncularine (38)

<sup>9</sup> S. Yu. Yunusov and S. T. Akramov, *Zhur. obshchei Khim.*, 1955, **25**, 1813 (*Chem. Abs.*, 1956, **50**, 7117); S. Yu. Yunusov and S. T. Akramov, *Zhur. obshchei Khim.*, 1960, **30**, 677, 3132 (*Chem. Abs.*, 1960, **54**, 24 831; 1961, **55**, 19 981); S. Yu. Yunusov and S. T. Akramov, *Doklady Akad. Nauk Uzbek. S.S.R.*, 1959, no. 4, 28 (*Chem. Abs.*, 1960, **54**, 11 028); M. Ribas, A. Landa, and I. Ribas, *Anales de Quim.*, 1968, **64B**, 515 (*Chem. Abs.*, 1968, **69**, 109 764).

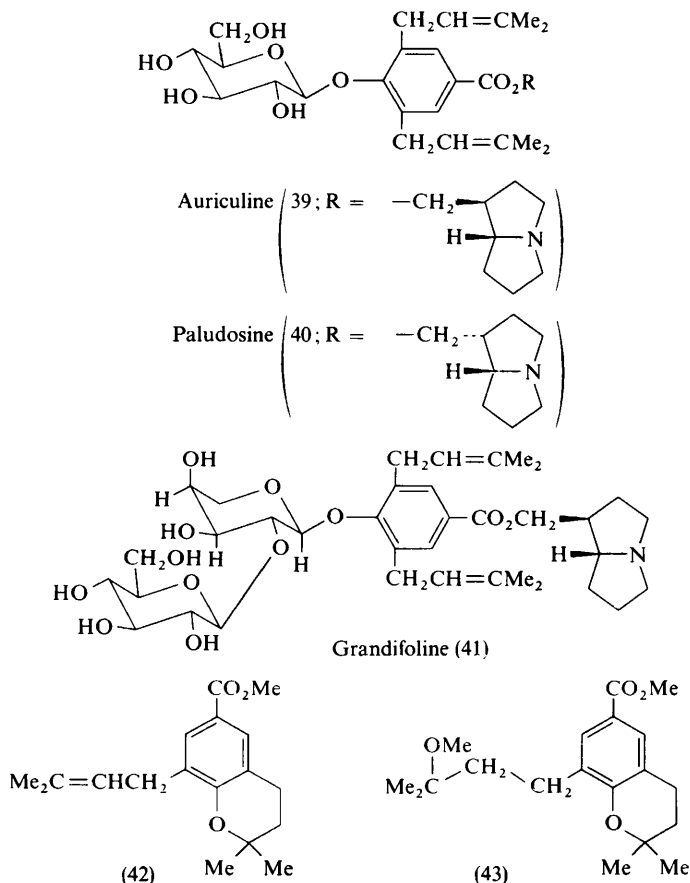
<sup>10</sup> J. A. S. McMillan, Ph.D. Thesis, University of Illinois, 1964; cited in ref. 11.

<sup>11</sup> R. B. Bates and S. R. Morehead, *Tetrahedron Letters*, 1972, 1629.

Peduncularine, an alkaloid of the roots and lower stems of the Tasmanian plant, *Aristolelia peduncularis* (Labill.) Hook. f. (Elaeocarpaceae), has been assigned the structure (38; relative configuration only) on the basis of physical evidence.<sup>12</sup> This alkaloid clearly belongs primarily to the indole series, but it should be noted that if a tryptamine residue is removed from the skeleton of (38), the remaining ten-carbon skeleton does not correspond to any of the hitherto encountered structural units derived from loganin.

### 3 The Ester Alkaloids

An alkaloid possessing a constitution identical with that proposed earlier<sup>13</sup> for auriculine (39) has been isolated from *Liparis loeselii* (L.) L. C. Rich.<sup>14</sup> A closely



<sup>12</sup> I. R. C. Bick, J. B. Bremner, N. W. Preston, and I. C. Calder, *Chem. Comm.*, 1971, 1155.

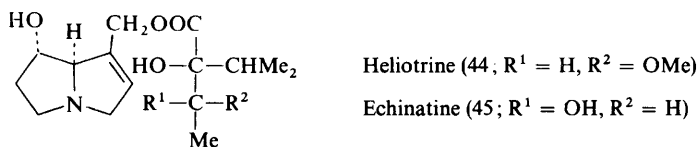
<sup>13</sup> K. Nishikawa, M. Miyamura and Y. Hirata, *Tetrahedron*, 1969, **25**, 2723.

<sup>14</sup> B. Lindström and B. Luning, *Acta Chem. Scand.*, 1971, **25**, 895.

related alkaloid, paludosine, from *Hammarbya paludosa* (L.) O.K., is presumably the epimer (40) of auriculine, since on alkaline hydrolysis it yields nervogenic acid and lindelofidine, while acidic hydrolysis affords glucose. No further information is available concerning a second alkaloid isolated from *H. paludosa*, but the similarity of its u.v. and i.r. spectra with those of (39) and (40) suggests that it is also very closely related.<sup>14</sup>

Another new glycosidic alkaloid in this group is grandifoline (41), an amorphous constituent of *Malaxis grandifolia* Schltr.,<sup>15</sup> which affords the two chroman derivatives (42) and (43), together with laburnine, D-glucose, and L-arabinose, on acid-catalysed methanolysis. The disaccharide component of the alkaloid was isolated by mild acidic hydrolysis and identified, following reduction with sodium borodeuteride, methylation, acidic hydrolysis, reduction with sodium borohydride, and acetylation, as 2-O- $\beta$ -D-glucopyranosyl-L-arabinose. The constitution of this previously unknown disaccharide was then confirmed by synthesis. Since on the basis of the optical rotation data for grandifoline and its component disaccharide the arabinoside linkage is believed to be  $\alpha$ , the complete structure for grandifoline is that given in (41).<sup>15</sup>

Two further *Heliotropium* species have been investigated. The dried leaves of *H. arguzioides* contain 1.2–2.05% alkaloids, the majority of which is heliotrine (44);<sup>16</sup> the same alkaloid occurs with incanine in *H. olgae*.<sup>17</sup> The aerial parts of *Paracynoglossum imeretinum* (Kusnez.) Popov (fam. Boraginaceae) also contain pyrrolizidine alkaloids; so far heliosupine, echinatine (45), and their *N*-oxides have been identified.<sup>18</sup>



In an earlier communication<sup>19</sup> the isolation of symphytine and echimidine from the roots of *Symphytum officinale* L. (comfrey) was described. Symphytine was presumed to be 7-angeloylretronecine viridiflorate; there was, however, some uncertainty as to whether angelic or tiglic acid is attached to the C-7 oxygen atom. Since the n.m.r. signals of the unsaturated acid component resemble those of tiglic acid much more closely than they resemble those of angelic acid, it is now concluded<sup>20</sup> that symphytine is a tiglic acid ester, and this has subsequently been confirmed by the isolation of tiglic acid together with retronecine on

<sup>15</sup> B. Lindström, B. Luning, and K. Sürala-Hansen, *Acta Chem. Scand.*, 1971, **25**, 1900.

<sup>16</sup> R. G. Medvedeva and Z. M. Zolotavina, *Trudy Inst. Bot., Akad. Nauk Kaz. S.S.R.*, 1971, **29**, 181 (*Chem. Abs.*, 1972, **76**, 56 583).

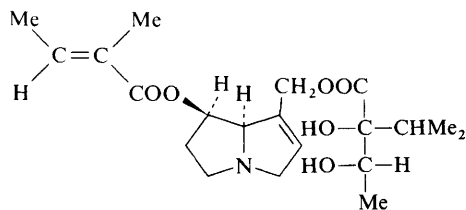
<sup>17</sup> G. P. Sheveleva, N. V. Plekhanova, and D. S. Sargazakov, *Mater. Nauch. Konf., Posvyashch. 100-[Sto]Letiyu Period. Zakona D. I. Mendeleeva*, 1969, 107 (*Chem. Abs.*, 1972, **76**, 23 067).

<sup>18</sup> I. V. Man'ko and L. G. Marchenko, *Khim. prirod. Soedinenii*, 1971, **7**, 537 (*Chem. Abs.*, 1971, **75**, 126 598).

<sup>19</sup> T. Furuya and K. Araki, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 2512.

<sup>20</sup> T. Furuya and M. Hikichi, *Phytochemistry*, 1971, **10**, 2217.

saponification of symphytine. Since hydrogenolysis affords (–)-viridifloric acid, the complete structure of symphytine is as given in (46), and it is the first pyrrolizidine alkaloid to contain a tiglic acid residue.<sup>20</sup>



Symphytine (46)

*Crotalaria sagittalis* L. (rattlebox) is reputed to be the oldest species known to cause crotalism in livestock, this property having been first noted as long ago as 1884. In particular, it produces a fatal cirrhosis of the liver in horses ingesting it, but in spite of this the plant appears not previously to have been investigated. The seeds have now been shown to contain the very toxic monocrotaline and its *N*-oxide, while t.l.c. has revealed the presence of three other alkaloids, together with an *N*-oxide.<sup>21</sup>

The identity of crotalaburnine,<sup>22</sup> from *Crotalaria laburnifolia*, with anacrotine, from the same and several other *Crotalaria* species, has been apparent for some time, but it has only recently been formally established by direct comparison.<sup>23</sup>

The *Senecio* genus continues to receive attention, but only one new alkaloid has been isolated during the year under review. Four species have been qualitatively investigated;<sup>24</sup> of these *S. vulgaris* L. (groundsel), *S. jacobaea* L. (ragwort), and *S. erucifolius* L. (hoary ragwort) contain, among others, two alkaloids in common, which may well be senecionine and seneciphylline on the basis of previous work. *S. adonidifolius* Lois, not previously examined, also contains four or five alkaloids, but these appear to be different from those present in the other three species. *S. kleinia* contains senkirkine (renardine),<sup>25</sup> *S. antieuphorbium* contains senkirkine and integerrimine,<sup>26</sup> while *S. tournefortii* contains platyphylline (47) and its *N*-oxide.<sup>27</sup>

The new alkaloid in this group is swazine (48),  $C_{18}H_{23}NO_6$ , m.p. 165°C,  $[\alpha]_D^{20} - 103.5^\circ$  (EtOH), which occurs together with retrorsine (49) in *S.*

<sup>21</sup> R. E. Willette and L. V. Cammarato, *J. Pharm. Sci.*, 1972, **61**, 122.

<sup>22</sup> J. Emmanuel and M. N. Ghosh, *Indian J. Pharm.*, 1964, **26**, 322; S. Snehlata, M. N. Ghosh, S. Nagarajan, and S. S. Subramanian, *Indian J. Pharm.*, 1966, **28**, 277; R. N. Gandhi, T. R. Rajagopalan, and T. R. Seshadri, *Current Sci.*, 1967, **36**, 363.

<sup>23</sup> R. S. Sawhney and C. K. Atal, *J. Indian Chem. Soc.*, 1971, **48**, 887.

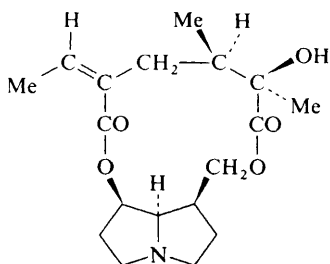
<sup>24</sup> S. Ferry, *Ann. pharm. franç.*, 1972, **30**, 145.

<sup>25</sup> F. D. Rodriguez and A. G. Gonzalez, *Farm. Nueva*, 1971, **36**, 803 (*Chem. Abs.*, 1972, **76**, 83 573).

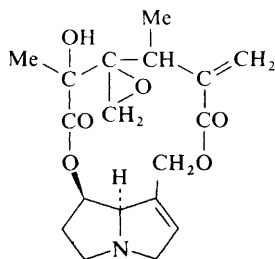
<sup>26</sup> F. D. Rodriguez and A. G. Gonzalez, *Farm. Nueva*, 1971, **36**, 810 (*Chem. Abs.*, 1972, **76**, 83 572).

<sup>27</sup> S. Valverde and F. Martin Panizo, *Anales de Quim.*, 1971, **67**, 425 (*Chem. Abs.*, 1971, **75**, 110 484).

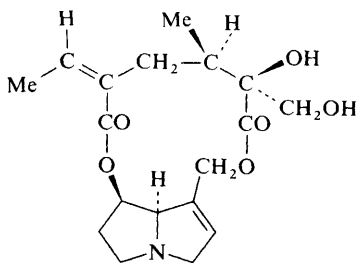
*swaziensis* Compton, from Swaziland.<sup>28</sup> Like its congener, retrorsine, swazine also affords retronecine (5) on acidic hydrolysis; the other product is a neutral, monounsaturated compound (50), which behaves on titration as a dilactone possessing non-equivalent lactone functions, one of which is  $\alpha\beta$ -unsaturated



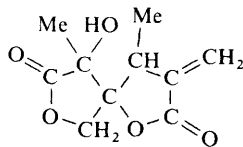
Platyphylline (47)



Swazine (48)



Retrorsine (49)



(50)

(i.r., u.v.). The constitution of (50) was elucidated by X-ray crystal structure determination of its *p*-bromobenzoate derivative, and its absolute configuration as (3*S*,4*S*,5*R*) by utilizing the anomalous scattering of the bromine atom. Of the possibilities for the structure of swazine itself, (48) is preferred; acidic hydrolysis of the ester functions is then accompanied by acid-catalysed opening of the epoxide ring, with subsequent lactone formation.<sup>28</sup>

The roots and leaves of *Farfugium japonicum* Kitam. (Compositae) have been shown to contain senkirkine (17).<sup>29</sup> A new alkaloid, emiline (51), also a derivative of otonecine, is a constituent of *Emilia flammea*.<sup>30</sup>

The structure (52), earlier assigned to clivorine,<sup>31</sup> has now been replaced by the structure (53), on the basis of an X-ray crystal structure determination.<sup>32</sup>

<sup>28</sup> C. G. Gordon-Gray, R. B. Wells, N. Hallak, M. B. Hursthouse, S. Neidle, and T. P. Toube, *Tetrahedron Letters*, 1972, 707.

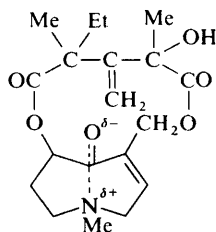
<sup>29</sup> T. Furuya, K. Murakami, and M. Hikichi, *Phytochemistry*, 1971, **10**, 3306.

<sup>30</sup> S. Kohlmueller and H. Tomczyk, *Diss. Pharm. Pharmacol.*, 1971, **23**, 419 (*Chem. Abs.*, 1972, **76**, 96 972).

<sup>31</sup> A. Klásek, P. Sedmera, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1970, **35**, 956.

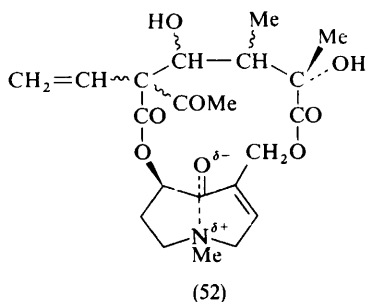
<sup>32</sup> K. B. Birnbaum, A. Klásek, P. Sedmera, G. Snatzke, L. F. Johnson, and F. Šantavý, *Tetrahedron Letters*, 1971, 3421.

The molecular formula of clivorine is  $C_{21}H_{27}NO_7$ , and the difference between this and the previously accepted molecular formula ( $C_{21}H_{29}NO_8$ ), is now known

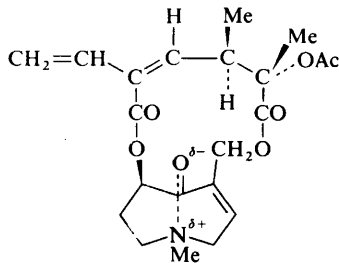


Emiline (51)

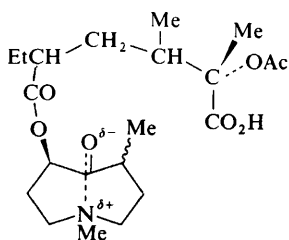
to be due to water of crystallization, which can be removed slowly when clivorine is dried at  $100^\circ\text{C}/0.04\text{ mm}$ . Structure (53) explains readily the facile loss of acetic acid on hydrolysis of clivorine, and is in accord with the presence in clivorine



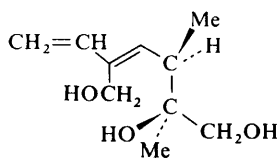
(52)



Clivorine (53)



Octahydroclivorine (54)



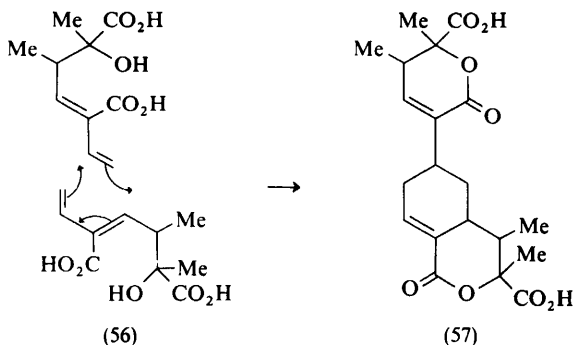
Clivonecinol (55)

of three carbon-carbon double bonds; two of the carbon atoms involved in these bonds carry no protons, and one carbonyl carbon atom is present in an  $\alpha\beta$ -unsaturated ester grouping ( $^{13}\text{C}$  n.m.r. spectrum). The presence of this last grouping was also deduced from the c.d. spectrum.

Octahydroclivorine is therefore (54), but the structures previously postulated<sup>31</sup> for clivonecinol (55) and its transformation products are still valid. The structure of the so-called acetylclivorine requires reinvestigation.

The internuclear distances in the otonecine component are of some interest.<sup>32</sup> In accord with the representation (53), which presupposes a transannular interaction, the  $N \cdots C-8$  distance is 1.993 Å, approximately 1 Å less than the sum of the nitrogen and carbon van der Waals radii, whereas the  $C \cdots O$  bond length is 1.258 Å, which is significantly longer than the normal  $C=O$  length (1.215 Å). This implies a rehybridization of C-8 to a state intermediate between  $sp^2$  and  $sp^3$ .

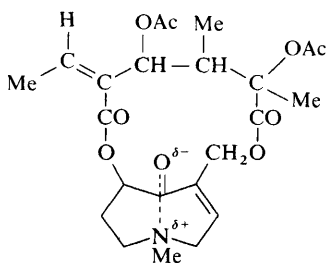
The acidic hydrolysis of clivorine affords a dilactonic dibasic acid, clivorinic acid,  $C_{20}H_{24}O_8$ , which on esterification with diazomethane gives a dimethyl ester. This acid is clearly a dimeric species obtained by union of two molecules of an unsaturated acid derived from hydrolysis of clivorine and elimination of acetic acid. According to the n.m.r. spectrum this product is an unsymmetrical dimer; thus, its dimethyl ester exhibits two methyl doublets ( $\delta$  1.145 and 1.00 p.p.m.), two coincident methyl singlets at 3.74 and 3.785 p.p.m., a one-proton quartet of doublets at 2.87 p.p.m., one proton at 3.55 p.p.m., and two olefinic protons at 7.280 and 6.11 p.p.m. (d,  $J = 3$  Hz). The higher field olefinic proton is coupled to the protons absorbing at 3.55 and 2.87 p.p.m., as is shown by double-resonance experiments. Irradiation of the signal at 2.87 p.p.m. reduces the signal at 6.11 p.p.m. to a singlet, and perturbs both the signal at 3.55 and the methyl doublet at 1.145 p.p.m. The second methine proton coupled with the methyl group at 1.00 p.p.m. ( $d, J = 6.5$  Hz) was located at 1.980 p.p.m., and is not coupled to any olefinic protons. The lower field olefinic signal at 7.280 p.p.m. is coupled to two aliphatic protons in the 2.4–2.6 p.p.m. region. From these data two structures, derived by Diels–Alder dimerization of two molecules of the dibasic acid (56), are possible; of these, structure (57) is preferred.<sup>33</sup>



Aside from its occurrence in *Ligularia clivorum* Maxim., clivorine has recently been isolated from *L. elegans* Cass. [*L. macrophylla* (Ledeb.) DC], *L. dentata* (A. Gray) Hara, and *L. brachyphylla* Hand.–Mazz.<sup>33</sup> These three species were also shown to contain a new, non-crystalline alkaloid, ligularine, while *L. dentata* and *L. brachyphylla* contain another new alkaloid, ligudentine, which is also amorphous.

<sup>33</sup> A. Klásek, P. Sedmera, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1971, **36**, 2205.

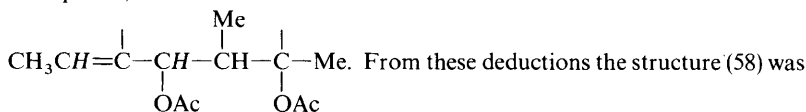
Ligularine,  $C_{23}H_{31}NO_9$ , is a base which exhibits a broad absorption band near  $1600\text{ cm}^{-1}$  (*cf.* clivorine), and on this basis is presumed to contain otonecine or an analogue in which there is transannular interaction between a basic nitrogen atom and an appropriately placed carbonyl group. This conclusion is supported by the mass spectrum, which discloses a fragmentation pattern analogous to that of clivorine, and different from the mass spectra of alkaloids containing a simple pyrrolizidine ring system.



Ligularine (58)

The n.m.r. spectrum of ligularine contains absorptions due to  $\text{MeCH}=\text{C}-$ ,

$\text{Me}-\text{C}-\text{O}-$ , two acetyl groups, one NMe group, and  $\text{Me}-\text{CH}=\text{C}-$ . Five protons in the region 3.0–6.3 p.p.m. form an ABKXY system, which are ascribed to the part-structure:  $-\text{N}-\text{CH}_2-\text{CH}=\text{C}-\text{CH}_2-\text{OCO}-$ , and a multiplet at 4.935 p.p.m. is ascribed to the C-7 proton in an otonecine component. Two other protons in the 5–6 p.p.m. region belong to the acid constituent of the alkaloid, and from their chemical shifts and multiplicities, together with other absorptions, were deduced to be contained in the structural unit:



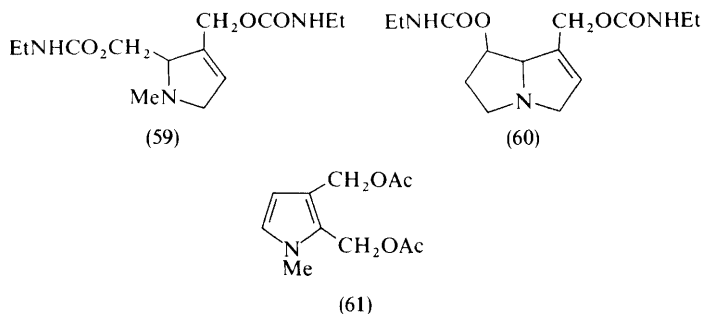
From these deductions the structure (58) was derived for ligularine; this is composed of otonecine and an acetylated hygrophyllineic acid (or stereoisomer).<sup>33</sup>

Owing to lack of material the second new alkaloid, ligudentine, has not yet been extensively investigated. The molecular formula has not yet been unequivocally established; the highest peak in its mass spectrum is at  $m/e$  406, but this appears not to be a molecular ion. From the i.r. spectrum, and in particular the absence of a broad band at  $1600\text{ cm}^{-1}$ , it is concluded that the basic component is not otonecine. The n.m.r. spectrum has not been completely analysed, but certain resemblances to the spectrum of clivorine suggest that the acidic component in ligudentine may be the same as that in clivorine.<sup>33</sup>



#### 4 Pharmacological Aspects

In connection with the toxicity of the pyrrolizidine alkaloids the toxic effects of the alkaloids themselves have been reproduced by dosing experimental animals with synthetic compounds. Because the most toxic alkaloids are esters which are resistant to enzymic hydrolysis, and which are converted *in vivo* into pyrrole derivatives, it was expected that simpler pyrrole esters would prove to exhibit the same toxic properties as the alkaloids.<sup>34</sup> This expectation was realised when it was shown that the dicarbamate (59) is rather more toxic than monocrotaline, and further that the tissue damage produced is histologically similar to that observed in cases of pyrrolizidine alkaloid poisoning. A compound of slightly lesser toxicity is the retronecine derivative (60).



In further experiments the synthetic pyrrole derivative (61) was shown also to produce the characteristic toxic effects of the poisonous pyrrolizidine alkaloids; this is the first time that this toxicity has been demonstrated in compounds containing a simple pyrrole ring.<sup>34</sup>

The relative susceptibilities of male and female rats to lasiocarpine and heliotrine have been studied.<sup>35</sup> Male rats proved to be more resistant than females to fatal hepatic lesions following repeated intraperitoneal injection of lasiocarpine, but the reverse was true when heliotrine was injected. Renal lipomatous tumours have also been shown to be produced in rats treated with *Heliotropium supinum*, *Amsinckia intermedia*, or retrorsine.<sup>36</sup>

In connection with the earlier suggestion that the pyrrolizidine alkaloids are converted into the toxic pyrrole metabolites *via* their *N*-oxides, Mattocks<sup>37</sup> has determined the respective toxicities of retrorsine (49) and retrorsine *N*-oxide. Although the LD<sub>50</sub> of retrorsine and its *N*-oxide are comparable when administered orally, retrorsine *N*-oxide appears to be much less toxic when injected intraperitoneally. The concentration of pyrrolic metabolites of retrorsine given orally or intraperitoneally reached a maximum in the liver of rats only one hour

<sup>34</sup> A. R. Mattocks, *Nature*, 1971, **232**, 476.

<sup>35</sup> M. V. Jago, *J. Pathol.*, 1971, **105**, 1.

<sup>36</sup> R. Schoental, G. C. Hard, and S. Gibbard, *J. Nat. Cancer Inst.*, 1971, **47**, 1037.

<sup>37</sup> A. R. Mattocks, *Xenobiotica*, 1971, **1**, 563.

after administration, but after a similar oral dose of retrorsine *N*-oxide the liver pyrrole level required 7—8 h to reach the same level. After intraperitoneal administration of retrorsine *N*-oxide the maximum concentration of pyrrole metabolites in the liver was reached after five hours, but it was only one quarter of the level observed with the oral dose. It was further noted that retrorsine *N*-oxide is reduced to retrorsine when incubated with rat gut contents. The indications are thus that the *N*-oxide of retrorsine, and possibly other *N*-oxides, are not hepatotoxic, but if they are they are probably not involved in the main pathway for the conversion of the toxic alkaloids into the pyrrolic metabolites.<sup>37</sup>

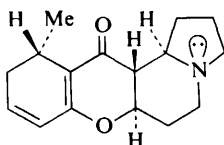
# 5

## The Indolizidine Group

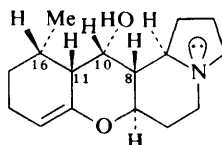
BY J. E. SAXTON

### 1 *Elaeocarpus* Alkaloids

Details of the work<sup>1</sup> on which the structures and absolute configurations of the alkaloids of *Elaeocarpus sphaericus* are based have now been published,<sup>2</sup> and the course of the sodium borohydride reduction of (+)-*elaecarpiline* (1) has been elucidated. The product of this reduction is a tetrahydro-derivative, which is now considered to be (2). The relative configurations at positions 10, 11, and 16

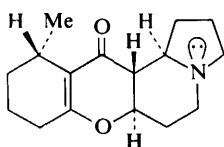


(+)-Elaecarpiline (1)

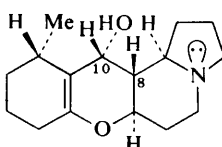


(2)

could not previously be assigned because of the complexity of the n.m.r. spectra; however, in view of the known configuration at C-16, it would be expected that addition of hydrogen from the  $\alpha$ -face of the molecule would be sterically hindered, with the result that reduction should result in the formation of (2). For similar reasons, (+)-13,14-dihydroelaecarpiline (3) should be reduced to the alcohol (4),



(+)-13,14-Dihydroelaecarpiline (3)



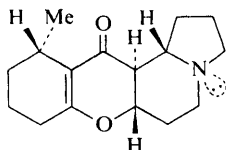
(4)

and in fact only one C-10 alcohol is obtained in this reaction. A study of molecular models indicates that the dihedral angle between the C-8 and C-10 protons in (4) is approximately zero, consistent with the observed coupling constant ( $J_{8,10} = 8.0$  Hz) for this product.

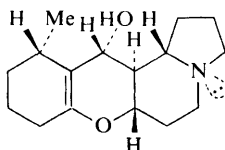
<sup>1</sup> S. R. Johns, J. A. Lamberton, A. A. Sioumis, H. Soares, and R. I. Willing, *Chem. Comm.*, 1970, 804.

<sup>2</sup> S. R. Johns, J. A. Lamberton, A. A. Sioumis, H. Soares, and R. I. Willing, *Austral. J. Chem.*, 1971, **24**, 1679.

The reduction of (–)-13,14-dihydroepielaecarpiline (5) is also dominated by the  $\alpha$ -methyl group at C-16, and leads, by  $\beta$ -addition of hydride ion, to a single C-10 alcohol (6). In this product, the C-8 and C-10 protons are oriented *trans*



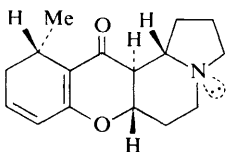
(–)-13,14-Dihydroepielaecarpiline (5)



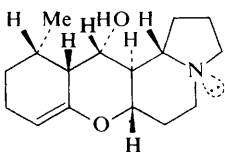
(6)

to each other, and the dihedral angle between them is approximately  $140^\circ$ , which is again consistent with the observed coupling constant ( $J_{8,10} = 8$  Hz). The identity of these coupling constants for *cis*- or *trans*-oriented protons at positions 8 and 10 obviously makes it impossible to determine the relative stereochemistry at these positions solely on the basis of the n.m.r. spectra.

A product whose stereochemistry still awaits clarification is the borohydride reduction product of (–)-epielaecarpiline (7). On the basis of the arguments used above, the product is tentatively considered to be (8).

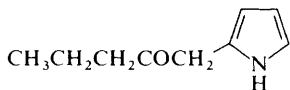


(–)-Epielaecarpiline (7)

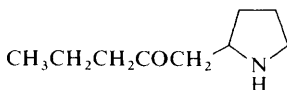


(8)

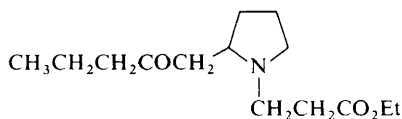
Full details are also available<sup>3</sup> of the structure elucidation of elaeokanines A–E, and elaeokanidines A–C, the leaf alkaloids of *E. kaniensis* Schltr.; further, the structures of elaeokanines A–C have been confirmed by synthesis. The reaction of the diazoketone prepared from butyryl chloride and diazomethane with pyrrole in the presence of copper powder gave the ketone (9), which was hydrogenated to the basic pyrrolidine ketone (10). Michael addition of ethyl acrylate



(9)



(10)

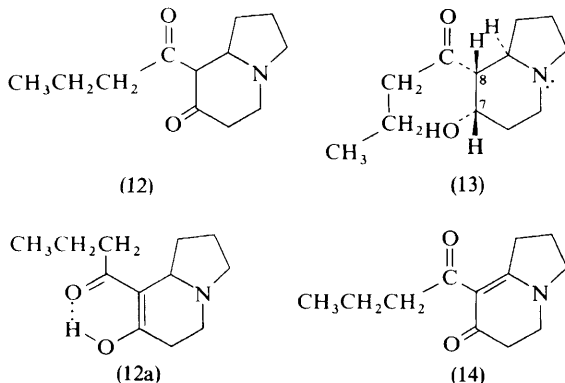


(11)

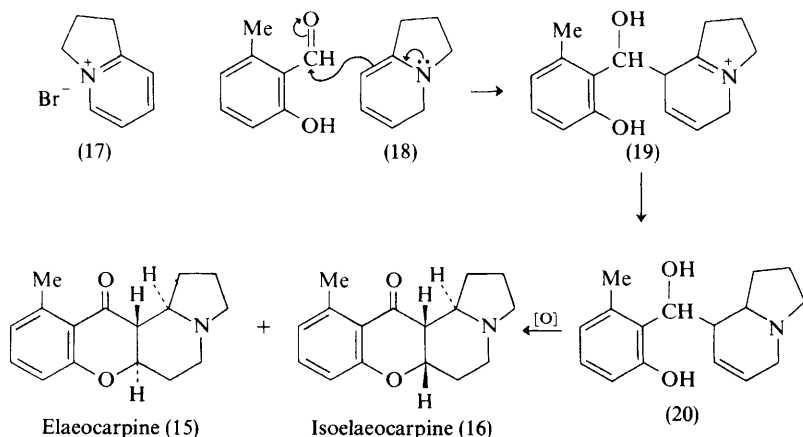
then gave the keto-ester (11), which was cyclized by means of sodium hydride in toluene to the crystalline  $\beta$ -diketone (12). Reduction of (12) proved to be a complex

<sup>3</sup> N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1972, **25**, 817.

reaction in which several products were formed; however, hydrogenation with platinum oxide in ethanol gave a 30% yield of ( $\pm$ )-8-n-butyryl-7-hydroxy-indolizidine (13), identical with elaeokanine C in all except optical properties.<sup>3</sup>



This synthesis of ( $\pm$ )-elaekokanine C confirms the structure deduced earlier, in particular the *cis* disposition of hydrogen atoms at C-7 and C-8, since hydrogenation presumably occurs on the enolic form (12a) of the  $\beta$ -diketone. Curiously, the major product (60%) from this hydrogenation is a crystalline *dehydrogenation* product, which was assigned the structure (14).



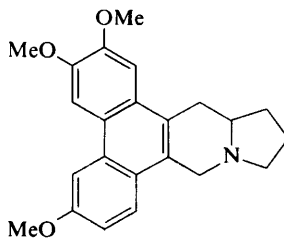
A second synthesis of elaeocarpine (15) and isoeleocarpine (16), by a direct, two-stage procedure, has been reported.<sup>4</sup> Reduction of 2,3-dihydro-1*H*-indolizinium bromide (17) with lithium aluminium hydride in the presence of 6-methylsalicylaldehyde afforded the condensation product (20), presumably *via* the dihydropyridine derivative (18) which, as a nucleophilic enamine, attacks the

<sup>4</sup> T. Onaka, *Tetrahedron Letters*, 1971, 4395.

carbonyl group in 6-methylsalicylaldehyde; reduction of the ammonium ion in the intermediate (19) then gives the observed product (20). Oxidation of the benzylic hydroxy-group in (20) by Jones' reagent was followed by acid-catalysed chromanone cyclization, to give a mixture of ( $\pm$ )-elaecarpine (15) and ( $\pm$ )-iso-elaecarpine (16).<sup>4</sup>

## 2 The Tylophorine Group

Predominantly racemic antofine (21),  $[\alpha]_D^{22} - 32^\circ$  ( $\text{CHCl}_3$ ), m.p. 212—214 °C, has been found to be the major alkaloid of the roots and leaves of *Ficus septica*.<sup>5</sup>



Antofine (21)

Further details of Rao's work<sup>6</sup> on *Tylophora* alkaloids have been published in a more readily accessible journal.<sup>7</sup> *T. indica* (Burm.) Merrill contains tylophorine, tylophorinine, Alkaloid A, Alkaloid B (which is a demethyltylophorine), and Alkaloid C (which is a demethyltylophorinine); this last base also occurs in *T. dalzellii* Hook. f.

<sup>5</sup> R. B. Herbert and C. J. Moody, *Phytochemistry*, 1972, **11**, 1184.

<sup>6</sup> K. V. Rao, U.S.P. 3 497 593 (*Chem. Abs.*, 1970, **72**, 125 054).

<sup>7</sup> K. V. Rao, R. A. Wilson, and B. Cummings, *J. Pharm. Sci.*, 1971, **60**, 1725.

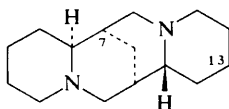
# 6

## The Quinolizidine Alkaloids

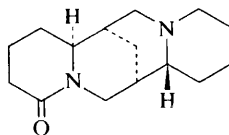
BY J. E. SAXTON

### 1 Occurrence, and Isolation of New Alkaloids

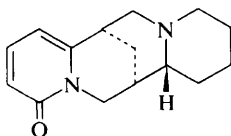
The leaves and terminal branches of the Western Australian 'blue bush', *Hovea elliptica* (Sm.) DC., contain (+)-sparteine (1), (–)-lupanine (2), (–)-anagryne (3), and (–)-cytisine (4).<sup>1</sup> The major alkaloid of the seeds is (–)-cytisine. The co-occurrence of these four alkaloids lends credence to Robinson's proposal,<sup>2</sup> as modified by Leete,<sup>3</sup> that cytisine is formed *in vivo* by oxidative degradation of sparteine, *via* lupanine and anagryne. Rhombifoline (5), the missing link in this sequence, has not so far been detected in this species.



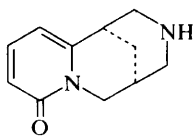
(+)-Sparteine (1)



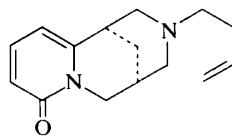
(–)-Lupanine (2)



(–)-Anagryne (3)



(–)-Cytisine (4)



Rhombifoline (5)

As noted previously, *Thermopsis lanceolata* R.Br. contains cytisine, *N*-methylcytisine, thermopsine, and pachycarpine [(+)-sparteine]. Young shoots also contain<sup>4</sup> rhombifoline and thermopsamine, m.p. 154–155 °C,  $[\alpha]_D + 26.4^\circ$  (EtOH), which is probably a 13-hydroxy derivative of (+)-sparteine, since oxidation affords a ketone, dehydration gives dehydrosparteine, and reduction with phosphorus and hydrogen iodide gives (+)-sparteine. The aerial parts, gathered during the seed-ripening period, contain also anagryne, argentine, and

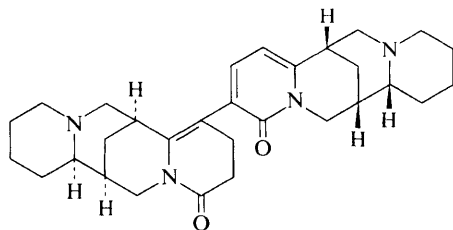
<sup>1</sup> J. R. Cannon, K. R. Joshi, and J. R. Williams, *Austral. J. Chem.*, 1971, **24**, 1537.

<sup>2</sup> R. Robinson, 'The Structural Relations of Natural Products', Clarendon Press, Oxford, 1955, p. 76.

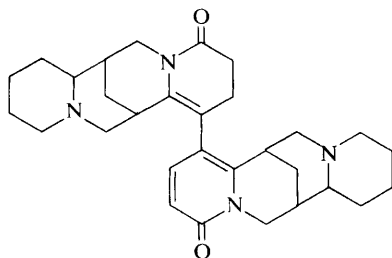
<sup>3</sup> E. Leete, in 'Biogenesis of Natural Compounds', ed. P. Bernfeld, 2nd edn. Pergamon Press, Oxford, 1967, p. 973.

<sup>4</sup> V. I. Vinogradova, S. Iskandarov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 463 (*Chem. Abs.*, 1972, **76**, 32 221).

two unidentified bases.<sup>5</sup> Ditermamine, a new dimeric alkaloid from the same plant, is formulated as an anagyrine dimer [(6) or (7)].<sup>6</sup>



(6)



(7)

Molloy and his collaborators have embarked on a survey of Bulgarian Leguminosae.<sup>7</sup> *Cytisus hirsutus* L., collected from the slopes of the Lozen mountains in May at the beginning of the blossoming period, contains (–)-sparteine, (+)-lupanine, 13-hydroxylupanine, and a new alkaloid, 7-hydroxy-sparteine. A specimen of the same species from the Pirin mountains contained the same alkaloids, with the exception of 13-hydroxylupanine. *C. supinus* from the Konyova mountains contained mainly (+)-lupanine, but *C. nigricans*, from Turnovo, contained insufficient alkaloids to warrant further study. *Genista sessilifolia* DC., collected in May on the Konyova mountains, was shown to contain retamine and anagyrine, and *Lotus aegaeus* Boiss., from the Kresnen Gorge, contains mainly lupanine.

The differences in alkaloid content in the bitter and fodder types of *Lupinus albus* L. have also been studied.<sup>8,9</sup> Both types contain sparteine, lupanine, and 13-hydroxylupanine, but they differ in regard to the other alkaloids present.<sup>9</sup>

<sup>5</sup> K. Orazgel'diev, K. A. Aslanov, A. S. Sadykov, and D. A. Abdullaeva, *Nauch. Trudy Samarkand Univ.*, 1969, no. 167, 154 (*Chem. Abs.*, 1971, **75**, 16 085).

<sup>6</sup> V. I. Vinogradova, S. Iskandarov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 87.

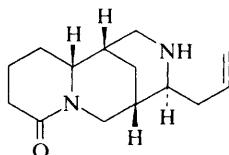
<sup>7</sup> N. M. Molloy, I. K. Ivanov, and P. P. Panov, *Doklady Bolg. Akad. Nauk*, 1971, **24**, 1657 (*Chem. Abs.*, 1972, **76**, 138 214).

<sup>8</sup> A. Scibor-Marchocka, *Acta Agrobot.*, 1970, **23**, 23 (*Chem. Abs.*, 1971, **75**, 115 950).

<sup>9</sup> W. Szymanska, *Acta Agrobot.*, 1970, **23**, 39 (*Chem. Abs.*, 1971, **75**, 115 860).



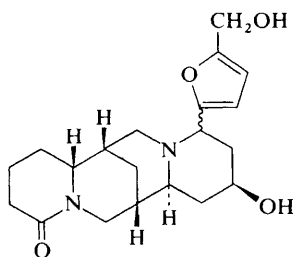
The bitter type contains angustifoline (8), multiflorine, and probably 13-epi-hydroxylupanine, although this last base is never found in the white variety. The fodder type contains possibly a ketosparteine and three other components,



Angustifoline (8)

so far unidentified. New *Lupinus* species that have been investigated include *L. paniculatus* Desr., which contains sparteine and lupanine,<sup>10</sup> and *L. meridensis* (*L. meridanus* Moritz?), the seeds and pods of which contain five alkaloids, but so far none has been identified.<sup>11</sup>

An interesting new alkaloidal artifact has been isolated from old extracts of the seeds of *L. angustifolius*.<sup>12</sup> It was observed that long storage (> 3 years) of the methanolic extract resulted in the disappearance of angustifoline (8), although the lupanine and 13-hydroxylupanine content remained unchanged. Extraction of the residue yielded a new base, 'pseudohydroxylupanine', C<sub>20</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>, m.p. 230 °C, [α]<sub>D</sub><sup>20</sup> + 138°, which contained two hydroxy-groups and a lactam function. It was suspected that this base was probably formed by condensation of angustifoline with an aldehyde, C<sub>5</sub>H<sub>5</sub>O<sub>2</sub>·CHO, which was probably 5-hydroxymethylfurfuraldehyde formed by degradation of carbohydrate material in the extract, since the remaining oxygen was neutral, and the n.m.r. spectrum of the base contained two superimposed doublets in the aromatic region (*J* ~ 4 Hz), appropriate to two β-furyl protons. This view was established as correct by the formation, in 50% yield, of 'pseudohydroxylupanine' (9) by the condensation of angustifoline hydrochloride with 5-hydroxymethylfurfuraldehyde.<sup>12</sup>



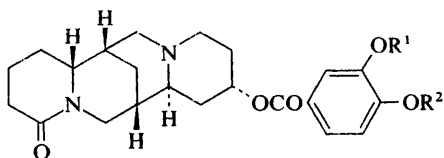
'Pseudohydroxylupanine' (9)

<sup>10</sup> C. A. Mammarella and J. Comin, *Anales Asoc. quim. argentina*, 1971, **59**, 239 (*Chem. Abs.*, 1972, **76**, 43 980).

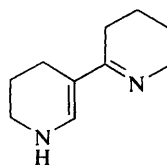
<sup>11</sup> A. Morales Mendez, *Rev. Fac. Farm., Univ. Los Andes*, 1970, **7**, 101 (*Chem. Abs.*, 1972, **76**, 110 251).

<sup>12</sup> M. D. Bratek-Wiewiórowska and M. Wiewiórowski, *Bull. Acad. polon. Sci. Sér. Sci. chim.*, 1971, **19**, 295.

Ten alkaloids have now been isolated from the branches of *Genista cinerea* DC.<sup>13</sup> These include six esters of 13-hydroxylupanine, four of which have been previously reported. The two esters recently isolated (from Provençal plants) are cinevanine (10), which is the vanillic acid ester of 13-hydroxylupanine, and 13-benzoyloxylupanine. The former had not previously been isolated from natural sources, but the latter had been found previously in *Lupinus angustifolius* and *L. albus*. The four remaining alkaloids of *Genista cinerea* are 13-hydroxylupanine, lupanine, anagyrine, and hystrine (11), a base which was first obtained from *G. hystrix* Lange.<sup>14</sup>



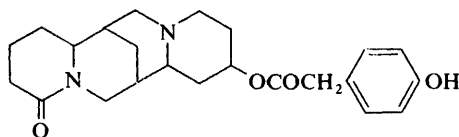
Cinevanine (10;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ )  
Isocinevanine (12;  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ )



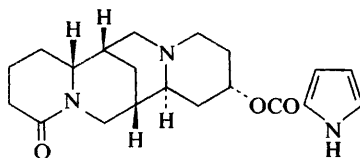
Hystrine (11)

*G. cinerea* thus proves to be a plant of some chemotaxonomic interest, because its major alkaloidal constituents are esters of 13-hydroxylupanine, compounds which are characteristic of the genus *Cytisus* rather than of *Genista*. In *Cytisus* species, for instance, the biosynthetic sequence: lupanine, 13-hydroxylupanine, 13-hydroxylupanine esters, is often observed. However, *G. cinerea* also contains alkaloids characteristic of the *Genista* genus, e.g. anagyrine and hystrine, although these are only present in very small amounts, and in fact anagyrine was not encountered in the extracts from some samples.<sup>13</sup>

New esters of 13-hydroxylupanine have also been found in other Leguminosae. Thus, isocinevanine (12) occurs in the branches of *Sarothamnus patens* (L.) Webb [*Cytisus striatus* (Hill) Rothm.], collected in the Spanish province of Pontevedra.<sup>15</sup> The leaves of *Cadia purpurea* Ait., a poisonous Ethiopian shrub, contain four alkaloids,<sup>16</sup> C I ( $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$ ), C II ( $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2$ ), cadiaine (C III), and C IV. Cadiaine is possibly the ester (13), although the position of the carbonyl group has not been thoroughly established, while C IV is calpurnine (14) or a stereoisomer.



Cadiaine? (13)



(+)-Calpurnine (14)

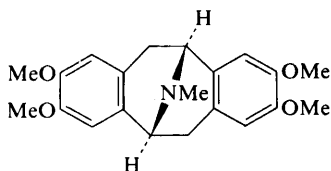
<sup>13</sup> G. Faugeras, *Ann. pharm. franç.*, 1971, **29**, 241.

<sup>14</sup> E. Steinegger and C. Moser, *Pharm. Acta Helv.*, 1967, **42**, 177.

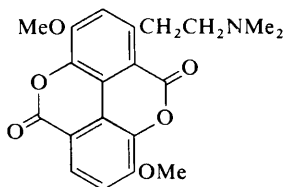
<sup>15</sup> G. Faugeras, R. R. Paris, and E. Valdes-Bermejo, *Compt. rend.*, 1971, **273**, C, 1372.

<sup>16</sup> J. L. Van Eijk and M. H. Radema, *Pharm. Weekblad*, 1972, **107**, 13.

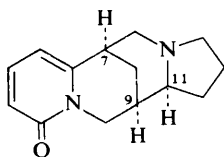
Three *Leontice* species have been investigated, and prove to contain a variety of alkaloids. The tubers of *L. smirnowii* Trautv. contain 4% alkaloids, three of which have been identified<sup>17</sup> as lupanine, (+)-argemone (15), and thaspine (16). The aerial parts of *L. alberti* Regel contain, among others, a new base, leontidine, for which the proposed structure (17) has been established by synthesis from cytisine.<sup>18</sup> Darvasamine, m.p. 102 °C,  $[\alpha]_D + 72^\circ$  (EtOH), a constituent of *L. darwasica* Regel, has been assigned<sup>19</sup> the structure (18).



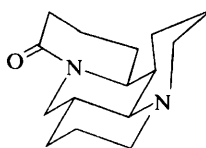
(+)-Argemone (15)



Thaspine (16)



Leontidine (17)



Darvasamine (18)

## 2 Tetracyclic Alkaloids

**Lupanine-Sparteine Group.**—A method has been developed<sup>20</sup> for the separation and identification of microgram quantities of quinolizidine alkaloids by the sequential use of t.l.c. or g.l.c. combined with mass spectrometry. In all, 22 alkaloids have been identified by this technique.

An improved route to the synthesis of anagryne (3), based on the earlier synthesis by Van Tamelen and Baran,<sup>21</sup> has been developed.<sup>22</sup> The condensation of methyl 2-pyridylacetate with triethyl orthoformate and acetic anhydride gave the crystalline quinolizone (19) directly. Hydrogenation of (19) in the presence of palladium charcoal afforded a mixture of stereoisomers [(20a) and (20b)?] which on equilibration with sodium methoxide-methanol gave a single product, presumably the stable equatorial isomer (20c). Reduction of (20c) by lithium aluminium hydride gave the corresponding primary alcohol, and the

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

<sup>18</sup> S. Iskandarov, R. A. Shaimardanov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, 7, 631, 636 (*Chem. Abs.*, 1972, 76, 99 884, 59 816).

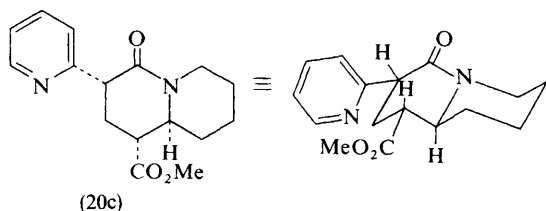
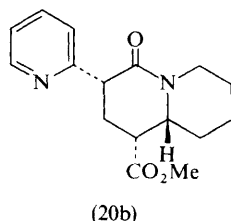
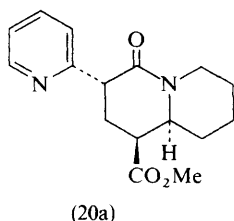
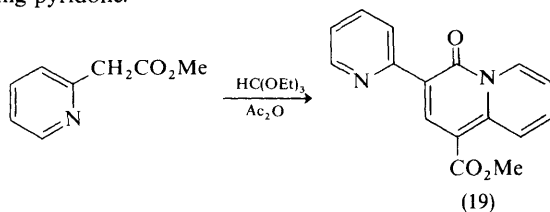
<sup>19</sup> A. Zunnunzhanov, S. Iskandarov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, 7, 851 (*Chem. Abs.*, 1972, 76, 124 144).

<sup>20</sup> Y. D. Cho and R. O. Martin, *Analyt. Biochem.*, 1971, 44, 49.

<sup>21</sup> E. E. van Tamelen and J. S. Baran, *J. Amer. Chem. Soc.*, 1958, 80, 4659.

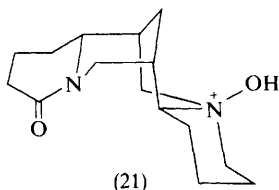
<sup>22</sup> S. I. Goldberg and A. H. Lipkin, *J. Org. Chem.*, 1972, 37, 1823.

synthesis was then completed by following the earlier procedure,<sup>21</sup> i.e. preparation of the primary bromide, internal quaternization, and finally oxidation to the corresponding pyridone.<sup>22</sup>



The utility of tris(dipivalomethanato)europium(III) as an n.m.r. shift reagent for compounds containing a lactam function, e.g. lupanine (2), has been demonstrated.<sup>23</sup> I.r. spectrographic evidence has also been presented which confirms that complexing with the n.m.r. shift reagent does not alter the position of the conformational equilibrium in the particular case of lupanine.<sup>24</sup>

Lupanine *N*-oxide perchlorate exists in anhydrous and hydrated forms; of these, the cation in the anhydrous form has been shown by X-ray crystal structure analysis to have the conformation depicted in (21).<sup>25</sup> Lupanine forms only one



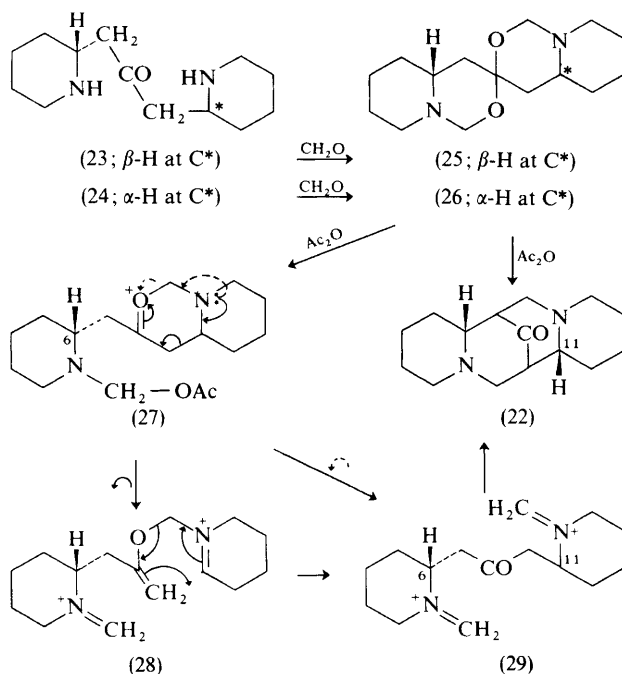
<sup>23</sup> J. Barciszewski, A. J. Rafalski, and M. Wiewiórowski, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1971, **19**, 545.

<sup>24</sup> J. Skolik, J. Barciszewski, A. J. Rafalski, and M. Wiewiórowski, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1971, **19**, 599.

*N*-oxide; no evidence could be obtained for the formation of an *N*-oxide from the conformation in which the C/D ring junction is *cis* in the free base.

The ability of ditertiary bases of the sparteine group to complex with alkali-metals and alkaline-earth metals has been further investigated by carrying out the Reformatsky reaction in the presence of (–)-sparteine.<sup>26</sup> In all the cases examined, a partial asymmetric synthesis of (*S*)-hydroxy-esters was achieved, the optical purity of the products ranging from 34–98%.

8-Oxo- $\alpha$ -isosparteine (22) may be synthesized<sup>27</sup> very simply by condensation of the racemic or *meso*-forms of anaferine [(23) and (24), respectively] with



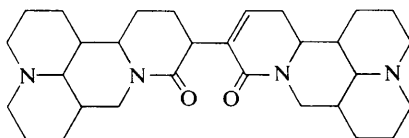
formaldehyde. The intermediate products are the spiranoid ketals (25) and (26), respectively, which are converted by treatment with acetic anhydride into 8-oxo- $\alpha$ -isosparteine (22). The transformation of (26) into (22) necessarily requires inversion at C-11; this may well occur by fission of the ketal function in (25) or (26) to give the intermediate (27), which can be transformed into 8-oxo- $\alpha$ -isosparteine (22) *via* (28) and (29) with destruction and re-creation of the asymmetric centre at C-11. Alternatively, the intermediate (29) may be formed directly from (27); in (29) and analogous compounds it seems likely that both C-6 and C-11 are vulnerable, and may suffer easy racemization.

<sup>25</sup> Z. Kaluski, A. I. Gusiev, Y. T. Sruchkov, J. Skolik, P. Baranowski, and M. Wiewiórowski, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1972, **20**, 1.

<sup>26</sup> M. Guetté, J. P. Guetté, and J. Capillon, *Tetrahedron Letters*, 1971, 2863.

<sup>27</sup> C. Schöpf, G. Benz, F. Dürsch, W. Burkhardt, and R. Rokohl, *Annalen*, 1972, **755**, 86.

**Matrine Group.**—From the residues of *Sophora pachycarpa* Schrenk obtained after removal of pachycarpine, Pakanaev and Sadykov<sup>28</sup> isolated a new alkaloid, goebeline, m.p. 231 °C,  $[\alpha]_D - 12.94^\circ$ , which was suspected to have the molecular formula  $C_{15}H_{22}N_2O$ . In later experiments<sup>29</sup> a distinct resemblance to matrine was observed in its chemical properties, and it was postulated to be a didehydromatrine or stereoisomer. In fact the molecular formula of goebeline, derived from its mass spectrum, is  $C_{30}H_{44}N_4O_2$  ( $M^+$  492). Goebeline is thus a dimeric alkaloid of the matrine group, and it is now considered to be (30).<sup>30</sup>



(30)

### 3 Alkaloids of Coccinellidae

Three compounds containing a quinolizidine ring system have recently been isolated from beetles belonging to the family Coccinellidae. The first of these is coccinellin,  $C_{13}H_{23}NO$ , which appears to be an effective constituent of the defensive secretion of the common ladybird, *Coccinella septempunctata* L.<sup>31</sup> Coccinellin is an *N*-oxide which can be reduced to the parent tertiary base, precoccinellin; the latter is also present in the haemolymph of the insect.

The n.m.r. spectra of coccinellin and precoccinellin exhibit a doublet owing to a methyl group attached to a saturated carbon atom. No olefinic protons are present, and since coccinellin gives no other evidence of unsaturation it must be tricyclic. Precoccinellin affords a methiodide which exhibits, in addition to the *N*-Me signal, a complex 3H absorption at 4.17 p.p.m., indicating the presence in the free base of only three protons on carbon atoms adjacent to the tertiary nitrogen atom.

Since coccinellin is optically inactive even at short wavelengths, it must either be racemic or a compound possessing a plane of symmetry. If the latter is correct, this plane must contain the nitrogen atom, one of its neighbouring carbon atoms, and the  $CH_3CH<$  group. The existence of such an element of symmetry is consistent with the proton-decoupled  $^{13}C$  n.m.r. spectrum, which is surprisingly simple, and contains only three singlets of relative intensity 1, and five singlets of relative intensity 2. The chemical shifts of these signals, and the absorptions

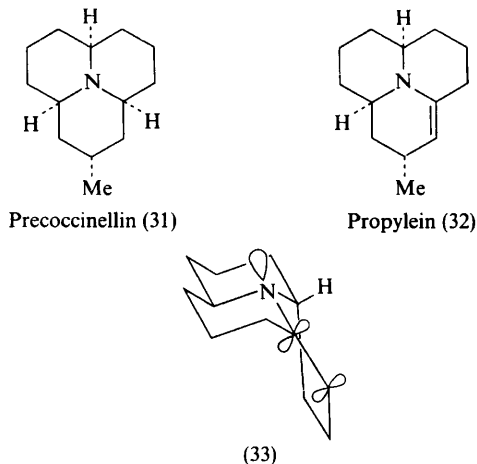
<sup>28</sup> Y. I. Pakanaev and A. S. Sadykov, *Zhur. obshchei Khim.*, 1961, **31**, 2428 (*Chem. Abs.*, 1961, **56**, 3522).

<sup>29</sup> Y. I. Pakanaev and A. S. Sadykov, *Zhur. obshchei Khim.*, 1963, **33**, 1374 (*Chem. Abs.*, 1963, **59**, 11 584).

<sup>30</sup> S. Iskandarov, B. Sadykov, Y. V. Rashkes, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 347.

<sup>31</sup> B. Tursch, D. Daloze, M. Dupont, J. M. Pasteels, and M. C. Tricot, *Experientia*, 1971, **27**, 1380; B. Tursch, D. Daloze, M. Dupont, C. Hootele, M. Kaisin, J. M. Pasteels, and D. Zimmermann, *Chimia (Switz.)*, 1971, **25**, 307.

exhibited in the off-resonance spectrum, are interpreted in terms of the gross structure (31) for precoccinellin,<sup>32</sup> and this, together with the stereochemistry depicted, has since been established as correct by an X-ray diffraction study.<sup>32</sup>



Propylein, the other alkaloid of this group, appears to be the sole alkaloid of the beetle *Propylaea quatuordecimpunctata* L.<sup>33</sup> Propylein is an amorphous, unstable, laevorotatory base of molecular formula  $C_{13}H_{21}N$  which affords precoccinellin on hydrogenation. Since the alkaloid contains one olefinic proton that is in an enamine system (n.m.r., i.r.), three dehydroprecoccinellin structures are possible for propylein. Two of these can be excluded, since propylein exhibits only end absorption in the u.v. It thus appears that in propylein the  $\pi$ -electron system of the double bond is so oriented that it cannot interact with the unshared electrons on the nitrogen atom. This leaves only one possible structure (32) for propylein [*cf.* conformation (33)].<sup>33</sup>

<sup>32</sup> D. Losman and R. G. Karlsson, unpublished work, quoted in ref. 33.

<sup>33</sup> B. Tursch, D. Daloze, and C. Hootele, *Chimia (Switz.)*, 1972, **26**, 74.

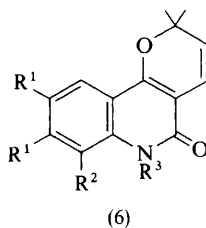
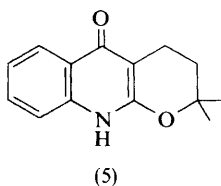
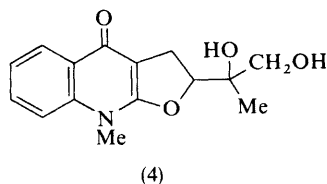
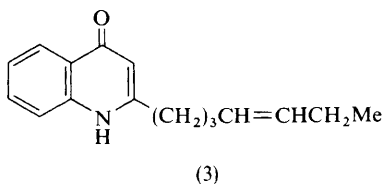
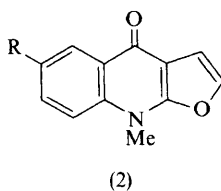
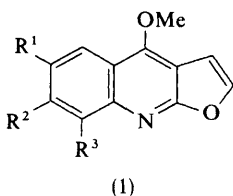
# Quinoline, Quinazoline, Acridone, and Related Alkaloids

BY V. A. SNIECKUS

A review concerning the use of n.m.r. spectroscopy in structural elucidation of Rutaceae alkaloids has appeared but is not readily accessible.<sup>1</sup>

## 1 Quinoline Alkaloids

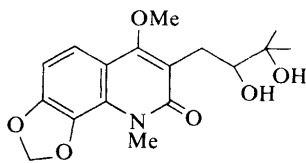
The only note dealing with quinoline derivatives of fungal origin is by way of confirming the well-known fact that viridicatin (3-hydroxy-4-phenyl-2-quinolone) is produced by *Penicillium cyclopium*.<sup>2</sup>



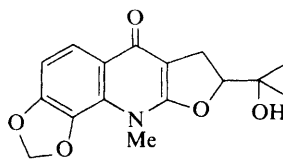
<sup>1</sup> M. Vlassa, *Stud. Cercet. Chim.*, 1971, **19**, 515 (*Chem. Abs.*, 1971, **75**, 118 427w).

<sup>2</sup> I. I. Guseva, A. G. Kozlovskii, and A. M. Bezborodov, *Priklad Biokhim. Mikrobiol.*, 1972, **8**, 259 (*Chem. Abs.*, 1972, **76**, 150 773n).

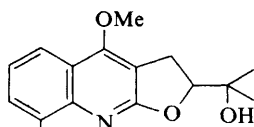




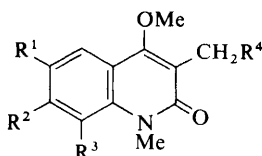
(7)



(8)



(9)



(10)

The Table summarizes recent isolation and structural elucidation work on quinoline and furoquinoline alkaloids of plant origin. The structure of folisine (4) from *Haplophyllum foliosum* was confirmed by synthesis.<sup>9</sup> Heating the methiodide of dubinidine (11) yielded folisine. The alkaloid distribution in *H. suaveolens* was extensively examined in leaf, stem, fruit with seeds, and root: kokusagine (1;  $R^1 = R^2 = \text{OMe}$ ,  $R^3 = \text{H}$ ) was found to be the major component in all parts.<sup>10</sup> Confusameline from *Melicope confusa* appears to be a phenolic furoquinoline alkaloid (1;  $R^1 = R^3 = \text{H}$ ,  $R^2 = \text{OH}$ ) which could be converted into evolitrine (1;  $R^1 = R^3 = \text{H}$ ,  $R^2 = \text{OMe}$ ) by treatment with diazomethane.<sup>13</sup> The structure of oricine (6;  $R^1 = \text{OMe}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{Me}$ ) from *Oricia suaveolens* was confirmed by a short and conventional synthesis.<sup>14</sup> Structural elucidation of alkaloids from *Ptelea trifoliata* was greatly facilitated by availability of similar

<sup>3</sup> X. A. Dominguez, D. Butruille, and J. Wapinsky, *Phytochemistry*, 1971, **10**, 2554.

<sup>4</sup> V. S. Asatiani, I. M. Kikvidze, I. A. Bessonova, K. S. Mudzhiri, and S. Yu. Yunusov, *Soobshch. Akad. Nauk Gruz. S.S.R.*, 1971, **64**, 85 (*Chem. Abs.*, 1972, **76**, 56 582c); I. M. Kikvidze, I. A. Bessonova, K. S. Mudzhiri, and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1971, **7**, 675 (*Chem. Abs.*, 1972, **76**, 124 107d).

<sup>5</sup> J. Kolodziejewski and L. Stecka, *Gdansk. Tow. Nauk., Rozpr. Wyzd.*, 1971, **3**, 125 (*Chem. Abs.*, 1971, **75**, 126 626a).

<sup>6</sup> F. Fish and P. G. Waterman, *Phytochemistry*, 1971, **10**, 3322.

<sup>7</sup> F. Fish and P. G. Waterman, *J. Pharm. Pharmacol.*, 1971, **23**, 132S.

<sup>8</sup> D. M. Gulyamova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1971, **7**, 850 (*Chem. Abs.*, 1972, **76**, 138 169n).

<sup>9</sup> I. A. Bessonova and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1971, **7**, 629 (*Chem. Abs.*, 1972, **76**, 72 684t).

<sup>10</sup> M. Ionescu, M. Vlassa, I. Mester, and E. C. Vicol, *Rev. Roumaine Biochim.*, 1971, **8**, 123 (*Chem. Abs.*, 1971, **75**, 115 908t).

<sup>11</sup> C. A. Mammarella and J. Comin, *An. Asoc. quim. argentina*, 1971, **59**, 239 (*Chem. Abs.*, 1972, **76**, 43 980f).

<sup>12</sup> M. N. S. Nayar, C. V. Sutar, and M. K. Bhan, *Phytochemistry*, 1971, **10**, 2843.

<sup>13</sup> T.-H. Yang, S.-T. Lu, S.-J. Wang, T.-W. Wang, J.-H. Lin, and I.-S. Chen, *J. Pharm. Soc. Japan*, 1971, **91**, 782 (*Chem. Abs.*, 1971, **75**, 95 382m).

<sup>14</sup> M. O. Abe and D. A. H. Taylor, *Phytochemistry*, 1971, **10**, 1167.

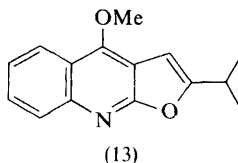
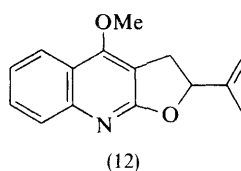
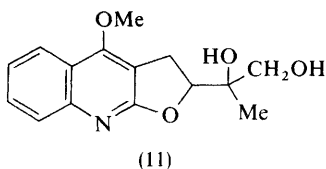
**Table** Isolation of quinoline and furoquinoline alkaloids

| Species  | Alkaloid (structure)   | Ref.                     |
|--|--|--------------------------|
| <i>Decatropis bicolor</i>                          | Dictamnine (1; $R^1 = R^2 = R^3 = H$ )<br>Skimmianine (1; $R^1 = H, R^2 = R^3 = OMe$ )   | 3                        |
| <i>Dictamnus caucasicus</i>                        | Dictamnine<br>6,8-Dimethoxydictamnine (1; $R^1 = R^3 = OMe, R^2 = H$ )<br>$\gamma$ -Fagarine <sup>a</sup> (1; $R^1 = R^2 = H, R^3 = OMe$ )<br>Isodictamnine (2; $R = H$ )<br>6-Methoxyisodictamnine (2; $R = OMe$ )<br>Robustine (1; $R^1 = R^2 = H, R^3 = OH$ )<br>Skimmianine (1; $R^1 = H, R^2 = R^3 = OMe$ )   | 4                        |
| <i>Echinops commutatus</i>                         | Echinorine (1-Methyl-4-methoxyisoquinolinium salt)   | 5                        |
| <i>Fagara lepreurii</i>                            | Skimmianine <sup>a</sup>   | 6                        |
| <i>F. rubescens</i>                                | Skimmianine  | 7                        |
| <i>Haplophyllum acutifolium</i>                    | Unnamed (3) <sup>b</sup>   | 8                        |
| <i>H. foliosum</i>                                 | Folisine (4)?  | 9                        |
| <i>H. suaveolens</i><br>( <i>Ruta suaveolens</i> ) | Dictamnine <sup>a</sup><br>Evoxine [1; $R^1 = H, R^2 = OCH_2CH(OH)C(OH)Me_2, R^3 = OMe$ ]<br>Haplofoline <sup>a</sup> (5)<br>Kokusaginine <sup>a</sup> (1; $R^1 = R^2 = OMe, R^3 = H$ )<br>Skimmianine <sup>a</sup><br>Alkaloids <sup>c</sup> H <sub>6</sub> , H <sub>7</sub> , H <sub>8</sub>   | 10                       |
| <i>Helietta longifoliata</i>                       | Dictamnine<br>Flindersiamine (1; $R^1 + R^2 = OCH_2O, R^3 = OMe$ )<br>Isodictamnine<br>Kokusaginine<br>Pteleine (6-methoxydictamnine) (1; $R^1 = OMe, R^2 = R^3 = H$ )<br>Skimmianine  | 11                       |
| <i>Hesperethusa crenulata</i>                      | 4-Methoxy-1-methyl-2-quinolone   | 12                       |
| <i>Melicope confusa</i>                            | Confusameline (1; $R^1 = R^3 = H, R^2 = OH$ )<br>Kokusaginine<br>Skimmianine   | 13                       |
| <i>Oricia suaveolens</i>                           | Oricine (6,7-dimethoxy-N-methylflindersine) (6; $R^1 = OMe, R^2 = H, R^3 = Me$ )   | 14                       |
| <i>Ptelea trifoliata</i>                           | Hydroxylunidine <sup>a</sup> (7)<br>Hydroxylunine <sup>a</sup> (8)<br>O-Methyl-luninium (9; $R = H, ^+NMe$ )<br>Pteleatinium chloride (9; $R = OH, ^+NMe Cl^-$ )<br>Ptelecortine (10; $R^1 + R^2 = OCH_2O, R^3 = OMe, R^4 = CH=Me_2$ )<br>Ptelefoline methyl ether [10; $R^1 = R^3 = OMe, R^2 = H, R^4 = CH(OMe)C(Me)=CH_2$ ]<br>Pteleoline [10; $R^1 = H, R^2 + R^3 = OCH_2O, R^4 = CH_2CH(Me)CO_2Me$ ] | 15<br>16<br>17<br>15, 17 |
| <i>Skimmia foremanii</i>                           | Dictamnine <sup>a</sup>  | 17                       |
| <i>Vinca herbacea</i>                              | Skimmianine  | 18<br>19                 |

<sup>a</sup> Previously isolated from this species.<sup>b</sup> Tentative structure.<sup>c</sup> Original literature not accessible for definition of structures.

compounds previously isolated from this species.<sup>15-17</sup> The alkaloid pteleatinium chloride (9;  $R = OH$ ,  $^+NMeCl^-$ ) is apparently responsible for activity against *Mycobacterium smegmatis* and *Candida albicans*.<sup>16</sup> *P. trifoliata* has now yielded more than twelve alkaloids in the past 2—3 years. Indications are that there may be additional alkaloids which await structural elucidation.<sup>15</sup>

The effect of added potential biosynthetic precursors on the formation of echinopsine (1-methyl-4-quinolone) in *Echinops shaerocephalus* grown on sterile culture media has been studied.<sup>20</sup> It was found that addition of tryptophan, nicotinic acid, phenylalanine, or methionine increased the amount of echinopsine produced in the plant. Cell cultures of *Ruta graveolens* grown in a liquid medium in continuous light have been shown to produce edulinine [ $10$ ;  $R^1 = R^2 = R^3 = H$ ,  $R^4 = CH(OH)C(OH)Me_2$ ], kokusaginine (1;  $R^1 = R^2 = OMe$ ,  $R^3 = H$ ), 6-methoxydictamnine (1;  $R^1 = OMe$ ,  $R^2 = R^3 = H$ ), and skimmianine (1;  $R^1 = H$ ,  $R^2 = R^3 = OMe$ ).<sup>21</sup>



Among the synthetic contributions this year, it is appropriate to discuss first the synthesis<sup>22</sup> of ( $\pm$ )-dubinidine (11), since the structure of this alkaloid had been in doubt for some time.<sup>23</sup> The synthesis was accomplished by treating ( $\pm$ )-platydesmine (9;  $R = H$ ) with triphenyl phosphite dibromide and potassium

<sup>15</sup> I. Novak, K. Szendrei, V. Papay, E. Minker, and M. Koltai, *Herba Hung.*, 1970, **9**, 23 (*Chem. Abs.*, 1971, **75**, 77 090k).

<sup>16</sup> L. A. Mitscher, M. S. Bathala, and J. L. Beal, *Chem. Comm.*, 1971, 1040.

<sup>17</sup> J. Reisch, K. Szendrei, I. Novak, E. Minker, J. Korosi, and K. Csedo, *Tetrahedron Letters*, 1972, 449.

<sup>18</sup> B. Weinstein and A. R. Craig, *Phytochemistry*, 1971, **10**, 2556.

<sup>19</sup> V. Yu. Vachnadze, V. M. Malikov, K. S. Mudzhiri, and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1971, **7**, 676 (*Chem. Abs.*, 1972, **76**, 110 298e).

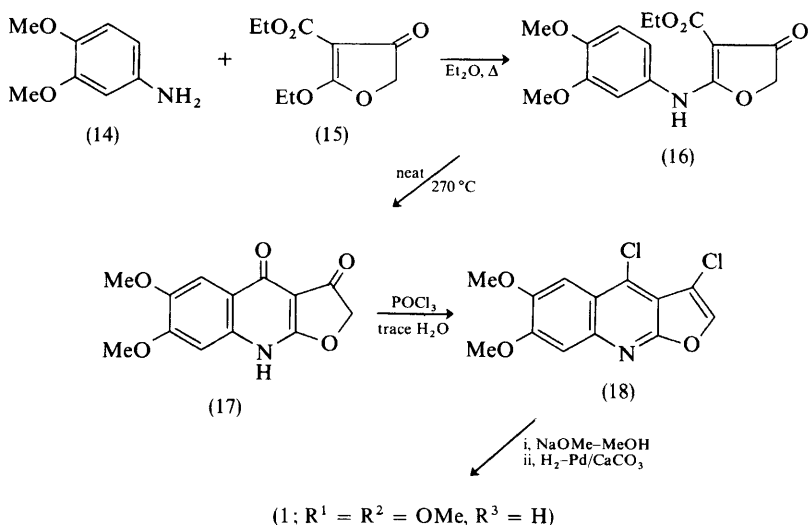
<sup>20</sup> V. P. Panina and N. A. Trofimova, Mater. Gor. Nauch. Konf. Molodykh Uch.-Med., 1st, 1967, ed. A. I. Ryzhov, Tomsk. Univ., Tomsk, USSR, 1969, 466 (*Chem. Abs.*, 1971, **75**, 126 693v; L. N. Berezenkovskaya and V. P. Serebryanskaya, *Nekotorye Vopr. Farmakogn. Dikorast. Kul'tiv. Rast. Sib.*, 1969, 122 (*Chem. Abs.*, 1971, **75**, 85 409m).

<sup>21</sup> W. Steck, B. K. Bailey, J. P. Shyluk, and O. L. Gamborg, *Phytochemistry*, 1971, **10**, 191.

<sup>22</sup> M. F. Grundon and K. J. James, *Tetrahedron Letters*, 1971, 4727.

<sup>23</sup> 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, Vol. 13, p. 407; Vol. 9, p. 254.

carbonate in refluxing isopropyl ether to give a mixture of olefins (12) and (13). Conventional reagents such as phosphorus tribromide were found to yield the thermodynamically more stable *endo*-olefin (13). Treatment of *exo*-olefin (12) with osmium tetroxide yielded ( $\pm$ )-dubininine (11).



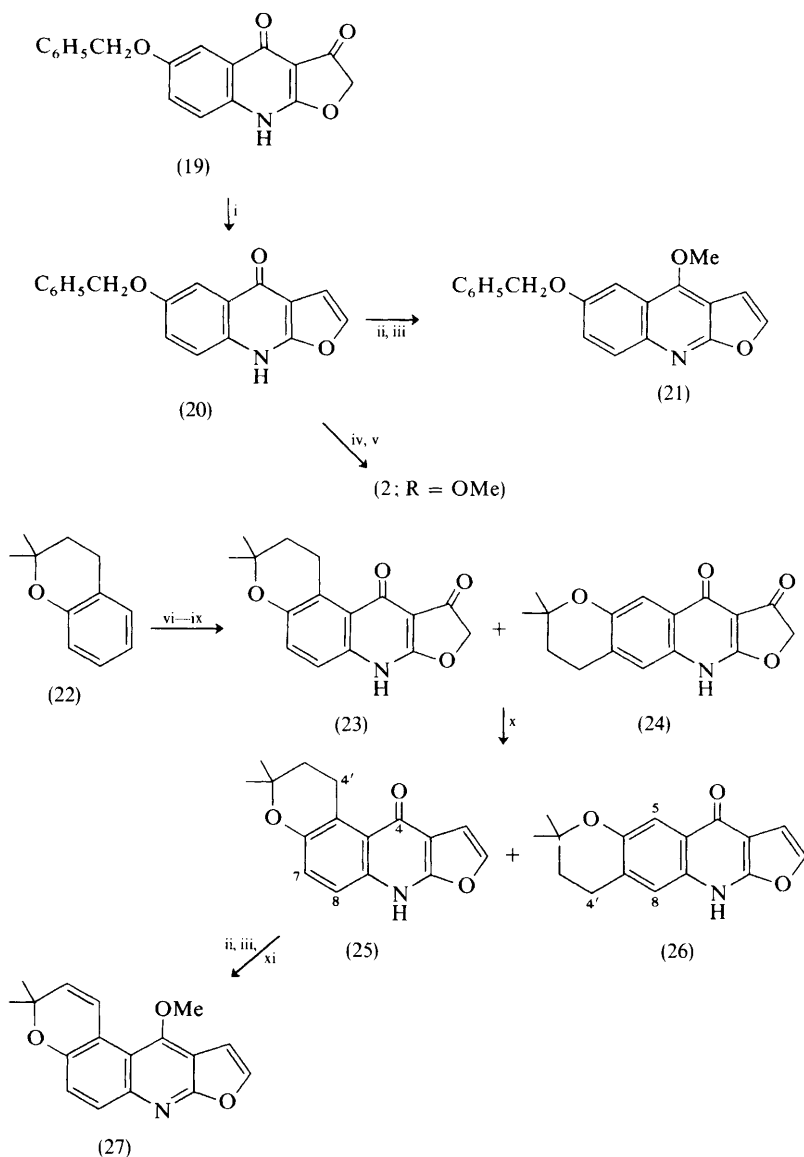
Scheme 1

A new total synthesis of kokusaginine (1;  $R^1 = R^2 = \text{OMe}$ ,  $R^3 = \text{H}$ ) was undertaken in order to provide a shorter and more economic route to this alkaloid than those previously available (Scheme 1).<sup>24</sup> Condensation of 4-aminoveratrole (14) with the dihydrofuran (15) (prepared *in situ*) gave compound (16) which was cyclized to the 4-quinolone derivative (17) in moderate yield (Tuppy and Böhm synthesis). Treatment of (17) with diazomethane failed to give the expected 4-methoxyquinoline derivative. In order to circumvent this problem, compound (17) was first converted into the dichlorofuroquinoline (18) which upon treatment with methanolic sodium methoxide followed by catalytic dehalogenation yielded kokusaginine (1;  $R^1 = R^2 = \text{OMe}$ ,  $R^3 = \text{H}$ ).

A further modification of the Tuppy and Böhm procedure has been used in the synthesis of medicosmine (27), a rare furoquinoline alkaloid from *Medicosa cunninghamii* (Scheme 2).<sup>25</sup> Although the 4-quinolone (19) was easily prepared by the reaction of 4-benzoyloxyaniline with compound (15), the diazomethane methylation step on (19) was again very unsatisfactory. However, treatment of (19) with an excess of sodium borohydride in basic solution yielded directly the furoquinolone (20). This reaction may be explained by a sequence of steps

<sup>24</sup> I. Mester and M. Ionescu, *Phytochemistry*, 1971, **10**, 2205.

<sup>25</sup> T. R. Govindachari, S. Prabhakar, V. N. Ramachandran, and B. R. Pai, *Indian J. Chem.*, 1971, **9**, 1031.

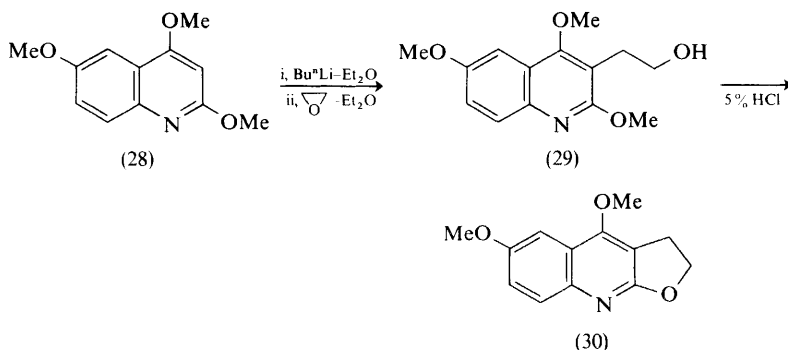


Reagents: *i*,  $\text{NaBH}_4\text{--MeOH--NaOH}$ ; *ii*,  $\text{POCl}_3$ ; *iii*,  $\text{NaOMe--MeOH}$ ; *iv*, conc.  $\text{HCl--MeOH}$ , room temp.; *v*,  $\text{Me}_2\text{SO}_4\text{--KOH--MeOH}$ ; *vi*, conc.  $\text{HNO}_3\text{--HOAc}$ ; *vii*,  $\text{H}_2\text{--PtO}_2\text{--MeOH--C}_6\text{H}_6$ ; *viii*,  $\text{NaCH}(\text{CO}_2\text{Et})_2\text{--ClCH}_2\text{COCl--Et}_2\text{O}$ ; *ix*,  $(\text{C}_6\text{H}_5)_2\text{O}$ ,  $250^\circ\text{C}$ ; *x*,  $\text{NaBH}_4\text{--EtOH--NaOH}$ ; *xi*,  $\text{DDQ--C}_6\text{H}_6$ .

Scheme 2

involving the reduction of the carbonyl followed by tautomerization of the 4-quinolone system and expulsion of hydroxide ion from the five-membered ring. Although the methoxyfuroquinoline (21) could be prepared in low yield, attempts to debenzylate it were unsuccessful. This route was not totally in vain, however, since debenzylation of (20) with methanolic hydrochloric acid gave the corresponding phenol which upon treatment with dimethyl sulphate and base produced 6-methoxyisodictamnine (2;  $R = \text{OMe}$ ), now known to be a *bona fide* alkaloid (see Table). The alternative route to medicosmine (27) proceeded from 2,2-dimethylchroman (22) which, in a series of standard steps, gave an inseparable mixture of tetracyclic compounds (23) and (24). Sodium borohydride reduction of this mixture under more vigorous conditions than those used in the case of (19) provided (25) and (26) which were separated and characterized by their n.m.r. spectra [(25):  $\delta$  7.0, dd, 2H,  $J = 9$  Hz, H-7 and H-8; 3.62, t, 2H, H-4', (26):  $\delta$  7.55, s, 1H, H-5; 7.45, s, 1H, H-8; 3.0, t, 2H, H-4']. Compound (25) was readily transformed into a 4-methoxyquinoline derivative [by analogy to the conversion of (20) into (21)] which upon dehydrogenation yielded medicosmine (27). The generality of the sodium borohydride reduction was investigated, and the successful synthetic scheme has apparently been extended to the preparation of 6-benzyloxydictamnine (1;  $R^1 = \text{OCH}_2\text{C}_6\text{H}_5$ ,  $R^2 = R^3 = \text{H}$ ), 6-benzyloxyisodictamnine (2;  $R = \text{OCH}_2\text{C}_6\text{H}_5$ ), and pteleine (1;  $R = \text{OMe}$ ,  $R^2 = R^3 = \text{H}$ ).<sup>25</sup>

Details of a new and generally useful approach to furoquinoline alkaloids involving lithiation of 2-alkoxyquinolines has been described.<sup>26</sup> After a successful model study, this reaction was applied to the preparation of dictamnine (1;  $R^1 = R^2 = R^3 = \text{H}$ ), dihydro- $\gamma$ -fagarine (1;  $R^1 = R^2 = \text{H}$ ,  $R^3 = \text{OMe}$ , dihydrofuran ring), and pteleine (1;  $R^1 = \text{OMe}$ ,  $R^2 = R^3 = \text{H}$ ); Scheme 3 shows the route for pteleine. Lithiation of the quinoline derivative (28) followed by treatment with ethylene oxide gave the alcohol (29), which upon treatment with mild acid underwent selective hydrolysis of the 2-methoxy-function and cyclization to give (30). The latter had been previously dehydrogenated to pteleine

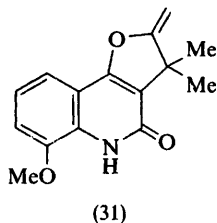


Scheme 3

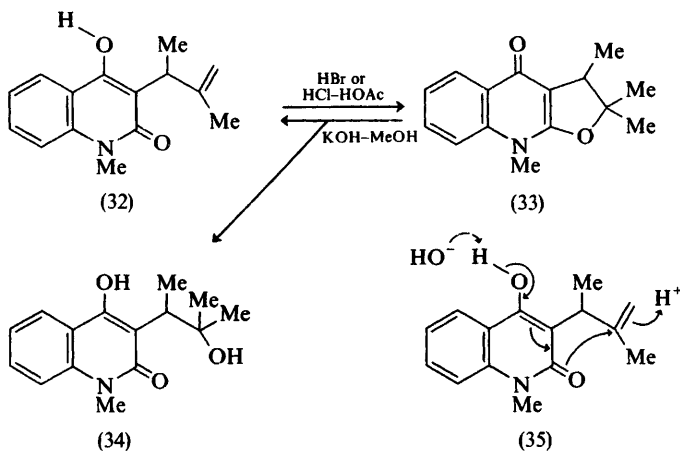
<sup>26</sup> N. S. Narasimhan, M. V. Paradkar, and R. H. Alurkar, *Tetrahedron*, 1971, **27**, 1351.

(1;  $R^1 = \text{OMe}$ ,  $R^2 = R^3 = \text{H}$ ). Stronger acidic conditions on compound (29) led to undesired cyclization of the side-chain alcohol to the C-4 oxygen function. The metalation of (28) and related quinolines appears to be selective and the overall yields of 3-substituted products are reasonable if based on recovered starting material. This paper also reports the preparation of edulitine (4,8-dimethoxy-2-quinolone) by mild acid hydrolysis of 2,4,8-trimethoxyquinoline.<sup>26</sup>

The reaction between the thallos salt of 4-hydroxy-2-quinolone and 3-chloro-3-methylbut-1-yne unexpectedly gave flindersine (6;  $R^1 = R^2 = R^3 = \text{H}$ ) in 28 % yield. This constitutes the shortest reported route for this alkaloid.<sup>27</sup> When 4-hydroxy-8-methoxy-2-quinolone was used in the same reaction, the corresponding methoxy-derivative (6;  $R^1 = R^3 = \text{H}$ ,  $R^2 = \text{OMe}$ ) was obtained together with the angularly cyclized derivative (31).



Treatment of (–)-ravenoline (32) with acid has been shown to give (–)-lemobiline (= spectabiline) (33) (Scheme 4).<sup>28</sup> This biogenetic-type process can be partially reversed by base. The other product in the base-catalysed reaction is the tertiary alcohol (34). Both ravenoline and alcohol (34) are stable to these basic



**Scheme 4**

<sup>27</sup> J. W. Huffman and T. M. Hsu, *Tetrahedron Letters*, 1972, 141.

<sup>28</sup> S. K. Talapatra, B. C. Maiti, and B. Talapatra, *Tetrahedron Letters*, 1971, 2683.

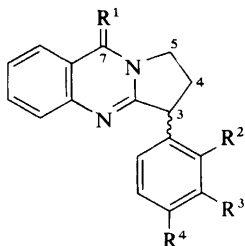
conditions, suggesting that ravenoline is not formed *via* the intermediacy of (34). Evidence is also presented that (–)-lemobiline is not an artifact arising from cyclization of (–)-ravenoline during the isolation procedure. A concerted mechanism (35) for the ravenoline → lemobiline transformation is likely.

Detailed experimental conditions for the DDQ dehydrogenation of dihydrodictamnine to dictamnine ( $1; R^1 = R^2 = R^3 = H$ ) have been reported.<sup>29</sup>

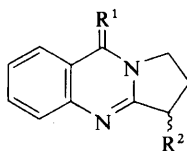
A potentiometric titration method for the determination of echinopsine (1-methyl-4-quinolone) in pharmaceutical preparations has been developed.<sup>30</sup>

## 2 Quinazoline Alkaloids

Aside from the known anisotine (36;  $R^1 = O, R^2 = H, R^3 = CO_2Me, R^4 = NHMe$ ) and peganine (37;  $R^1 = H_2, R^2 = OH$ ), three new alkaloids, adhatodine (36;  $R^1 = H_2, R^2 = H, R^3 = CO_2Me, R^4 = NHMe$ ), vasicolinone (36;  $R^1 = O, R^2 = NMe_2, R^3 = R^4 = H$ ), and vasicoline (36;  $R^1 = H_2, R^2 = NMe_2, R^3 = R^4 = H$ ), have been isolated from *Adhatoda vasica*.<sup>31</sup> Their structures were elucidated by extensive spectral analysis. For example, the 100 MHz n.m.r. spectrum of vasicoline (36;  $R^1 = H_2, R^2 = NMe_2, R^3 = R^4 = H$ ) showed, aside from the aromatic multiplet at  $\delta$  6.8–7.3 (8H), a singlet at  $\delta$  4.60 (2H) assigned to the C-7 methylene protons overlapping with a triplet at  $\delta$  4.50 (1H) due to the C-3 methine hydrogen. The remaining methylene hydrogens at C-4 and C-5 appeared as multiplets at  $\delta$  3.1–3.4 (2H), 1.6–2.1 (1H), and 2.25–3.8 (1H). A singlet at  $\delta$  2.67 (6H) was readily assigned to the dimethylamino-function. The mass spectrum of vasicoline showed two interesting major and minor fragmentation pathways, (38) → (39) and (38) → (40), respectively. Both vasicoline (36;  $R^1 = H_2, R^2 = NMe_2, R^3 = R^4 = H$ ) and adhatodine (36;  $R^1 = H_2, R^2 = H, R^3 = CO_2Me, R^4 = NHMe$ ) were easily air-oxidized under the conditions of isolation to vasicolinone and (36;  $R^1 = O, R^2 = H, R^3 = CO_2Me, R^4 = NHMe$ ) respectively. These observations raise the question as to how these alkaloids exist in the C-7 unoxidized state in the plant. The interesting hypothesis advanced in this paper that this group of alkaloids, now numbering four (anisotine



(36)



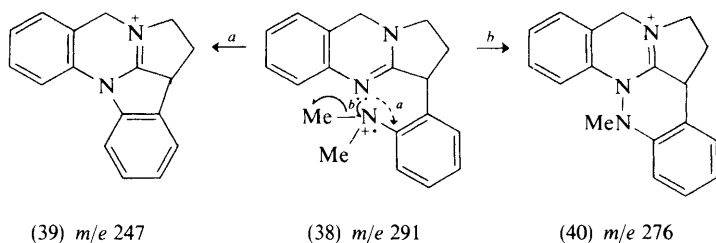
(37)

<sup>29</sup> F. Piozzi, P. Venturella, and A. Bellino, *Org. Prep. Proced. Internat.*, 1971, 3, 223.

<sup>30</sup> A. P. Kreshkov, T. V. Maksimova, and V. A. Drozdov, *Farmatsiya*, 1972, 21, 56 (*Chem. Abs.*, 1972, 76, 158 410n).

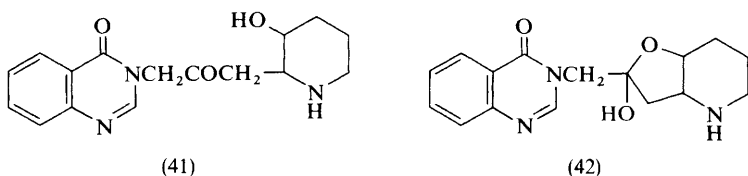
<sup>31</sup> S. John, D. Groeger, and M. Hesse, *Helv. Chim. Acta.*, 1971, 54, 826.





had been previously isolated from *Anisotes sessiliflorus*), may be biogenetically derived from peganine (37;  $R^1 = H_2$ ,  $R^2 = OH$ ) and anthranilic acid derivatives, has received some support from synthetic work (see below).

Apparently, febrifugine (41) and isofebrifugine (42) isolated from *Dichroa febrifuga*<sup>32,33</sup> have anti-moth activity.<sup>33</sup> *Peganum harmala* has been shown to elaborate a new alkaloid, pegalol (37;  $R^1 = H$ ,  $OH$ ,  $R^2 = H$ ).<sup>34</sup> The seasonal patterns of peganine (37;  $R^1 = H_2$ ,  $R^2 = OH$ ) distribution in the roots and ripe seeds of *P. harmala* have been determined.<sup>35</sup>



Preparative results in this area are limited to a single but significant report dealing with the biogenetic-type synthesis of vasicinone (37;  $R^1 = O$ ,  $R^2 = OH$ ) and anisessine (43).<sup>36</sup> In the elaboration of these alkaloids, anthranilic acid or 3-hydroxyanthranilic acid was condensed with *O*-methylbutyrolactim (44) to give the quinazoline derivatives (45;  $R^1 = R^2 = H$ ) and (45;  $R^1 = OH$ ,  $R^2 = H$ ) in high yield. Compound (45;  $R^1 = R^2 = H$ ), on treatment with *N*-bromosuccinimide and benzoyl peroxide, produced mainly the monobrominated product (45;  $R^1 = H$ ,  $R^2 = Br$ ). Sodium acetate-acetic acid solvolysis of this compound followed by hydrolysis gave vasicinone (37;  $R^1 = O$ ,  $R^2 = OH$ ). Alternatively, treatment of (45;  $R^1 = H$ ,  $R^2 = Br$ ) with ethyl anthranilate gave anisessine (43). In an attempt to generalize this sequence to the preparation of sessiflorine, for which structure [45;  $R^1 = OMe$ ,  $R^2 = N(Me)C_6H_5$ ] had been

<sup>32</sup> E. S. Zabolotnaya and L. N. Safronich, *Trudy Vses. Nauch.-Issled. Inst. Lekarstv. Aromat. Rast.*, 1969, **15**, 356 (*Chem. Abs.*, 1971, **75**, 20 733t).

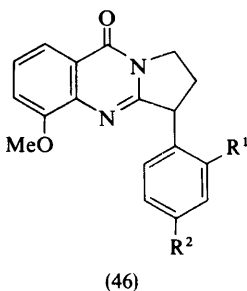
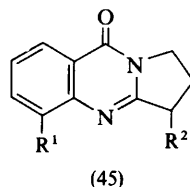
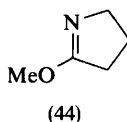
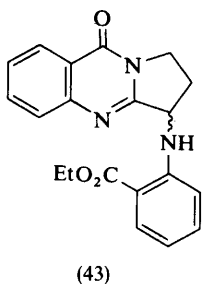
<sup>33</sup> E. S. Zabolotnaya and L. N. Safronich, *Lekarstv. Rasteniy*, 1969, 356 (*Chem. Abs.*, 1972, **76**, 32 240p).

<sup>34</sup> M. V. Telezhenetskaya, Kh. N. Kashimov, and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1971, **7**, 849 (*Chem. Abs.*, 1972, **76**, 110 310c).

<sup>35</sup> Kh. N. Khashimov, M. V. Telezhenetskaya, N. N. Sharakhimov, and S. Yu. Yunusov, *Khim. prirod Soedinenii*, 1971, **7**, 382 (*Chem. Abs.*, 1971, **75**, 115 865b).

<sup>36</sup> T. Onaka, *Tetrahedron Letters*, 1971, 4387.

proposed, the bromo-derivative (45;  $R^1 = \text{OMe}$ ,  $R^2 = \text{Br}$ ), prepared by successive treatment of (45;  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ) with diazomethane and NBS, was allowed to react with methylaniline. A compound was obtained which showed spectral data consistent with the expected structure [45;  $R^1 = \text{OMe}$ ,  $R^2 = \text{N}(\text{Me})\text{C}_6\text{H}_5$ ]. However, comparison of the synthetic material with the natural product in spectral and t.l.c. properties showed significant differences. The i.r. spectrum of natural sessiflorine showed a band at  $3290\text{ cm}^{-1}$  (NH) and its n.m.r. spectrum showed absorption at  $\delta$  4.66, t, 1H,  $J = 6$  Hz. On the other hand, the synthetic compound exhibited a corresponding one-proton triplet ( $J = 8.2$  Hz) at  $\delta$  5.47 and no NH i.r. absorption. This information, taken in consort with n.m.r. data of other known 3-phenylquinazoline alkaloids, indicated that sessiflorine of natural origin must be represented by either (46;  $R^1 = \text{H}$ ,  $R^2 = \text{NHMe}$ ) or (46;  $R^1 = \text{NHMe}$ ,  $R^2 = \text{H}$ ). The presence of an  $A_2$  part of  $A_2B_2$  pattern at  $\delta$  7.0–6.7 (2H) and the unshielded nature of the *N*-methyl signal ( $\delta$  2.95) favours structure (46;  $R^1 = \text{H}$ ,  $R^2 = \text{NHMe}$ ) for the alkaloid sessiflorine.



### 3 Acridone Alkaloids

The lack of any reviews on this group noted in Volume 1 has been amply corrected. General reviews on the structural elucidation,<sup>37,38</sup> synthesis,<sup>39</sup> and

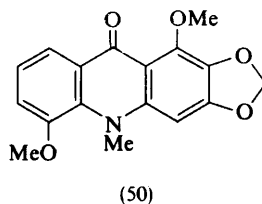
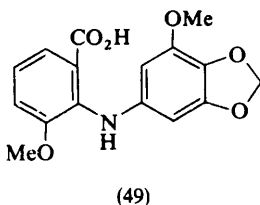
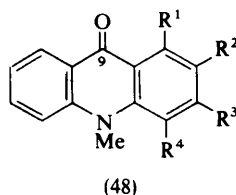
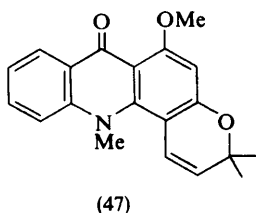
<sup>37</sup> I. Hopartean, *Stud. Cercet. Chim.*, 1971, **19**, 695 (*Chem. Abs.*, 1971, **75**, 148 458z).

<sup>38</sup> J. Reisch, K. Szendrei, E. Minker, and I. Novak, *Pharmazie*, 1972, **27**, 208.

<sup>39</sup> S. Johnne and D. Groeger, *Pharmazie*, 1972, **27**, 195.

biological activity<sup>37,39</sup> have become available. A discussion of acronycine (47) is included in a review of alkaloids with anti-tumour properties.<sup>40</sup>

Two substituted acridones, (48;  $R^1 = OH$ ,  $R^2 = R^4 = H$ ,  $R^3 = OMe$ ) and (48;  $R^1 = OH$ ,  $R^2 = R^3 = OMe$ ,  $R^4 = H$ ), have been isolated from *Fagara lepreurii* and *F. rubescens*.<sup>6,7</sup> Arborinine (48;  $R^1 = OH$ ,  $R^2 = R^3 = OMe$ ,  $R^4 = H$ ) has been obtained from *Lemonia spectabilis*<sup>28</sup> and *Monnieria trifolia*.<sup>41</sup> The biogenetically unusual acridone (48;  $R^1 = OH$ ,  $R^2 = R^3 = R^4 = H$ ) has been extracted from *Ruta graveolens*.<sup>42</sup>



A conventional synthesis of tecleanthine (50) has been executed.<sup>43</sup> Ullmann reaction of 2-amino-3-methoxybenzoic acid with 3-methoxy-4,5-methylenedioxyiodobenzene gave the diphenylamine (49). Compound (49) was converted by cyclization ( $POCl_3$ ), hydrolysis ( $HCl$ ), and methylation into tecleanthine (50). The Ullmann condensation was also used to prepare the natural acridones (48;  $R^1 = R^2 = R^3 = R^4 = OMe$ ) and xanthoxoline (48;  $R^1 = OH$ ,  $R^2 = R^3 = R^4 = H$ , *N*-demethyl).<sup>44</sup> The corresponding 9-thioketones were also synthesized.

The structure of a binary compound formed from the reaction of acridine and  $K_2HgI_4$  has been established.<sup>45</sup>

<sup>40</sup> G. H. Svoboda, *Pharmacogn. Phytochem.*, Internat. Congr., 1st, 1970, ed. H. Wagner, Springer, Berlin, 1971, p. 166.

<sup>41</sup> A. Cave, J. I. Ramos de Souza, and R. R. Paris, *Plant. Med. Phytother.*, 1971, 5, 327 (*Chem. Abs.*, 1972, 76, 150 988m).

<sup>42</sup> J. Reisch, K. Szendrei, I. Novak, E. Minker, and Z. Rozsa, *Experientia*, 1971, 27, 1005.

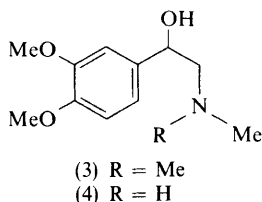
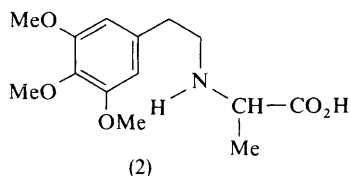
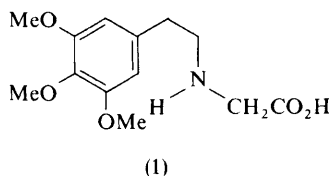
<sup>43</sup> V. N. Ramachandran, B. R. Pai, and R. Santhanam, *Indian J. Chem.*, 1972, 10, 14.

<sup>44</sup> M. Ionescu and M. Vlassa, *Rev. Roumaine Chim.*, 1971, 16, 743 (*Chem. Abs.*, 1971, 75, 49 372k).

<sup>45</sup> G. Szasz and L. Buda, *Acta Pharm. Hung.*, 1971, 41, 241 (*Chem. Abs.*, 1972, 76, 25 446g).

**$\beta$ -Phenethylamines and Simple Isoquinolines.**—Tyramine and  $\beta$ -phenethylamine have been isolated from *Prosopis alba* Gris. (Leguminosae).<sup>1</sup> The alkaloids of fourteen species of *Trichocereus* cacti have been reported. Eight previously known phenethylamines, viz. tyramine, *N*-methyltyramine, hordenine, 3-methoxytyramine, 3,4-dimethoxyphenethylamine, *N*-methyl-3-methoxytyramine, 3-hydroxy-4,5-dimethoxyphenethylamine, and mescaline were identified in these species. Mescaline was found to occur in *T. cuzcoensis*, *T. fulvilanus*, *T. taquimbalensis*, and *T. validus*. Mescaline was also present in small amounts in *Stetsonia coryne* together with traces of anhalidine and anhalonidine. 3-Hydroxy-4-methoxyphenethylamine was identified in *Pachycereus pecten-aboriginum*. 3-Methoxytyramine was found to be the major alkaloid of *Trichocereus cuzcoensis*.<sup>2</sup>

Mescaloxylic (1) and mescaloruvic (2) acids, two novel amino-acid analogues of mescaline, have been firmly identified in peyote extracts.<sup>3</sup>



The isolation, structure, synthesis, and absolute configuration of the new hydroxylic  $\beta$ -phenethylamine, (–)-macromerine (3), has been reported.<sup>4</sup> The same cactus, *Coryphantha macromeris*, also contains (–)-normacromerine (4).<sup>5</sup>

<sup>1</sup> M. N. Graziano, G. E. Ferraro, and J. D. Coussio, *Lloydia*, 1971, **34**, 453.

<sup>2</sup> S. Agurell, J. G. Bruhn, J. Lundström, and U. Svensson, *Lloydia*, 1971, **34**, 183.

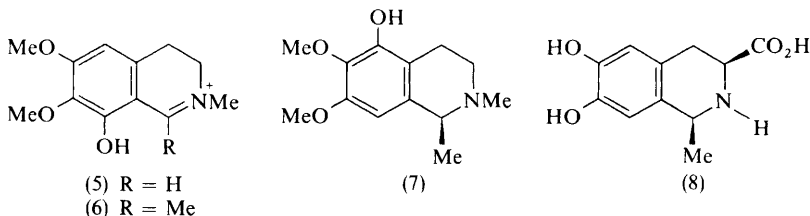
<sup>3</sup> G. J. Kapadia, M. H. Hussain, and G. Subba Rao, *J. Pharm. Sci.*, 1972, **61**, 1172.

<sup>4</sup> S. D. Brown, J. E. Hodgkins, and M. G. Reinecke, *J. Org. Chem.*, 1972, **37**, 773.

<sup>5</sup> W. J. Keller and J. L. McLaughlin, *J. Pharm. Sci.*, 1972, **61**, 147.

The pharmacology of hallucinogens such as mescaline and related bases has been reviewed<sup>6</sup> and the cardiovascular and renal actions of dopamine have been discussed with a view to potential clinical applications.<sup>7</sup> The proceedings of a symposium on the regulation of catecholamine metabolism in the sympathetic nervous system have appeared.<sup>8</sup> The mass spectra of ephedrine derivatives have been discussed.<sup>9,10</sup>

Anhalidine is present in the cactus *Pelecyphora aselliformis*.<sup>2</sup> The new quaternary bases anhalotine (5) and peyotine (6) have been found in *Lophophora williamsii* var. *caespitosa* which also contains pellotine, anhalidine, anhalonidine, anhalamine, and lophophorine.<sup>11</sup>



The structure of the giant-cactus alkaloid gigantine (7) is now firmly established by synthesis,<sup>12-14</sup> and the absolute configuration has been settled through inter-relationship with (–)-salsolidine.<sup>14</sup> The velvet bean *Mucuna deeringiana* (Bort.) Merr. (Leguminosae) produces the amino-acid (8)<sup>15</sup> which has been synthesized starting with L-dopa.<sup>15,16</sup> This new amino-acid differs by only a methyl group from the one isolated from the seed of *M. mutisiana*.<sup>17</sup>

An X-ray crystallographic study of (–)-anhalonine hydrobromide and (+)-O-methylanhalonidine hydrobromide has established the absolute configuration of (–)-anhalonine, (–)-lophophorine, and (+)-O-methylanhalonidine.<sup>18</sup>

A full paper has now appeared on the sulphur dioxide dehydrative cyclization of *NN*-dimethylphenethylamine *N*-oxides to yield tetrahydroisoquinolines.<sup>19</sup> An interesting method for the functionalization of tetrahydroisoquinolines at C-4

<sup>6</sup> P. Brawley and J. C. Duffield, *Pharm. Rev.*, 1972, **24**, 31.

<sup>7</sup> L. I. Goldberg, *Pharm. Rev.*, 1972, **24**, 1.

<sup>8</sup> *Pharm. Rev.*, 1972, **24**, 163.

<sup>9</sup> H. M. Fales, G. W. A. Milne, and N. C. Law, *Arch. Mass Spectral Data*, 1971, **2**, 632.

<sup>10</sup> K. Serck-Hanssen and E. Martensson, *Arch. Mass Spectral Data*, 1971, **2**, 760.

<sup>11</sup> M. Fujita, H. Itokawa, J. Inoue, Y. Nozu, N. Goto, and K. Hasegawa, *J. Pharm. Soc. Japan*, 1972, **92**, 482.

<sup>12</sup> G. J. Kapadia, G. S. Rao, M. B. E. Favez, B. K. Chowdhury, and M. L. Sethi, *Chem. and Ind.*, 1970, 1593.

<sup>13</sup> A. M. Choudhury, *Chem. and Ind.*, 1971, 578.

<sup>14</sup> S. D. Brown, J. E. Hodgkins, J. L. Massingill, jun., and M. G. Reinecke, *J. Org. Chem.*, 1972, **37**, 1825.

<sup>15</sup> M. E. Daxenbichler, R. Kleiman, D. Weisleder, C. H. VanEtten, and K. D. Carlson, *Tetrahedron Letters*, 1972, 1801.

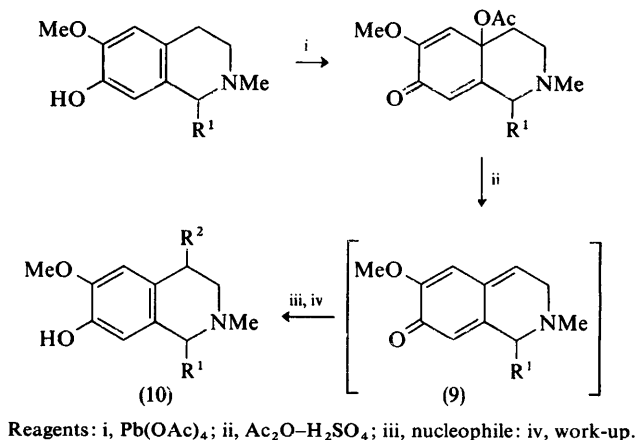
<sup>16</sup> A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, 1972, **55**, 15.

<sup>17</sup> E. A. Bell, J. R. Nulu, and C. Cone, *Phytochemistry*, 1971, **10**, 2191.

<sup>18</sup> A. Brossi, J. F. Blount, J. O'Brien, and S. Teitel, *J. Amer. Chem. Soc.*, 1971, **93**, 6248.

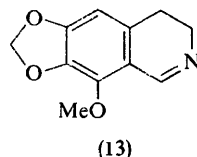
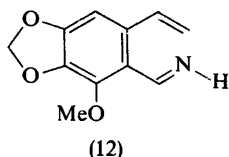
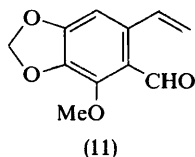
<sup>19</sup> P. A. Bather, J. L. Lindsay Smith, and R. O. C. Norman, *J. Chem. Soc. (C)*, 1971, 3060.

has been developed (Scheme 1). The nucleophile which adds to the quinone methide (9) may result in  $R^2$  being OAc, OR, SR,  $NR_2$ , CN,  $CH_2NO_2$ ,  $CH(CN)_2$ ,  $CH(CO_2Et)_2$ , etc., in the tetrahydroisoquinoline (10).<sup>20-24</sup>



Scheme 1

The alkali-catalysed disproportionation of pseudo-bases in the simple tetrahydroisoquinoline series is assumed to be a heteroanalogous Cannizzaro reaction, intermediate between the acid-catalysed disproportionation of benzhydrols and the alkali-catalysed Cannizzaro reaction.<sup>25</sup> The benzenoid derivatives (11) and (12) react with ammonium hydroxide under pressure to give norcotarnine (13).<sup>26</sup> 6,7-Dihydroxylated tetrahydroisoquinolines can be readily prepared by aqueous hydrobromic acid hydrolysis of the corresponding 6,7-dimethoxy-compounds.<sup>27</sup>



<sup>20</sup> B. Umezawa, O. Hoshino, Y. Terayama, K. Ohshima, Y. Yamanashi, T. Inoue, and T. Toshioka, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2138.

<sup>21</sup> B. Umezawa, O. Hoshino and Y. Yamanashi, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2147.

<sup>22</sup> B. Umezawa, O. Hoshino, and Y. Yamanashi, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2154.

<sup>23</sup> O. Hoshino, Y. Yamanashi, and B. Umezawa, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2161.

<sup>24</sup> O. Hoshino, Y. Yamanashi, T. Toshioka, and B. Umezawa, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2166.

<sup>25</sup> G. Habermehl and J. Schunk, *Annalen*, 1971, **750**, 128.

<sup>26</sup> D. Korbonits, S. Holly, and K. Harsanyi, *Magyar Kém. Folyóirat*, 1971, **77**, 353 (*Chem. Abs.*, 1971, **75**, 110 482).

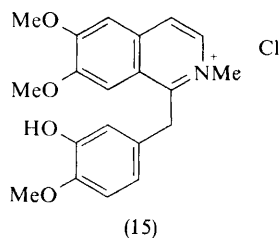
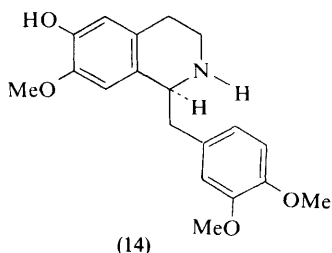
<sup>27</sup> S. Teitel, J. O'Brien, and A. Brossi, *J. Medicin. Chem.*, 1972, **15**, 845.

The functionalization of salsolidine through alkylation or acylation at the nitrogen atom has been described.<sup>28</sup>

A systematic study of the n.m.r. spectra of some simple tetrahydroisoquinolines has appeared.<sup>29</sup>

**Benzylisoquinolines.**—An extensive review of *Thalictrum* alkaloids has appeared. These include benzylisoquinolines, bisbenzylisoquinolines, isoquinolones, aporphines, aporphine-benzylisoquinoline dimers, phenanthrenes, protoberberines, protopines, pavines, and isopavines.<sup>30</sup> The alkaloids of the Lauraceae have also been summarized.<sup>31</sup>

New benzylisoquinoline alkaloids are (+)-*N*-norprotosinomenine (14), found in *Erythrina lithosperma* Blume (Leguminosae),<sup>32</sup> and *N*-methylpalaudinium chloride (15), isolated from *Thalictrum polygamum* Muhl. (Ranunculaceae).<sup>33</sup>



New sources for known alkaloids are: (+)-reticuline, *Litsea xylanica* (Lauraceae)<sup>34</sup> and *Hernandia jamaicensis* (Hernandiaceae) (see ref. 87); coclaurine, *Sarcopetalum harveyanum* Muell. (Menispermaceae);<sup>35</sup> (–)-armepavine, *Euonymus europaeus* (Celastraceae);<sup>36</sup> (+)-armepavine *N*-metho-salt, *Xanthoxylum inerme* Koidz. (*Fagara boninensis* Koidz.) (Rutaceae).<sup>37</sup>

The Bischler-Napieralski cyclization can be properly directed by means of bromination of ring A of the amide precursor,<sup>38</sup> and a biogenetically patterned

<sup>28</sup> A. L. Mndzhoyan, L. Sh. Pirdzhanov, and M. T. Bkhiyan, *Armenian. khim. Zhur.*, 1971, **24**, 995 (*Chem. Abs.*, 1972, **76**, 127 207).

<sup>29</sup> F. Schenker, R. A. Schmidt, T. Williams, and A. Brossi, *J. Heterocyclic Chem.*, 1971, **8**, 665.

<sup>30</sup> N. M. Mollov, H. B. Dutschewska, and V. St. Georgiev, 'Recent Developments in the Chemistry of Natural Products', ed. R. Bognár, V. Bruckner, and Cs. Szántay, Akadémiai Kiadó, Budapest, 1971, Vol. 4.

<sup>31</sup> O. R. Gottlieb, *Phytochemistry*, 1972, **11**, 1537.

<sup>32</sup> S. Ghosal, S. K. Majumdar, and A. Chakraborti, *Austral. J. Chem.*, 1971, **24**, 2733.

<sup>33</sup> M. Shamma and J. L. Moniot, *J. Pharm. Sci.*, 1972, **61**, 295.

<sup>34</sup> T. Kametani, Y. Satoh, K. Fukumoto, and B. R. Pai, *Indian J. Chem.*, 1971, **9**, 770.

<sup>35</sup> B. O. Sowemimo, J. L. Beal, R. W. Doskotch, and G. H. Svoboda, *Lloydia*, 1972, **35**, 90.

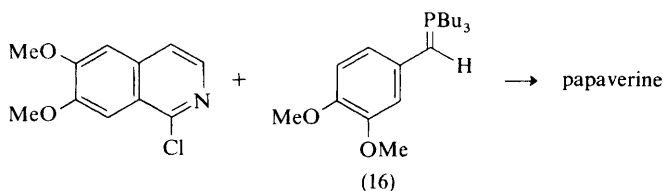
<sup>36</sup> D. W. Bishay, Z. Kowalewski, and J. D. Phillipson, *J. Pharm. Pharmacol.*, 1971, **23** (Suppl.), 233 (S).

<sup>37</sup> H. Ishii, H. Ohida, and J. Haginiwa, *J. Pharm. Soc. Japan*, 1972, **92**, 118.

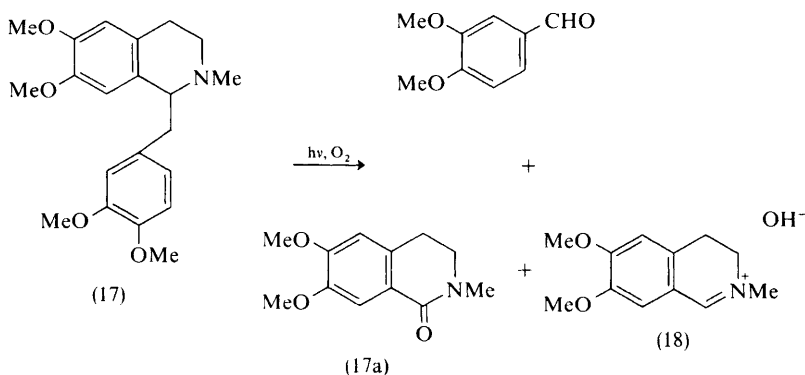
<sup>38</sup> T. Kametani, T. Nakano, K. Shishido, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 3350.

synthesis of (+)-laudanose from (–)-dopa has been described.<sup>39</sup> New syntheses of petaline are available.<sup>40,41</sup>

A new procedure for the elaboration of benzyloquinolines has been developed. Treatment of 6,7-dimethoxy-1-chloroisoquinoline with the Wittig reagent (16) prepared from veratryl chloride and tri-*n*-butylphosphine furnished, after work-up, a 74% yield of papaverine.<sup>42</sup>



A potentially useful oxidation of a tetrahydrobenzyloquinoline involves irradiation with u.v. light in the presence of oxygen; in this fashion laudanose (17) gave veratraldehyde, *N*-methylcorydaldine (17a), and the carbinolamine (18), which was isolated as its NaBH<sub>4</sub>-reduction product.<sup>43</sup>



Enzymic phenolic oxidation of reticuline has given a 4% yield of the corresponding tetrahydrobenzyloquinoline hydroxylated at the C- $\alpha$  site.<sup>44</sup> An interesting case of selective oxidation of a tetrahydrobenzyloquinoline involves ferricyanide oxidation of (19) to a mixture of diastereoisomeric dienones (20). Acid-catalysed rearrangement then gave the penta-oxygenated derivative (21).<sup>45</sup>

<sup>39</sup> S. Yamada, M. Konda, and T. Shioiri, *Tetrahedron Letters*, 1972, 2215.

<sup>40</sup> B. C. Uff, J. R. Kershaw, and S. R. Chhabra, *J. C. S. Perkin I*, 1972, 479.

<sup>41</sup> T. Kametani, T. Kobari, K. Fukumoto, and M. Fujihara, *J. Chem. Soc. (C)*, 1971, 1796.

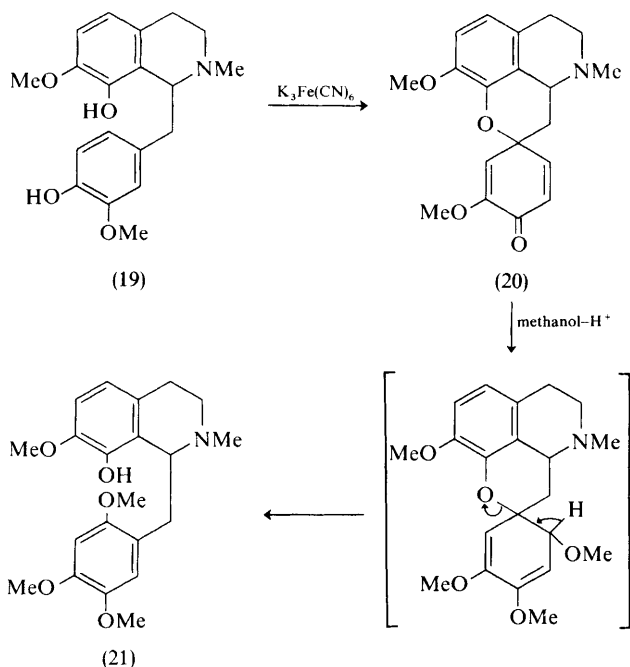
<sup>42</sup> E. C. Taylor and S. F. Martin, *J. Amer. Chem. Soc.*, 1972, **94**, 2874.

<sup>43</sup> I. R. C. Bick, J. B. Bremner, and J. Wiriachitra, *Tetrahedron Letters*, 1971, 4795.

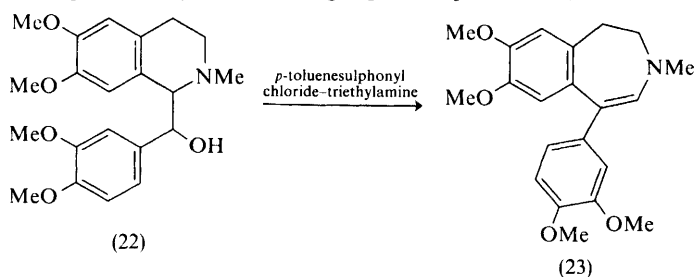
<sup>44</sup> T. Kametani, S. Takano, and T. Kobari, *J. Chem. Soc. (C)*, 1971, 1030.

<sup>45</sup> A. H. Jackson and G. W. Stewart, *Tetrahedron Letters*, 1971, 4941.





Rearrangement of the C- $\alpha$ -hydroxylated tetrahydrobenzylisoquinoline (22) apparently gave a 3% yield of the ring-expansion product (23).<sup>46</sup>



Additional studies of the acid-catalysed rearrangement of 1,2-dihydroisoquinolines have been carried out, and it has been shown that a C-1 allyl group migrates more readily than a benzylic function.<sup>47</sup>

The absolute configuration of (+)-isococlaurine has been proved by its transformation to (-)-*O*-methylnarmepavine.<sup>48</sup> The sign of rotation of a nortetrahydrobenzylisoquinoline at the sodium D line usually changes upon *N*-methyla-

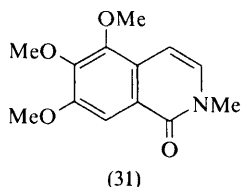
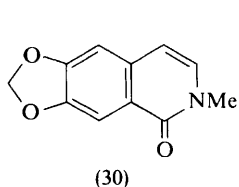
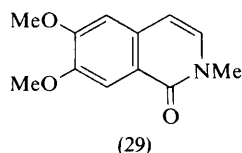
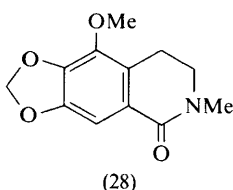
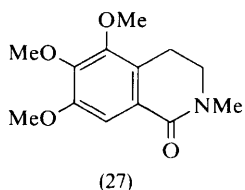
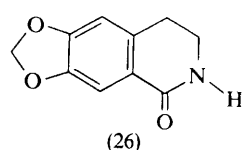
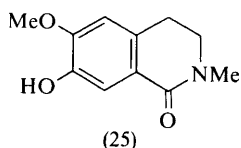
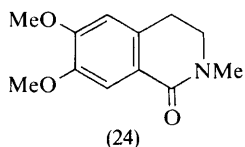
<sup>46</sup> T. Kametani, S. Hirata, S. Shibuya, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 1927.

<sup>47</sup> S. F. Dyke, R. G. Kinsman, J. Knabe, and H. D. Holtje, *Tetrahedron*, 1971, **27**, 6181.

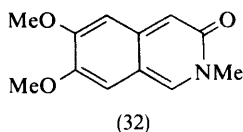
<sup>48</sup> D. S. Bhakuni, S. Satish, and M. M. Dhar, *Tetrahedron*, 1972, **28**, 1093.

tion to generate the tertiary amine. No upfield shift of the C-8 proton of a tetrahydrobenzylisoquinoline occurs when the C-7 substituent is hydroxyl.<sup>49</sup>

**Isoquinolones.**—Known isoquinolones obtained from natural sources are *N*-methylcorydaldine (24), thalifoline (25), noroxyhydrastinine (26), *N*-methylthalidaldine (27), thalflavine (28),<sup>50</sup> *N*-methyl-6,7-dimethoxyisoquinolone (29), doryanine (30), and thalactamine (31). A general preparation of 6,7-dioxygenated



3(2*H*)-isoquinolones such as (32) from 2-hydroxymethylarylacetic acid lactones has been described.<sup>51</sup>



**Pavines and Isopavines.**—(–)-Norargemonine and (–)-bisnorargemonine have been isolated from the roots of *Eschscholtzia californica*, *E. douglassi*, and *E. glauca* (Papaveraceae).<sup>52</sup>

Following the first recorded hydration of a 1,2-dihydroisoquinoline to a 4-hydroxy-1,2,3,4-tetrahydroisoquinoline, a synthesis of *O*-methylthalisopavine (33) has been achieved.<sup>53</sup>

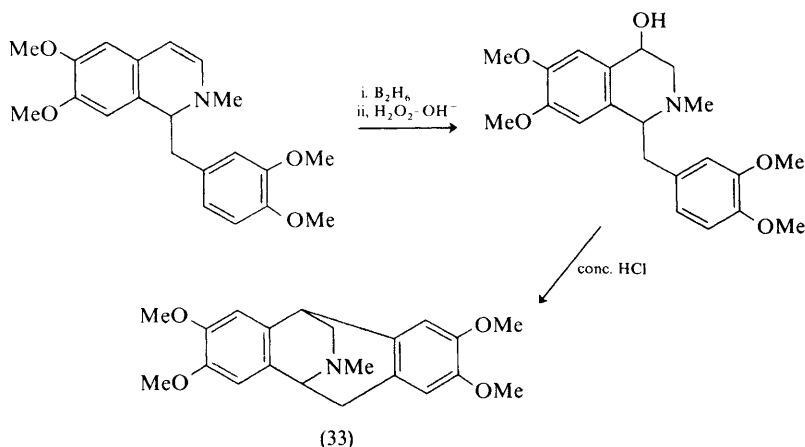
<sup>49</sup> V. St. Georgiev and N. M. Mollov, *Compt. rend. Acad. bulg. Sci.*, 1971, **24**, 1329.

<sup>50</sup> For a reference to thalflavine see N. M. Mollov, D. Sc. Thesis, Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia, 1972.

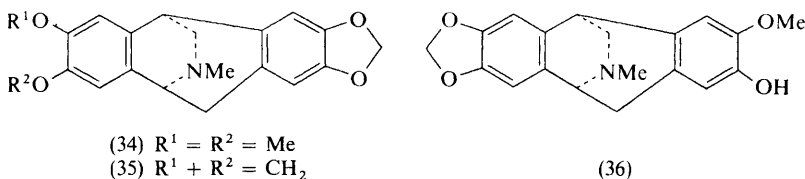
<sup>51</sup> N. J. McCorkindale and A. W. McCullough, *Tetrahedron*, 1971, **27**, 4653.

<sup>52</sup> J. Slavik and L. Slavikova, *Coll. Czech. Chem. Comm.*, 1971, **36**, 2067.

<sup>53</sup> S. F. Dyke and A. C. Ellis, *Tetrahedron*, 1971, **27**, 3803.



The isopavines reframine (34) and reframidine (35) have been synthesized by established routes.<sup>53</sup> The details of the conventional synthesis of the pavine bisnorargemonine and related isomers have been given, together with the appropriate n.m.r. spectral characteristics.<sup>54,55</sup>



The absolute configuration of the isopavine alkaloids has been established by means of the useful aromatic chirality method, and (–)-amurensine possesses the absolute configuration depicted in structure (36).<sup>56</sup> The fact that the pavines and isopavines have the identical absolute configuration points to the possibility of a common biogenetic precursor, such as a 4-hydroxytetrahydrobenzylisoquinoline, for these alkaloids.<sup>56</sup>

**Bisbenzylisoquinolines.**—A review of recent developments has been written.<sup>57</sup> New sources for known alkaloids are: thalmetine, *Thalictrum minus* (Ranunculaceae);<sup>58</sup> cycleanine, *Stephania glabra* (Menispermaceae);<sup>59</sup> dauricine and daurinolone, *Menispermum canadense* L. (Menispermaceae) (see ref. 90).

<sup>54</sup> C.-H. Chen, T. O. Soine, and K.-H. Lee, *J. Pharm. Sci.*, 1971, **60**, 1634.

<sup>55</sup> C.-H. Chen and T. O. Soine, *J. Pharm. Sci.*, 1972, **61**, 55.

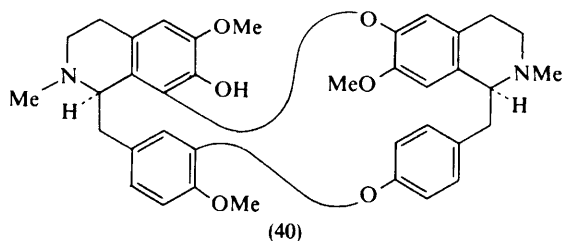
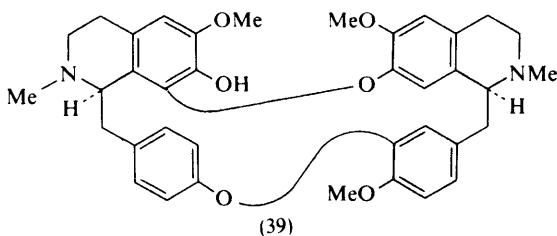
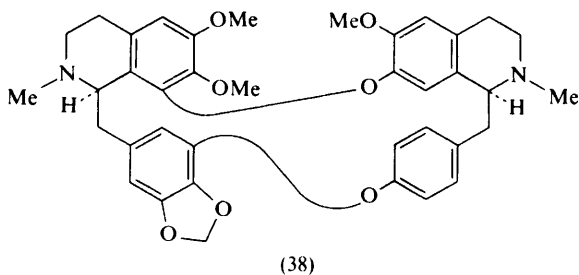
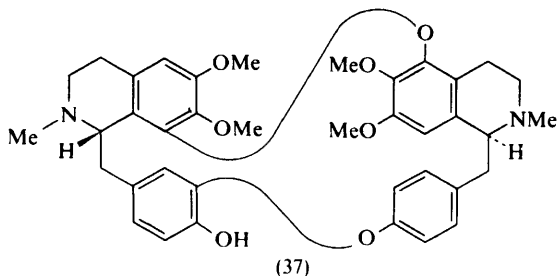
<sup>56</sup> M. Shamma, J. L. Moniot, W. K. Chan, and K. Nakanishi, *Tetrahedron Letters*, 1971, 3425.

<sup>57</sup> M. Curcumelli-Rodostamo, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1971, Vol. 13, p. 303.

<sup>58</sup> H. B. Allayarov, V. G. Khodzhaev, and Z. F. Ismailov, *Izvest. Akad. Nauk Turkmen. S.S.R., Ser. fiz.-tekh., khim. geol. Nauk*, 1971, **6**, 121.

<sup>59</sup> I. I. Fadeeva, A. D. Kuzovkov, and T. N. Il'inskaya, *Trudy Vses. nauch.-issled. Inst. lek. aromat. Rast.*, 1969, **15**, 334.

The structure of thalfoetidine has now been conclusively proved to be as in formula (37),<sup>60</sup> and the structure of the new alkaloid (+)-isotenuipine, isolated from a *Daphnandra* species, is as shown in (38).<sup>61</sup> Another new bisbenzylisoquinoline is (+)-thalrugosamine (39), obtained from *Thalictrum rugosum* Ait. (Ranunculaceae), and possessing weak *in vitro* activity against mycobacteria.<sup>62</sup> *N'*-Desmethyldauricine is also a new alkaloid (see ref. 90).



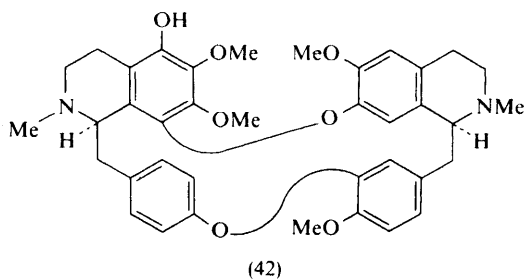
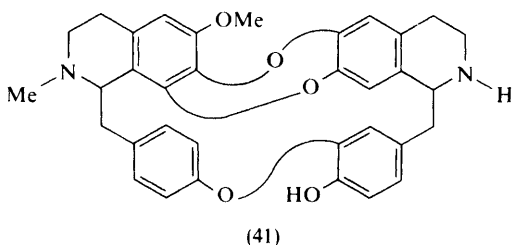
<sup>60</sup> V. St. Georgiev and N. M. Mollov, *Phytochemistry*, 1971, **10**, 2161.

<sup>61</sup> I. R. C. Bick and W. I. Taylor, *J. Chem. Soc. (C)*, 1971, 3779.

<sup>62</sup> L. A. Mitscher, W. Wu, and J. L. Beal, *Experientia*, 1972, **28**, 500.

A useful method for labelling the site of the diphenyl ether linkage has been developed in connection with the structural elucidation of the new bisbenzylisoquinoline (–)-belarine (40), isolated from the bark of *Berberis laurina* Billb. (Berberidaceae): the sodium cleavage is carried out in  $\text{ND}_3$ .<sup>63</sup> An alternative method for the determination of the position of the diphenyl ether linkage consists in treatment of the O-methylated dimer with 3% DCl in  $\text{D}_2\text{O}$  at  $120^\circ\text{C}$  in a sealed tube for several days. Under these conditions only protons *ortho* to methoxy-groups are exchanged for deuterium. Subsequent cleavage of the dimer by sodium in liquid ammonia and characterization of the resulting tetrahydrobenzylisoquinolines shows that an aromatic hydrogen *ortho* to a methoxy-group indicates the original site of attachment of the diaryl ether bond.<sup>64</sup>

The structure of the alkaloid micranthine, from *Daphnandra micrantha* Benth. (Monimiaceae), has been revised and is now represented by formula (41), which is related to trilobine,<sup>65</sup> whereas thalisopine is now believed to be as in (42).<sup>66</sup>



Full details of the synthesis of (+)-O-methylthalicberine are now available.<sup>67</sup>

As with the monomeric tetrahydrobenzylisoquinolines, u.v. irradiation of a non-phenolic bisbenzylisoquinoline in the presence of oxygen leads to oxidative

<sup>63</sup> M. R. Falco, J. X. de Vries, Z. Macchió, and I. R. C. Bick, *Chem. Comm.*, 1971, 1056.

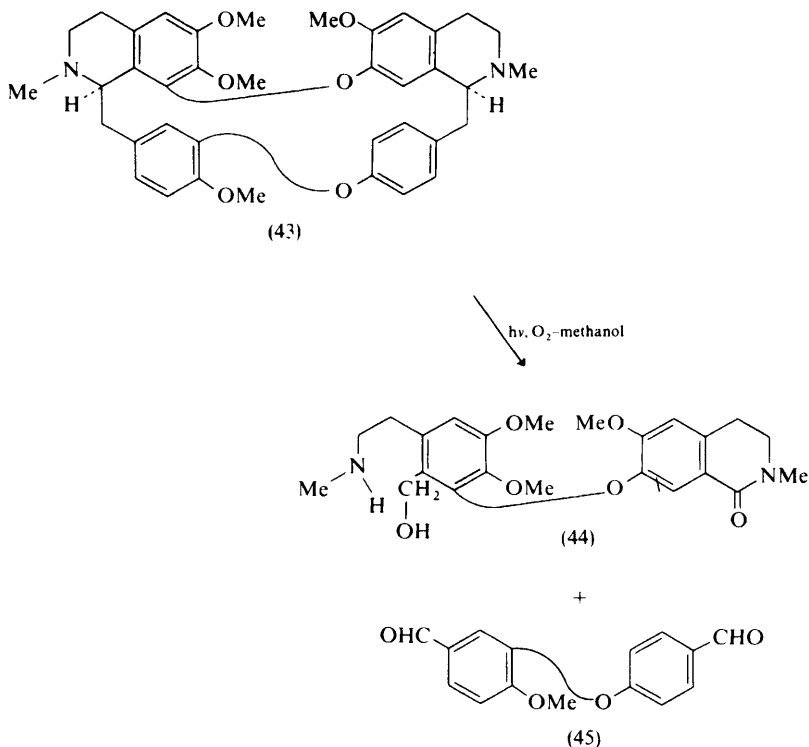
<sup>64</sup> Y. Inubushi, T. Kikuchi, T. Ibuka, and I. Saji, *Tetrahedron Letters*, 1972, 423.

<sup>65</sup> I. R. C. Bick, J. B. Bremner, H. M. Leow, and P. Wiriyachitra, *Tetrahedron Letters*, 1972, 33.

<sup>66</sup> Kh. G. Pulatova, S. Kh. Maekh, Z. F. Ismailov, and S. Yu. Yunusov, *Chem. Natural Compounds*, 1968, 4, 336; *Khim. prirod. Soedinenii*, 1968, 4, 394.

<sup>67</sup> E. Fujita, A. Sumi, and Y. Yoshimura, *Chem. and Pharm. Bull. (Japan)*, 1972, 20, 368.

cleavage at the benzylic centres. Isotetrandrone (43) gave as major products the lactam amino-alcohol (44) (30%) and the dialdehyde (45) (50%).<sup>43</sup>



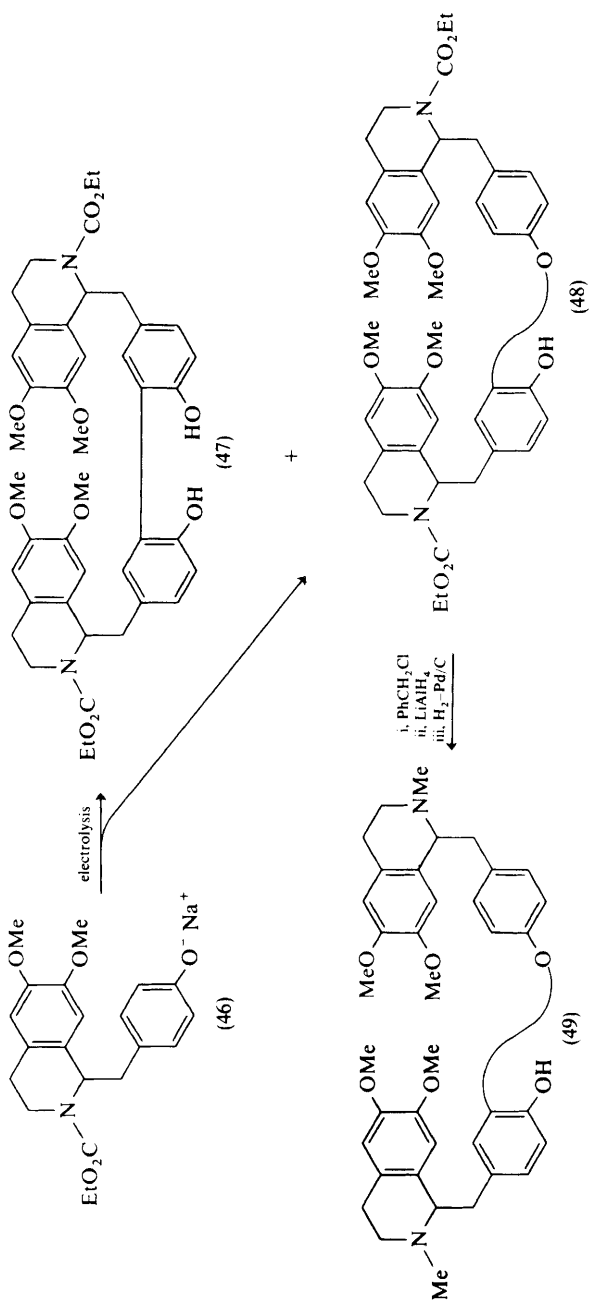
The electrolytic oxidation of the sodium salt of ( $\pm$ )-*N*-ethoxycarbonyl-*N*-norarmepavine (46) led to the dimeric mixtures (47) and (48). The latter mixture was converted into a mixture of dauricine analogues (49) *via* *O*-benzylation, reduction with lithium aluminium hydride, and hydrogenolytic debenzoylation. This transformation represents the first preparation of an analogue of a natural bisbenzylisoquinoline by oxidation of a phenolic monomeric benzylisoquinoline.<sup>68</sup> Detailed studies on the mass-spectral cleavage patterns of bisbenzylisoquinolines have appeared.<sup>69-71</sup>

<sup>68</sup> J. M. Bobbitt and R. C. Hallcher, *Chem. Comm.*, 1971, 543.

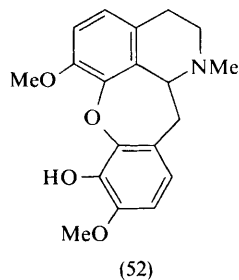
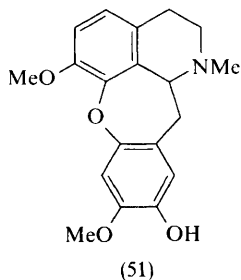
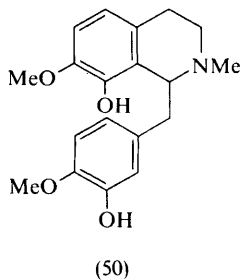
<sup>69</sup> J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, *J. C. S. Perkin I*, 1972, 592.

<sup>70</sup> J. Baldas, I. R. C. Bick, M. R. Falco, J. X. de Vries, and Q. N. Porter, *J. C. S. Perkin I*, 1972, 597.

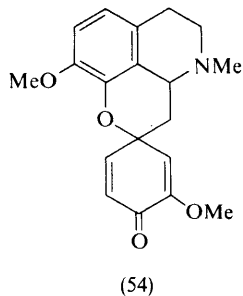
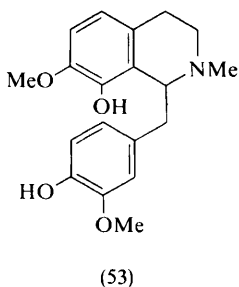
<sup>71</sup> J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, *J. C. S. Perkin I*, 1972, 599.



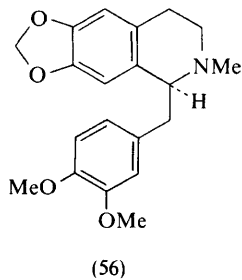
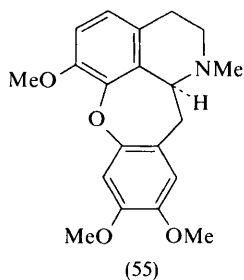
**Cularines.**—Ferricyanide oxidation of the tetrahydrobenzylisoquinoline (50) gave the cularine analogues (51) and (52) in 2.5% and 5% yield respectively. ( $\pm$ )-Cularine was then obtained from (51) by O-methylation.<sup>72</sup> Analogous



oxidation of the tetrahydrobenzylisoquinoline (53) led to formation of the two diastereoisomeric enediones (54) in 2.5% and 3.85% yield (see also the section on aporphines below).<sup>72</sup>



The absolute configuration of naturally occurring (+)-cularine (55) has been firmly established by its chemical correlation with (+)-romneine (56) of established absolute configuration.<sup>73</sup>

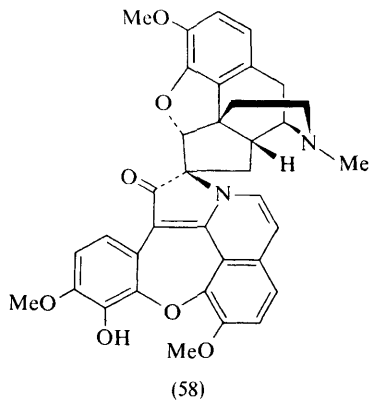
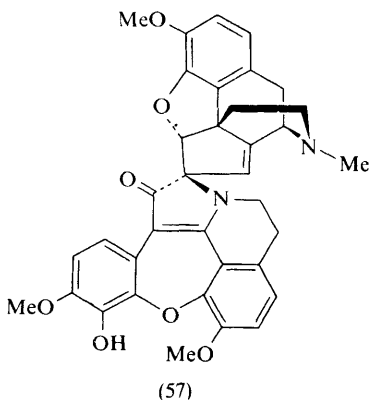


<sup>72</sup> T. Kametani, K. Fukumoto, and M. Fujihara, *Bio-org. Chem.*, 1971, **1**, 40.

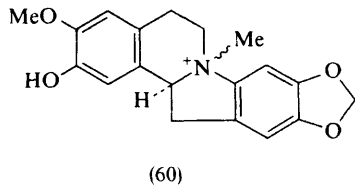
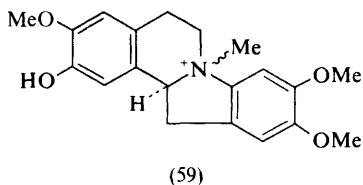
<sup>73</sup> J. Kunitomo, K. Morimoto, K. Yamamoto, Y. Yoshikawa, K. Azuma, and K. Fujitani, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2197.



**Cularine-Morphine Dimers.**—A full paper on cancentrine has appeared, which also incorporates a possible biogenetic pathway.<sup>74</sup> The structures of the related dehydrocancentrine-A (57) and -B (58) have been elucidated by a combination of physical and chemical methods.<sup>75</sup>



**Dibenzopyrrocolines.**—Several syntheses of the two alkaloids of this group, (–)-cryptaustoline (59) and (–)-cryptowoline (60), or of their analogues, are now available.<sup>76–79</sup> It is interesting to note, however, that although the absolute configuration is known for both alkaloids, the stereochemistry of the B/C ring fusion, though probably *cis*, has not been formally proved.



**Proaporphines.**—New sources for the known proaporphine stepharine are *Stephania glabra* (Menispermaceae),<sup>59</sup> *Sarcopetalum harveyanum* Muell. (Menispermaceae),<sup>35</sup> and *Annona purpurea* L. (Annonaceae) (see ref. 85). *A. purpurea* also produces glaziovine (62) (see ref. 85).

Several syntheses of glaziovine (62) and other simple proaporphines are now available. Photolysis of the 8-bromotetrahydrobenzylisoquinoline (61) gave a

<sup>74</sup> R. Rodrigo, R. H. F. Manske, D. B. MacLean, L. Baczynskyj, and J. K. Saunders, *Canad. J. Chem.*, 1972, **50**, 853.

<sup>75</sup> D. B. MacLean, L. Baczynskyj, R. Rodrigo, and R. H. F. Manske, *Canad. J. Chem.*, 1972, **50**, 852.

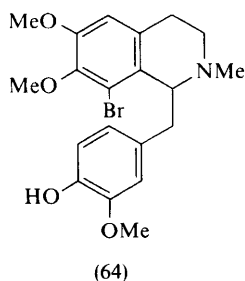
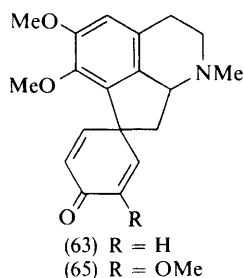
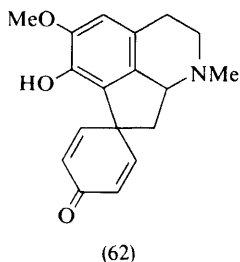
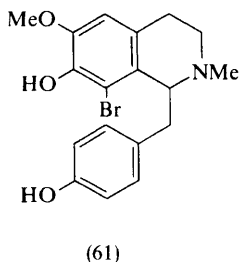
<sup>76</sup> R. Robinson and S. Sugawara, *J. Chem. Soc.*, 1932, 789.

<sup>77</sup> C. Schöpf and K. Thierfelder, *Annalen*, 1932, **497**, 22.

<sup>78</sup> T. Kametani and K. Ogasawara, *J. Chem Soc. (C)*, 1967, 2208.

<sup>79</sup> F. Bennington and R. D. Morin, *J. Org. Chem.*, 1967, **32**, 1050.

7% yield of ( $\pm$ )-glaziovine (62). Alternatively a 1% yield of (62) was obtained by ferricyanide oxidation of (61).<sup>80</sup> ( $\pm$ )-Pronuciferine (63) has been prepared by an analogous photochemical route.<sup>81,82</sup> Similarly, photolysis of (64) afforded a mixture of ( $\pm$ )-*O*-methylorientalinone and ( $\pm$ )-*O*-methyloiso-orientalinone (65).<sup>81</sup>



**Aporphines.**—Recently reported sources for aporphines are shown in Table 1.

**Table 1**

| Alkaloid       | Source  | Ref. |
|----------------|---|------|
| Glaucine       | <i>Glaucium flavum</i> (Papaveraceae)           | 83   |
|                | <i>Annona squamosa</i> L. (Annonaceae)          | 84   |
| Isocorydine    | <i>Glaucium flavum</i> (Papaveraceae)           | 83   |
|                | <i>Annona squamosa</i> L. (Annonaceae)          | 84   |
|                | <i>Annona purpurea</i> L. (Annonaceae)          | 85   |
|                | <i>Nandina domestica</i> Thunb. (Berberidaceae) | 86   |
|                | <i>Hernandia jamaicensis</i> (Hernandiaceae)    | 87   |
| Norisocorydine | <i>Annona squamosa</i> L. (Annonaceae)          | 84   |
| Corydine       | <i>Annona squamosa</i> L. (Annonaceae)          | 84   |
| Norcorydine    | <i>Annona squamosa</i> L. (Annonaceae)          | 84   |

<sup>80</sup> T. Kametani, S. Shibuya, T. Nakano, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 3818.

<sup>81</sup> T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem. Comm.*, 1971, 724.

<sup>82</sup> Z. Horii, Y. Nakashita, and C. Iwata, *Tetrahedron Letters*, 1971, 1167.

<sup>83</sup> L. D. Yakhontova, *Trudy Vses. nauch.-issled. Inst. lek. aromat. Rast.*, 1969, **15**, 348.

<sup>84</sup> D. S. Bhakuni, S. Tewari, and M. M. Dhar, *Phytochemistry*, 1972, **11**, 1819.

<sup>85</sup> P. E. Sonnet and M. Jacobson, *J. Pharm. Sci.*, 1971, **60**, 1254.

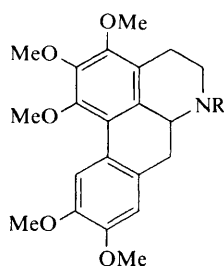
<sup>86</sup> J. Kunitomo, K. Morimoto, S. Tanaka, and S. Hayata, *J. Pharm. Soc. Japan*, 1972, **92**, 207.

<sup>87</sup> M. P. Cava and A. Venkateswarlu, *Tetrahedron*, 1971, **27**, 2639.

Table 1—cont.

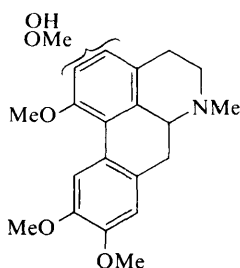
| Alkaloid                    | Source  | Ref. |
|-----------------------------|---|------|
| Boldine                     | <i>Litsea glutenosa</i> var. <i>glabraria</i> Hook. (Lauraceae) | 88   |
| Norboldine                  | <i>Litsea glutenosa</i> var. <i>glabraria</i> Hook. (Lauraceae) | 88   |
| Isoboldine                  | <i>Litsea xylanica</i> (Lauraceae)                              | 34   |
| Norisoboldine               | <i>Litsea xylanica</i> (Lauraceae)                              | 34   |
| Laurifoline                 | <i>Zanthoxylum ocumarensense</i> (Rutaceae)                     | 89   |
| O-Methyldomesticine         | <i>Nandina domestica</i> Thunb. (Berberidaceae)                 | 86   |
| Laurotetanine               | <i>Litsea glutenosa</i> var. <i>glabraria</i> Hook. (Lauraceae) | 88   |
|                             | <i>Hernandia jamaicensis</i> (Hernandiaceae)                    | 87   |
| N-Methyl-laurotetanine      | <i>Litsea glutenosa</i> var. <i>glabraria</i> Hook. (Lauraceae) | 88   |
| Actinodaphnine              | <i>Litsea glutenosa</i> var. <i>glabraria</i> Hook. (Lauraceae) | 88   |
| N-Methylactinodaphnine      | <i>Litsea glutenosa</i> var. <i>glabraria</i> Hook. (Lauraceae) | 88   |
| Magnoflorine                | <i>Menispermum canadense</i> L. (Menispermaceae)                | 90   |
| OO-Dimethylcorytuberine     | <i>Hernandia jamaicensis</i> (Hernandiaceae)                    | 87   |
| N-Methyl-lindcarpine        | <i>Menispermum canadense</i> L. (Menispermaceae)                | 90   |
| methiodide (a new alkaloid) |   |      |
| Xanthoplanine               | <i>Hernandia ovigera</i> L. (Hernandiaceae)                     | 91   |
| Anonaine                    | <i>Annona squamosa</i> L. (Annonaceae)                          | 84   |
| Roemerine                   | <i>Stephania glabra</i> (Roxb.) Miers (Menispermaceae)          | 92   |
|                             | <i>Annona squamosa</i> L. (Annonaceae)                          | 84   |
| Asimilobine                 | <i>Melodorum punctulatum</i> (Annonaceae)                       | 93   |
| Norushinsunine              | <i>Melodorum punctulatum</i> (Annonaceae)                       | 93   |
| Hernovine                   | <i>Hernandia ovigera</i> L. (Hernandiaceae)                     | 91   |
|                             | <i>Hernandia jamaicensis</i> (Hernandiaceae)                    | 87   |
| Hernangerine                | <i>Hernandia ovigera</i> L. (Hernandiaceae)                     | 91   |
| N-Methylhernangerine        | <i>Hernandia ovigera</i> L. (Hernandiaceae)                     | 91   |
| Nandigerine                 | <i>Hernandia jamaicensis</i>                                    | 87   |
| N-Methylnandigerine         | <i>Hernandia jamaicensis</i>                                    | 87   |
| Ovigerine                   | <i>Hernandia jamaicensis</i> (Hernandiaceae)                    | 87   |
| N-Methylovigerine           | <i>Hernandia jamaicensis</i> (Hernandiaceae)                    | 87   |

New aporphines are norpurpureine (66), purpureine (67), and O-demethyl-purpureine (68), obtained from *Annona purpurea* L. (Annonaceae),<sup>85</sup> and dehydroocopodine (69), isolated from *Ocotea macropoda*.<sup>87</sup>

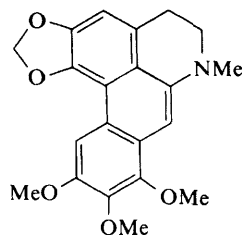


(66) R = H

(67) R = Me



(68)



(69)

<sup>88</sup> S. Tewari, D. S. Bhakuni, and M. M. Dhar, *Phytochemistry*, 1972, **11**, 1149.

<sup>89</sup> D. Della Casa de Marcano, M. Hasegawa, and A. Castaldi, *Phytochemistry*, 1972, **11**, 1531.

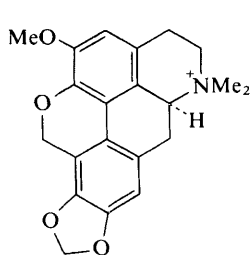
<sup>90</sup> R. W. Doskotch and J. E. Knapp, *Lloydia*, 1971, **34**, 292.

<sup>91</sup> H. Furukawa, F. Ueda, M. Ito, K. Ito, H. Ishii, and J. Haginiwa, *J. Pharm. Soc. Japan*, 1972, **92**, 150.

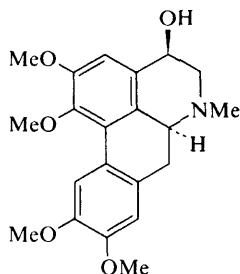
<sup>92</sup> N. V. Thu and P. Nuhn, *Pharmazie*, 1971, **26**, 504.

<sup>93</sup> I. R. C. Bick and N. W. Preston, *Austral. J. Chem.*, 1971, **24**, 2187.

An unusual new aporphine alkaloid is (+)-thalphenine (70), obtained from *Thalictrum polygamum* Muhl. (Ranunculaceae), whose structure and absolute configuration were confirmed by spectral evidence and by X-ray analysis of the iodide salt. Thalphenine is the first aporphine possessing a methylenedioxy-bridge.<sup>94</sup> Another new aporphine of interest is (+)-cataline (71), found in *Glaucium flavum* Cr. var. *vestitum* (Papaveraceae), and corresponding to 4-hydroxyglaucine.<sup>95</sup>

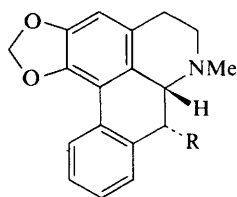


(70)



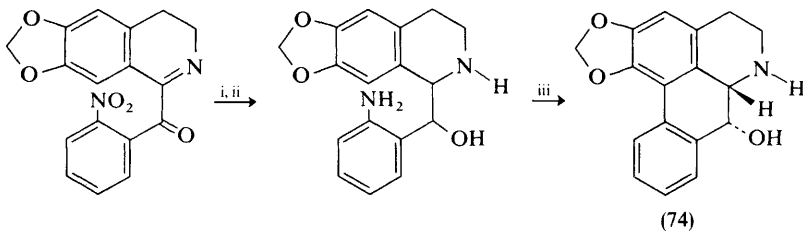
(71)

The absolute configuration of ushinsunine (72) has now been established through its catalytic hydrogenolysis to (–)-roemerine (73) of known chirality. (±)-Michelalbine [ $\equiv$ (±)-norushinsunine] (74) has been synthesized by the route shown in Scheme 2.<sup>96</sup>



(72) R = OH

(73) R = H



Reagents: i, Raney Ni; ii, NaBH<sub>4</sub>; iii, Pschorr.

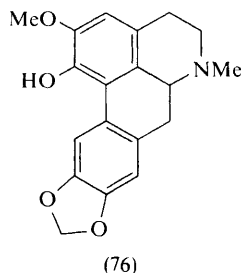
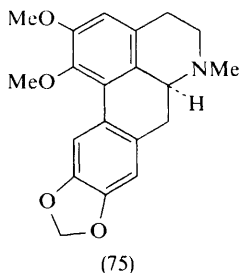
**Scheme 2**

<sup>94</sup> M. Shamma, J. L. Moniot, S. Y. Yao, and J. A. Stanko, *J. C. S. Chem. Comm.*, 1972, 408.

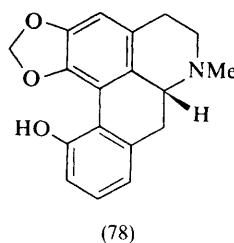
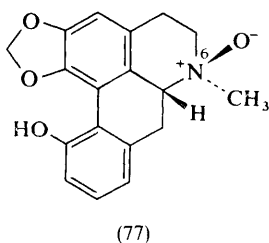
<sup>95</sup> I. Ribas, J. Sueiras, and L. Castedó, *Tetrahedron Letters*, 1972, 2033.

<sup>96</sup> J. Kunitomo, M. Miyoshi, E. Yage, T.-H. Yang, and C.-M. Chen, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1502.

Selective O-demethylation of (+)-O-methyldomesticine (75) with 36% HBr leads to a 37.7% yield of racemic domesticine (76), but O-demethylation with sodium thioethoxide in DMF affords a 71.4% yield of (+)-domesticine.<sup>86</sup>



The aporphine (–)-laurepukine (77) from *Laurelia novae-zelandiae* (Lauraceae) has conclusively been shown to correspond to one of the two N-oxides of (–)-pukateine (78), oxidation of the latter alkaloid with hydrogen peroxide furnishing laurepukine (77) and 6-epilaurepukine.<sup>97</sup>



Green oxidation products of the Pellagri reaction have apparently been obtained only with those aporphines possessing a phenolic group at C-1 or at C-11.<sup>98</sup> The N-demethylation of tertiary aporphines can be achieved in about 25% yield by treatment of the N-oxide with sulphur dioxide followed by hydrochloric acid.<sup>99</sup>

Aporphines synthesized by the Pschorr procedure include nuciferine,<sup>100</sup> sparsiflorine and apoglaziovine,<sup>101</sup> thalicmidine,<sup>102</sup> bracteoline,<sup>103</sup> apomorphine,<sup>104</sup> and 9,10-dihydroxyaporphine.<sup>105</sup> Treatment of the tetrahydrobenzyl-

<sup>97</sup> Ek. Weiss, K. Bernauer, and A. Girardet, *Helv. Chim. Acta*, 1971, **54**, 1342.

<sup>98</sup> V. Preininger, J. Hrbek, jun., Z. Samek, and F. Šantavý, *Acta Univ. Palacki. Olomuc., Fac. Med.*, 1969, **52**, 5; *Arch. Pharm.*, 1969, 392, 808 (*Chem. Abs.*, 1970, **72**, 55 710).

<sup>99</sup> M. P. Cava and M. Srinivasan, *J. Org. Chem.*, 1972, **37**, 330.

<sup>100</sup> J. Kunitomo, M. Miyoshi, M. Toyoko, and E. Yage, *J. Pharm. Soc. Japan*, 1971, **91**, 896.

<sup>101</sup> S. Narayanaswami, B. R. Pai, and C. S. Swaminathan, *Indian J. Chem.*, 1971, **9**, 509.

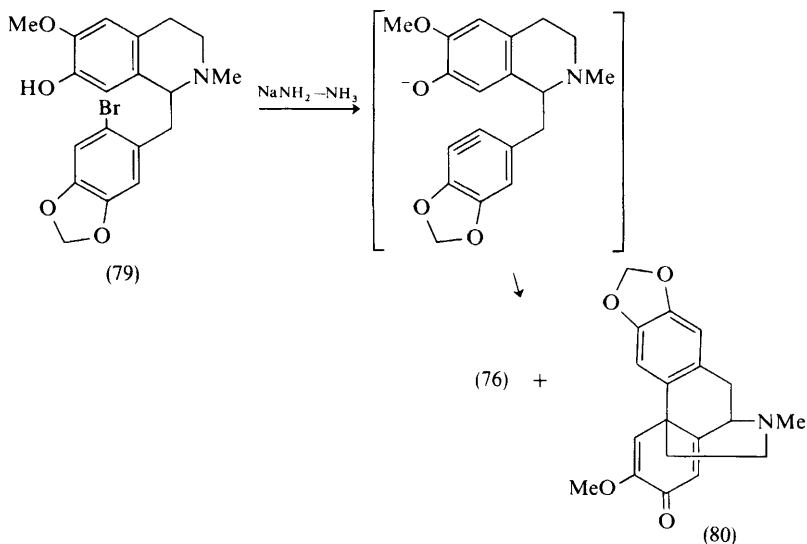
<sup>102</sup> R. W. Doskotch, J. D. Phillipson, A. B. Ray, and J. L. Beal, *J. Org. Chem.*, 1971, **36**, 2409.

<sup>103</sup> P. Kerekes, K. Délenk-Heydenreich, and S. Pfeifer, *Chem. Ber.*, 1972, **105**, 609.

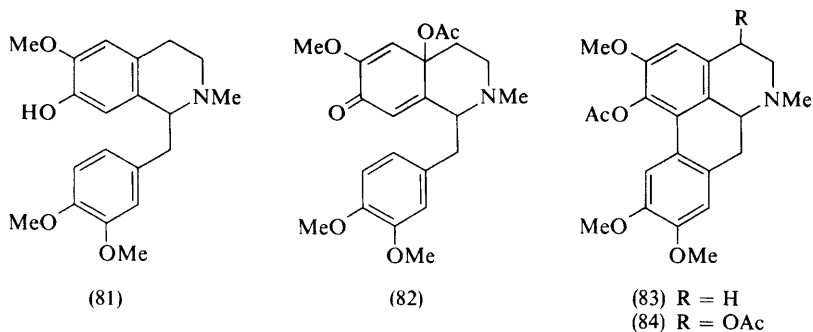
<sup>104</sup> J. L. Neumeyer, B. R. Neustadt, and K. K. Weinhardt, *J. Pharm. Sci.*, 1970, **59**, 1850.

<sup>105</sup> J. G. Cannon and M. A. Aleem, *J. Heterocyclic Chem.*, 1972, **8**, 305.

isoquinoline (79) with sodium amide in liquid ammonia gave domesticine (76) and amurine (80) in a reaction which involves a benzyne intermediate.<sup>106</sup>



A new route to aporphines involves treatment of codamine (81) with lead tetra-acetate to yield the *p*-quinol acetate (82). Further treatment with acetic anhydride and sulphuric acid generates *O*-acetylthaliporphine (83) (14%) and 4-acetoxy-*O*-acetylthaliporphine (84) (6%).<sup>107</sup>

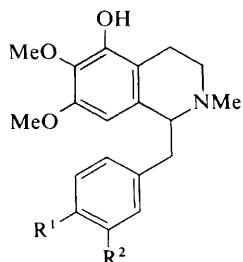


Phenolic oxidative coupling of the benzylisoquinoline (85) gave the aporphine (86) which led to the non-phenolic thalicsimidine upon *O*-methylation. Alternatively, oxidative coupling of (87) gave rise to a mixture of dienones (88) which on acid-catalysed dienone-phenol rearrangement furnished the aporphines (89) and

<sup>106</sup> T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Chem. Soc. (C)*, 1971, 2712.

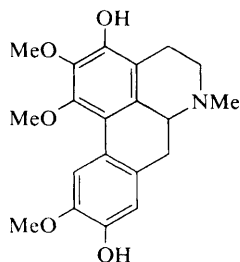
<sup>107</sup> O. Hoshino, T. Tadashi, and B. Umezawa, *Chem. Comm.*, 1971, 1533.

(90). The aporphine (90) also afforded thalicsimidine after treatment with diazomethane.<sup>108</sup>

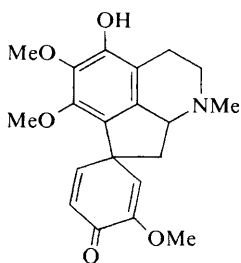


(85)  $R^1 = \text{OMe}, R^2 = \text{OH}$

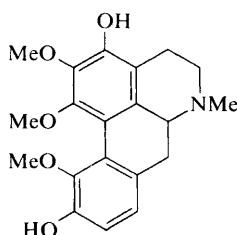
(87)  $R^1 = \text{OH}, R^2 = \text{OMe}$



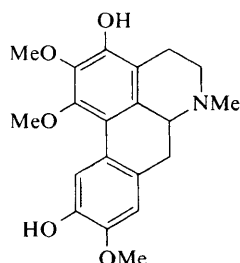
(86)



(88)

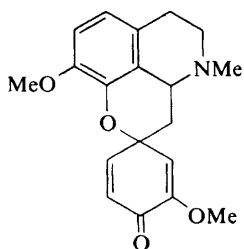


(89)

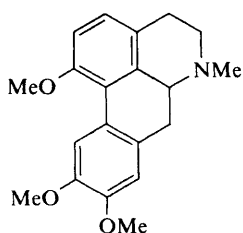


(90)

Acid-catalysed rearrangement of the quinol ether (91), itself obtained by phenolic oxidative coupling, unexpectedly gave an aporphine which on O-methylation afforded 1,9,10-trimethoxyaporphine (92).<sup>109</sup> Ferricyanide oxidation of reticuline supplied isoboldine and the morphinandienone pallidine.<sup>110</sup>



(91)



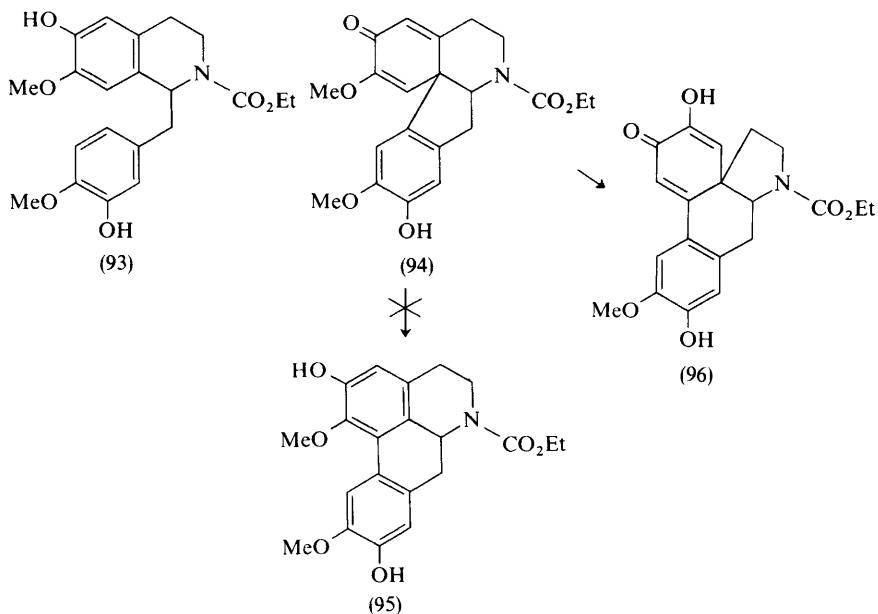
(92)

<sup>108</sup> T. Kametani, K. Takahashi, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 3617.

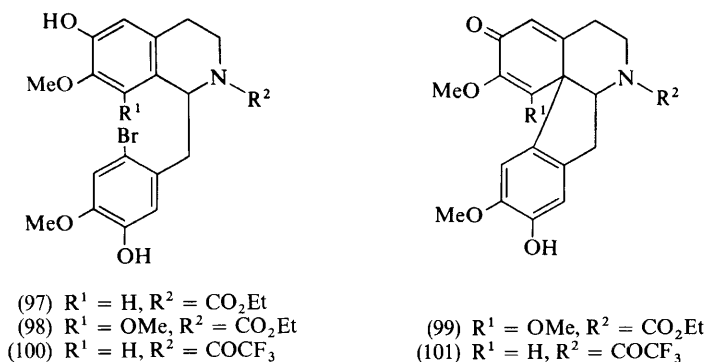
<sup>109</sup> T. Kametani, K. Fukumoto, and M. Fujihara, *J. C. S. Perkin I*, 1972, 394.

<sup>110</sup> T. Kametani, K. Fukumoto, K. Kigasawa, and K. Wakisaka, *Chem. and Pharm. Bull. (Japan)*, 1971, 19, 714.

In another study, ferricyanide oxidative coupling of the urethane (93) gave a 2% yield of the dienone (94) which in acid apparently did not rearrange to the aporphine (95), but instead furnished the dienone (96).<sup>111</sup>



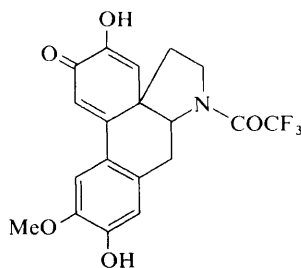
In attempts at photolytic cyclization, it was found that photolysis of the brominated tetrahydrobenzylisoquinoline (97) provided a 12% yield of the dienone (96). Similarly, photolysis of (98) and (100) gave (99) (8%) and (101)



<sup>111</sup> T. Kametani, R. Charubala, M. Ihara, M. Koizumi, K. Takahashi, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 3315.

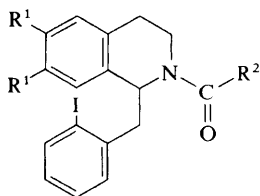


(4%), respectively. Acid-catalysed rearrangement of (101) again did not lead to an aporphine, but gave rise to a material formulated as the dienone (102).<sup>112</sup>

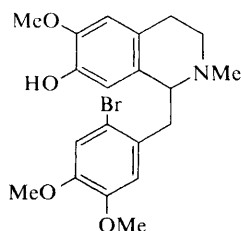


(102)

Three useful photolytic syntheses of aporphine are presently available. Photolysis of iodinated tetrahydrobenzylisoquinolines of type (103), where the basic nitrogen is protected as the *N*-acetyl, *N*-benzoyl, *N*-ethoxycarbonyl, or *N*-phenoxycarbonyl derivative, in the presence of sodium thiosulphate yields *N*-acylated aporphines in yields of 30–67%. *N*-Acetylated derivatives of nora-porphine and nornuciferine were prepared by such a route.<sup>113</sup> Secondly, photolysis of the bromophenol (104) in basic solution affords a 52% yield of the corresponding aporphine, thaliporphine.<sup>114</sup> The third efficient photochemical route



(103)



(104)

to the aporphines involves, as an example, irradiation of the bromourethane (105) in the presence of potassium *t*-butoxide. The *N*-ethoxycarbonyldehydro-aporphine (106) was thus obtained in a surprising 72% yield. This method is a distinct improvement over the original use of calcium carbonate in place of potassium *t*-butoxide as the acid scavenger.<sup>115</sup>

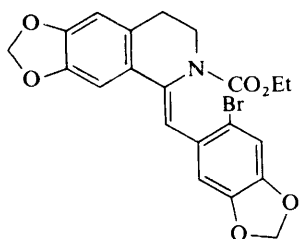
*N*-Methyl-lindcarpine and isocorydine have been obtained by the photo-Pschorr cyclization, whereas bulbocapnine was better prepared by the classical

<sup>112</sup> T. Kametani, T. Honda, M. Ihara, and K. Fukumoto, *Chem. and Ind.*, 1972, 119.

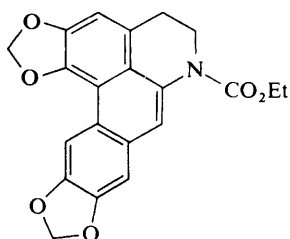
<sup>113</sup> S. M. Kupchan, J. L. Moniot, R. M. Kanojia, and J. B. O'Brien, *J. Org. Chem.*, 1971, 36, 2413.

<sup>114</sup> R. J. Spangler and D. C. Boop, *Tetrahedron Letters*, 1971, 4851.

<sup>115</sup> M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, 1970, 35, 175; M. P. Cava, personal communication.

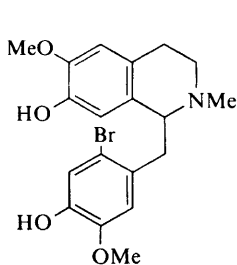


(105)

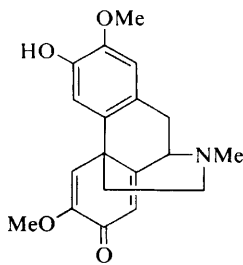


(106)

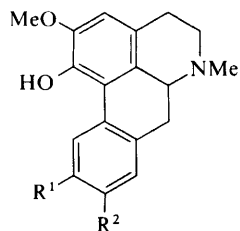
Pschorr cyclization.<sup>116</sup> Bracteoline has similarly been obtained by photo-Pschorr cyclization,<sup>117,118</sup> and so has *NO*-dimethylhernovine.<sup>119</sup> Photolysis of 6'-bromo-orientalinone (107) yielded flavinantine (108) (2%) and bracteoline (109) (10%). Amurine (80) (5%) and domesticine (76) (7%) were similarly obtained from the corresponding phenolic tetrahydrobenzylisoquinoline (110).<sup>120</sup> Isoboldine (111) has also been obtained *via* photolysis of brominated tetrahydrobenzylisoquinolines.<sup>118</sup>



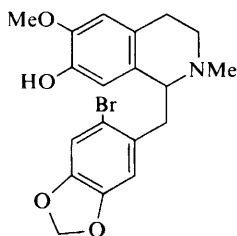
(107)



(108)



(109)  $R^1 = OH, R^2 = OMe$   
 (111)  $R^1 = OMe, R^2 = OH$



(110)

<sup>116</sup> T. Kametani, T. Sugahara, and K. Fukumoto, *Tetrahedron*, 1971, **27**, 5367.

<sup>117</sup> T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1513.

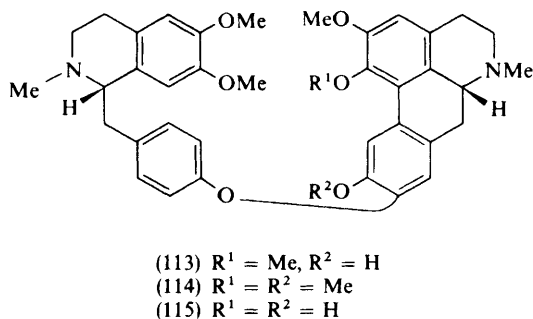
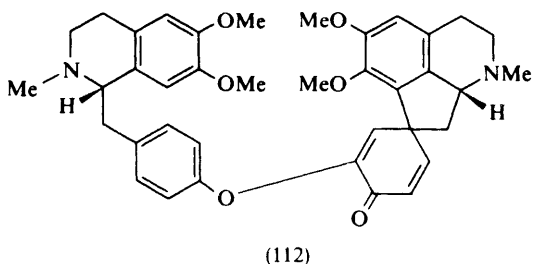
<sup>118</sup> T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Tetrahedron*, 1971, **27**, 5375.

<sup>119</sup> T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 1923.

<sup>120</sup> T. Kametani, S. Shibuya, O. Kusama, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 2446.

A gas-chromatographic study of aporphines and their trimethylsilyl derivatives has been carried out, and a relationship drawn between oxygenation pattern and retention time.<sup>121</sup> A fluoroscopic technique has been developed that measures submicrogram quantities of apomorphine in brain tissue.<sup>122</sup> The u.v. spectrum of a monophenolic aporphine shows a strong absorption between 315 and 330 nm in basic solution if the phenolic group is situated at C-9.<sup>123</sup> A tabulation of chemical shifts for the n.m.r. spectra of a variety of aporphine alkaloids has appeared.<sup>84</sup>

**Proaporphine-Benzyloisoquinoline Dimers.**—The first known proaporphine-benzyloisoquinoline dimer, pakistanamine (112), has been isolated from *Berberis baluchistanica* Ahrendt (Berberidaceae). Dienone-phenol rearrangement of pakistanamine (112) using dilute hydrochloric acid gave rise to the phenolic aporphine-benzyloisoquinoline dimer (113), and O-methylation of this product with diazomethane provided *OO*-dimethylpakistanine (114) of known structure and stereochemistry.<sup>124</sup>



**Aporphine-Benzyloisoquinoline Dimers.**—The known aporphine-benzyloisoquinoline dimer (+)-thalicarpine (116) has been found in *Hernandia ovigera* L.

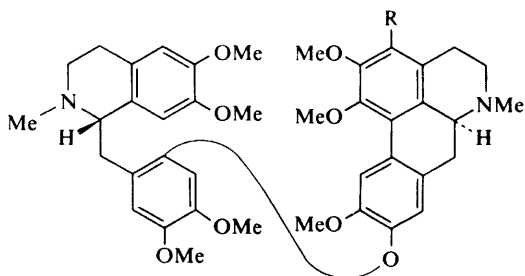
<sup>121</sup> K. Ito, H. Furukawa, N. Nakashima, and A. Hayakawa, *J. Pharm. Soc. Japan*, 1971, **91**, 841.

<sup>122</sup> W. K. van Tyle and A. M. Burkman, *J. Pharm. Sci.*, 1971, **60**, 1736.

<sup>123</sup> M. Shamma, S. Y. Yao, B. R. Pai, and R. Charubala, *J. Org. Chem.*, 1971, **36**, 3253.

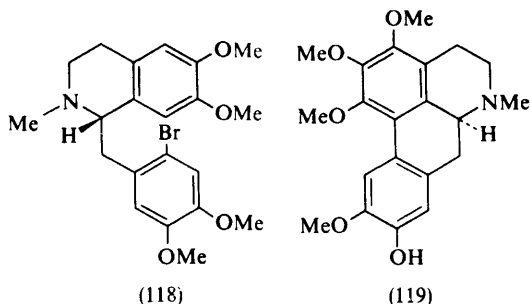
<sup>124</sup> M. Shamma, J. L. Moniot, S. Y. Yao, G. A. Miana, and M. Ikram, *J. Amer. Chem. Soc.*, 1972, **95**, 1381.

(Hernandiaceae)<sup>91</sup> and in *Thalictrum foetidum* (Ranunculaceae).<sup>125</sup> A total synthesis of (+)-adiantifoline (117) has been described involving, in the final step, the joining by the Ullmann condensation of the two components (+)-(*S*)-6'-bromolaudanosine (118) and (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (119), thus confirming the structure earlier assigned on the basis of spectroscopic evidence.<sup>102</sup>



(116) R = H

(117) R = OMe



(118)

(119)

An interesting new synthesis of (+)-thalicarpine (116) *via* synthetic hernandaine (120) has appeared and is described in Scheme 3.<sup>126</sup>

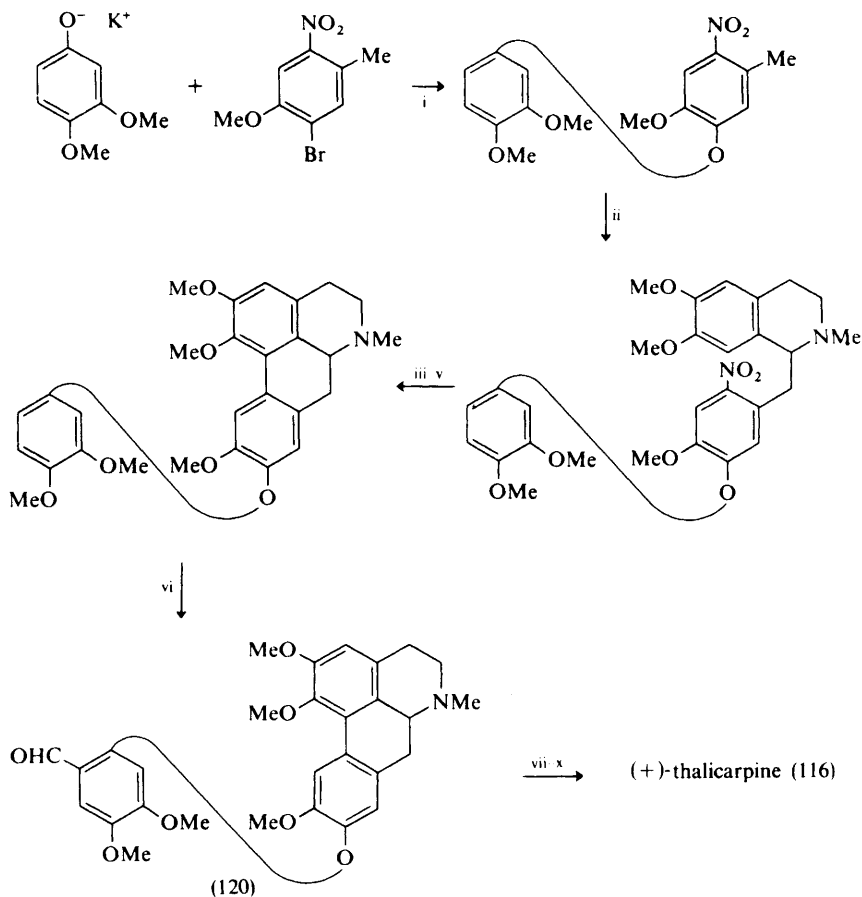
The structure originally given to the alkaloid fetidine,<sup>127</sup> isolated from *Thalictrum foetidum* (Ranunculaceae), has been revised, and has been shown to correspond to structure (121).<sup>125</sup> Fetidine is thus the first example of an aporphine-benzylisoquinoline dimer possessing a 2',3',4'-trioxygenated benzyl unit.<sup>125</sup>

The new aporphine-benzylisoquinoline dimer (+)-pakistanine (115), found in *Berberis baluchistanica* Ahrendt, represents another new class of dimeric isoquinoline alkaloid. Cleavage of *OO*-dimethylpakistanine (114) by sodium in liquid ammonia yielded (−)-2,10-dimethoxyaporphine and L-(+)-armepavine. The fact that pakistanine and pakistanamine are found in the same plant lends

<sup>125</sup> M. P. Cava and K. Wakisaka, *Tetrahedron Letters*, 1972, 2309.

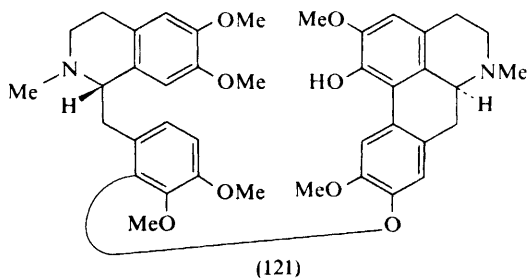
<sup>126</sup> S. M. Kupchan and A. J. Liepa, *Chem. Comm.*, 1971, 599.

<sup>127</sup> Z. F. Ismailov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1966, 2, 43.



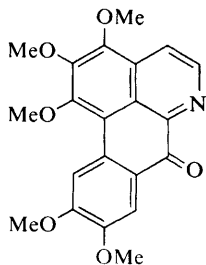
Reagents: i, MeCN,  $\Delta$ , 40 h; ii, 2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide-NaH; iii,  $H_2$ -Pd/C; iv, HONO; v,  $H_3PO_4$ ; vi,  $POCl_3$ -DMF; vii, resolution; viii, Reissert condensation; ix, Zn-HOAc; x, N-methylation.

Scheme 3

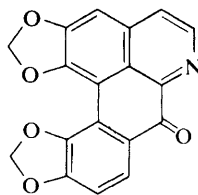


substantial support to the biogenetic scheme involving the sequence bisbenzylisoquinoline  $\rightarrow$  proaporphine-benzylisoquinoline dimer  $\rightarrow$  aporphine-benzylisoquinoline dimer in the pakistanamine-pakistanine series.<sup>124</sup>

**Oxoaporphines.**—Recent sources for known oxoaporphines are: liriodenine, *Melodorum punctulatum* (Annonaceae);<sup>93</sup> *O*-methylatheroline and cassamedine, *Annona purpurea* L. (Annonaceae);<sup>85</sup> and dicentrinone, *Ocotea macropoda* (Lauraceae).<sup>87</sup> New oxoaporphines are oxopurpureine (122), isolated from *Annona purpurea* L.,<sup>85</sup> and hernandonine (123) found in *Hernandia ovigera*<sup>128</sup> and *H. jamaicensis* (Hernandiaceae).<sup>87</sup>

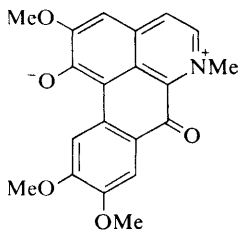


(122)

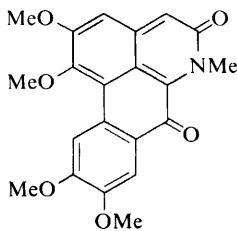


(123)

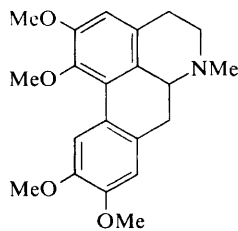
Two new oxoaporphines of interest are corunnine (124) and pontevedrine (125) which were found in *Glaucium flavum* Cr. var. *vestitum* (Papaveraceae) together with 1,2,9,10-tetramethoxyoxoaporphine. The two new alkaloids were characterized spectroscopically, and treatment of glaucine (126) with a large



(124)



(125)



(126)

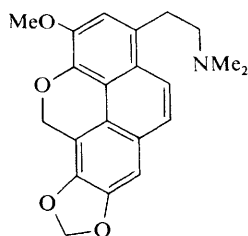
excess of chromium trioxide-pyridine complex gave in low yield a mixture of dehydroglaucine, corunnine, pontevedrine, and 1,2,9,10-tetramethoxyoxoaporphine. In an attempt to quaternize 1,2,9,10-tetramethoxyoxoaporphine with methyl iodide in commercial acetone, it was found that instead corunnine and pontevedrine were unexpectedly produced. Shorter reaction times led mostly to the desired methiodide salt, and subsequent refluxing of an acetone solution of this salt afforded corunnine as the only reaction product.<sup>129</sup>

<sup>128</sup> K. Ito and H. Furukawa, *Tetrahedron Letters*, 1970, 3023.

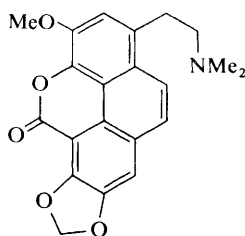
<sup>129</sup> I. Ribas, J. Sueiras, and L. Castedo, *Tetrahedron Letters*, 1971, 3093.

Oxoylophine corresponds to the known lanuginosine, which is 1,2-methylenedioxy-9-methoxyoxoaporphine.<sup>130-132</sup>

**Phenanthrenes.**—Two interesting new phenanthrene alkaloids are thaliglucine (127) and thaliglucinone (128). Thaliglucine was found independently in *Thalictrum rugosum* Ait.<sup>133</sup> and in *T. polygamum* Muhl. (Ranunculaceae).<sup>94</sup> The structure of thaliglucine was established by spectral means,<sup>94,133</sup> as well as by a direct chemical correlation with the aporphine (+)-thalphenine (70), the biogenetic precursor, which was found in *T. polygamum*.<sup>94</sup> The  $\delta$ -lactone thaliglucinone (128) was found in *T. rugosum* and was obtained as a light-yellow crystalline substance. Dichromate oxidation of thaliglucine (127) afforded thaliglucinone (128).<sup>133</sup>

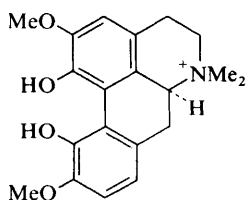


(127)

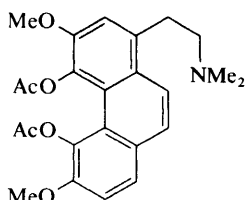


(128)

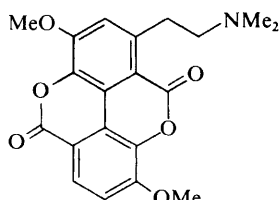
**Taspine.**—A biogenetically patterned conversion of the aporphine quaternary salt magnoflorine (129) into the optically inactive dilactonic alkaloid taspine has been carried out. Ozonization of diacetylmagnoflorine methine (130) followed by oxidation and lactonization afforded taspine (131).<sup>134</sup> This is the first synthesis of taspine to be reported.



(129)



(130)



(131)

<sup>130</sup> S. M. Kupchan, M. I. Suffness, and E. M. Gordon, *J. Org. Chem.*, 1970, **35**, 1682.

<sup>131</sup> S. K. Talapatra, A. Patra, and B. Talapatra, *Chem. and Ind.*, 1969, 1056.

<sup>132</sup> T. Govindachari, N. Viswanathan, S. Narayanaswami, and B. R. Pai, *Indian J. Chem.*, 1970, **8**, 475.

<sup>133</sup> N. M. Mollov, L. N. Thuan, and P. P. Panov, *Compt. rend. Acad. bulg. Sci.*, 1971, **24**, 1047.

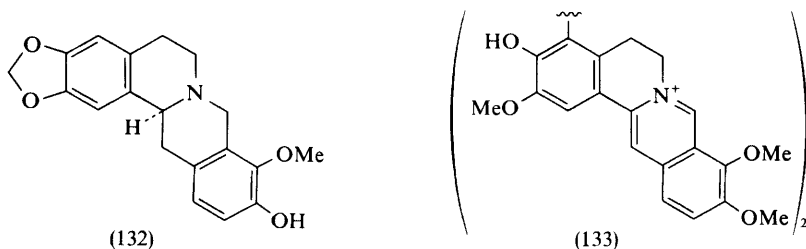
<sup>134</sup> M. Shamma and J. L. Moniot, *Chem. Comm.*, 1971, 1065.

**Protoberberines.**—New sources for known protoberberines are shown in Table 2.

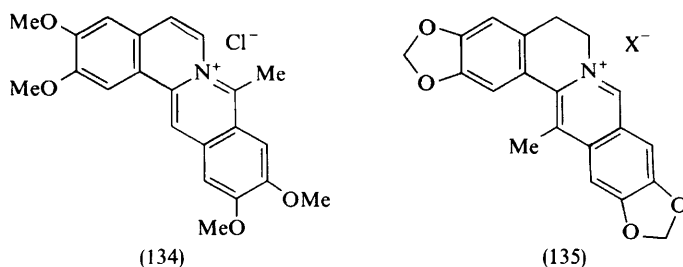
**Table 2**

| Alkaloid                | Source  | Ref.   |
|-------------------------|---|--------|
| Berberine               | <i>Berberis lycium</i> (Berberidaceae)  | 135    |
|                         | <i>Corydalis campulicarpa</i> Hayata (Fumariaceae)                                | 136    |
|                         | <i>Coptis japonica</i> Makino var. <i>dissecta</i> (Yatabe) Nakai (Ranunculaceae) | 137    |
|                         |   |        |
| Ophiocarpine            | <i>Corydalis campulicarpa</i> Hayata  | 136    |
| Tetrahydropalmatine     | <i>Stephania glabra</i> (Roxb.) Miers (Menispermaceae)                            | 59, 92 |
| N-Methylcanadine        | <i>Zanthoxylum ocumarensense</i> (Rutaceae)                                       | 89     |
| Dehydrocheilanthifoline | <i>Menispermum canadense</i> L. (Menispermaceae)                                  | 90     |

A new tetrahydroprotoberberine alkaloid is tetrahydrothalifendine (132), found in *Thalictrum fendleri* Engelm. ex Gray (Ranunculaceae).<sup>138</sup> The first known dimeric protoberberine alkaloid is bisjatrorrhizine (133), obtained from the root of *Jatrorrhiza palmata* (Lam.) Miers (Menispermaceae) and synthesized by oxidative dimerization of jatrorrhizine.<sup>139</sup>



A practical preparation of the compound called coralyne chloride (134) has appeared,<sup>140</sup> and a synthesis of 13-methyl-ψ-coptisine (135) has been reported. The latter salt may correspond to the alkaloid worenine.<sup>141</sup>



<sup>135</sup> R. K. Sehdev, K. L. Handa, and P. R. Rao, *Indian J. Chem.*, 1971, **9**, 503.

<sup>136</sup> S.-T. Lu, S.-J. Wang, and T.-S. Su, *J. Pharm. Soc. Japan*, 1971, **91**, 778.

<sup>137</sup> T. Furuya, K. Syōno, and A. Ikuta, *Phytochemistry*, 1972, **11**, 175.

<sup>138</sup> M. Shamma and Sr. M. A. Podczasy, *Tetrahedron*, 1971, **27**, 727.

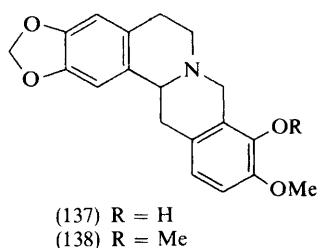
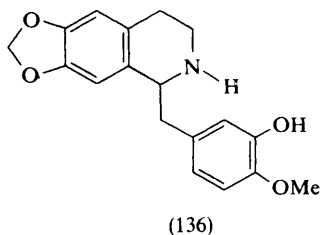
<sup>139</sup> M. L. Carvalhas, *J. C. S. Perkin I*, 1972, 327.

<sup>140</sup> K. Y. Zee-Cheng and C. C. Cheng, *J. Pharm. Sci.*, 1972, **61**, 969.

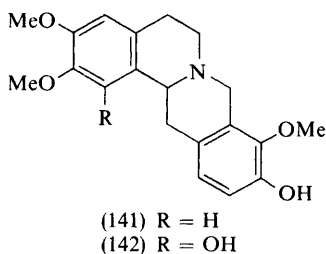
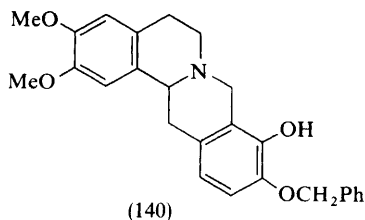
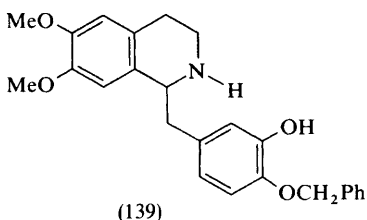
<sup>141</sup> T. R. Govindachari, K. Nagarajan, S. Natarajan, and B. R. Pai, *Indian J. Chem.*, 1971, **9**, 1313.



Condensation of the tetrahydrobenzylisoquinoline (136) with formaldehyde at pH 1.2 gave a 71% yield of nandinine (137) which was O-methylated to give



canadine (138).<sup>142</sup> Additionally, Mannich condensation of (139) with formaldehyde gave a 52% yield of the tetrahydroprotoberberine (140). O-Methylation followed by O-debenzylation then furnished ( $\pm$ )-kikemanine (141).<sup>143</sup> ( $\pm$ )-



Capaurimine (142) was prepared by a parallel route.<sup>144</sup> The structure of capaurimine was also confirmed by an X-ray analysis of capaurimine mono-*p*-bromobenzoate.<sup>145</sup>

Two somewhat similar syntheses of the unusually substituted ( $\pm$ )-caseadine (143) are now available, in which a bromine atom is used to direct the Bischler-Napieralski cyclization.<sup>146,147</sup>

<sup>142</sup> T. Kametani, K. Fukumoto, T. Terui, K. Yamaki, and E. Taguchi, *J. Chem. Soc. (C)*, 1971, 2709.

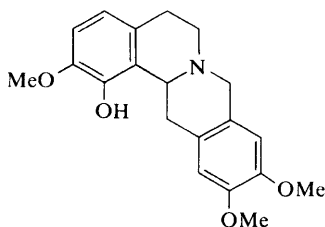
<sup>143</sup> T. Kametani, T. Honda, and M. Ihara, *J. Chem. Soc. (C)*, 1971, 3318.

<sup>144</sup> T. Kametani, T. Honda, and M. Ihara, *J. Chem. Soc. (C)*, 1971, 2396.

<sup>145</sup> T. Kametani, M. Ihara, T. Honda, H. Shimanouchi, and Y. Sasada, *J. Chem. Soc. (C)*, 1971, 2541.

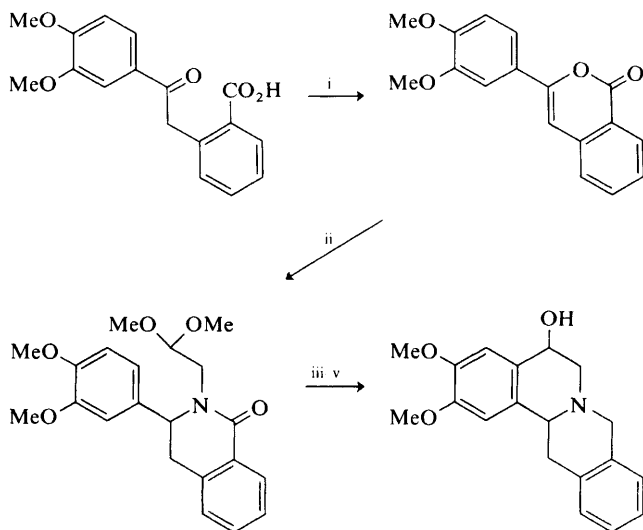
<sup>146</sup> T. Kametani, T. Nakano, K. Shishido, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 3350.

<sup>147</sup> H. Iida, H.-C. Hsu, H. Miyano, and T. Kikuchi, *J. Pharm. Soc. Japan*, 1971, **91**, 795.



(143)

A full paper has now appeared on the preparation of 5-hydroxylated tetrahydroprotoberberines utilizing the Pomeranz–Fritsch cyclization.<sup>148</sup> An alternative way of preparing 5-hydroxytetrahydroprotoberberines involves the use of isocoumarin intermediates (Scheme 4). The relative stereochemistry of these protoberberines may be deduced from spectral data.<sup>149</sup>



Reagents: i,  $\Delta$ ; ii, aminoacetaldehyde dimethyl acetal; iii,  $\text{LiAlH}_4$ ; iv,  $\text{NaBH}_4$ ; v, 6N-HCl.

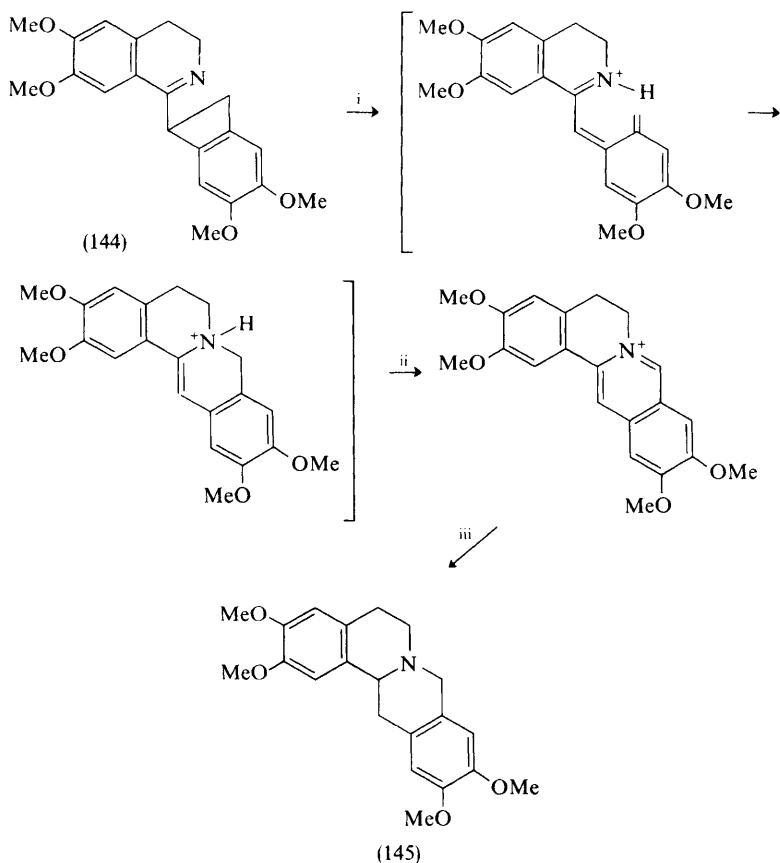
Scheme 4

( $\pm$ )-Xylopinine (145) has been synthesized from the 1-benzocyclobutenylisoquinoline (144) in good yield by thermolysis (Scheme 5) in what amounts to a new approach to protoberberines.<sup>150</sup>

<sup>148</sup> S. F. Dyke, D. W. Brown, M. Sainsbury, and G. Hardy, *Tetrahedron*, 1971, **27**, 3495.

<sup>149</sup> D. W. Brown, S. F. Dyke, M. Sainsbury, and G. Hardy, *J. Chem. Soc. (C)*, 1971, 3219.

<sup>150</sup> T. Kametani, K. Ogasawara, and T. Takahashi, *J. C. S. Chem. Comm.*, 1972, 675.



Reagents: i,  $N_2$ ,  $155^\circ C$ ; ii, work-up; iii,  $H_2-PtO_2$ .

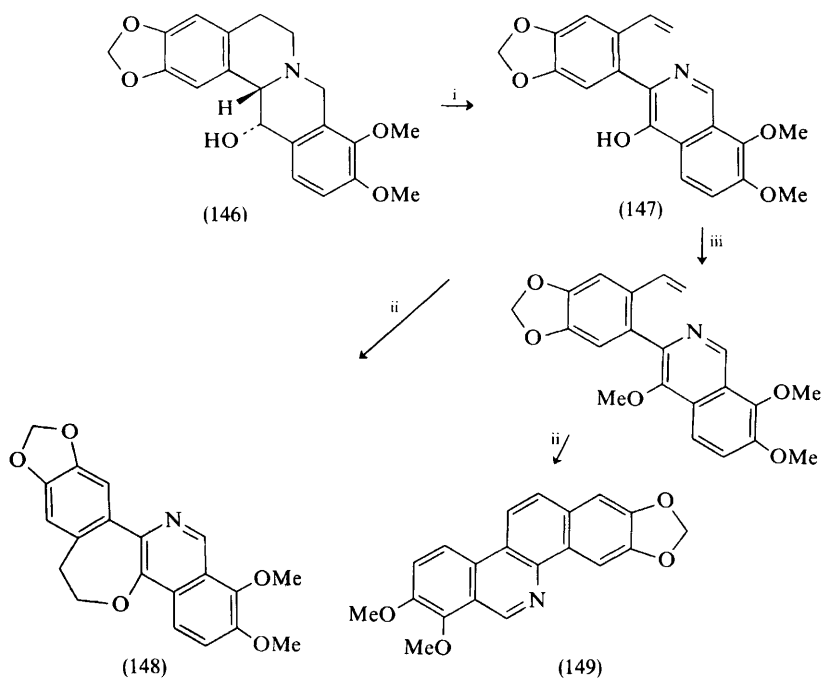
**Scheme 5**

Some interesting new reactions of protoberberines have been studied. Oppenauer oxidation of ( $\pm$ )-opiocarpine (146) was carried out to yield the isoquinoline (147) which on photolysis afforded the dihydrobenzoxepine (148). But photolysis of the methyl ether of (147) produced *N*-norchelerythrine (149) (Scheme 6). This is the second known conversion of a protoberberine into a benzophenanthridine.<sup>151</sup>

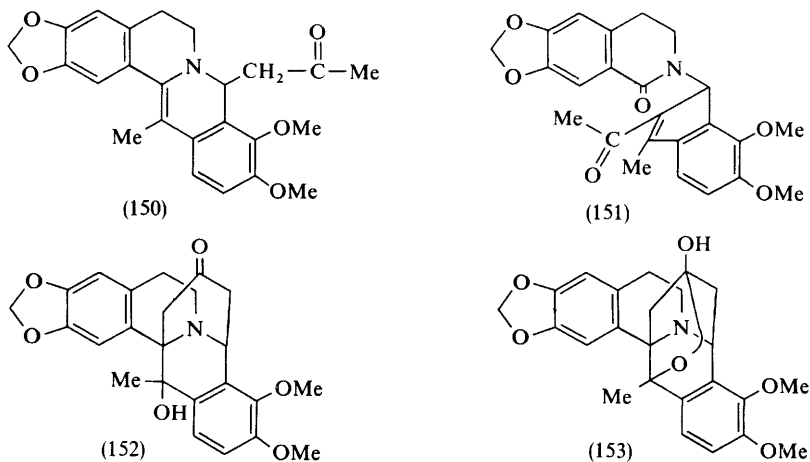
Permanganate oxidation of 13-methylacetoneberberine (150) gave a 30% yield of the lactam (151), a 1% yield of the expected product (152), and a 4% yield of the hemiketal (153).<sup>152</sup>

<sup>151</sup> V. Šmula, R. H. F. Manske, and R. Rodrigo, *Canad. J. Chem.*, 1972, **50**, 1544.

<sup>152</sup> S. Naruto, H. Nishimura, and H. Kaneko, *Tetrahedron Letters*, 1972, 2127.



Scheme 6



The mass spectra of scoulerine and coramine have been studied.<sup>153</sup>

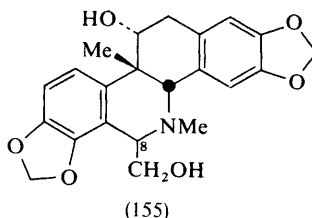
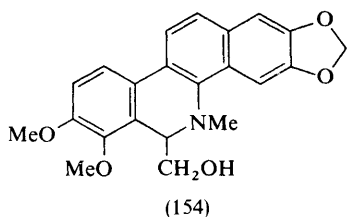
<sup>153</sup> M. S. Yunusov, Ya. V. Rashkes, M. U. Ibragimova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, 7, 380.

**Benzophenanthridines.**—Recently published sources for known benzophenanthridines are shown in Table 3.

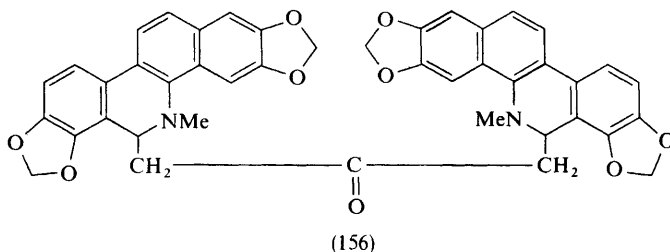
Table 3

| Alkaloid         | Source   | Ref. |
|------------------|--|------|
| Sanguinarine     | <i>Corydalis stricta</i> (Fumariaceae)   | 154  |
| Chelerythrine    | <i>Fagara chalybea</i> Engl. ( <i>Zanthoxylum chalybeum</i> Engl.)             | 155  |
|                  | <i>Zanthoxylum ocumarensis</i> (Rutaceae)                                      | 89   |
| Nitidine         | <i>F. chalybea</i> Engl.   | 155  |
|                  | <i>Zanthoxylum inerme</i> Koidz. ( <i>Fagara boninensis</i> Koidz.) (Rutaceae) | 37   |
| Avicine          | <i>Zanthoxylum inerme</i> Koidz. ( <i>Fagara boninensis</i> Koidz.)            | 37   |
| Corynoline       | <i>Corydalis incisa</i> Pers. (Fumariaceae)                                    | 156  |
| Acetylcorynoline |  |      |
| Isocorynoline    |  |      |
| Corynoloxine     |  |      |

Bocconoline, a minor alkaloid from *Bocconia cordata* Willd., (Papaveraceae) has structure (154). Corynolamine (155), isolated from *Corydalis incisa* Pers. (Fumariaceae) together with corynoline and corynoloxine, is structurally related to bocconoline since it too possesses a C-8 hydroxymethyl function.<sup>157</sup>



A new dimeric base is chelidimerine, which corresponds to *meso*-1,3-bis-(11-hydrosanguinarinyl)acetone (156). This compound may or may not be an artefact, and was found in an extract of *Chelidonium majus* L. (Papaveraceae).<sup>158</sup>



<sup>154</sup> Kh. Sh. Balsheva and B. K. Rostotskii, *Trudy Vses. nauch.-issled. Inst. lek. aromat. Rast.*, 1969, **15**, 376.

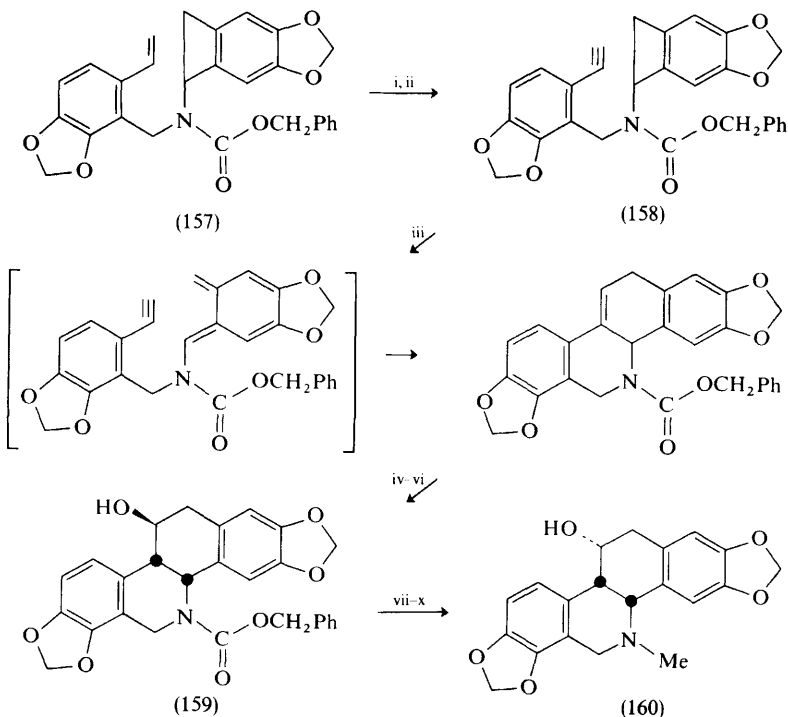
<sup>155</sup> F. Fish and P. G. Waterman, *Phytochemistry*, 1972, **11**, 1866.

<sup>156</sup> T. Kametani, M. Ihara, and T. Honda, *Phytochemistry*, 1971, **10**, 1881.

<sup>157</sup> H. Ishii, K. Hosoya, and N. Yakao, *Tetrahedron Letters*, 1971, 2429.

<sup>158</sup> M. Tin-Wa, H. K. Kim, H. H. S. Fong, N. R. Farnsworth, J. Trojáněk, and D. J. Abraham, *Lloydia*, 1972, **35**, 87.

An interesting first synthesis of ( $\pm$ )-chelidone (160) has appeared. Bromination and dehydrobromination of the urethane olefin (157) provided the acetylenic urethane (158). Pyrolysis and Brown hydroboration furnished two diastereoisomeric alcohols which were separated. The *cis* *b/c* fused isomer (159) upon oxidation and reduction, removal of the urethane group, and *N*-methylation gave ( $\pm$ )-chelidone, itself a natural product (Scheme 7).<sup>159</sup>



Reagents: i,  $\text{Br}_2$ ; ii, base; iii,  $\Delta$ ; iv,  $\text{B}_2\text{H}_6$ ; v,  $\text{H}_2\text{O}_2$ ; vi, separation of isomers; vii,  $\text{CrO}_3$ ; viii,  $\text{NaBH}_4$ ; ix,  $\text{H}_2$ -Pd/C; x, *N*-methylation.

**Scheme 7**

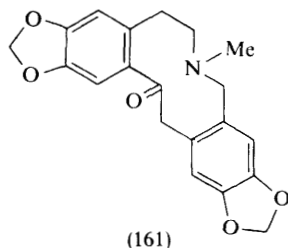
**Protopines.**—Recently published sources for protopines are shown in Table 4.

**Table 4**

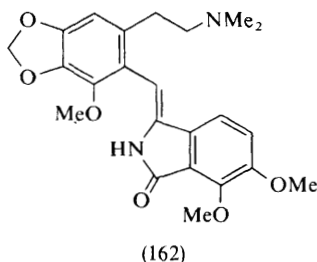
| Alkaloid                 | Source  | Ref. |
|--------------------------|---|------|
| Protopine                | <i>Corydalis incisa</i> (Pers.) (Fumariaceae) | 156  |
|                          | <i>Corydalis campulicarpa</i> Hayata          | 136  |
|                          | <i>Corydalis stricta</i>                      | 154  |
|                          | <i>Corydalis fimbriifera</i>                  | 154  |
| Corycavine               | <i>Corydalis incisa</i> (Pers.)               | 156  |
| $\alpha$ -Allocryptopine | <i>Corydalis campulicarpa</i> Hayata          | 136  |

<sup>159</sup> W. Oppolzer and K. Keller, *J. Amer. Chem. Soc.*, 1971, **93**, 3836.

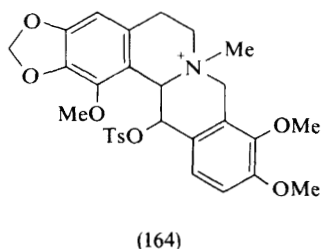
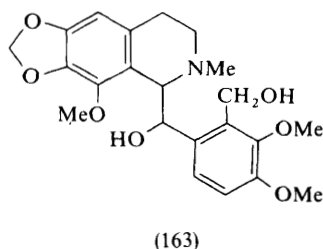
The structure of the new alkaloid pseudoprotopine (161), found in *Zanthoxylum conspersipunctatum* Merr. and Perry (Rutaceae), has been confirmed by synthesis.<sup>160</sup>



**Phthalideisoquinolines.**—The new alkaloid narceine imide (162) has been obtained from extracts of *Papaver somniferum* L. (Papaveraceae).<sup>161</sup> Gnoscopine [(±)-narcotine] has been synthesized by a classical route.<sup>162</sup>



Epimerization of phthalideisoquinolines at C-1 can be brought about by successive treatment with BrCN and mineral acid.<sup>163</sup> Alternatively, this transformation can be achieved by treatment with triphenylmethylammonium butylate.<sup>164</sup> Treatment of α-narcotinediol (163) with toluene-*p*-sulphonyl



<sup>160</sup> R. M. Sotelo and D. Giacomello, *Austral. J. Chem.*, 1972, **25**, 385.

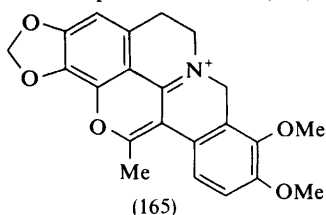
<sup>161</sup> J. Hodková, Z. Veselý, Z. Koblicová, J. Holubek, and J. Trojánek, *Lloydia*, 1972, **35**, 61.

<sup>162</sup> P. Kerekes and R. Bognár, *J. prakt. Chem.*, 1971, **313**, 923.

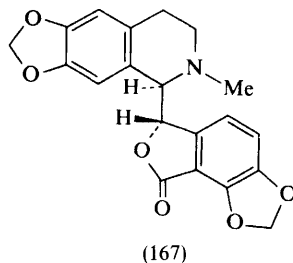
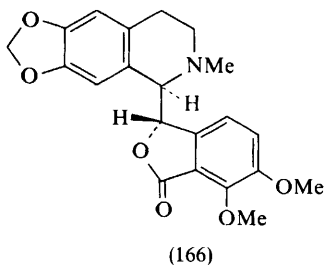
<sup>163</sup> G. Gaál, P. Kerekes, and B. Bognár, *J. prakt. Chem.*, 1971, **313**, 935.

<sup>164</sup> G. Gaál, P. Kerekes, P. Gorecki, and R. Bognár, *Pharmazie*, 1971, **26**, 431; *Magyar Kém. Folyóirat*, 1971, **77**, 286.

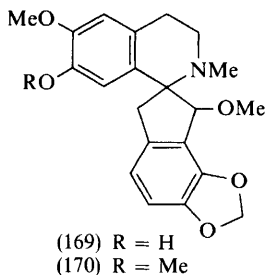
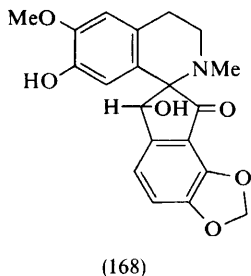
chloride yields the tetrahydroprotoberberine salt (164) which reacts with acetic anhydride and sodium iodide to produce the salt (165).<sup>165</sup>



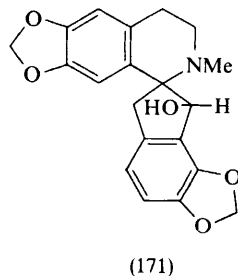
The two methoxy-groups of (–)-β-hydrastine (166) can be selectively hydrolysed using pyridine hydrochloride, whereas boron tribromide in methylene chloride also hydrolyses the methylenedioxy-function to yield a tetraphenol. This tetraphenol can be converted into (–)-bicuculline (167) using methylene chloride, DMSO, and sodium hydroxide. It follows that lactonic phthalideisoquinolines may be chemically interrelated, especially bearing in view the C-1 isomerization described in the previous paragraph and the known isomerization at C-9 brought about by hot alkali. The structure of (–)-bicuculline was confirmed by an X-ray analysis of its hydrobromide salt.<sup>166</sup>



**Spirobenzylisoquinolines.**—A review on the spirobenzylisoquinolines has appeared.<sup>167</sup> New alkaloids are fumarofine (168) found in *Fumaria officinalis* L.,<sup>168</sup>



(170) R = Me



<sup>165</sup> V. Šimanek and A. Klásek, *Tetrahedron Letters*, 1971, 4133.

<sup>166</sup> S. Teitel, J. O'Brien, and A. Brossi, *J. Org. Chem.*, 1972, 37, 1879.

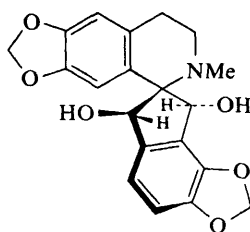
<sup>167</sup> M. Shamma in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1971, Vol. 13, p. 165.

<sup>168</sup> C. K. Yu, J. K. Saunders, D. B. MacLean, and R. H. F. Manske, *Canad. J. Chem.*, 1971, 49, 3020.

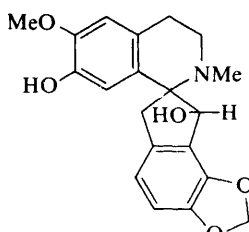


fumaritridine (169) from *F. rostellata*,<sup>169</sup> fumaritrine (170) from 'Herba Fumaria',<sup>169</sup> and corydaine (171) from *Corydalis paczoskii* (Fumariaceae).<sup>170</sup> The alkaloid corpaïne, found in *C. paczoskii*,<sup>170</sup> may possibly correspond to fumaritrine (173).

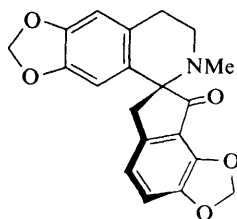
Two syntheses of ( $\pm$ )-ochrobirine (172) by the indanone approach have appeared.<sup>171,172</sup> Indanones have also been used in the preparation of fumaritrine (173) and fumariline (174),<sup>173</sup> as well as in the synthesis of other spirobenzylisoquinoline analogues.<sup>174</sup>



(172)



(173)



(174)

The conditions for the deep-seated protoberberine  $\rightarrow$  spirobenzylisoquinoline  $\rightarrow$  dibenzocyclopent[*b*]azepine rearrangement have been defined.<sup>175</sup> Base-catalysed rearrangement of the dihydroprotoberberine salt (175) yields the dibenzocyclopent[*b*]azepine (177) by the mechanism indicated in Scheme 8. The intermediacy of the aziridinium ion (176) should be noted. The rearrangement stops at the spirobenzylisoquinoline stage when a phenolic function is present in the bottom ring.<sup>175</sup>

<sup>169</sup> N. M. Mollov, H. G. Kiryakov, and G. I. Yakimov, *Phytochemistry*, 1972, **11**, 2331.

<sup>170</sup> D. A. Fesenko and M. E. Perel'son, *Khim. prirod. Soedinenii*, 1971, **7**, 166.

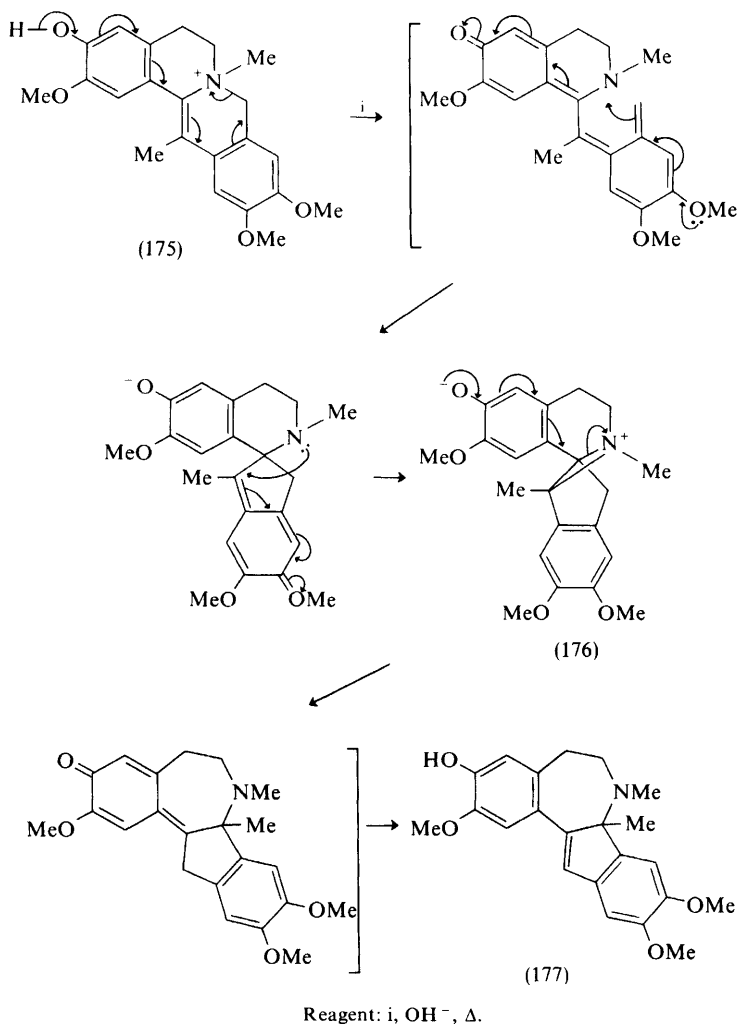
<sup>171</sup> T. Kametani, S. Hibino, and S. Takano, *Chem. Comm.*, 1971, 925; *J. C. S. Perkin I*, 1972, 391.

<sup>172</sup> B. Nalliah, Q. A. Ahmed, R. H. F. Manske, and R. Rodrigo, *Canad. J. Chem.*, 1972, **50**, 1819.

<sup>173</sup> S. Uyeo and T. Kishimoto, *J. Chem. Soc. (C)*, 1971, 1644.

<sup>174</sup> T. Kametani, S. Hibino, S. Shibuya, and S. Takano, *J. Heterocyclic Chem.*, 1972, **9**, 47.

<sup>175</sup> M. Shamma and J. F. Nugent, *Chem. Comm.*, 1971, 1642.



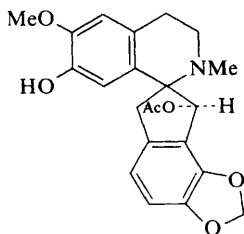
Scheme 8

Pyrolysis of fumarophycine (178) is reported to give the enamine (179),<sup>176</sup> although expression (179a) may be a more logical representation of the product since an aziridinium ion intermediate must again be involved.

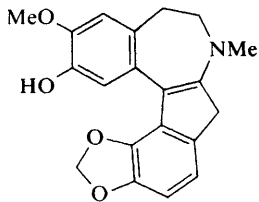
The absolute configurations of ochotensine, ochotensimine, ochrobirine, and lumaritine have been established using the aromatic chirality method. In each case, the methylenedioxy-group in ring D is below the mean plane of the molecule

<sup>176</sup> N. M. Mollov and G. I. Yakimov, *Compt. rend. Acad. bulg. Sci.*, 1971, **24**, 1325.

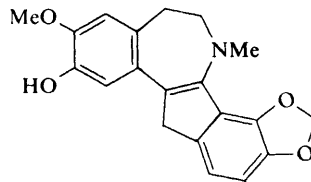
as it is usually drawn.<sup>177</sup> The mass spectra of a variety of spirobenzylisoquinolines have been discussed.<sup>178</sup>



(178)

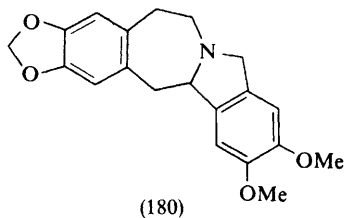


(179)



(179a)

**Rhoeadines and Papaverrubines.**—Schöpf's base (180) has been synthesized by a photochemical route.<sup>179</sup>



(180)

The interesting conversion of nornarceine (181) into the rhoeadine analogues (187) and (188) has been carried out as shown in Scheme 9. Nornarceine (181), obtained from (–)- $\alpha$ -narcotine, was heated in base to afford the enamine (182) which readily cyclized in dilute acetic acid to the  $\gamma$ -lactone (183). Upon standing, (183) was oxidized to the ketone (184). Lithium borohydride reduction led to the *cis*-acid (185). The derived *cis*-fused lactone (186) was then reduced to the hemiacetal (187) which upon O-methylation with trimethyl orthoformate gave (188). The structure of the methiodide salt of (187) was confirmed by an X-ray analysis.<sup>180</sup> The phthalideisoquinoline alkaloid (–)-bicuculline (189) was then converted into naturally occurring (+)-rhoeadine (190) by an analogous route. Since (–)-bicuculline was obtained from (–)- $\beta$ -hydrastrine, whose synthesis had been reported in 1950, this transformation represents the first total synthesis of a rhoeadine alkaloid.<sup>181</sup>

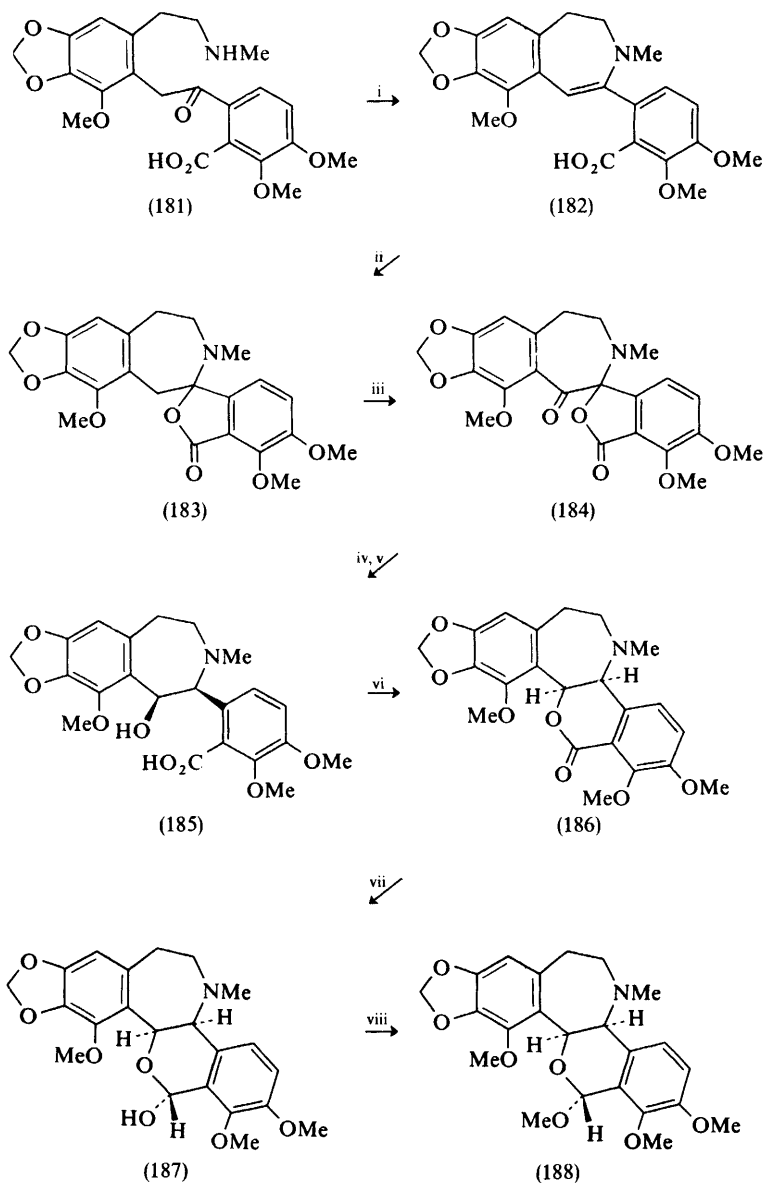
<sup>177</sup> M. Shamma, J. L. Moniot, R. H. F. Manske, W. K. Chan, and K. Nakanishi, *J. C. S. Chem. Comm.*, 1972, 310.

<sup>178</sup> C. K. Yu and D. B. MacLean, *Canad. J. Chem.*, 1971, **49**, 3025.

<sup>179</sup> H. O. Bernhard and V. Snieckus, *Tetrahedron Letters*, 1971, 4867.

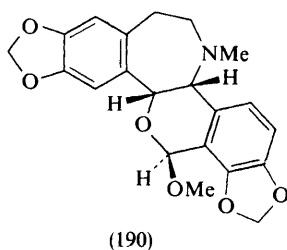
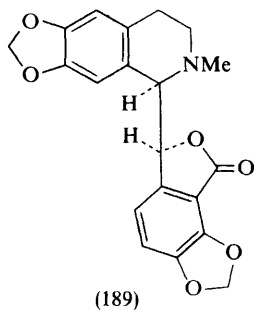
<sup>180</sup> A. Brossi, W. Klötzer, S. Teitel, and J. F. Blount, *J. Amer. Chem. Soc.*, 1971, **93**, 4321.

<sup>181</sup> W. Klötzer, S. Teitel, and A. Brossi, *Helv. Chim. Acta*, 1971, **54**, 2057; W. Klötzer, S. Teitel, J. F. Blount, and A. Brossi, *Monatsh.*, 1972, **103**, 435.

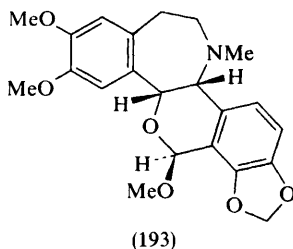
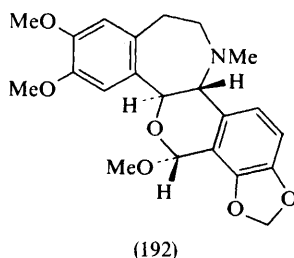
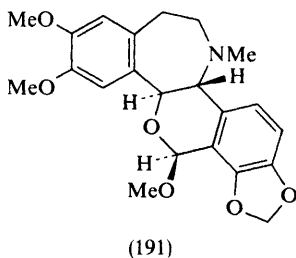


Reagents: i,  $\text{OH}^-$ ; ii,  $\text{HOAc-H}_2\text{O}$ ; iii, air; iv,  $\text{LiBH}_4$ ; v,  $\text{HOAc}$ ; vi, dil. acid; vii, sodium bis-(2-methoxyethoxy)aluminium hydride; viii, trimethyl orthoformate-methanol.

Scheme 9



The absolute configurations of all the rheadine and papaverrubine alkaloids have now been elucidated using the aromatic chirality method. For instance, (+)-glaudine is represented by structure (191), (+)-epiglaudine by (192), and (+)-oreodine by (193).<sup>182</sup>



**Morphines and Morphinandienones.**—Reviews on the alkaloids of the genus *Papaver*<sup>183</sup> and the family Papaveraceae<sup>184</sup> have appeared, and a recent detailed review of the morphine alkaloids is now available.<sup>185</sup> Reviews on the synthesis of morphinanandienone alkaloids have also been published.<sup>186,187</sup>

<sup>182</sup> M. Shamma, J. L. Moniot, W. K. Chan, and K. Nakanishi, *Tetrahedron Letters*, 1971, 4207.

<sup>183</sup> S. Pfeifer, *Pharmazie*, 1971, **26**, 328; S. Pfeifer and D. Thomas, *ibid*, 1972, **27**, 48.

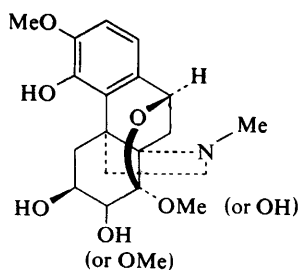
<sup>184</sup> F. Šantavý in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1970, Vol. 12, p. 333.

<sup>185</sup> K. W. Bentley in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1971, Vol. 13, p. 1.

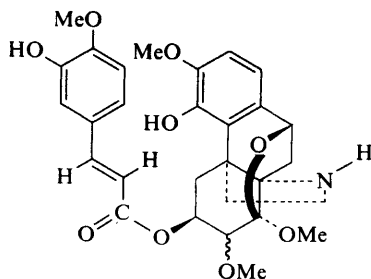
<sup>186</sup> T. Kametani and K. Fukumoto, *J. Heterocyclic Chem.*, 1971, **8**, 341.

<sup>187</sup> K. Fukumoto, *J. Jap. Chem.* 1971, Suppl. No. **94**, 133.

Sinoacutine and pallidine are found in *Corydalis incisa* (Pers.) (Fumariaceae),<sup>156</sup> and the former alkaloid is also found in *Stephania glabra* (Menispermaceae).<sup>59</sup> The chlorine-containing alkaloids acutumine and acutumidine are present in *Menispermum canadense* L. (Menispermaceae),<sup>90</sup> and a full paper describing the isolation and structural elucidation of these two bases has been published.<sup>188</sup> Hernandine (194)<sup>189</sup> and hernandifoline (195)<sup>190</sup> have been obtained from *Stephania hernandifolia*.

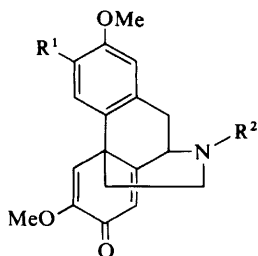
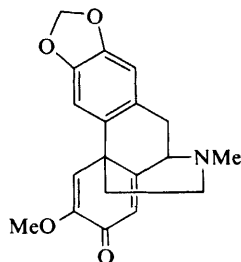


(194)



(195)

A new alkaloid from opium is 16-hydroxythebaine.<sup>191</sup> Salutaridine has been prepared in 1% yield by photolysis of 2'-bromoreticuline,<sup>192</sup> and the morphin-andienones (196)<sup>111</sup> and flavinanthine (197)<sup>117</sup> are available in low yields by a

(196)  $R^1 = \text{OMe}, R^2 = \text{CO}_2\text{Et}$ (197)  $R^1 = \text{OH}, R^2 = \text{Me}$ 

(198)

photo-Pschorr cyclization. Amurine (198) has been prepared by the benzyne reaction, as well as by phenolic oxidative coupling of the appropriate tetrahydrobenzylisoquinoline precursor.<sup>106</sup>

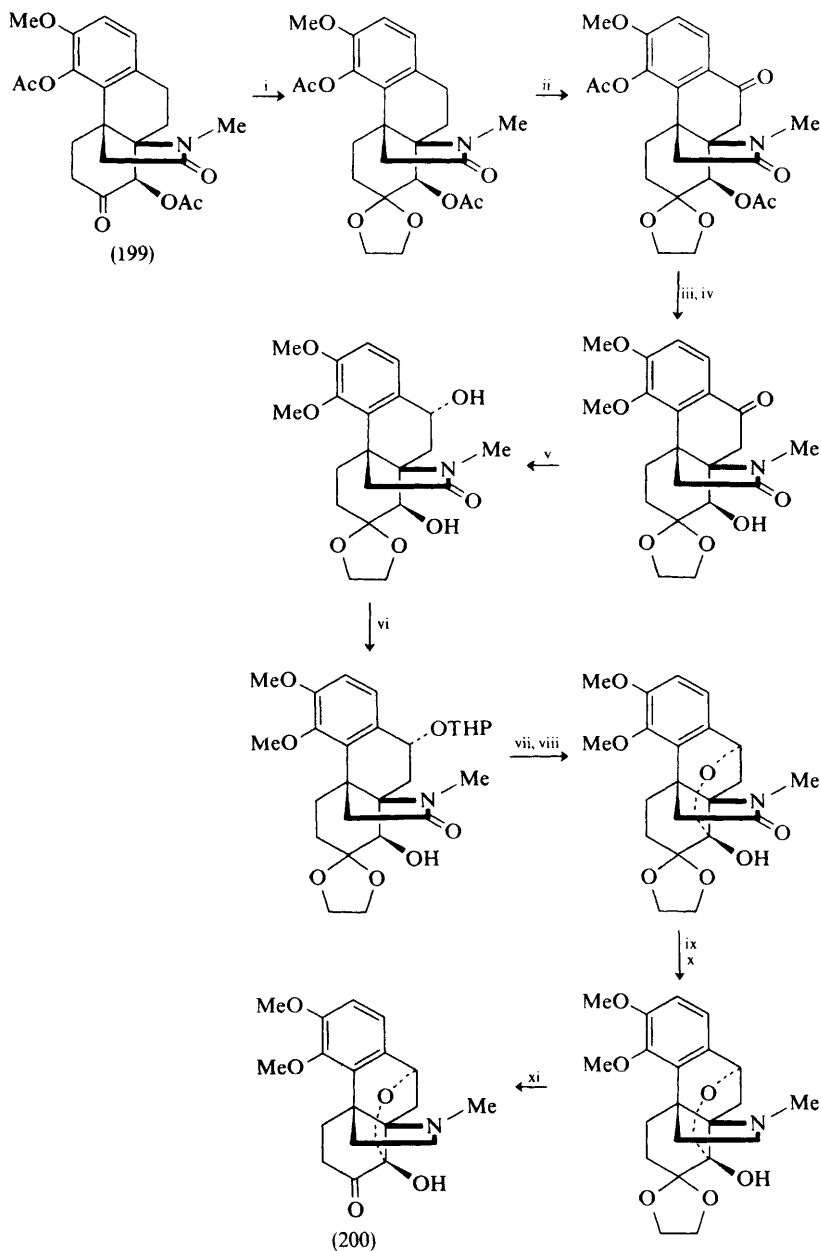
<sup>188</sup> M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, and K. Goto, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 770.

<sup>189</sup> T. N. Il'inskaya, D. A. Fesenko, I. I. Perel'son, and O. N. Tolkachev, *Khim. prirod. Soedinenii*, 1971, **7**, 480.

<sup>190</sup> D. A. Fesenko, I. I. Fadeeva, T. N. Il'inskaya, M. E. Perel'son, and O. N. Tolkachev, *Khim. prirod. Soedinenii*, 1971, **7**, 158.

<sup>191</sup> E. Brochmann-Hanssen, A. Y. Leung, and W. J. Richter, *J. Org. Chem.*, 1972, **37**, 1881.

<sup>192</sup> T. Kametani, H. Nemoto, T. Nakano, S. Shibuya, and K. Fukumoto, *Chem. and Ind.*, 1971, 788.

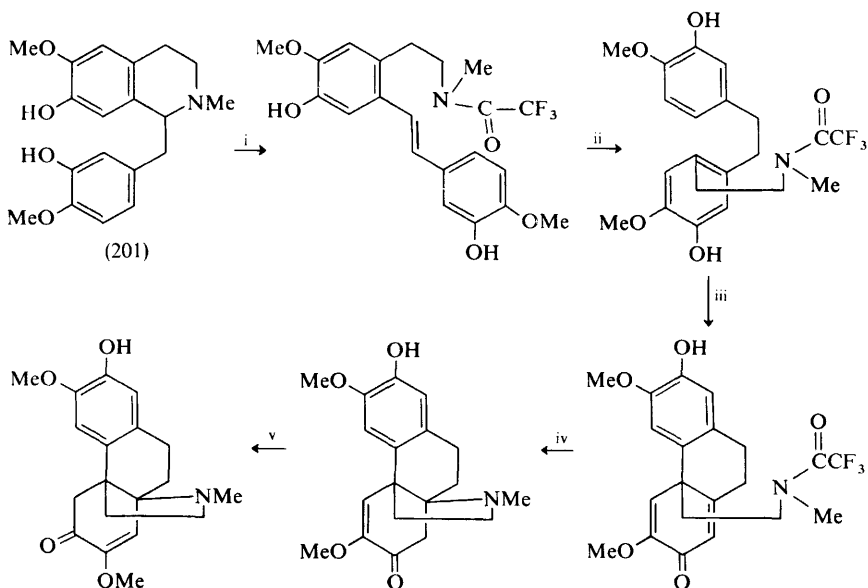


Reagents: i, ethylene glycol- $\text{H}^+$ ; ii,  $\text{CrO}_3\text{-HOAc}$ ; iii, base; iv,  $\text{CH}_2\text{N}_2$ ; v,  $\text{Al(OPr)}_3\text{-Pr}^i\text{OH-toluene}$ ; vi, dihydropyran; vii, bipyridine-chromium oxide; viii, aq.  $\text{HOAc}$ ; ix,  $\text{Et}_3\text{O}^+ \text{BF}_4^-$ ; x,  $\text{NaBH}_4$ ; xi,  $\text{H}_3\text{O}^+$ .

Scheme 10

The complete details of the total synthesis of the hasubanan base ( $\pm$ )-cepharamine have been revealed,<sup>193</sup> and this work has been followed by a total synthesis of ( $\pm$ )-metaphanine (200) starting with the known keto-lactam (199) (Scheme 10).<sup>194</sup>

A new approach to the hasubanan ring system has been developed, starting with reticuline (201) (Scheme 11),<sup>195</sup> and the sequence has been extended to the construction of ( $\pm$ )-cepharamine (202).<sup>196</sup>



Reagents: i, trifluoroacetic anhydride; ii,  $H_2$ -Pt; iii,  $VOCl_3$ ; iv, aq.  $K_2CO_3$ ; v,  $MeOH-HCl$ .

Scheme 11

Acid treatment of 7-hydroxydihydrocodeinone dimethyl acetal gave sino-meninone (203).<sup>197</sup>



<sup>193</sup> Y. Inubushi, M. Kitano, and T. Ibuka, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1820.

<sup>194</sup> T. Ibuka, K. Tanaka, and Y. Inubushi, *Tetrahedron Letters*, 1972, 1393.

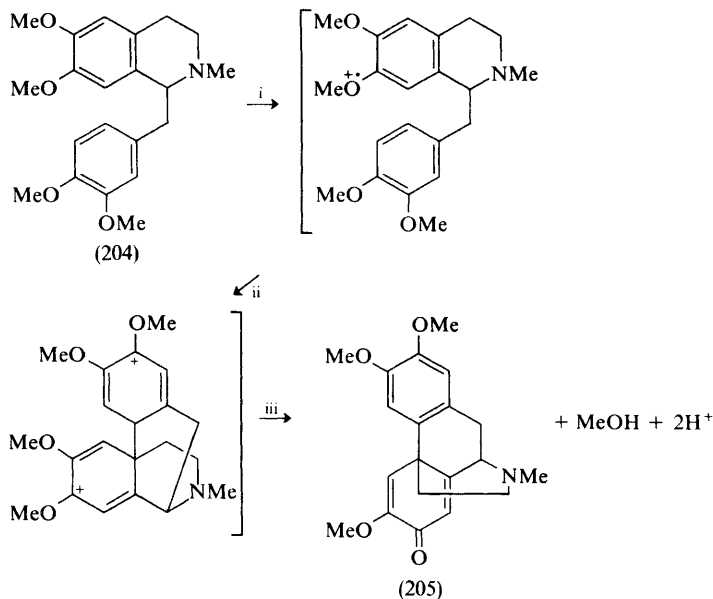
<sup>195</sup> T. Kametani, T. Kobari, and K. Fukumoto, *J. C. S. Chem. Comm.*, 1972, 288.

<sup>196</sup> T. Kametani, H. Nemoto, T. Kobari, K. Shishido, and K. Fukumoto, *Chem. and Ind.*, 1972, 538.

<sup>197</sup> W. Fleischhacker and H. Markut, *Monatsh.*, 1971, **102**, 643.



A short and efficient synthesis of a morphinandienone involves the electrolysis of the non-phenolic laudanosine (204) at a platinum electrode, to afford a 52% yield of *O*-methylflavinantine (205) (Scheme 12).<sup>198</sup>

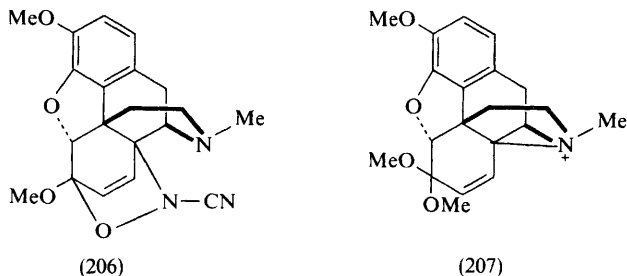


Reagents: i,  $-e$ , Pt electrode, 1.1 V; ii,  $-e$ ; iii,  $H_2O$ .

**Scheme 12**

A Diels-Alder adduct (206) was obtained when thebaine was treated with nitrosyl chloride and silver cyanide, the reactive intermediate probably being nitrosyl cyanide, ONCN.<sup>199</sup>

Solvolysis of 7- $\beta$ -iodoneopinone dimethyl acetal or of 14-bromocodeinone dimethyl acetal gives the common aziridinium ion intermediate (207) which can lead to 9-substituted indolinocodeinones.<sup>200</sup>



<sup>198</sup> L. L. Miller, F. R. Stermitz, and F. R. Falck, *J. Amer. Chem. Soc.*, 1971, **93**, 5941.

<sup>199</sup> P. Horswood and G. W. Kirby, *Chem. Comm.*, 1971, 1139.

<sup>200</sup> R. M. Allen and G. W. Kirby, *Chem. Comm.*, 1971, 1121.

Thebaine-maleimide adducts have been prepared,<sup>201</sup> and the Diels-Alder reaction of thebaine with cyclic azo-dienophiles has been investigated.<sup>202</sup> Nitrosation of thebaine hydrochloride with nitrosyl chloride or pentyl nitrite in methanol or ethanol gives 7-hydroxyiminoneopinone dimethyl or diethyl acetal.<sup>203</sup> The chemistry of 14-bromocodeinone and its dimethyl acetal has been studied in some detail, including catalytic hydrogenation,<sup>204</sup> methanolysis,<sup>205</sup> debromination,<sup>206</sup> dehydrobromination,<sup>207</sup> and solvolysis.<sup>208</sup> Efforts are continuing in the preparation of novel analgesics in the morphine-thebaine series.<sup>209-216</sup>

New morphine derivatives have also been prepared by treating 6-*O*-tosyl-codeine or 3-*O*-acetyl-6-*O*-tosylmorphine with KSCN in acetone,<sup>217</sup> and the behaviour of 7-methoxyneopinone dimethyl acetal methoperchlorate in acidic solution has been studied.<sup>218</sup> Morphine, upon electrochemical oxidation on a platinum anode at O.S.B., gave the dimeric pseudomorphine in 73% yield.<sup>219</sup> The conformation of ring C of a number of morphine derivatives has been determined from i.r. spectral data.<sup>220</sup>

[*Me*-<sup>3</sup>H<sub>3</sub>]Morphine has been prepared by reductive methylation of normorphine with [<sup>3</sup>H]paraformaldehyde and formic acid,<sup>221</sup> and the *N*-demethylation of codeine has been achieved using oxygen, u.v. light, and Bengal Red.<sup>222</sup> The mass spectra of some morphines have been recorded,<sup>223,224</sup> and quantum mechanical calculations have been carried out for some 64 morphine derivatives.<sup>225</sup>

<sup>201</sup> O. Hromatka, G. Sengtschmid, and K. Eichinger, *Monatsh.*, 1971, **102**, 1015.

<sup>202</sup> O. Hromatka and G. Sengtschmid, *Monatsh.*, 1971, **102**, 1022.

<sup>203</sup> K. W. Bentley, G. W. Kirby, A. P. Price, and S. Singh, *J. C. S. Perkin I*, 1972, 302.

<sup>204</sup> W. Fleischhacker and H. Markut, *Monatsh.*, 1971, **102**, 569.

<sup>205</sup> G. Heinisch, V. Klintz, and F. Vieboeck, *Monatsh.*, 1971, **102**, 530.

<sup>206</sup> W. Reusser and F. Vieboeck, *Monatsh.*, 1971, **102**, 1101.

<sup>207</sup> W. Fleischhacker and H. Markut, *Monatsh.*, 1971, **102**, 587.

<sup>208</sup> K. Abe, Y. Nakamura, and M. Onda, *Tetrahedron*, 1971, **27**, 4495.

<sup>209</sup> J. W. Lewis, M. J. Readhead, I. A. Selby, C. B. Alan, and C. A. Young, *J. Chem. Soc. (C)*, 1971, 1158.

<sup>210</sup> J. W. Lewis and M. J. Readhead, *J. Chem. Soc. (C)*, 1971, 2296.

<sup>211</sup> J. W. Lewis and M. J. Readhead, *J. Chem. Soc. (C)*, 1971, 2298.

<sup>212</sup> K. W. Bentley, J. W. Lewis, and A. C. B. Smith, *J. C. S. Perkin I*, 1972, 870.

<sup>213</sup> D. I. Haddelsey, J. W. Lewis, P. A. Mayor, and G. R. Young, *J. C. S. Perkin I*, 1972, 872.

<sup>214</sup> D. I. Haddelsey, J. W. Lewis, and P. A. Mayor, *J. C. S. Perkin I*, 1972, 875.

<sup>215</sup> J. W. Lewis, M. J. Readhead, and A. C. B. Smith, *J. C. S. Perkin I*, 1972, 878.

<sup>216</sup> J. W. Lewis and M. J. Readhead, *J. C. S. Perkin I*, 1972, 881.

<sup>217</sup> R. Bognár, S. Makleit, T. Mile, and L. Radics, *Monatsh.*, 1972, **103**, 143.

<sup>218</sup> G. Heinisch and F. Vieboeck, *Monatsh.*, 1971, **102**, 770.

<sup>219</sup> H. Isaka, *J. Pharm. Soc. Japan*, 1971, **91**, 1027.

<sup>220</sup> Z. Dinya, S. Makleit, S. Szabo, T. Mile, and R. Bognár, *Magyar Kém. Folyóirat*, 1971, **77**, 265.

<sup>221</sup> G. Werner and O. Von der Heyde, *J. Labelled Compounds*, 1971, **7**, 233.

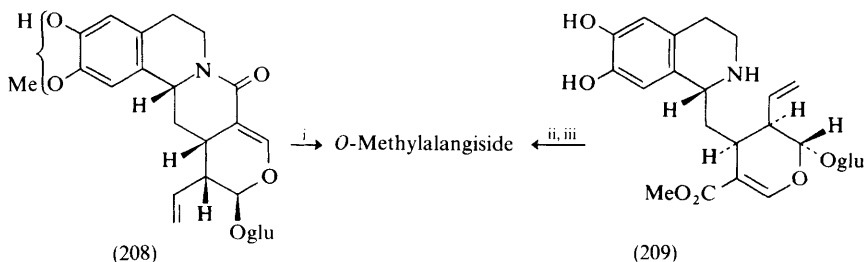
<sup>222</sup> J. H. E. Lindner, H. J. Kuhn, and K. Gollnick, *Tetrahedron Letters*, 1972, 1705.

<sup>223</sup> H. M. Fales, G. W. A. Milne, and N. C. Law, *Arch. Mass Spectral Data*, 1971, **2**, 608.

<sup>224</sup> F. Vane, *Arch. Mass Spectral Data*, 1971, **2**, 724.

<sup>225</sup> Z. Dinya, S. Makleit, R. Bognár, and P. Jekel, *Acta Chim. Acad. Sci. Hung.*, 1972, **71**, 125.

**Emetine and Related Alkaloids.**—A review on the ipecac alkaloids has appeared.<sup>226</sup> (–)-Alangiside (208) is a terpenoidal lactam recently isolated from *Alangium lamarckii* Thw. (Alangiaceae). The structure was proven by chemical correlation with desacetylpecoside (209) (Scheme 13).<sup>227</sup>

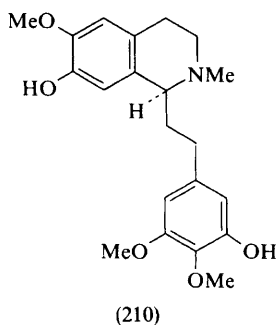


Reagents: i,  $\text{CH}_2\text{N}_2$ ; ii,  $\text{Na}_2\text{CO}_3$  or  $\text{NH}_3$ ; iii,  $\text{CH}_2\text{N}_2$ .

**Scheme 13**

Emetine has been used in the treatment of amebiasis since 1912. It has now been shown that it blocks protein synthesis directly, and not as a result of altered nucleic acid function.<sup>228</sup>

**Simple Phenethylisoquinolines.**—The alkaloid (–)-autumnaline (210) from *Colchicum cornigerum* (Liliaceae, subfamily Wurmbaeoidae) possesses the absolute configuration shown, and its synthesis has been carried out.<sup>229</sup>



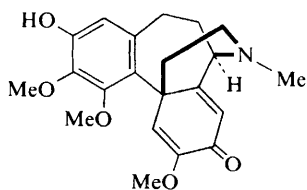
**Androcymbine Analogues and the Homomorphines.**—*C. cornigerum* possesses a variety of new alkaloids derived from autumnaline among which are CC-10 (211), CC-20 (212), CC-2 (213), whose structure was proven by X-ray analysis of its *O*-acetyl methiodide, CC-3b (214), and (–)-kreysiginine (216).<sup>229</sup>

<sup>226</sup> A. Brossi, S. Teitel, and R. J. Parry in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1971, Vol. 13, p. 189.

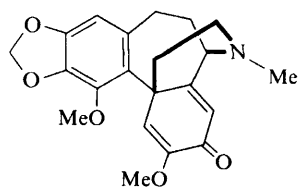
<sup>227</sup> R. S. Kapil, A. Shoeb, S. P. Popli, A. R. Burnett, G. D. Knowles, and A. R. Battersby, *Chem. Comm.*, 1971, 904.

<sup>228</sup> T. M. Cashman, K. A. Conklin, and S. C. Chou, *Experientia*, 1972, **28**, 520.

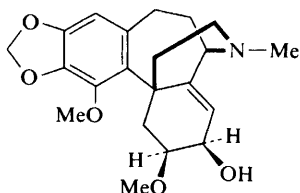
<sup>229</sup> A. R. Battersby, R. Ramage, A. F. Cameron, C. Hannaway, and F. Šantavý, *J. Chem. Soc. (C)*, 1971, 3514.



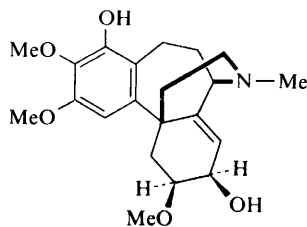
(211)



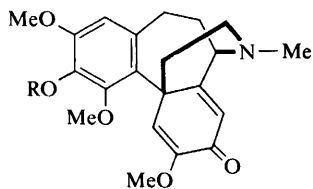
(212)



(213)

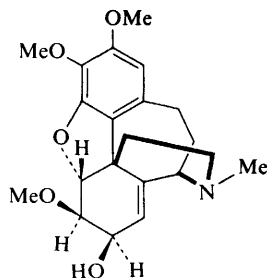


(214)



(215) R = H

(217) R = Me



(216)

(±)-Androcymbine (215) and (±)-*O*-methylandrocymbine (217) have been synthesized both by a photo-Pschorr cyclization<sup>119,230</sup> and by photolysis of the appropriate 2'-bromophenethylisoquinoline.<sup>231,232</sup>

**Homoaporphines and Homoproaporphines.**—A new homoaporphine from *C. cornigerum* is CC-24 (219).<sup>229</sup> Photolysis of the appropriate bromotetrahydrophenethylisoquinolines can lead to racemic multifloramine (218), kreysigine (220), or *O*-methylkreysigine (221). In each of these syntheses the bromine is situated either at C-8 or at C-2' of the tetrahydrophenethylisoquinoline precursor.<sup>81,231–233</sup>

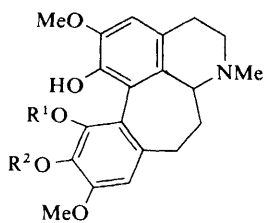
<sup>230</sup> T. Kametani, M. Koizumi, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 1792; *J. Org. Chem.*, 1971, **36**, 3729.

<sup>231</sup> T. Kametani, Y. Satoh, S. Shibuya, M. Koizumi, and K. Fukumoto, *J. Org. Chem.*, 1971, **36**, 3733.

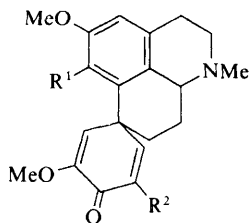
<sup>232</sup> T. Kametani and M. Koizumi, *J. Chem. Soc. (C)*, 1971, 3976.

<sup>233</sup> T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, and K. Fukumoto, *Tetrahedron*, 1971, **27**, 5993.

The photo-Pschorr cyclization has been utilized to prepare kreysigine (220)<sup>119</sup> and the homoproaporphine (222).<sup>230</sup>

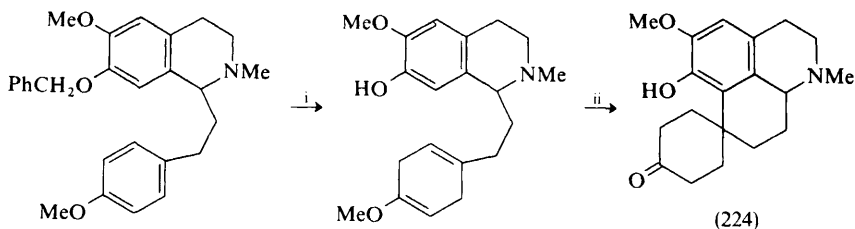


- (218) R<sup>1</sup> = Me, R<sup>2</sup> = H  
 (219) R<sup>1</sup> = H, R<sup>2</sup> = Me  
 (220) R<sup>1</sup> = Me, R<sup>2</sup> = Me



- (221) R<sup>1</sup> = OMe, R<sup>2</sup> = H  
 (222) R<sup>1</sup> = OH, R<sup>2</sup> = OMe

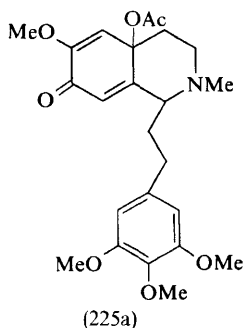
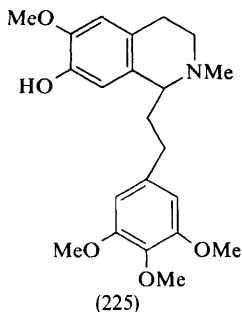
A new method for the synthesis of reduced homoproaporphines involves Birch reduction of the phenethyltetrahydroisoquinoline (223). Further treatment with hot H<sub>3</sub>PO<sub>4</sub> furnishes the tetracyclic species (224) (Scheme 14).<sup>234</sup>



Reagents: i, Li-NH<sub>3</sub>-THF-Bu<sup>t</sup>OH; ii, H<sub>3</sub>PO<sub>4</sub>.

Scheme 14

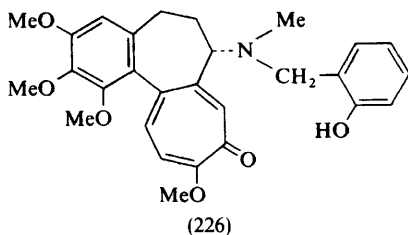
The synthetic method using *p*-quinol acetates to prepare aporphines has been extended to the synthesis of (±)-kreysigine (220). Treatment with acid of the *p*-quinol acetate (225a) derived from (±)-(225) gave (±)-*O*-acetylkreysigine in 18% yield.<sup>235</sup>



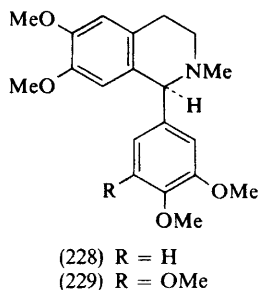
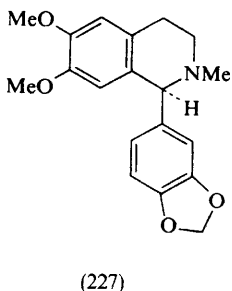
<sup>234</sup> W. V. Curran, *Chem. Comm.*, 1971, 478.

<sup>235</sup> O. Hoshino, T. Toshioka, and B. Umezawa, *J. C. S. Chem. Comm.*, 1972, 740.

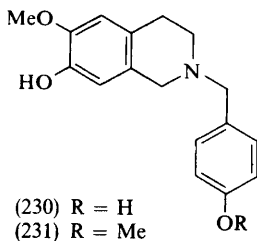
**Colchicine and Related Alkaloids.**—The structure of speciosine (226) was deduced by spectroscopic methods and confirmed by synthesis from demecolcine and 2-bromomethylphenyl acetate.<sup>236</sup> *N*-Formyldemecolcine is a new alkaloid found in *Colchicum cornigerum*.<sup>229</sup>



**Phenyltetrahydroisoquinolines.**—(+)-Cryptostyline I, II, and III (227)—(229) have been synthesized by the Bischler–Napieralski approach followed by a resolution using (–)diacetone-2-keto-L-gulonic acid, and reductive N-methylation. The o.r.d. and c.d. spectra have been described in detail<sup>237,238</sup> and the absolute configuration has been confirmed by an X-ray analysis of unnatural (–)-cryptostyline II.HBr.<sup>237</sup>



***N*-Benzyltetrahydroisoquinolines.**—A new alkaloid is corgoine (230) found in *Corydalis gortschakovii* (Fumariaceae). Selective O-methylation with diazomethane produced the known alkaloid sendaverine (231).<sup>239</sup>



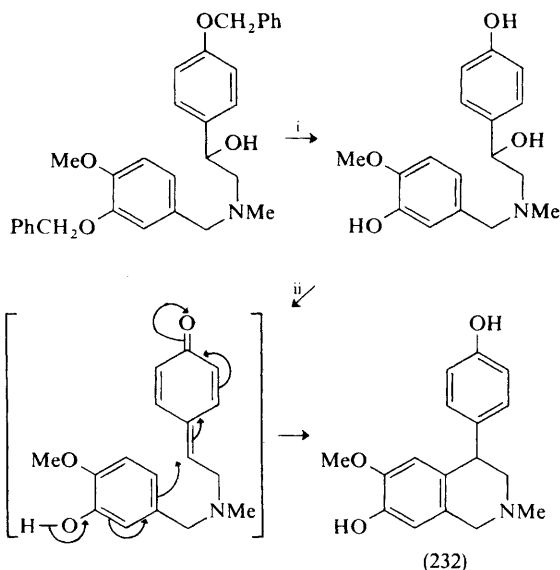
<sup>236</sup> R. Ramage, *Tetrahedron*, 1971, **27**, 1499.

<sup>237</sup> A. Brossi and S. Teitel, *Helv. Chim. Acta*, 1971, **54**, 1564.

<sup>238</sup> See also T. Kametani, H. Sugi, H. Yagi, and S. Shibuya, *J. Chem. Soc. (C)*, 1970, 2213.

<sup>239</sup> M. U. Ibragimova, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 211.

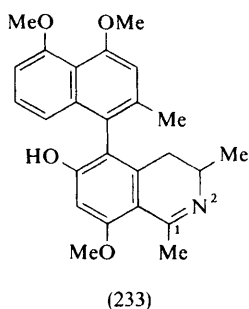
**Cherylline.**—An interesting biogenetically patterned synthesis of ( $\pm$ )-cherylline (232) has been carried out (Scheme 15).<sup>240</sup>



Reagents: i,  $\text{H}_2\text{-Pd/C}$ ; ii,  $\text{NH}_4\text{OH}$ .

**Scheme 15**

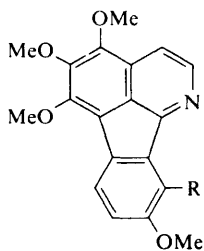
**Naphthalenoisoquinolines.**—A new base related to the unusual alkaloid (–)-ancistrocladine is (–)-ancistrocladinine (233), also found in *Ancistrocladus heyneanus* Wall. (Ancistrocladaceae), and which corresponds to (–)-1,2-dehydroancistrocladine.<sup>241</sup>



<sup>240</sup> M. A. Schwartz and S. W. Scott, *J. Org. Chem.*, 1971, **36**, 1827.

<sup>241</sup> T. R. Govindachari, P. C. Parthasarathy, and H. K. Desai, *Indian J. Chem.*, 1971, **9**, 1421.

**Azafluoranthenes.**—Two alkaloids of a novel type are imeluteine (234) and rufescine (235), isolated from the Amazonian vines *Abuta imene* and *A. rufescens* (Menispermaceae). The structures of both alkaloids were confirmed by synthesis using the Bischler–Napieralski and Pschorr sequences.<sup>242</sup>



(234) R = OMe

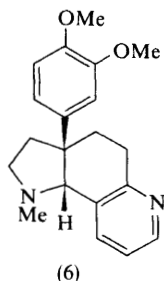
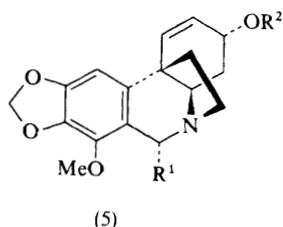
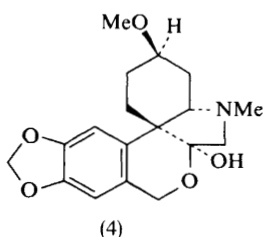
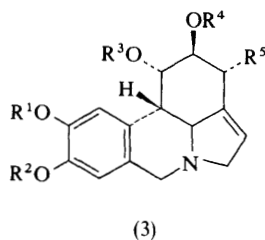
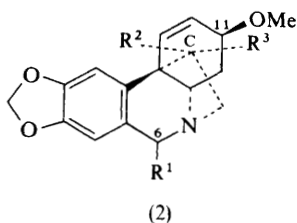
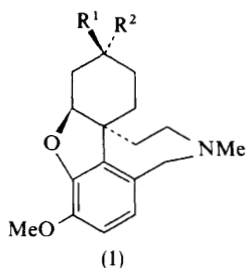
(235) R = H

<sup>242</sup> M. P. Cava, K. T. Buck, and A. I. daRocha, *J. Amer. Chem. Soc.*, 1972, **94**, 5931.



The pharmacological properties of galanthamine and other Amaryllidaceae alkaloids have been reviewed.<sup>1</sup>

New isolation and structural elucidation studies are summarized in the Table. The unnamed alkaloid isolated from *Chlidanthus fragrans* appears to be galanthamine *O*-methyl ether (1;  $R^1 = \text{OMe}$ ,  $R^2 = \text{H}$ ) on the basis of limited spectral data and conversion into galanthamine (1;  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ) by sodium-isoamyl alcohol reduction.<sup>2</sup> Conversion of galanthamine into epigalanthamine (1;  $R^1 = \text{H}$ ,  $R^2 = \text{OH}$ ) with mineral acid followed by successive treatment of the



latter with thionyl chloride and sodium methoxide yielded the alkaloid from *C. fragrans*. Spectroscopic studies as well as Hofmann degradation to the amino acid (10) provided the information necessary to assign the structure of epihaemantamine (2;  $R^1 = R^3 = \text{H}$ ,  $R^2 = \text{OH}$ ).<sup>3</sup>

<sup>1</sup> P. Cordier, *Bull. Soc. Pharm. Strasbourg*, 1971, **14**, 9 (*Chem. Abs.*, 1972, **77**, 27d).

<sup>2</sup> C. Nogueiras, W. Doepke, and G. Lehmann, *Tetrahedron Letters*, 1971, 3249.

<sup>3</sup> C. Nogueiras, W. Doepke, E. Gruendemann, and G. Lehmann, *Tetrahedron Letters*, 1971, 2743.

Table. Isolation of Amaryllidaceae and related alkaloids

| Species   | Alkaloid (Structure)   | Ref. |
|---|--|------|
| <i>Chlidanthus fragrans</i>   | Galanthamine <i>O</i> -methylether (1; $R^1 = \text{OMe}, R^2 = \text{H}$ )      | 2    |
| <i>Haemanthus katherinae</i>  | Epiphaemanthamine (2; $R^1 = R^3 = \text{H}, R^2 = \text{OH}$ )                  | 3    |
| <i>Hippeastrum equestre</i><br>( <i>Amaryllis belladonna</i> )                    | Lycorine (3; $R^1 + R^2 = \text{CH}_2, R^3 = R^4 = R^5 = \text{H}$ )             | 4    |
|   | Pseudolycorine (3; $R^1 = R^3 = R^4 = R^5 = \text{H}, R^2 = \text{Me}$ )         |      |
|   | Tazettine (4)  | 5    |
| <i>H. johnsonii</i>   | Lycorine   |      |
|   | Pseudolycorine   |      |
|   | Tazettine  |      |
| <i>Narcissus tazetta</i><br>var. <i>florepleno</i> and<br>var. <i>panizzianus</i> | Isorhamnetin*  | 6    |
|   | Lycorine (narcissine)†   |      |
| <i>Nerine bowdenii</i>  | 6-Hydroxybuphanidrine (5; $R^1 = \text{OH}, R^2 = \text{Me}$ )                   | 7    |
|   | 6-Hydroxypowelline (5; $R^1 = \text{OH}, R^2 = \text{H}$ )                       |      |
| <i>Sceletium namaquense</i>   | Alkaloid A <sub>4</sub> (6)  | 8    |
| <i>S. strictum</i>  | <i>N</i> -Demethylmesembranol (7)  | 9    |
|   | <i>N</i> -Demethylmesembrenol (7; C-4—C-5 double bond)                           |      |
| <i>S. tortuosum</i>   | Alkaloid A <sub>4</sub>  | 10   |
|   | Tortuosamine (8)   |      |
| <i>Sternbergia lutea</i>  | Galanthamine (1; $R^1 = \text{OH}, R^2 = \text{H}$ )                             | 11   |
|   | Galanthine (3; $R^1 = R^2 = \text{OMe}, R^3 = R^5 = \text{H}, R^4 = \text{Me}$ ) |      |
|   | Haemanthidine† (2; $R^1 = R^3 = \text{OH}, R^2 = \text{H}$ )                     |      |
|   | Hippeastrine (9)   |      |
|   | Lycorine†  |      |
|   | Tazettine†   |      |
| <i>Ungernia trisphaera</i>  | Hippeastrine†  | 12   |
|   | Lycorine†  |      |
|   | Tazettine†   |      |

\* Inaccessibility of original literature prevented definition of structure.

† Known alkaloid, previously isolated from the same species but usually from a different locality.

The structure and absolute configuration of 6-hydroxybuphanidrine (5;  $R^1 = \text{OH}, R^2 = \text{Me}$ ) was established by its conversion into the known buphanidrine (5;  $R^1 = \text{H}, R^2 = \text{Me}$ ).<sup>7</sup> The location of the hydroxy-group was ascertained from the i.r. (3595  $\text{cm}^{-1}$ , weak H-bonding) and n.m.r. ( $\delta$  5.31, s, 1H) spectra, and its configuration was assigned on the basis of steric and electronic

<sup>4</sup> R. V. K. Rao and R. Vimaladevi, *Planta Med.*, 1972, **21**, 142.

<sup>5</sup> R. V. K. Rao, N. Ali, and R. Vimaladevi, *Indian J. Pharm.*, 1971, **33**, 56 (*Chem. Abs.*, 1972, **76**, 23 005p).

<sup>6</sup> A. Sh. Shikhiev and S. V. Serkerov, *Aktual. Probl. Izuch. Efirnomaslich. Rast. Efirn. Masel*, 1970, 149 (*Chem. Abs.*, 1972, **76**, 89 931u).

<sup>7</sup> W. C. Wildman and M. R. Slabaugh, *J. Org. Chem.*, 1971, **36**, 3202.

<sup>8</sup> P. W. Jeffs, P. A. Luhan, A. T. McPhail, and N. H. Martin, *Chem. Comm.*, 1971, 1466.

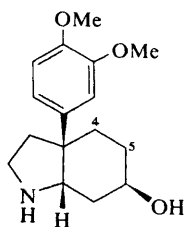
<sup>9</sup> P. E. J. Kruger and R. R. Arndt, *J.S. African Chem. Inst.*, 1971, **24**, 235 (*Chem. Abs.*, 1971, **75**, 151 942h).

<sup>10</sup> F. O. Snyckers, F. Strelow, and A. Wiechers, *Chem. Comm.*, 1971, 1467.

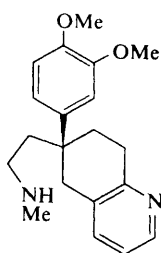
<sup>11</sup> G. Foka, *Pharm. Delt., Epistem. Ekdosis*, 1971, **1**, 9 (*Chem. Abs.*, 1972, **77**, 2773t).

<sup>12</sup> Kh. Allayarov and Kh. A. Abduazimov, *Probl. Osvoeniya Pustyn*, 1970, 83 (*Chem. Abs.*, 1971, **75**, 148 488j).

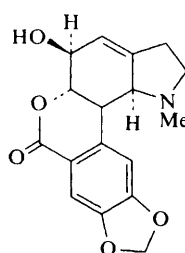
considerations. Similarly, the structure of 6-hydroxypowelline (5;  $R^1 = OH$ ,  $R^2 = H$ ) was assigned and confirmed by correlation with powelline (5;  $R^1 = R^2 = H$ ), a known alkaloid. Several interesting reactions of the new alkaloids were also reported.<sup>7</sup> In contrast to other 5,10b-ethanophenanthridine



(7)

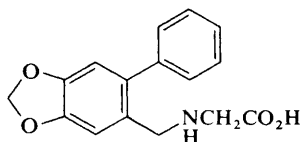


(8)

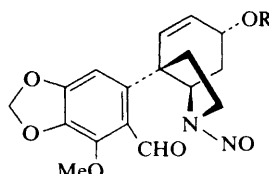


(9)

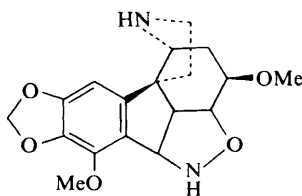
alkaloids which possess C-11 hydroxy-groups, both 6-hydroxybuphanidrine and 6-hydroxypowelline showed no tendency to epimerize at the C-6 position even when refluxed in acidic or basic media. However, treatment with sodium nitrite in acetic acid did produce the *N*-nitroso-aldehydes (11;  $R = Me$ ) and (11;  $R = H$ ), respectively. Interestingly, treatment of 6-hydroxybuphanidrine with hydroxylamine hydrochloride yielded the isoxazolidine derivative (12). This result appears to be another example of the well-documented addition reaction of oximes to double bonds.



(10)



(11)

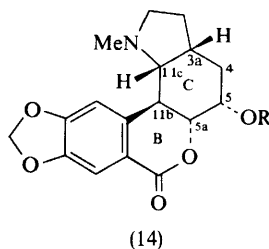
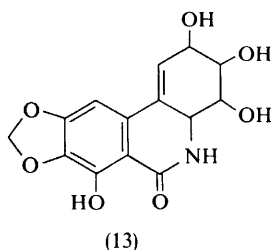


(12)

The *Sceletium* Alkaloid  $A_4$  (6) has been shown to be an interesting structural variant of the mesembrine group of alkaloids by Jeffs and co-workers.<sup>8</sup> The 220 MHz n.m.r. spectrum showed two AMX patterns ( $\delta$  8.48, dd,  $J$  5.0 and 2.0 Hz,  $H_A$ ; 7.56, dd,  $J$  7.8 and 2.0 Hz,  $H_M$ ; 7.15 dd,  $J$  5.0 and 7.8 Hz,  $H_X$ ; and  $\delta$  6.70, d,  $J$  8.0 Hz,  $H_{A'}$ ; 6.65, d,  $J$  2.0 Hz,  $H_{M'}$ ; 6.56, dd,  $J$  2.0 and 8.0 Hz,  $H_{X'}$ ) which clearly

established the presence of 2,3-disubstituted pyridine and 3,4-disubstituted phenyl rings, respectively. Additional n.m.r. as well as u.v., i.r., and mass spectral evidence allowed six possible structures to be written for Alkaloid  $A_4$ —a good graduate seminar problem—although structure (6) was favoured on biogenetic grounds. Direct X-ray crystallographic analysis confirmed this structure. Comparable spectral evidence was presented by Wiechers and co-workers in their independent assignment of the structure of Alkaloid  $A_4$  isolated from *Sceletium tortuosum*.<sup>10</sup> In addition, these workers isolated tortuosamine (8) which was also obtained by catalytic hydrogenolysis (Pd-C) of Alkaloid  $A_4$ , thus confirming its structure.

The structural assignment of the antimitotic agent narciclasine (13) has been previously discussed.<sup>13</sup> The <sup>13</sup>C n.m.r. spectrum of narciclasine has now fully confirmed this assignment.<sup>14</sup>



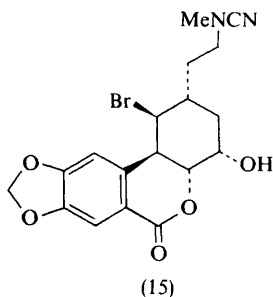
The classical method of structural elucidation of Amaryllidaceae alkaloids possessing the [2]benzopyrano[3,4-g]indole skeleton [e.g. (9)] involves their conversion into alkaloids bearing the better characterized lycorine-type skeleton [e.g. (3)]. This method fails for clivonine (14; R = H) since the derived product represents a stereochemical modification in the lycorine series which is unknown. However, Jeffs, Doepke, and co-workers have shown that extensive application of mass spectral and n.m.r. methods produces sufficient information to define fully the structure and stereochemistry of clivonine.<sup>15</sup> Its n.m.r. spectrum showed a multiplet at  $\delta$  4.18 (1H) [ $\delta$  5.38 in the acetate 14; R = Ac] assigned to C-5 hydrogen whose equatorial orientation was indicated by the width at half-height (< 10 Hz). A double doublet at  $\delta$  4.06 was assigned to the C-5a hydrogen on the basis of decoupling studies on the acetate. Irradiation of the  $\delta$  5.35 signal gave a clean doublet at  $\delta$  4.16 and afforded the coupling constants,  $J_{5a,5a}$  3.0 Hz and  $J_{5a,11b}$  12.5 Hz. The 12.5 Hz coupling implies that the C-5a and C-11b hydrogens are *trans* and thus that clivonine possesses a *trans* B/C ring junction. The 3.0 Hz coupling indicates that the C-5 and C-5a oxygen functions are *cis*, as inferred earlier from rates of the periodic acid cleavage reaction. Furthermore, the spectrum of clivonine showed double doublets at  $\delta$  3.23 ( $J_{5a,11b}$  12.0,  $J_{11b,11c}$  9.5 Hz) and at  $\delta$  2.87 ( $J_{11b,11c}$  9.5 Hz,  $J_{11c,3a}$  5.8 Hz) which could be assigned to the C-11b

<sup>13</sup> V. A. Snieckus, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1972, vol. 2, ch. 9.

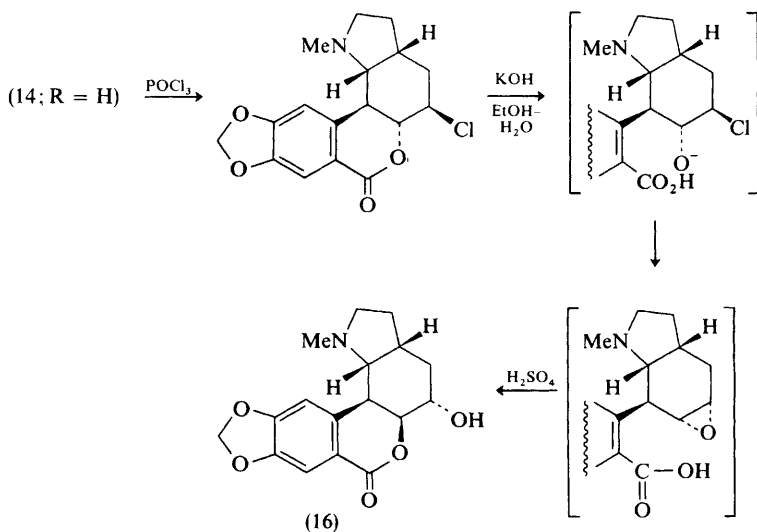
<sup>14</sup> L. Zetta, G. Gatti, and G. Fuganti, *Tetrahedron Letters*, 1971, 4447.

<sup>15</sup> P. W. Jeffs, J. F. Hansen, W. Doepke, and M. Bienert, *Tetrahedron*, 1971, 27, 5065.

and C-11c protons, respectively. The 9.5 Hz coupling in the C-11b signal implies a *trans* relationship of the C-11b and C-11c protons. Therefore the C-11c hydrogen must be axial and  $J_{11c,3a}$  5.8 Hz must be interpreted in terms of an equatorially oriented *cis*-C-3a hydrogen. These assignments were corroborated by a similar analysis of the n.m.r. spectrum of *O*-acetylclivonine (14; R = Ac) and by von Braun degradation of clivonine which gave (15) as the sole product in good yield. Attempts to use compound (15) to confirm the stereochemical assignments



made on the basis of the n.m.r. study were unsuccessful. However, conversion of clivonine into 5 $\alpha$ -hydroxymasan-7-one (16) ( $\alpha$ -dihydrohippeastrine; see the proposed new nomenclature<sup>15</sup>) was effected (Scheme 1). A mechanism for this

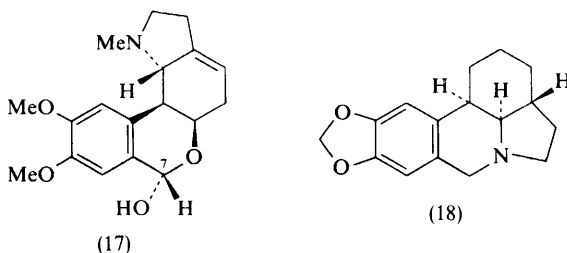


**Scheme 1**

conversion was also proposed, as shown. Since the structure and absolute configuration of (16) are known, this conversion established the absolute stereochemistry of clivonine as represented by (14; R = H).

An X-ray crystallographic analysis of lycorenine (17) methiodide has established the  $\alpha$ -configuration of the C-7 hydroxy-group.<sup>16</sup> On the basis of this information, and specific and molecular rotation studies of analogous alkaloids and their 7-oxo-derivatives, the related alkaloids oduline, nerinine, krigeine, unsevine, and krigenamine may also be assigned C-7  $\alpha$ -configurations.

A second X-ray crystal structural analysis of narcissidine (3;  $R^1 = R^2 = R^4 = \text{Me}$ ,  $R^3 = \text{H}$ ,  $R^5 = \text{OH}$ ) methiodide has been published.<sup>17</sup> A discussion of the influence of allylic oxygen functions on transoid diene c.d. spectra includes mention of lycorine derivatives.<sup>18</sup>



The past year has witnessed a vast number of synthetic achievements. Details of the previously discussed<sup>13</sup> synthesis of  $\delta$ -lycorane (18) have been reported.<sup>19</sup> In a novel and possibly general approach to lycorine-type alkaloids, the readily available compound (19) was directly cyclized to a single pentacyclic hydroxyketone (20) (Scheme 2).<sup>20</sup> The identity of (20) was established by its four-step conversion into  $\gamma$ -lycorane (21), whose stereochemistry had been elucidated previously.

The stereoselective total synthesis of ( $\pm$ )-elwesine (dihydrocrinine) (22;  $R^1 = \text{H}$ ,  $R^2 = \text{OH}$ ) has been previously reviewed;<sup>13</sup> details of this synthesis have now appeared.<sup>21</sup> This report also presents i.r. and n.m.r. spectral evidence similar to that adduced by other workers<sup>13</sup> which supports a rigid half-chair conformation with the bulky aryl group in an axial configuration for several synthetic mesembrine-like intermediates (23). Irradiation of the readily available  $\beta$ -phenethylamine derivatives (24;  $R^1 = \text{OMe}$ ,  $R^2 + R^3 = \text{OCH}_2\text{O}$ ) and (24;  $R^1 = \text{H}$ ,  $R^2 = \text{OMe}$ ,  $R^3 = \text{OH}$ ) gave 2-methoxy-3-oxocrinine (25;  $R^1 = \text{OMe}$ ,  $R^2 + R^3 = \text{OCH}_2\text{O}$ ) and 8-demethyl-3-oxomaritidine (25;  $R^1 = \text{H}$ ,  $R^2 = \text{OMe}$ ,  $R^3 = \text{OH}$ ), respectively, in very low yields.<sup>22,23</sup> Since the oxomaritidine derivative prepared by an alternative route has been converted into ( $\pm$ )-maritidine (26) as previously discussed,<sup>24</sup> the above results also constitute a formal total

<sup>16</sup> W. C. Wildman, J. Clardy, and J. A. Chan, *J. Org. Chem.*, 1972, **37**, 49.

<sup>17</sup> A. Immirzi and C. Fuganti, *J. Chem. Soc. (B)*, 1971, 1218.

<sup>18</sup> A. F. Beecham, *Tetrahedron*, 1971, **27**, 5207.

<sup>19</sup> H. Irie, Y. Nishitani, M. Sugita, K. Tamoto, and S. Uyeyo, *J. C. S. Perkin I*, 1972, 588.

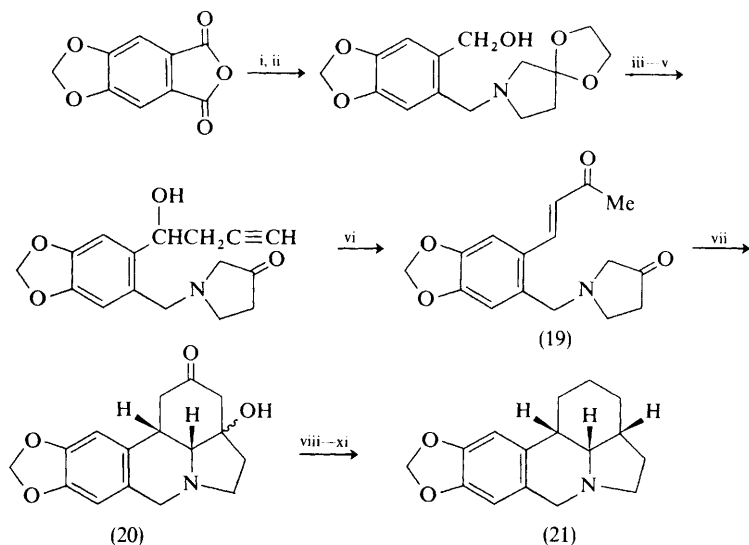
<sup>20</sup> B. Ganem, *Tetrahedron Letters*, 1971, 4105.

<sup>21</sup> R. V. Stevens, L. E. DuPree, jun., and P. L. Loewenstein, *J. Org. Chem.*, 1972, **37**, 977.

<sup>22</sup> T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, *Chem. Comm.*, 1971, 774.

<sup>23</sup> T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, *Tetrahedron*, 1971, **27**, 5441.

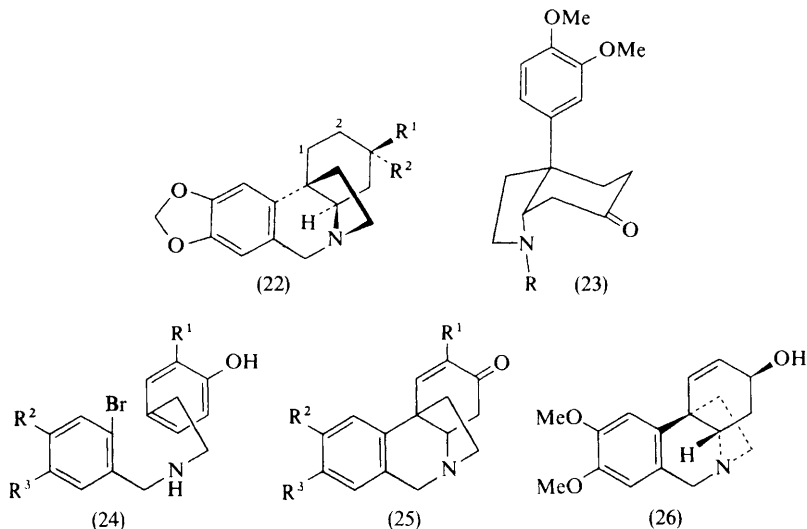
<sup>24</sup> V. A. Snieckus, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1971, vol. 1, pp. 140—141.



Reagents: i, 3-pyrrolidone ethylene ketal-THF; ii,  $\text{LiAlH}_4$ -THF; iii, Jones oxidation; iv,  $\text{HC}\equiv\text{CCH}_2\text{Br}$ - $\text{HgCl}_2$ -Al; v, 10 % HCl; vi,  $\text{HgSO}_4$ -dil.  $\text{H}_2\text{SO}_4$ ; vii,  $\text{K}_2\text{CO}_3$ - $\text{H}_2\text{O}$ -MeOH- $\text{CHCl}_3$ ; viii, TsOH; ix,  $\text{H}_2$ -Pd/C; x,  $\text{H}_2$ , NNHTs; xi,  $\text{NaBH}_3\text{CN}$

### Scheme 2

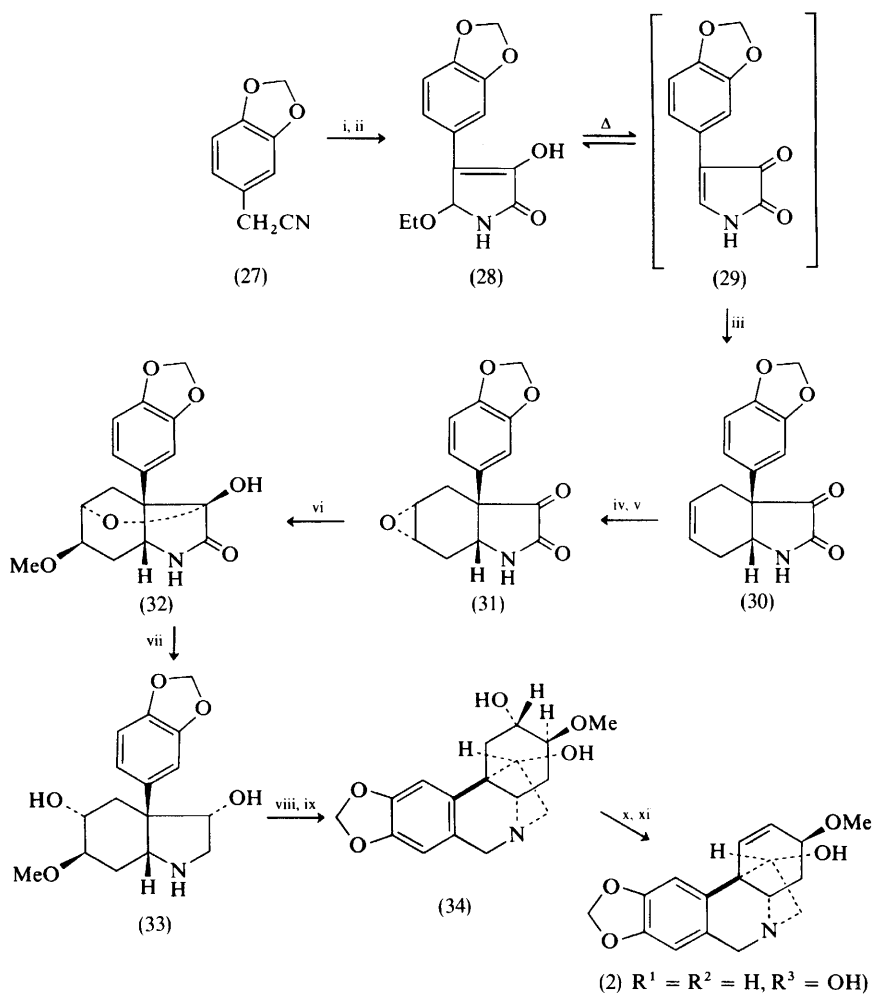
synthesis of this alkaloid. Slight modification of the structure of the starting material (24;  $R^1 = H$ ,  $R^2 + R^3 = OCH_2O$ ) led to the photochemical synthesis of (+)-oxocrinine (25;  $R^1 = H$ ,  $R^2 + R^3 = OCH_2O$ ) in 5% yield.<sup>25</sup> Lithium



<sup>25</sup> T. Kametani and T. Kohno, *Tetrahedron Letters*, 1971, 3155.

aluminium hydride reduction of ( $\pm$ )-oxocrine afforded ( $\pm$ )-epicrine (22;  $R^1 = OH, R^2 = H$ ; C-1—C-2 double bond), which was identified by comparison with an authentic sample. A more efficient route to crinine-like compounds has been developed (see below).

A stereoselective total synthesis of haemanthamine (2,  $R^1 = R^2 = H, R^3 = OH$ ) utilizing as the key step the Diels–Alder reaction of the  $\Delta^2$ -pyrrole-4,5-dione

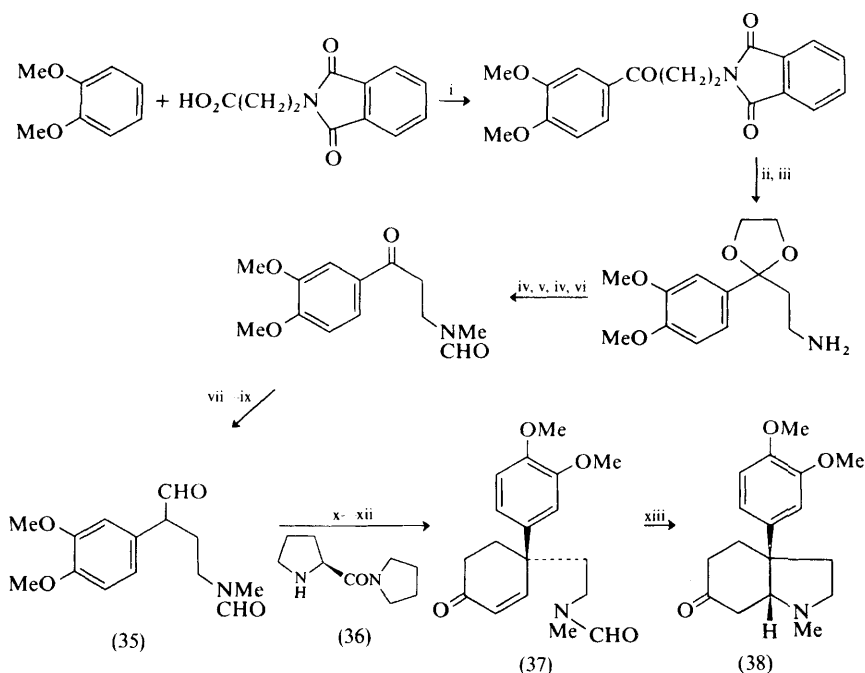


Reagents: i,  $(CO_2Et)_2-NaOEt$ ; ii,  $H_2$ -Raney Ni, 40 psi, 70 °C,  $EtOH-Et_2O$ ; iii,  $CH_3=CHCH=CH_2$ -DMSO (or DMF), 170 °C; iv,  $MeCONHBr$ -dioxan- $HClO_4$ ; v,  $MeONa-MeOH$ ; vi,  $BF_3, Et_2O-MeOH$ ; vii,  $LiAlH_4$ ; viii,  $HCHO-MeOH$ ; ix,  $HOAc$ ; x,  $TsCl$ ; xi,  $DBN-DMSO$ , heat.

Scheme 3



derivative (29) with butadiene has been described (Scheme 3).<sup>26</sup> The unstable dienophile (29) could be generated by the thermal decomposition of its ethanol adduct (28), which in turn was obtained from the nitrile (27). When the thermolysis of (28) was carried out in the presence of butadiene, a 70% yield of the adduct (30) was obtained, which was then converted into the epoxy-ketone (31) in two further steps. Acid-catalysed epoxide ring-opening in methanol gave the methoxy-acetal (32) as the major product, together with the corresponding isomer resulting from ring-opening in the other available direction. Metal hydride reduction then provided a single diol (33), which upon Pictet–Spengler cyclization followed by acid treatment yielded the ethanophenanthridine (34). This compound was converted into ( $\pm$ )-haemanthamine (2;  $R^1 = R^2 = H$ ,  $R^3 = OH$ ) in high yield to complete the synthesis. The Diels–Alder reaction as exemplified by the transformation (29)  $\rightarrow$  (30) has potential utility for the synthesis of mesembrane as well as several other unrelated groups of alkaloids.<sup>27</sup>



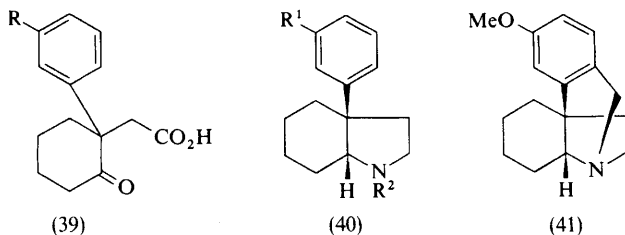
Reagents: i, PPA; ii,  $\text{HOCH}_2\text{CH}_2\text{OH}$ -TsOH; iii,  $\text{N}_2\text{H}_4$ ; iv,  $\text{HCO}_2\text{H}$ - $\text{Ac}_2\text{O}$ ; v,  $\text{LiAlH}_4$ ; vi,  $\text{MeCOMe}$ -TsOH; vii,  $\text{ClCH}_2\text{CO}_2\text{Me}$ - $\text{Bu}^t\text{OK}$ ; viii, NaOH; ix, HOAc, heat; x, (36),  $\text{C}_6\text{H}_6$ , heat; xi,  $\text{CH}_2=\text{CHCOMe}$ ; xii, HOAc- $\text{H}_2\text{O}$ -pyrrolidine; xiii, 10% HCl-EtOH.

Scheme 4

<sup>26</sup> Y. Tsuda and K. Isobe, *Chem. Comm.*, 1971, 1555.

<sup>27</sup> Y. Tsuda, K. Isobe, and A. Ukai, *Chem. Comm.*, 1971, 1554.

Synthetic work on the mesembrine group will no doubt be further stimulated by reports on their central nervous system activity<sup>28</sup> and somewhat surprising biosynthesis.<sup>29</sup> An interesting asymmetric synthesis of unnatural (+)-mesembrine (38) has been announced (Scheme 4).<sup>30</sup> The key intermediate (35), prepared in nine steps from 1,2-dimethoxybenzene, was treated with L-proline pyrrolidide (36) under conditions typical for the preparation of enamines. The product was not isolated but subjected to reaction with methyl vinyl ketone followed by acid treatment to give the cyclohexenone (37) in 38% overall yield. The last step in the synthesis [(37) → (38)] was based on previous synthetic work on mesembrine alkaloids. The synthetic (+)-mesembrine (38) was shown to exhibit a positive Cotton effect and thus an antipodal relationship to natural (–)-mesembrine. The mesembrine analogues (40; R<sup>1</sup> = H or OMe, R<sup>2</sup> = H, Me, or CH<sub>2</sub>Ph) have



been prepared by condensation of the corresponding cyclohexanone carboxylic acids (39; R = H or OMe) with the requisite amines, followed by catalytic and metal hydride reduction reactions.<sup>31</sup> One of these (40; R<sup>1</sup> = OMe, R<sup>2</sup> = H) was subjected to the Pictet–Spengler reaction with formaldehyde to yield the crinine analogue (41). Extensive application of n.m.r. spectroscopy defined<sup>31</sup> the stereochemistry and unusual conformation of these compounds in this study (see also ref. 21).

A neat biogenetic-type synthesis of (±)-cherylline (46) has been described (Scheme 5).<sup>32</sup> Condensation of (±)-O-benzyl octopamine hydrochloride (42) (prepared by lithium aluminium hydride reduction of *p*-benzyloxybenzaldehyde cyanohydrin) with *O*-benzylisovanillin (43), followed by reduction, gave the amine (44). Compound (44) was readily converted into (±)-hydroxy-*ON*-dimethylnorbelladine (45), which upon treatment with mild base gave (±)-cherylline (46) in 79% yield. An even shorter efficient synthesis of (46) starting with debenzylated octopamine and isovanillin was also presented.<sup>32</sup> A new preparation of 1,2,3,4-tetrahydro-4-phenylisoquinoline may also hold potential for the synthesis of cherylline.<sup>33</sup>

<sup>28</sup> A. Oishi and H. Kugita, *Jap. P.* 71 43 538 (*Chem. Abs.*, 1972, **76**, 59 442t); A. Oishi and H. Kugita, *Jap. P.* 71 43 539 (*Chem. Abs.*, 1972, **76**, 59 443u).

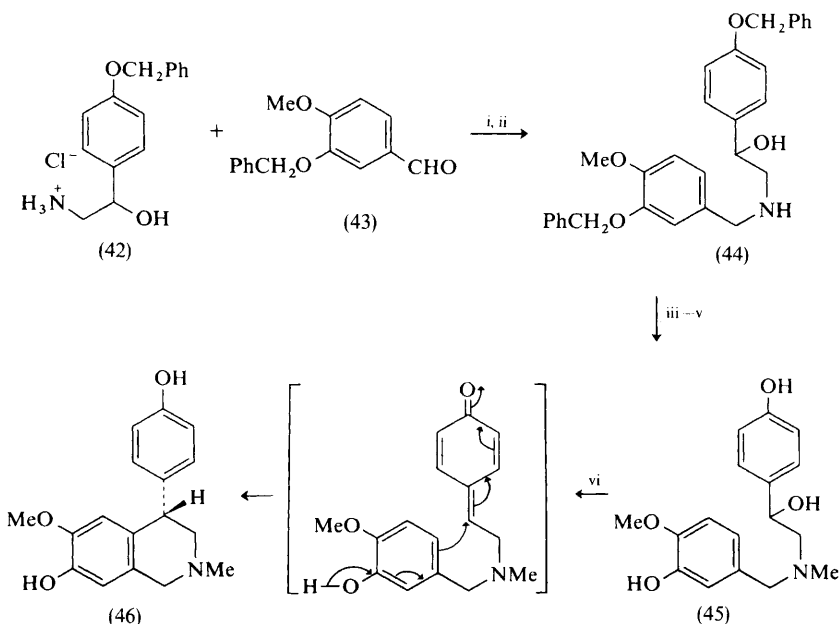
<sup>29</sup> P. W. Jeffs, H. F. Campbell, D. S. Farrier, and G. Molina, *Chem. Comm.*, 1971, 228.

<sup>30</sup> S. Yamada and G. Otani, *Tetrahedron Letters*, 1971, 1133.

<sup>31</sup> M. Langlois, C. Guillonau, J. Meingan, and J. Maillard, *Tetrahedron*, 1971, **27**, 5641.

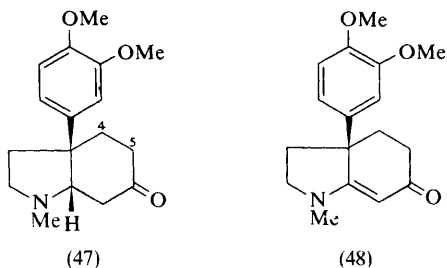
<sup>32</sup> M. A. Schwartz and S. W. Scott, *J. Org. Chem.*, 1971, **36**, 1827.

<sup>33</sup> T. J. Schwan, *J. Heterocyclic Chem.*, 1971, **8**, 839.



Scheme 5

Mesembrine (47) and mesembrinone (47; C-4—C-5 double bond) have been converted into the dehydrogenated derivatives (48) and (48; C-4—C-5 double bond), respectively, by treatment with diethyl azidodicarboxylate.<sup>34</sup> Attack at the *N*-methyl function, another expected reaction of this reagent with tertiary amines, did not occur.



A method for quantitative determination of galanthamine (1;  $\text{R}^1 = \text{OH}$ ,  $\text{R}^2 = \text{H}$ ) in biological material has been devised.<sup>35</sup>

<sup>34</sup> P. W. Jeffs, H. F. Campbell, and R. L. Hawks, *Chem. Comm.*, 1971, 1338.

<sup>35</sup> V. Mikhno and G. K. Levitskaya, *Farm. Zhur. (Kiev)*, 1971, **26**, 26 (*Chem. Abs.*, 1972, **76**, 122 476z).

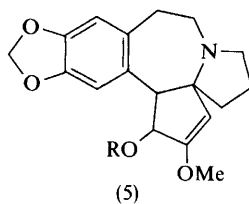
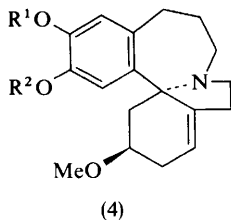
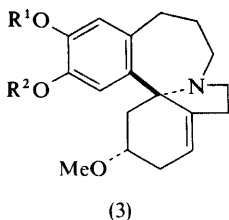
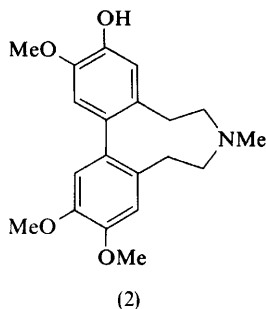
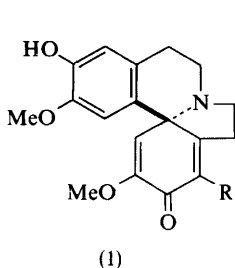
# 10

## Erythrina and Related Alkaloids

BY V. A. SNIECKUS

Erysodienone (1;  $R = H$ ), a compound previously unknown in Nature, has been isolated from *Erythrina lithosperma*.<sup>1</sup> The isolation of erybidine (2) from *E. xbidwilli* Lindl. is of biogenetic interest.<sup>2</sup> Its structure was determined by spectral studies, Hofmann degradation, and synthesis from erysodienone (1;  $R = H$ ). This species has been shown previously to elaborate *Erythrina* alkaloids.

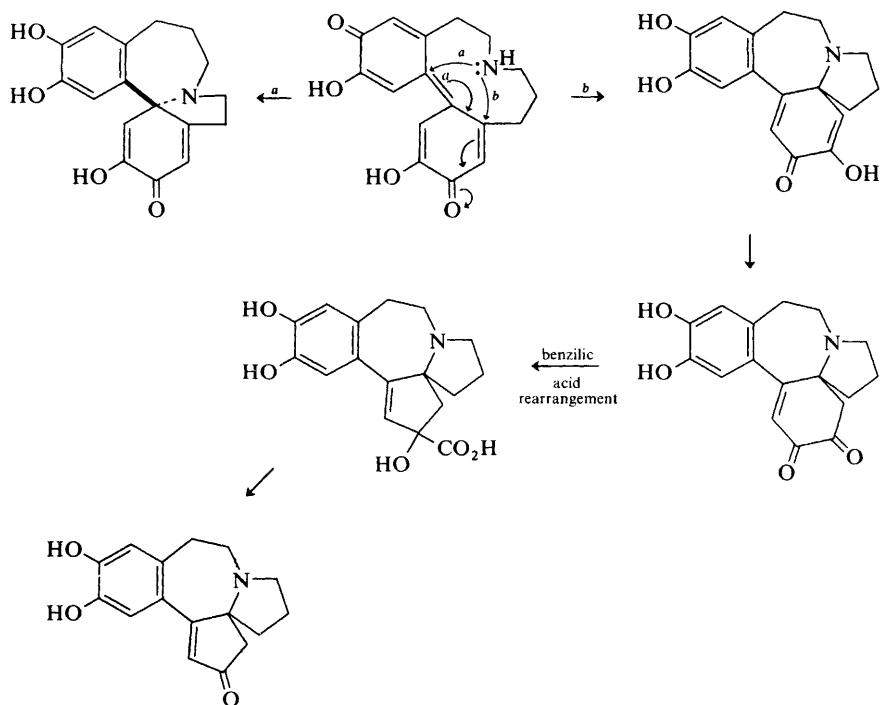
The known Homoerythrina alkaloids B (3;  $R^1 = Me$ ,  $R^2 = H$ ) and E (3;  $R^1 + R^2 = OCH_2O$ ) have been isolated from *Schelhammera undulata*.<sup>3</sup> These have been previously obtained from *S. pedunculata* and *S. multiflora*.



<sup>1</sup> S. Ghosal, S. K. Majumdar, and A. Chakraborti, *Austral. J. Chem.*, 1971, **24**, 2733.

<sup>2</sup> K. Ito, H. Furukawa, and H. Tanaka, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1509.

<sup>3</sup> A. A. Sioumis, *Austral. J. Chem.*, 1971, **24**, 2737.



Scheme 1

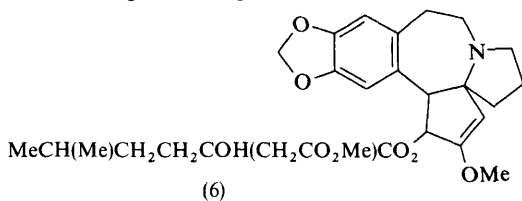
Five Homoerythrina alkaloids (3;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ), (3;  $R^1 + R^2 = \text{OCH}_2\text{O}$ ), (3;  $R^1 = R^2 = \text{Me}$ ), (4;  $R^1, R^2 = \text{H}, \text{Me}$ ), and (4;  $R^1 = R^2 = \text{Me}$ ) have been shown to co-occur with cephalotaxine (5;  $R = \text{H}$ ) and its ester derivatives in *Cephalotaxus harringtonia* var. *harringtonia*.<sup>4</sup> The structures of the minor Homoerythrina alkaloids were established by spectroscopic studies and comparison with the known alkaloids (3;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) and (3;  $R^1 + R^2 = \text{OCH}_2\text{O}$ ) which had been previously isolated from *Schelhammera pedunculata* and whose structures and absolute chemistry had been established.<sup>3</sup> The co-occurrence of Homoerythrina and *Cephalotaxus* alkaloids makes it most attractive to propose<sup>4,5</sup> that both types are derived from a common dienone (Scheme 1). An alternative biogenetic scheme for the formation of cephalotaxine (5;  $R = \text{H}$ ) from an *Erythrina* precursor has been previously offered as speculation.<sup>6</sup> Deoxyharringtonine (6), a new alkaloid with antileukemic activity of the same order of magnitude as the other known cephalotaxine alkaloids, has been

<sup>4</sup> R. G. Powell, *Phytochemistry*, 1972, **11**, 1467.

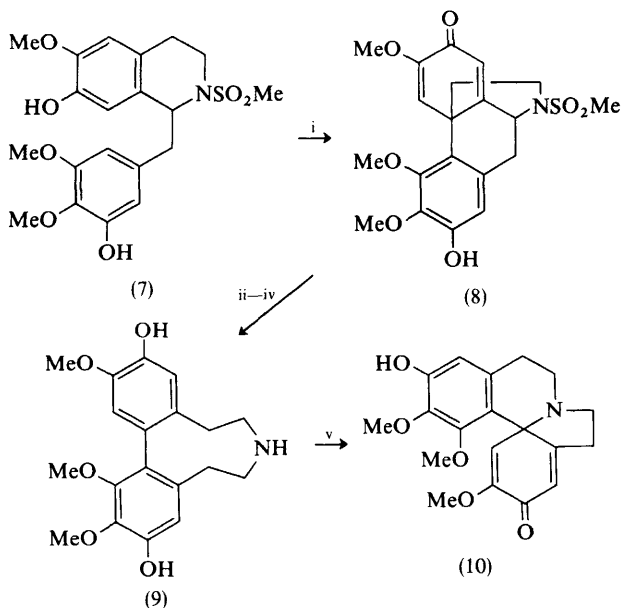
<sup>5</sup> J. S. Fitzgerald, S. R. Johns, J. A. Lambertson, and A. A. Sioumis, *Austral. J. Chem.*, 1969, **22**, 2187.

<sup>6</sup> V. A. Snieckus, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1970, Vol. 1, Chap. 12.

isolated also from *Cephalotaxus harringtonia* var. *harringtonia*.<sup>7</sup> That the dicarboxylic acid component in deoxyharringtonine is attached to cephalotaxine (5; R = H) via a tertiary ester link was shown by synthesis of the two half-esters,  $\text{RC(OH)(CH}_2\text{CO}_2\text{Me)CO}_2\text{H}$  and  $\text{RC(OH)(CH}_2\text{CO}_2\text{H)CO}_2\text{Me}$  [R =  $\text{MeCH(Me)CH}_2\text{CH}_2$ ]. Treatment of the latter with natural cephalotaxine gave a diastereomeric mixture of esters neither of which was identical with deoxyharringtonine. Therefore deoxyharringtonine must be represented by formula (6). Attempts to prepare (6) using the tertiary carboxylic acid half-ester have not been successful. If achieved, such a synthesis would offer a temporary solution to the lack of material for biological testing.



The influence of allylic oxygen functions on application of the transoid diene rule in c.d. spectra of *Erythrina* bases has been discussed.<sup>8</sup>



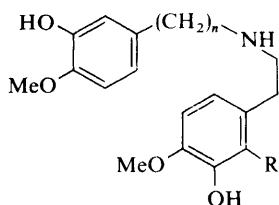
Reagents: i,  $\text{VOCl}_3$ ; ii,  $\text{BF}_3$ ,  $\text{Et}_2\text{O}$ ,  $20^\circ\text{C}$ ; iii,  $\text{H}_2$ -Pt/C-MeOH; iv, Li-liq.  $\text{NH}_3$ ; v,  $\text{K}_3\text{Fe(CN)}_6$ .

#### Scheme 2

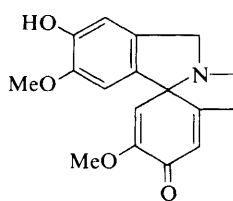
<sup>7</sup> K. L. Mikolajczak, R. G. Powell, and C. R. Smith, jun., *Tetrahedron*, 1972, **28**, 1995.

<sup>8</sup> A. F. Beecham, *Tetrahedron*, 1971, **27**, 5207.

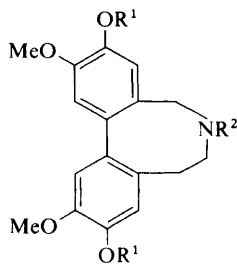
A new biogenetic-type synthesis of *Erythrina* alkaloids based in large part on previous experience in this field has been described (Scheme 2).<sup>9</sup> Oxidation of the nor-reticuline derivative (7) gave the morphinandienone (8), which upon mild acid treatment followed by two reductive steps yielded the biphenyl (9). This compound was subjected to the phenol oxidative coupling reaction to give 14-methoxyerysodienone (10) in 61% yield. The transformation (8)  $\rightarrow$  (9) is proposed as a step in the biosynthesis of the *Erythrina* alkaloids. Of the two possible modes of oxidative coupling available to the secondary amine (11; R = OMe,  $n = 2$ ), only that leading to the erythrinadienone (1; R = OMe) has been shown to occur.<sup>10</sup> Norerythrinadienone (12) was similarly prepared from (11; R = H,  $n = 1$ ), reduced with sodium borohydride, and the resulting product subjected to the dienone-phenol rearrangement (acetic anhydride-sulphuric acid) to give the dibenz[*c,e*]azocine (13; R<sup>1</sup> = R<sup>2</sup> = Ac).<sup>11</sup> The tetramethoxy-derivative (13; R<sup>1</sup> = Me, R<sup>2</sup> = Ac) was readily obtained from (13; R<sup>1</sup> = R<sup>2</sup> = Ac) and also by an alternative synthesis.



(11)



(12)



(13)

A facile one-step synthesis<sup>11a</sup> of ( $\pm$ )-*cis*- and *trans*-16-hydroxy-15-methoxyerythrinanone (14; R<sup>1</sup> = OMe, R<sup>2</sup> = OH, X = O) and (15; R<sup>1</sup> = OMe, R<sup>2</sup> = OH, X = O) by the condensation of 2-(ethoxycarbonylmethyl)methylcyclohexanone with 3-hydroxy-4-methoxy- $\beta$ -phenethylamine in refluxing ethanol without acid catalysis, reported by Kametani and co-workers, has been discussed

<sup>9</sup> B. Franck and V. Teetz, *Angew. Chem. Internat. Edn.*, 1971, **10**, 411.

<sup>10</sup> T. Kametani and T. Kohno, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2102.

<sup>11</sup> T. Kametani, K. Takahashi, S. Shibuya, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 1800.

<sup>11a</sup> T. Kametani, H. Agui, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 1285; T. Kametani, H. Agui, K. Saito, and K. Fukumoto, *J. Heterocyclic Chem.*, 1969, **6**, 453.

those obtained for (14;  $R^1 = \text{OMe}$ ,  $R^2 = \text{OH}$ ,  $X = \text{O}$ ) and (15;  $R^1 = \text{OMe}$ ,  $R^2 = \text{OH}$ ,  $X = \text{O}$ ) and their derivatives, synthesized independently in Mondon's laboratory, has cast serious doubt on the original claim.<sup>12</sup> For example, Kametani<sup>11a</sup> assigned the *cis*-structure (14;  $R^1 = \text{OMe}$ ,  $R^2 = \text{OH}$ ,  $X = \text{O}$ ) to a compound, m.p. 124–125 °C (chloroform), which exhibited singlets at  $\delta$  6.74, 6.81, 6.73, and 6.80, whereas the pure *cis*-compound, m.p. 116–118 °C (methanol–ether with one mole of  $\text{H}_2\text{O}$  of crystallization), originally synthesized by Mondon in 1960 by acid-catalysed cyclization of (16;  $R = \text{H}$ ), showed the expected two aromatic singlets of  $\delta$  6.69 and 6.89. Furthermore, Kametani's *trans*-isomer, m.p. 143–144 °C, as its methyl ether (15;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{O}$ ) exhibited a singlet at  $\delta$  6.76, which is in better agreement with structure (16;  $R = \text{Me}$ ) since the former would be expected to exhibit signals for C-14 and C-17 hydrogens typically shifted to lower fields at  $\delta$  7.22 and 6.66 (see below). On the basis of this information and particularly mass spectral data, it appears that Kametani *et al.*<sup>11a</sup> were dealing with a mixture of products containing (16;  $R = \text{H}$ ) and, in part, cyclized *cis* material (14;  $R^1 = \text{OMe}$ ,  $R^2 = \text{OH}$ ,  $X = \text{O}$ ) resulting from contact with acid during the silica gel chromatography or crystallization. The compound (17;  $R = \text{H}$ ) also described by Kametani appears to be incorrectly assigned.<sup>12</sup>

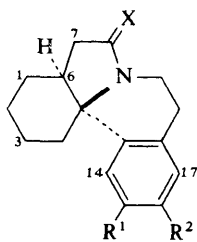
Additional examples of *trans* *Erythrina* derivatives, e.g. (15;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{O}$  or  $\text{H}_2$ ), have been synthesized in Mondon's laboratories.<sup>13</sup> Catalytic hydrogenation of the diene–lactam (18;  $X = \text{O}$ ) over platinum in acetic acid gave a 70:30 mixture of the *cis*- and *trans*-lactams (14;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{O}$ ) and (15;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{O}$ ), respectively. When the reduction was carried out over palladium on carbon in methanolic solution only the *cis*-lactam (14;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{O}$ ) was obtained. These and other experiments suggest that the hydrogenation is not stereospecific and leads initially to a mixture of the unsaturated lactams (17;  $R = \text{Me}$ ) and (19;  $R = \text{OMe}$ ,  $X = \text{O}$ ). Since it was known that the conjugated lactam (17;  $R = \text{Me}$ ) is catalytically hydrogenated only to the *cis*-lactam (14;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{O}$ ), the *trans*-lactam (15;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{O}$ ) must be formed *via* the unconjugated lactam (19;  $R = \text{OMe}$ ,  $X = \text{O}$ ). On the other hand, catalytic reduction of the base (18;  $X = \text{H}_2$ ) over palladium–carbon in methanol gave exclusively the unconjugated amine (19;  $X = \text{H}_2$ ,  $R = \text{OMe}$ ), which upon further reduction with platinum in acetic acid gave the *trans*-base (15;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{H}_2$ ). Comparison of the n.m.r. spectra of the *cis*- and *trans*-bases (14;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{H}_2$ ) and (15;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{H}_2$ ) shows significant differences in the aromatic proton region. In the *cis*-base, absorption at  $\delta$  6.71 (1H) and 6.50 (1H) was assigned to the C-14 and C-17 hydrogens, respectively. On the other hand, the *trans*-base showed one-proton singlets at  $\delta$  7.18 and 6.63 due to these hydrogens, the appreciable shift to lower field for the C-14 hydrogen being attributed to its steric interaction with the axial C-1 and C-3 hydrogens. Resolution of the *trans*-base (15;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{H}_2$ ) with (+)- and (–)-dibenzoyltartaric acid

<sup>12</sup> A. Mondon, *Chem. Ber.*, 1971, **104**, 2960.

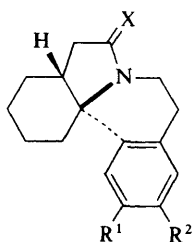
<sup>13</sup> A. Mondon and P. R. Seidel, *Chem. Ber.*, 1971, **104**, 2937.



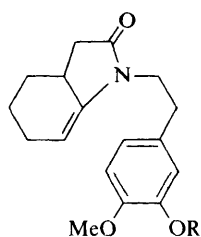
was effected and the (+)-form was assigned the 5*S*,6*R* configuration by comparison of c.d. spectra with those of *Erythrina* alkaloids of known absolute configuration. Interestingly, both the *cis*- and *trans*-bases in all their four optical modifications showed little difference in curare-like activity, leading to the conclusion that the pharmacological activity is neither structure- nor configuration-specific.



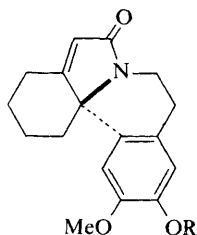
(14)



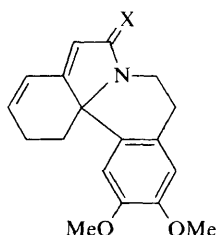
(15)



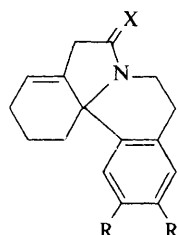
(16)



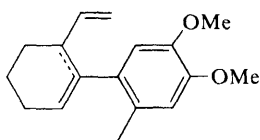
(17)



(18)



(19)



(20)

Confirmation of the conclusions drawn above for the *cis*- and *trans*-isomers (14;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{H}_2$ ) and (15;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{H}_2$ ) from physical and spectroscopic data was obtained by exhaustive Hofmann degradation.<sup>13</sup> As required, both isomers yielded the same mixture of isomeric non-nitrogenous compounds (20). Finally, *trans*-base (15;  $R^1 = R^2 = \text{OMe}$ ,  $X = \text{H}_2$ ) was converted into the dedimethoxy-compound (15;  $R^1 = R^2 = \text{H}$ ,  $X = \text{H}_2$ ) for comparison with the *cis*-dedimethoxy derivative (14;  $R^1 = R^2 = \text{H}$ ,  $X = \text{H}_2$ ) which had been prepared by Belleau.<sup>14</sup> Treatment of (15;  $R^1 = R^2 = \text{OMe}$ ,

<sup>14</sup> B. Belleau, *J. Amer. Chem. Soc.*, 1953, **75**, 5765.

X = H<sub>2</sub>) with hydrobromic acid followed by esterification of the resulting diphenol with diethyl phosphite gave an intermediate diester which, upon lithium-liquid ammonia reduction, provided the *trans*-base (15; R<sup>1</sup> = R<sup>2</sup> = H, X = H<sub>2</sub>). Spectral comparison with the *cis*-dedimethoxy-base (14; R = H, X = H<sub>2</sub>), whose preparation has been summarized,<sup>6</sup> was fully described.

The most recent volume<sup>1</sup> in the Manske series contains reviews of carbazole alkaloids<sup>1a</sup> and the alkaloids of the Calabar bean.<sup>1b</sup> A useful review<sup>2</sup> of the monoterpene indole alkaloid structural types brings together established biogenetic relationships and reasonable chemical analogy to build up a structurally sub-classified total picture of the currently recognized skeletal types. Laboratory transformations between some of the skeletal types in this group, patterned on established or postulated biogenetic interconversions, have been reviewed.<sup>3</sup> The alkaloidal content of sixty-nine African *Strychnos* species has been reviewed.<sup>4</sup> It has been pointed out<sup>5</sup> that it is inadvisable to use methylene chloride in work with indole alkaloids because some alkaloids form quaternary chloromethyl chlorides by reacting with this solvent.

The material in this Report is organized in the same way as in last year's Report.<sup>6</sup>

### 1 Simple Alkaloids

**Non-tryptamines.**—The simple indoles in barley and tomato shoots have been identified;<sup>7</sup> amongst others, 3-formylindole, 5-hydroxytryptamine, and of course indole-3-acetic acid were common to both; only barley had 3-aminomethyl- and 3-methylaminomethyl-indoles, gramine, *N*<sub>6</sub>-methyltryptamine, and 5-hydroxy-*N*<sub>6</sub>-methyltryptamine. The seeds of *Monodora tenuifolia*, which are used to flavour food in West Africa, contain<sup>8</sup> 6-(3-methylbuta-1,3-dienyl)indole.

Details of the work on heptaphylline<sup>9c</sup> have been given.<sup>10</sup> It has been suggested,<sup>11</sup> on the basis of analogy with the now revised structure (1) for cannabi-

<sup>1</sup> (a) R. H. F. Manske, 'The Alkaloids', Academic Press, New York, 1971, Vol. XIII, chap. 6; (b) *ibid.*, Vol. XIII, Chap. 4.

<sup>2</sup> I. Kompis, M. Hesse, and H. Schmid, *Lloydia*, 1971, **34**, 269.

<sup>3</sup> E. Winterfeldt, *Chimia (Switz.)*, 1971, **25**, 394.

<sup>4</sup> N. G. Bisset and J. D. Phillipson, *Lloydia*, 1971, **34**, 1.

<sup>5</sup> R. Besselièvre, N. Langlois, and P. Potier, *Bull. Soc. chim. France*, 1972, 1477; J. D. Phillipson and N. G. Bisset, *Phytochemistry*, 1972, **11**, 2547.

<sup>6</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. 224; (c) *ibid.*, p. 229; (d) *ibid.*, p. 231; (e) *ibid.*, p. 237; (f) *ibid.*, p. 240.

<sup>7</sup> E. A. Schneider, R. A. Gibson, and F. Wightman, *J. Exp. Bot.*, 1972, **23**, 152.

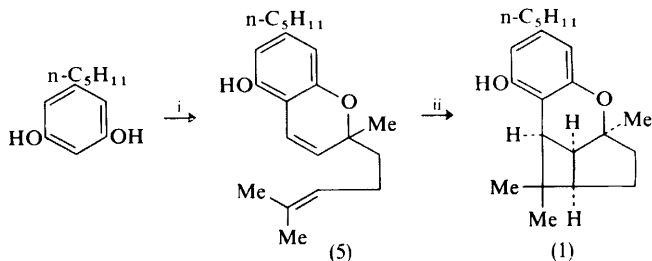
<sup>8</sup> M. N. Nwaji, S. O. Onyirinka, and D. A. H. Taylor, *J. C. S. Chem. Comm.*, 1972, 327.

<sup>9</sup> (a) J. A. Joule, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1, p. 150; (b) *ibid.*, p. 152; (c) *ibid.*, p. 154; (d) *ibid.*, p. 155; (e) *ibid.*, p. 158; (f) *ibid.*, p. 168; (g) *ibid.*, p. 164; (h) *ibid.*, p. 162; (i) *ibid.*, p. 198; (j) *ibid.*, p. 176; (k) *ibid.*, p. 177; (l) *ibid.*, p. 180; (m) *ibid.*, p. 183; (n) *ibid.*, p. 184; (o) *ibid.*, p. 191; (p) *ibid.*, p. 194; (q) *ibid.*, p. 197.

<sup>10</sup> B. S. Joshi, V. N. Kamat, D. H. Gawad, and T. R. Govindachari, *Phytochemistry*, 1971, **11**, 2065.

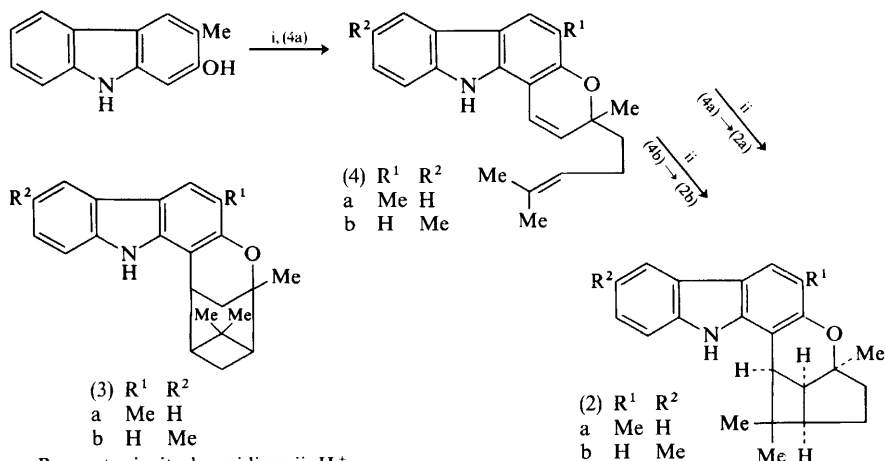
<sup>11</sup> M. J. Begley, D. G. Clarke, L. Crombie, and D. A. Whiting, *Chem. Comm.*, 1970, 1547.

cyclol, that bicyclomahanimbine and bicyclomahanimbicine may well have structures (2a) and (2b), and not (3a)<sup>9b</sup> and (3b)<sup>6a</sup> respectively. The analogy seems



Reagents: i, citral-pyridine; ii,  $\text{H}^+$

close; thus not only can mahanimbine (4a) be obtained by pyridine-catalysed condensation of a precursor phenolic carbazole with citral, as cannabichromene (5) can be obtained from olivetol, but each chromene [cannabichromene, mahanimbine, and mahanimbicine (4b)] can be cyclized by a comparable acid treatment (to cannabicyclol, bicyclomahanimbine, and bicyclomahanimbicine, respectively).



Reagents: i, citral-pyridine; ii,  $\text{H}^+$

Glycozolidine<sup>9a</sup> can be produced by thermal-oxidative cyclization of a diphenylamine.<sup>12</sup>

**Non-isoprenoid Tryptamines.**—There have been more descriptions of  $\beta$ -carbolines and dihydro- and tetrahydro-derivatives from *Virola*<sup>13</sup> and *Phalaris*<sup>14</sup> species. One such compound, reported earlier<sup>9c</sup> as 6-methoxy-2,9-dimethyl-1,2,3,4-

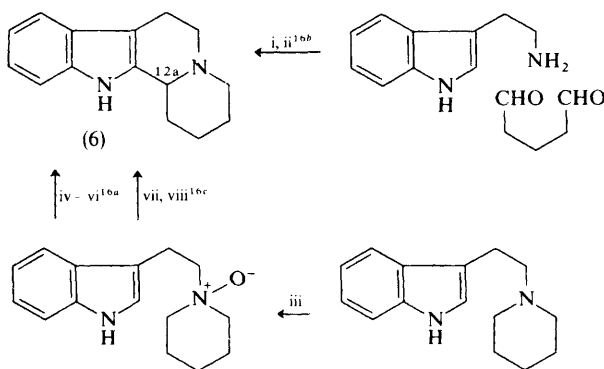
<sup>12</sup> A. Islam, P. Bhattacharyya, and D. P. Chakraborty, *J. C. S. Chem. Comm.*, 1972, 1537.

<sup>13</sup> J. M. Cassady, G. E. Blair, R. F. Raffauf, and V. E. Tyler, *Lloydia*, 1971, 34, 161.

<sup>14</sup> (a) J. L. Frahn and D. F. O'Keefe, *Austral. J. Chem.*, 1971, 24, 2189; (b) P. V. R. Shannon and W. M. Leyshon, *J. Chem. Soc. (C)*, 1971, 2837.

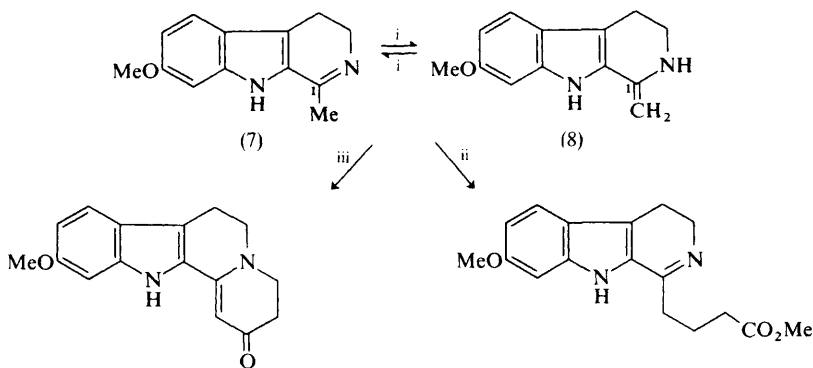
tetrahydro- $\beta$ -carboline, in fact turns out<sup>14b</sup> to be 6-methoxy-2-methyl-1,2,3,4-tetrahydro- $\beta$ -carboline, a structure with one less (!) carbon atom than that originally postulated. The revised structure was established by synthesis.

All the carbon atoms of the simple tetracyclic tetrahydro- $\beta$ -carboline (6) can be picked out by <sup>13</sup>C n.m.r.<sup>15</sup> This technique may provide an alternative means for assigning stereochemistry at the sometimes tricky (see for example p. 196) C-3 position [the equivalent of C-12a in (6)] of tetrahydro- $\beta$ -carboline alkaloids. Three more syntheses of ( $\pm$ )-(6) have been reported (Scheme 1).<sup>16</sup>



Reagents: i, H<sub>2</sub>O, RT, 10 days; ii, NaBH<sub>4</sub>-EtOH; iii, 30% H<sub>2</sub>O<sub>2</sub>-EtOH; iv, aq. FeSO<sub>4</sub>-MeOH-AcOH, heat; v, H<sub>2</sub>S; vi, NaBH<sub>4</sub>; vii, (CF<sub>3</sub>CO)<sub>2</sub>O-CH<sub>2</sub>Cl<sub>2</sub>; viii, H<sup>+</sup>

Scheme 1



Reagents: i, MeOH solution; ii, CH<sub>2</sub>=CHCO<sub>2</sub>Me, RT, 3 days; iii, CH<sub>2</sub>=CHCO<sub>2</sub>Me-PhH-MeOH, heat

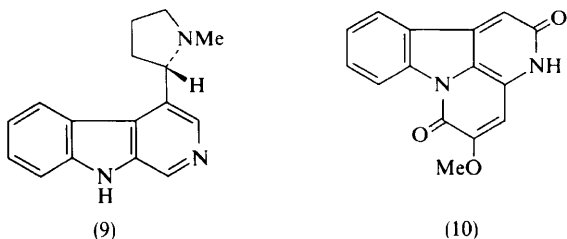
Scheme 2

<sup>15</sup> G. W. Gribble, R. B. Nelson, G. C. Levy, and G. L. Nelson, *J. C. S. Chem. Comm.*, 1972, 703.

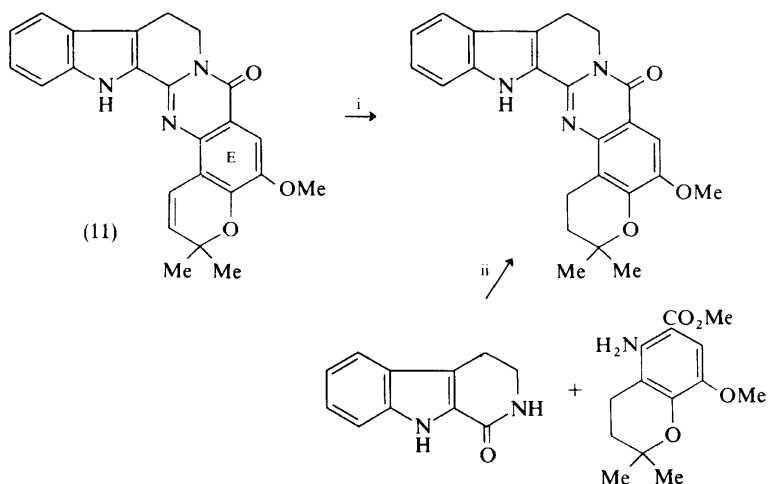
<sup>16</sup> (a) C. A. Scherer, C. A. Dorschel, J. M. Cook, and P. W. Le Quesne, *J. Org. Chem.*, 1972, 37, 1083; (b) G. W. Gribble, *ibid.*, p. 1833; (c) H.-P. Husson, L. Chevelot, Y. Langlois, C. Thal, and P. Potier, *J. C. S. Chem. Comm.*, 1972, 930.

The equilibrium between imine (7) and enamine (8) forms of harmaline has been demonstrated<sup>17</sup> by exchange at the C-1 methyl group in methanolic solution and the enamine reactivity of tautomer (8) by alkylation, as in the reaction with methyl acrylate under mild conditions. Intramolecular enamine acylation occurs after initial alkylation at N<sub>6</sub> in reactions at higher temperature (Scheme 2).

The absolute configuration of brevicolline (9) has been established<sup>18</sup> by a multistep oxidative degradation to hygrinic acid.



Indacanthinone<sup>19</sup> from *Samadera indica* has been given the structure (10). Euxylophoricine C and euxylophorine B are<sup>20a</sup> of the conventional quinazolino-carboline type; paraensine (11) from the same plant, *Euxylophora paraensis*, is a



Reagents: i, H<sub>2</sub>-Pd-C, EtOH; ii, POCl<sub>3</sub>-PhMe, heat

Scheme 3

<sup>17</sup> Atta-ur-Rahman, *J. C. S. Perkin I*, 1972, 731, 736.

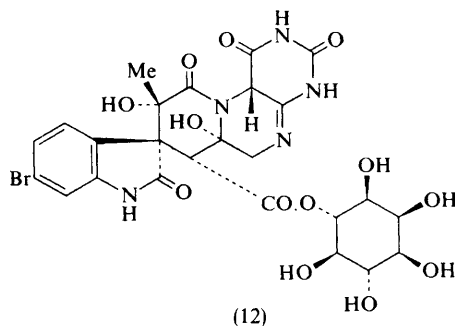
<sup>18</sup> K. Blaha, Z. Koblicová, J. Pospíšek, and J. Trojānek, *Coll. Czech. Chem. Comm.*, 1971, **36**, 3448.

<sup>19</sup> V. S. Iyer and S. Rangaswami, *Current Sci.*, 1972, **41**, 140 (*Chem. Abs.*, 1972, **76**, 140 585p).

<sup>20</sup> (a) B. Danieli, P. Manitto, F. Ronchetti, G. Russo, and G. Ferrari, *Phytochemistry*, 1972, **11**, 1833; (b) B. Danieli, P. Manitto, F. Ronchetti, G. Russo, and G. Ferrari, *Experientia*, 1972, **28**, 249.

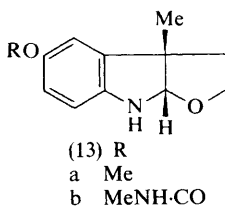
new variation,<sup>20b</sup> incorporating an isoprene unit fused to the E-ring. The dihydro-derivative was synthesized as shown in Scheme 3.

The story behind surugatoxin (12),<sup>21a</sup> which is a mydriatic, is fascinating. This toxin occurs in the gut of the gastropod *Babylonia japonica*, but only in those



specimens caught in Suruga Bay near Mount Fuji. Animals living in other waters, or Suruga Bay creatures allowed to live elsewhere for a while, do not contain the toxin; conversely, non-poisonous specimens acquire the toxicity after spending some time living in Suruga Bay. The structure (12), established by *X*-ray analysis of the heptahydrate, reveals the molecule as an entirely novel 6-bromo-oxindale type, the indole portion of which is possibly derived from tryptophan by the insertion of a methyl group in the ethanamine side-chain, as in indolmycin<sup>21b</sup> and others.

An intermediate (13a), previously converted into physovenine (13b), can be obtained<sup>22</sup> from 5-methoxy-3-methylindolylmagnesium bromide by reaction with ethylene oxide.



An intriguing way<sup>23</sup> of making the tricyclic ring system of the eserine alkaloids, which probably involves an arene oxide type intermediate, uses the reaction of a tryptamine, in the presence of u.v. light, with pyridine *N*-oxide as an oxygen donor (Scheme 4).

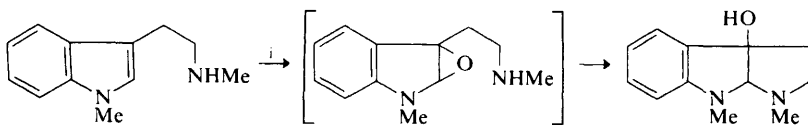
A total synthesis<sup>24</sup> of brevicarine<sup>9d</sup> has been claimed.

<sup>21</sup> (a) T. Kosuge, H. Zenda, A. Ochiai, N. Masaki, M. Noguchi, S. Kimura, and H. Nanita, *Tetrahedron Letters*, 1972, 2545; (b) U. Hornemann, L. H. Horley, M. K. Speedie, and H. G. Floss, *J. Amer. Chem. Soc.*, 1971, **93**, 3078.

<sup>22</sup> T. Onaka, *Tetrahedron Letters*, 1971, 4391.

<sup>23</sup> M. Nakagawa, T. Kaneko, and H. Yamaguchi, *J. C. S. Chem. Comm.*, 1972, 603.

<sup>24</sup> K. I. Kuchkova, A. A. Semenov, and I. V. Terenteva, *Acta Chim. Acad. Sci. Hung.*, 1971, **69**, 367 (*Chem. Abs.*, 1971, **75**, 118 433v).

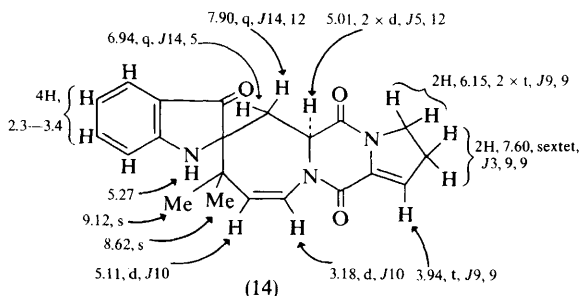


Reagents: i, pyridine *N*-oxide,  $h\nu$  at 253 nm,  $\text{CH}_2\text{Cl}_2$

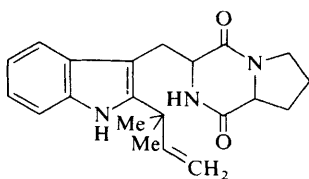
Scheme 4

## 2 Isoprenoid Tryptamine and Tryptophan Alkaloids

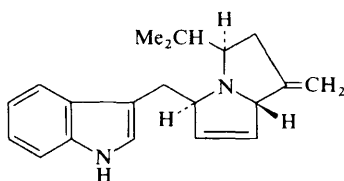
**Non-terpenoid Alkaloids.**—The structure (14) adduced<sup>25a</sup> for austamide, a metabolite from *Aspergillus ustus*, is based principally on a thorough n.m.r. analysis [see data on (14)]. Like the brevianamides<sup>9e,25b</sup> it is made up of proline,



isoprene, and tryptophan moieties although the last, as in brevianamide A, is in a rearranged indoxyl orientation. Deoxybrevianamide E (15a), a compound obtained during the chemical degradation<sup>9e</sup> of brevianamide E, was isolated<sup>25</sup>



(15a)



(16)

as a natural compound from *A. ustus* and is clearly a likely *in vivo* precursor for austamide and perhaps for the brevianamides too.\*

Peduncularine, though made up of a tryptamine unit and a residual  $\text{C}_{10}$ -portion, does not seem<sup>26</sup> to be of a standard type. In the structure (16) which has been proposed for the compound, only one isoprene unit can be discerned, leaving the remaining five carbon atoms in a straight chain.

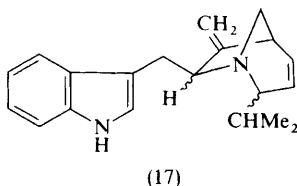
\* See note added in proof, on p. 225.

<sup>25</sup> (a) P. S. Steyn, *Tetrahedron Letters*, 1971, 3331; (b) A. J. Birch and R. A. Russell, *Tetrahedron*, 1972, **28**, 2999.

<sup>26</sup> I. R. C. Bick, J. B. Bremner, N. W. Preston, and I. C. Calder, *Chem. Comm.*, 1971, 1155.



The indole  $\beta$ -substitution is substantiated only by the chemical shift ( $\tau$ 2.95 in  $\text{CDCl}_3\text{-MeOH}$ ) of the other hetero-ring C-hydrogen. Having no exchangeable N-hydrogen and taking up two moles of hydrogen on hydrogenation, the non-indolic portion is seen to comprise a bicyclic ring system. The presence of indolyl- $\text{CH}_2$ , exocyclic methylene, and isopropyl groups seems irrefutably established by n.m.r. and m.s. These data, together with the recognition of a spin-coupled  $-\text{CH}_2-\text{CH}-$  system at  $\tau$ 7.69 (2H, assigned adjacent to  $\text{C}=\text{CH}_2$ ) and  $\tau$ 7.18 (1H, assigned adjacent to N) led to the formulation (16) shown. This Reporter feels that further confirmation would be appropriate; a structure (17)



for example, which *does* contain a conventional monoterpene unit, would seem to fit the data so far presented; other structures having  $\text{C}_{10}$ -skeletons of the rearranged-monoterpene type found in other indole alkaloids should also be considered.

Isoetoclavine has been synthesized<sup>27</sup> using an advanced intermediate from an earlier lysergic acid synthesis.

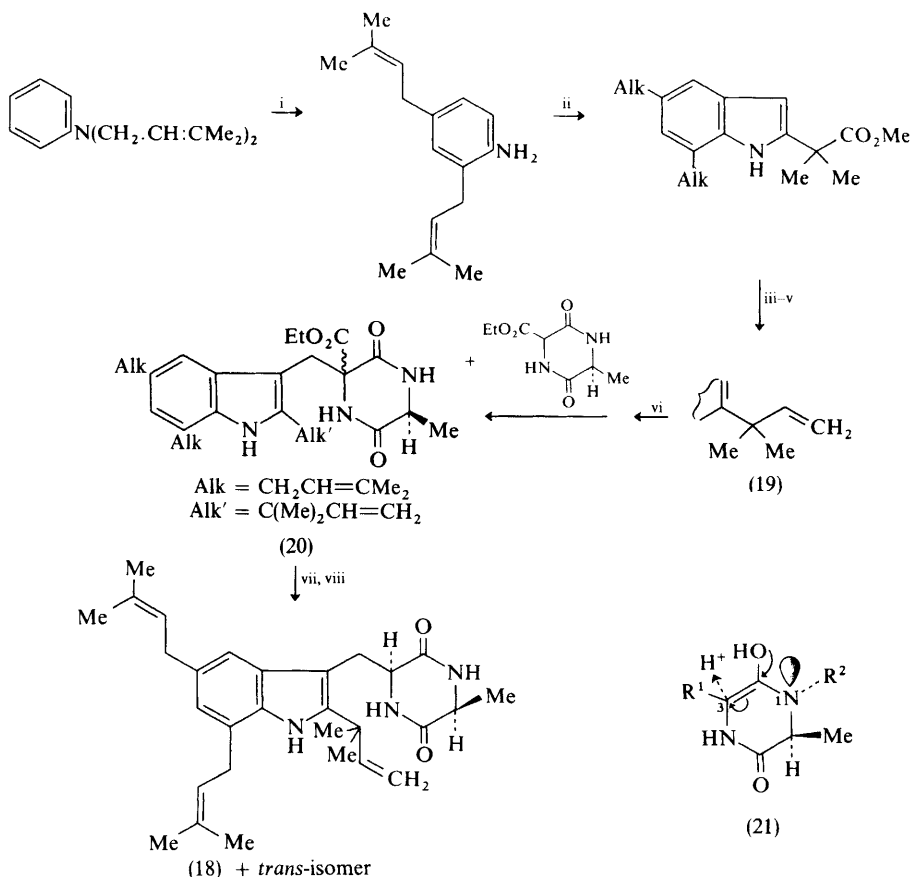
Oxidative degradation has confirmed<sup>28</sup> that the amino-acid units in echinulin (18) are derived from acids in the L-series. The total synthesis (Scheme 5) of (18) has been announced;<sup>29c</sup> it uses a previously established method<sup>29d</sup> for producing an appropriately  $\alpha$ -substituted indole and newly developed methods for the introduction<sup>29b</sup> of benzene ring substituents and the formation,<sup>29a</sup> with partial selectivity, of the desired *cis*-substituted diketopiperazine ring.

The Lewis-acid-catalysed rearrangement of *NN*-di-(3,3-dimethylallyl)aniline gave an acceptable yield of 2,4-di-(3,3-dimethylallyl)aniline. After formation of the requisite  $\alpha$ -substituted indole (19) from this aniline, a 2-ethoxycarbonyl-5-methyl-3,6-diketopiperazin-2-ylmethyl substituent was introduced into the indole  $\beta$ -position by way of a Mannich base. Decarboxylation of the acid corresponding to this product (20) gave predominantly the *cis*-isomer, echinulin (18). It was shown<sup>29a</sup> that the stereoselectivity of this decarboxylation process is general and it was suggested that this might be the result of a preferred C-3 protonation of an intermediate enol, shown in general form (21), from the bottom face owing to steric hindrance by the N-1 lone-pair to protonation from the top. An alternative explanation would seem desirable.

<sup>27</sup> E. C. Kornfeld and N. J. Bach, *Chem. and Ind.*, 1971, 1233.

<sup>28</sup> R. Nakashima and G. P. Slater, *Tetrahedron Letters*, 1971, 2649.

<sup>29</sup> (a) Y. Kishi, S. Nakatsuka, T. Fakayama, and T. Goto, *Tetrahedron Letters*, 1971, 4657; (b) N. Takamatsu, S. Inoue, and Y. Kishi, *ibid.*, p. 4661; (c) N. Takamatsu, S. Inoue, and Y. Kishi, *ibid.*, p. 4665; (d) E. Houghton and J. E. Saxton, *Tetrahedron Letters*, 1968, 5475.



Reagents: i,  $\text{ZnCl}_2$ -xylene-heat; ii,  $\text{BrCH}_2\text{CO}\cdot\text{CMe}_2\text{CO}_2\text{Me}$ ; iii,  $\text{LiAlH}_4$ ; iv,  $\text{DMSO}-\text{Ac}_2\text{O}$ ; v,  $\text{Ph}_3\text{P}=\text{CH}_2$ ; vi,  $\text{CH}_2\text{O}-\text{Me}_2\text{NH}-\text{AcOH}$ ; vii, 0.1N aq.  $\text{NaOH}$ ; viii, dioxan, heat

**Scheme 5**

**Monoterpenoid Alkaloids.**—*Yohimbine-Corynantheine-Heteroyohimbine (and Related Oxindoles) Group*. Holeyine<sup>30a</sup> from *Bleekeria vitiensis*<sup>30</sup> (and *Ochrosia sandwichensis*) is isoreserpiline metho-salt; the former source contains, *inter alia*, 10,11-dimethoxyalstonine.<sup>30a</sup>

*Ochrosia balansae*<sup>31a</sup> contains 10,11-dimethoxypicrephylline, and *O. oppositifolia*<sup>31b</sup> 3,4-dehydroreserpiline (ochroposine) and 10,11-dimethoxydihydro-corynantheol (ochroposinine, stereochemistry at C-20 unspecified).

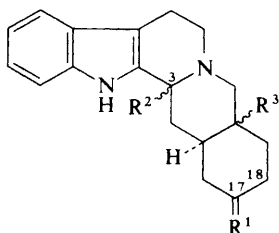
<sup>30</sup> (a) M. Sainsbury and B. Webb, *Phytochemistry*, 1972, **11**, 2337; (b) K. N. Kilminster, M. Sainsbury, and B. Webb, *ibid.*, p. 389.

<sup>31</sup> (a) J. Bruneton, J. L. Pousset, and A. Cavé, *Compt. rend.*, 1971, **273**, C, 442; J. Bruneton and A. Cavé, *Phytochemistry*, 1971, **10**, 846; (b) N. Peube-Locou, M. Koch, M. Plat, and P. Potier, *ibid.*, 1972, **11**, 2109.

Ervine<sup>32</sup> is a heteroyohimbine alkaloid in which the C-D ring junction is *trans*, the D-E *cis*, and in which the C-19 methyl group is  $\beta$ -oriented.

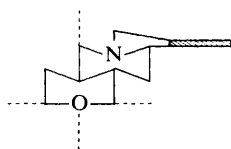
A full structural analysis<sup>33</sup> of an alkaloid from *Vinca elegantissima* led to the assignment of a structure previously given<sup>9f</sup> to isomajdine. The melting points reported for the two alkaloids are effectively identical.

In a study<sup>34</sup> of the chiroptical properties of yohimbanes (22a—d) and yohimbones (22e—h) the Cotton effects of aromatic and 17-keto-chromophores were



| (22) | R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> |
|------|----------------|----------------|----------------|
| a    | H <sub>2</sub> | $\alpha$ -H    | $\beta$ -H     |
| b    | H <sub>2</sub> | $\beta$ -H     | $\beta$ -H     |
| c    | H <sub>2</sub> | $\alpha$ -H    | $\alpha$ -H    |
| d    | H <sub>2</sub> | $\beta$ -H     | $\alpha$ -H    |
| e    | O              | $\alpha$ -H    | $\beta$ -H     |
| f    | O              | $\beta$ -H     | $\beta$ -H     |
| g    | O              | $\alpha$ -H    | $\alpha$ -H    |
| h    | O              | $\beta$ -H     | $\alpha$ -H    |

analysed. Thus subtraction of the curves for the yohimbanes from those of the corresponding yohimbones revealed the contribution from the carbonyl chromophore. One interesting and diagnostically useful aspect to emerge from the study pertains to the differences in the carbonyl Cotton effect observed in neutral and acidic solutions: positively charged nitrogen makes an anti-octant contribution. This is to say that in whichever octant the conformation of the molecule places the basic nitrogen, the contribution, positive or negative, to the Cotton effect will be reduced, *i.e.* will be less positive or less negative, in acidic than in neutral solution. The neutral and acidic solution c.d. curves (Figure) for the carbonyl chromophores of yohimban-17-one (22e) illustrate this effect. The projection formula (23) for this ketone shows the nitrogen in a negative octant.



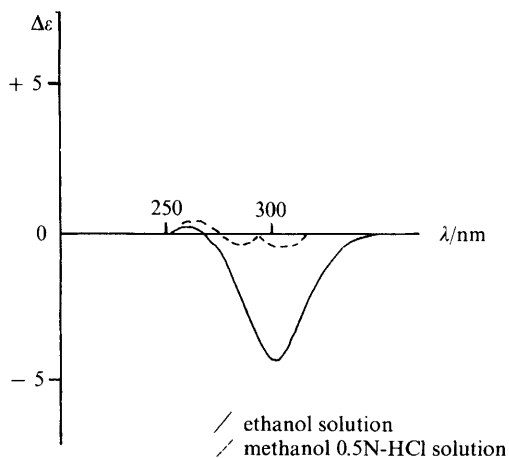
(23)

The chiroptical properties and conformations inferred therefrom were correlated<sup>34</sup> with n.m.r. and dehydrogenation (at C-3—N-4) measurements, the traditional methods for the analysis of configuration and conformation in these systems. The C-3 equilibration of all the yohimbane and yohimban-17-ones was studied. One interesting point which emerged was the differences observed between equilibrium positions determined by the usual organic acid method and

<sup>32</sup> I. A. Ismailov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 346 (*Chem. Abs.*, 1970, **73**, 66 766t).

<sup>33</sup> J. Bhattacharyya and S. C. Pakrashi, *Tetrahedron Letters*, 1972, 159.

<sup>34</sup> L. Bartlett, N. J. Dastoor, J. Hrbek, W. Klyne, H. Schmid, and G. Snatzke, *Helv. Chim. Acta*, 1971, **54**, 1238.



Figure

those achieved by treatment with potassium *t*-butoxide in *t*-butanol. Such differences are of vital relevance to studies in which conformation and/or configurational assignments on piperidines are made on the basis of such equilibration studies. To exemplify such differences one can cite the relative percentages of isomers alloyohimbine (22c) and 3-epialloyohimbine (22d). Base-catalysed equilibration gave a ratio of 54 : 46, whereas acid-catalysed equilibration gave 34 : 66. The allo-isomer is more stable in acetic acid solution but the epiallo-isomer more stable in basic *t*-butyl alcohol. Such differences are attributed to the size of the hydrogen-bonded system ( $N_b^+ - H \cdots^- OAc$ ) in acetic acid solution, a factor not present in basic solution.

The conversion of 18-hydroxymethyl-yohimban-17-ones into pyrazoles has been described.<sup>35</sup>

Three independent investigations<sup>36</sup> have led to the conclusion that the relative stereochemistry at C-3 in the pair of biosynthetically crucial bases (24a) and (24b) must be revised.

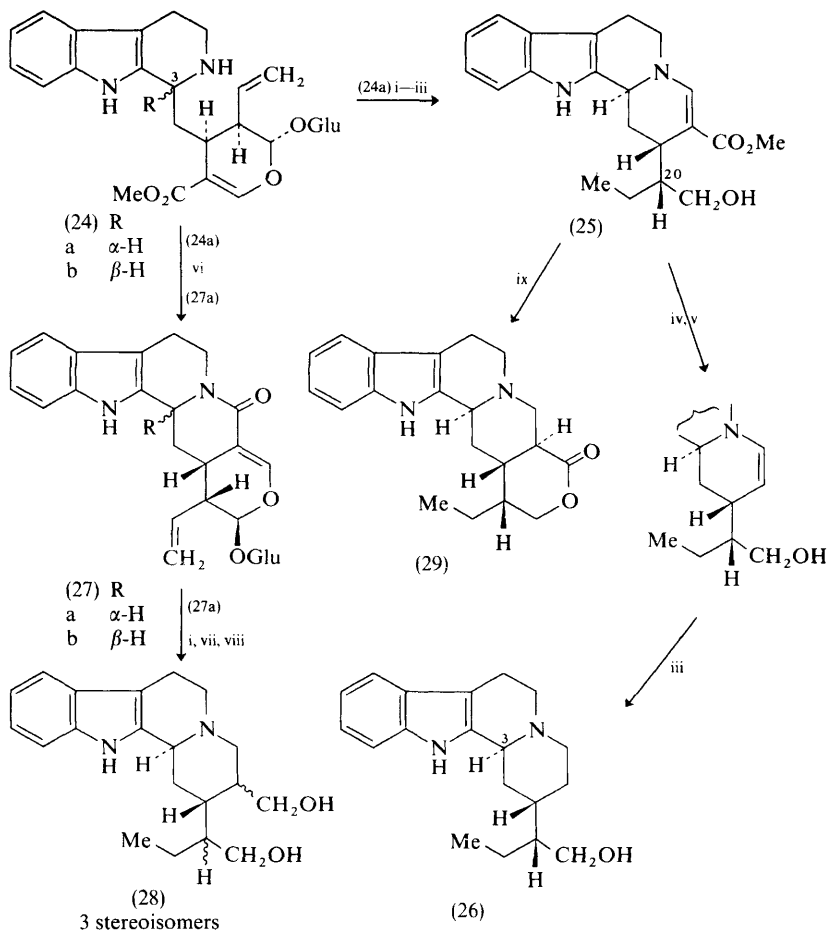
The seemingly definitive<sup>9g</sup> chemical correlation of the *N*-acetyl derivative of ipecoside, the tetrahydroisoquinoline counterpart of (24a) or (24b), with (–)-dihydroprotoemetine, must involve inversion of the crucial centre at some stage, for an *X*-ray analysis of the dimethyl ether of ipecoside showed the hydrogen in question to have a  $\beta$ -orientation and not  $\alpha$  as was previously believed. Application of the optical-rotation-based argument<sup>9g</sup> then confirmed<sup>36a</sup> the reformulations, arrived at by rigorous chemical correlations as described below. Thus

<sup>35</sup> J. D. Albright, N. H. Conroy, L. Goldman, and A. C. Osterberg, *J. Medicin. Chem.*, 1971, **14**, 571.

<sup>36</sup> (a) O. Kennard, P. J. Roberts, N. W. Isaacs, F. H. Allen, W. D. S. Motherwell, K. H. Gibson, and A. R. Battersby, *Chem. Comm.*, 1971, 899; (b) K. T. D. De Silva, G. N. Smith, and K. E. H. Warren, *ibid.*, p. 905; (c) W. P. Blackstock, R. T. Brown, and G. K. Lee, *ibid.*, p. 910.

vincoside is correctly represented by (24b) and isovincoside, now to be known as strictosidine, the name it was given when originally isolated,<sup>9g</sup> has structure (24a).

In a thoroughly worked-out set of correlations,<sup>36b</sup> strictosidine was converted (Scheme 6) *via* tetrahydrovallesiachotamine (25) into dihydroantirrhine (26) of established<sup>9h</sup> C-3 stereochemistry.



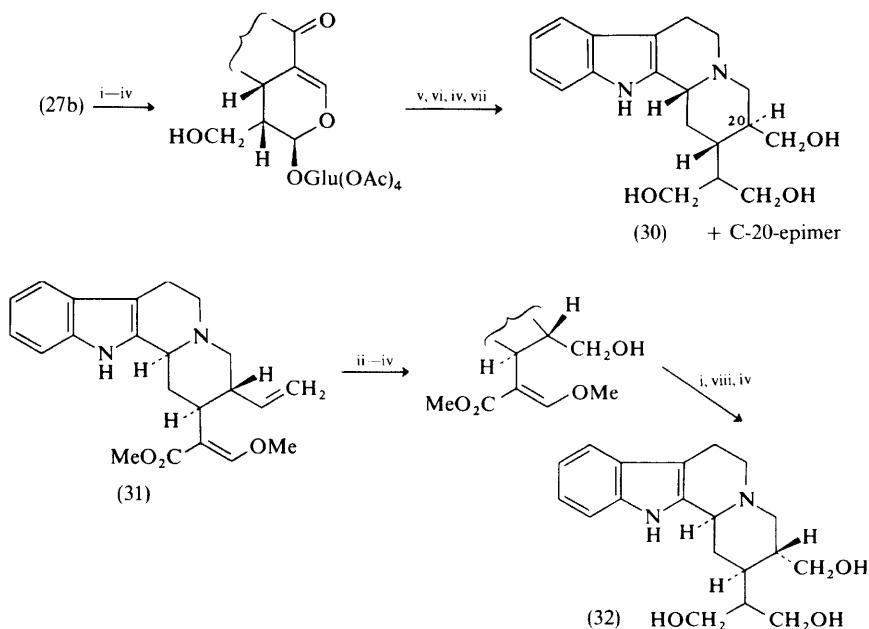
Reagents: i, catalytic reduction; ii, controlled hydrolysis; iii,  $\text{NaBH}_4$ ; iv, mild basic hydrolysis; v, controlled acid-catalysed decarboxylation; vi, base; vii,  $\beta$ -D-glucosidase; viii,  $\text{LiAlH}_4$ ; ix,  $\text{NaBH}_4$ -AcOH

Scheme 6

Studies on strictosamide<sup>36b</sup> (27a) from *Rhazya stricta* (which may be an artefact for it is formed from strictosidine under mild conditions) and vincoside lactam<sup>36c</sup> (27b) have also been adduced in support of the revised formulations.

Strictosamide was converted<sup>36b</sup> (Scheme 6) into a stereoisomeric mixture of tetracyclic diols (28). These in turn were obtained from tetrahydrovallesiachotamine (25) and its C-20-epimer by a series of reductions beginning with reduction of the enamide grouping, as shown for (25)  $\rightarrow$  (29).

Vincoside lactam (27b), isolated from *Adina rubescens*, was converted (Scheme 7)<sup>36c</sup> into a triol (30). Corynantheine (31) was degraded to a triol (32) which proved to be enantiomeric with the major vincoside lactam degradation product (30).



Reagents: i, Ac<sub>2</sub>O; ii, OsO<sub>4</sub>; iii, NaIO<sub>4</sub>; iv, NaBH<sub>4</sub>; v, MeONa–MeOH; vi,  $\beta$ -D-glucosidase; vii, LiAlH<sub>4</sub>; viii, HCl–Me<sub>2</sub>CO

**Scheme 7**

Rubescine,<sup>37</sup> also from *A. rubescens*, is the 3,4-dihydroxycinnamate of vincoside lactam, where the extra acyl residue is at the 3-position of the glucose unit.

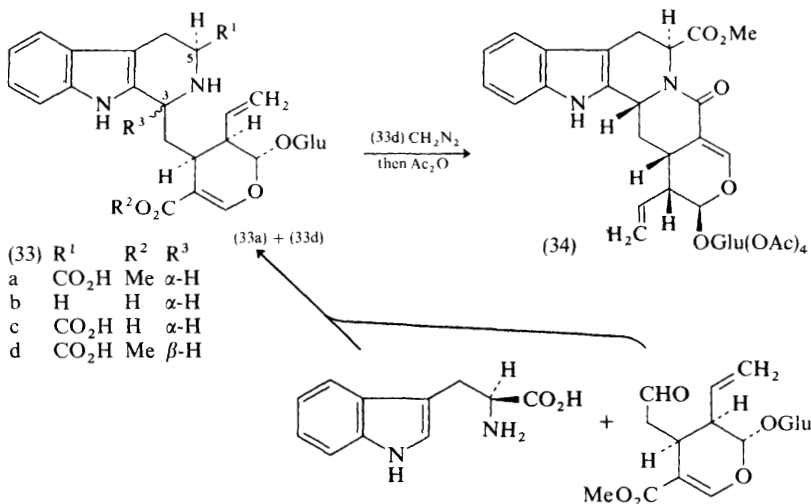
L-Tryptophan was shown to be incorporated with high efficiency into 5 $\alpha$ -carboxystrictosidine (33a)<sup>38</sup> in *Rhazya orientalis*, from where it was originally isolated. It joins the small group of indole alkaloids which retain the carboxyl of precursor tryptophan. The di-acid (33c) and the acid (33b), corresponding to strictosidine, were also isolated in this study.

In analogy with the synthesis<sup>9g</sup> of strictosidine and vincoside from tryptamine, a mixture of 5 $\alpha$ -carboxystrictosidine (33a) (major) and 5 $\alpha$ -carboxyvincoside (33d) could be obtained by condensation of L-tryptophan with secologanin. Again in

<sup>37</sup> W. P. Blackstock and R. T. Brown, *Tetrahedron Letters*, 1971, 3727.

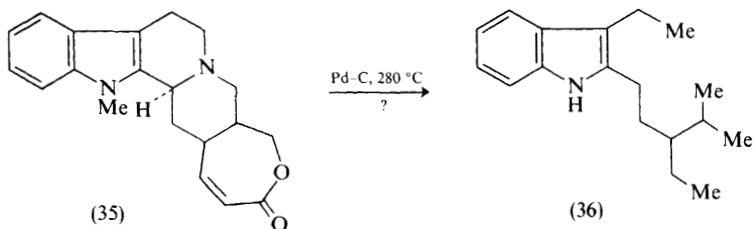
<sup>38</sup> K. T. D. De Silva, D. King, and G. N. Smith, *Chem. Comm.*, 1971, 908.

parallel with vincoside chemistry, 5 $\alpha$ -carboxyvincoside was easily converted into a lactam (34).



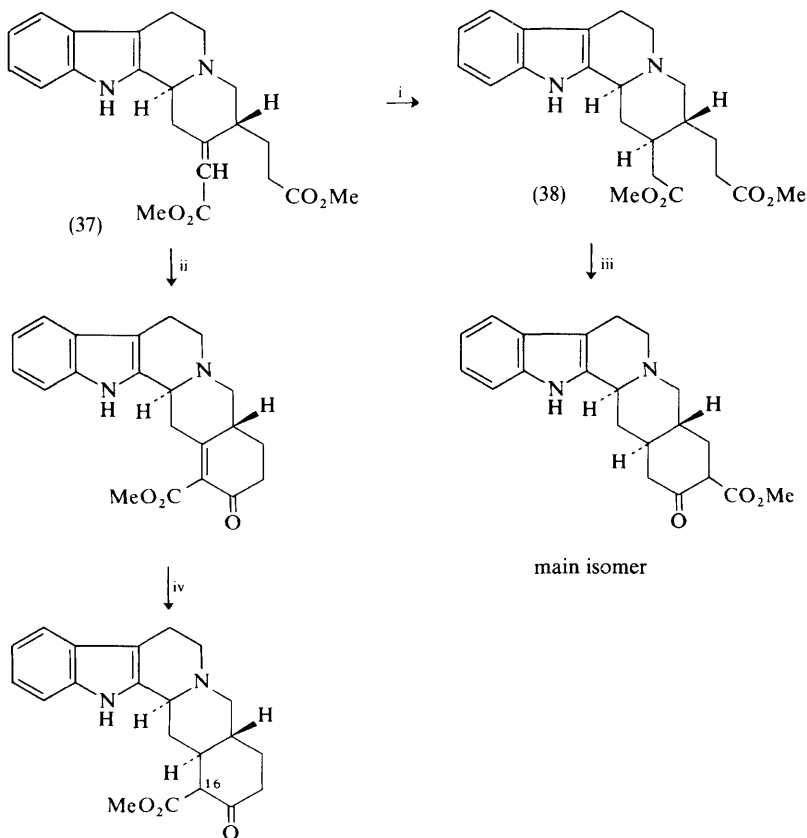
In the course of investigating the stereochemistry at C-3 in 5 $\alpha$ -carboxystrictosidine, epimerizations at C-5 were carried out in alkaloid and model series. A diagnostically useful feature emerged: it was shown that only isomers in which the C-3 and C-5 hydrogen atoms are *cis* have a downfield signal, probably the C-5 proton ( $\tau$  3.9–4.1 in  $\text{C}_6\text{D}_6$ ).

Cannaguine,  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$ , one of nineteen bases isolated from cranberries, *Vaccinium oxycoccus*, has been given<sup>39</sup> the structure (35) which, if it proves to be correct, would place the alkaloid in a unique structural category. However, the evidence presented so far seems to this Reporter to fall far short of supporting the formulation suggested. For example, the reported u.v. absorption  $\lambda_{\text{max}}$  338 nm, is certainly not typical of a simple 1,2,3-trisubstituted indole as is claimed. Perhaps most difficult to believe is that Pd-C dehydrogenation could give as described the indole (36), containing all but one of the skeletal carbon atoms of the suggested structure, in a saturated form, and what is more having lost the  $\text{N}_\alpha$ -methyl group!



<sup>39</sup> K. Jankowski, J. Boudreau, and I. Jankowska, *Experientia*, 1971, 27, 1141.

Two routes<sup>40</sup> to the pentacyclic yohimbine skeleton carrying ester groups at C-16 have been described. Dieckman cyclization<sup>40a</sup> (Scheme 8) of (37), a synthetic precursor of (38), leads to a major product in which closure occurs in the desired sense, in contrast to a comparable reaction on (38).



Reagents: i,  $H_2$ -Pd; ii, NaH-THF, RT; iii,  $MeSOCH_2Na$ -DMSO; iv,  $H_2$ -Pd-MeOH

Scheme 8

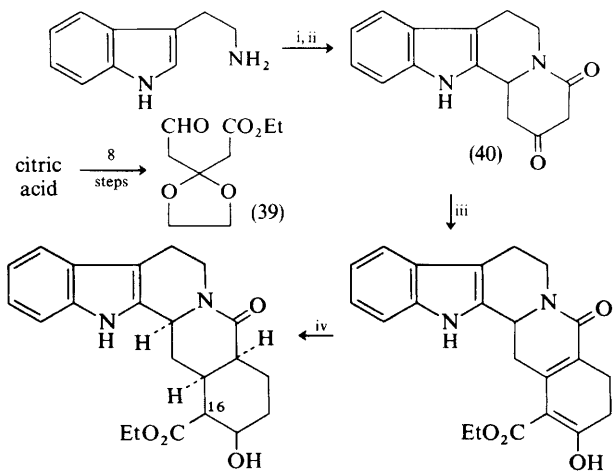
Condensation of tryptamine (Scheme 9)<sup>40b</sup> with the aldehydo-ester (39), readily available from citric acid in eight steps, gives an intermediate (40) to which the E-ring can be added in one step.

( $\pm$ )-19,20-Dihydronorfluorocurine (41) has been synthesized<sup>41</sup> starting with 3,4-dihydro- $\beta$ -carboline (Scheme 10). The mechanism envisaged for the one-step

<sup>40</sup> (a) Cs. Szantay, K. Honaty, L. Toke, A. Buzas, and J. P. Jacquet, *Tetrahedron Letters*, 1971, 4871; (b) F. V. Brutcher, W. D. Vanderwerff, and B. Dreikorn, *J. Org. Chem.*, 1972, **37**, 297.

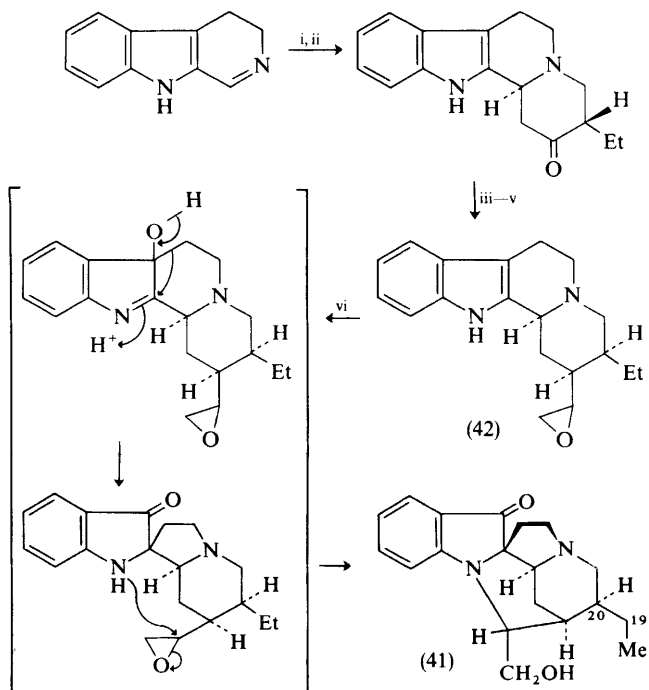
<sup>41</sup> D. D. O'Rell, F. G. H. Lee, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1972, **94**, 3205.





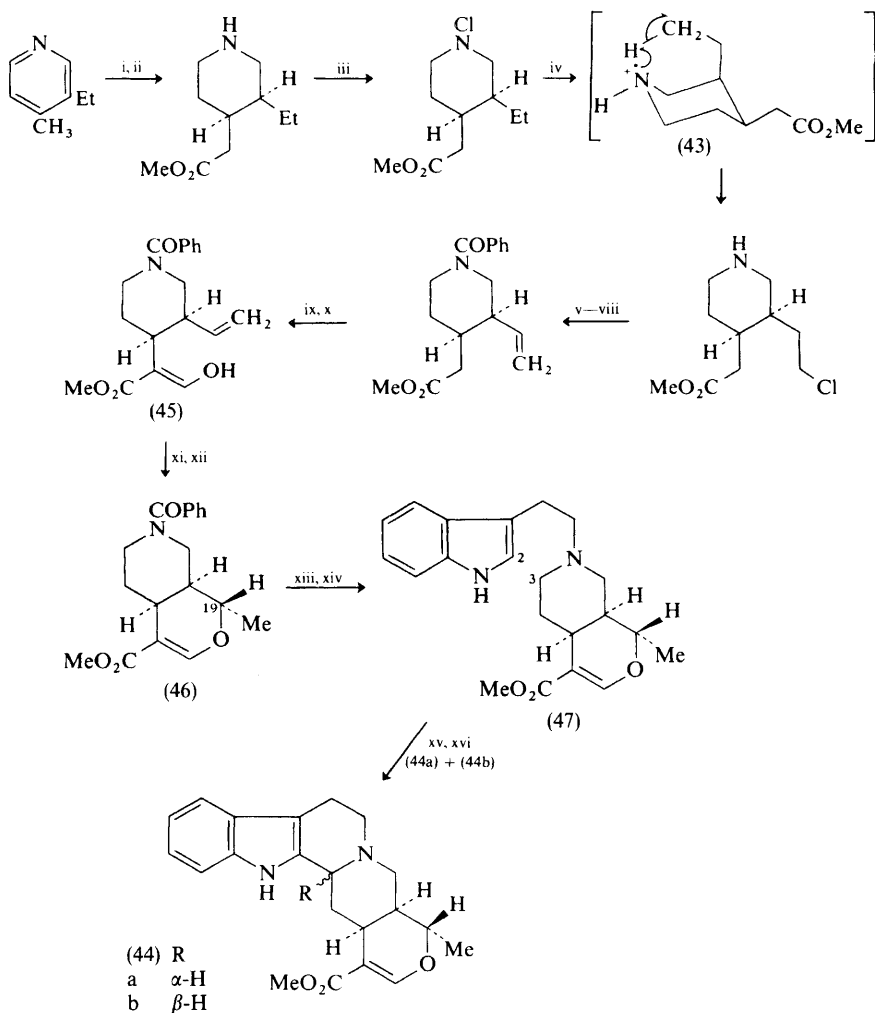
Reagents: i, AcOH, heat; ii, 10% aq. H<sub>2</sub>SO<sub>4</sub>; iii, CH<sub>2</sub>=CH.CO.CH<sub>2</sub>CO<sub>2</sub>Et-KOH-MeOH; iv, H<sub>2</sub>-Pt

Scheme 9



Reagents: i, MeCO.CH(Et).CO<sub>2</sub>Et-aq. CH<sub>2</sub>O-AcOH-EtOH, heat; ii, aq. H<sub>2</sub>SO<sub>4</sub>-EtOH, heat; iii, Ph<sub>3</sub>P=CHOMe-THF; iv, 3N aq. HCl, RT; v, Me<sub>2</sub>SO.Me<sup>+</sup>I<sup>-</sup>-NaH-DMSO; vi, O<sub>2</sub>-NaH-DMSO

Scheme 10



Reagents: i,  $(\text{MeO})_2\text{CO-LiN}(\text{Pr})_2\text{-THF}$ ; ii,  $\text{H}_2\text{-Pt}$  on  $\text{HCl}$  salt; iii,  $N$ -chlorosuccinimide- $\text{Et}_2\text{O}$ ; iv,  $h\nu$ ,  $\text{CF}_3\text{CO}_2\text{H}$ ; v,  $\text{PhCOCl}$ ; vi,  $\text{KOH-MeOH}$ , RT; vii,  $\text{Bu}^t\text{OK-DMSO-PhH}$ ,  $70^\circ\text{C}$ ; viii,  $\text{CH}_3\text{N}_2$ ; ix,  $(\text{Me}_2\text{N})_2\text{CHOBu}^t$ ; x, acid-catalysed hydrolysis; xi,  $\text{Hg}(\text{OAc})_2\text{-DMF}$ ; xii,  $\text{NaBH}_4\text{-MeOH}$ ; xiii, remove benzoyl group; xiv, 3-indolyl- $\text{CH}_2\text{CH}_2\text{Br-K}_2\text{CO}_3\text{-DMF}$ ; xv, excess  $\text{Hg}(\text{OAc})_2\text{-edta}$  di-Na salt; xvi,  $\text{NaBH}_4$ .

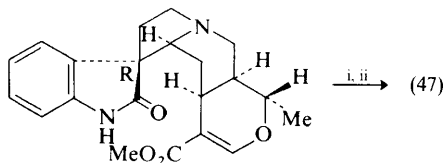
Scheme 11

conversion of (42) into (41) is illustrated: formation of a 3-hydroxy-3*H*-indole is suggested as a first step, followed by rearrangement and finally intramolecular nucleophilic attack on the epoxide. The  $(\pm)$ -dihydronorfluorocurine was transformed into  $(\pm)$ -dihydromavacurine by the standard sequence of borohydride and then acid.

The esters of *cis*- and *trans*-*N*-benzoyl-3-vinyl-4-piperidine-acetic acids have been utilized in syntheses<sup>42b</sup> of ( $\pm$ )-ajmalicine, ( $\pm$ )-19-epiajmalicine, ( $\pm$ )-tetrahydroalstonine, and ( $\pm$ )-akuammigine. One synthesis of the *cis*-piperidine was described<sup>9i</sup> previously; now both isomers have been made<sup>42a</sup> by parallel, new routes, in which the crucial feature is the overall dehydrogenation of a 3-ethyl group in precursor *cis*- and *trans*-3-ethyl-4-piperidine-acetic acid esters involving initial functionalization of the ethyl group using the Hofmann–Loeffler–Freitag reaction. This step works best for the *cis*-isomer, for only one substituent (the ethyl group) is axially oriented, as opposed to two for the *trans*-isomer, in the transition state (43) for the reaction.

To show the way in which one of the piperidine isomers was synthesized and how each was utilized to make heteroyohimbine alkaloids, the full synthesis of ( $\pm$ )-tetrahydroalstonine (44a) and ( $\pm$ )-akuammigine (44b) is detailed in Scheme 11. As well as the effective dehydrogenation of the ethyl group, notable in the sequence is the intramolecular oxymercuration, (45)  $\rightarrow$  (46), which in the *cis*-series leads, by kinetic control, only to the 19 $\beta$ -isomer. Also of interest is the absence, apparently, of 'inside' isomers (such as have been reported in other similar cyclizations, see below) in the closure of the C-ring, *i.e.* (47)  $\rightarrow$  (44).

The transformation of indole into corresponding oxindole alkaloids has been possible for some time; now the reverse sequence has been achieved. The type of 2,3-*seco*-intermediate (47) arrived at by total synthesis above has been produced<sup>43a</sup> and then cyclized, in both heteroyohimbine (Scheme 12) and yohimbine



Reagents: i,  $\text{Et}_3\text{O}^+ \text{BF}_4^-$ ; ii,  $\text{NaBH}_4\text{-AcOH}$

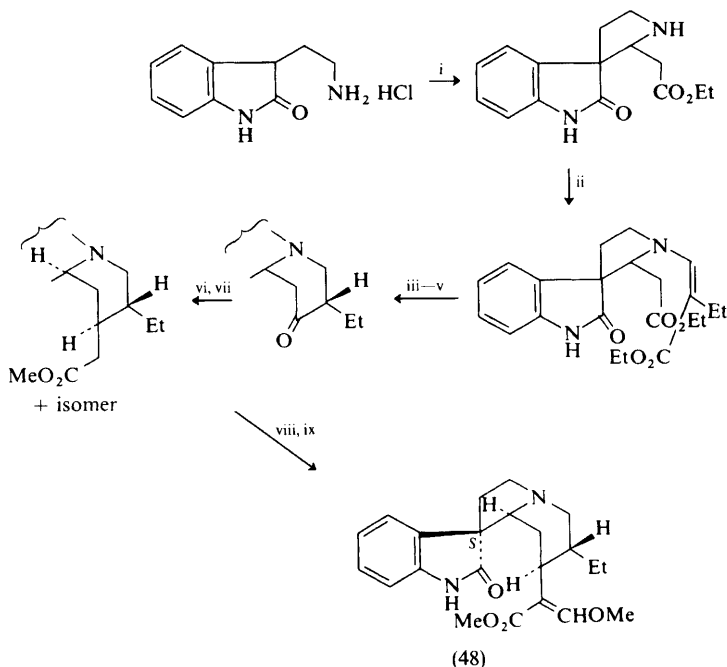
**Scheme 12**

series, by partial synthesis from oxindole types. Thus the reduction of the imino-ethers<sup>43b</sup> of oxindole alkaloids (or oxindole rearrangement products, *e.g.* of yohimbine) with a borohydride-acetic acid combination gives indoles in the 2,3-*seco*-series. Mercuric acetate oxidative cyclization resulted again only in the natural skeletal types from ring E hetero-precursors, but interestingly, did give 'inside' isomers<sup>43c</sup> from 2,3-*seco*yohimbine. Treatment of 2,3-*seco*-akuammigine *N*-oxide with trifluoroacetic anhydride, another way<sup>43d,16c</sup> of producing immonium species, gave only akuammigine and no tetrahydroalstonine or 'inside' isomer.

<sup>42</sup> (a) M. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Amer. Chem. Soc.*, 1971, **93**, 5902; (b) J. Gutzwiller, G. Pizzolato, and M. Uskoković, *ibid.*, p. 5907.

<sup>43</sup> (a) N. Aimi, E. Yamanaka, J. Endo, S. Sakai, and J. Haginawa, *Tetrahedron Letters*, 1972, 1081; (b) A. J. Gaskell, H.-E. Radunz, and E. Winterfeldt, *Tetrahedron*, 1970, **26**, 5353; (c) see, for example, G. C. Morrison, W. Cetenko, and J. Shavel, *J. Org. Chem.*, 1967, **32**, 4089; (d) A. Ahond, A. Cavé, C. Kan-Fan, and P. Potier, *Bull. Soc. chim. France*, 1970, 2707.

The total synthesis<sup>44</sup> of ( $\pm$ )-isorhynchophylline (48) is detailed in Scheme 13.



Reagents: i, 2 moles  $\text{NaOCH}=\text{CH}\cdot\text{CO}_2\text{Et}$ -50% aq.  $\text{EtOH}$ , 50 °C, 2 days; ii,  $\text{EtCH(CHO)}\cdot\text{CO}_2\text{Et}\cdot\text{PhH}$  ( $-\text{H}_2\text{O}$ ); iii,  $\text{H}_2\text{-Pt-AcOH}$ ; iv,  $\text{NaH-PhMe}$ , heat (using major isomer); v, aq.  $\text{HCl}$ , heat; vi,  $\text{NaH-diglyme-(EtO)}_2\text{PO}\cdot\text{CH}_2\text{CO}_2\text{Me}$ ; vii,  $\text{H}_2\text{-Pd-C-EtOH}$ ; viii,  $\text{HCO}_2\text{Et-NaN(SiMe}_3)_2$ ; ix,  $\text{CH}_2\text{N}_2$

**Scheme 13**

*Sarpagine-Ajmaline-Picraline Group.* Raucaffrinoline from *Rauwolfia caffra* has been tentatively assigned<sup>45</sup> a structure corresponding to 21,21-O-dihydroperakine.

Vincarine<sup>46</sup> from *Vinca erecta* is 12-methoxypicalinal. Gelseverine<sup>47</sup> has been shown to be  $N_a$ -methoxygelsemine; it was converted into gelsemine by treatment with lithium-ammonia.

Voachalotine (49) (Scheme 14) undergoes<sup>48a</sup> von Braun degradation to give an ether (50) of the taberpsychine<sup>9j</sup> type. Oxidation<sup>48b</sup> of this alkaloid with

<sup>44</sup> Y. Ban, M. Seto, and T. Oishi, *Tetrahedron Letters*, 1972, 2113.

<sup>45</sup> M. Ataullah Khan and S. Siddiqui, *Experientia*, 1972, **28**, 127.

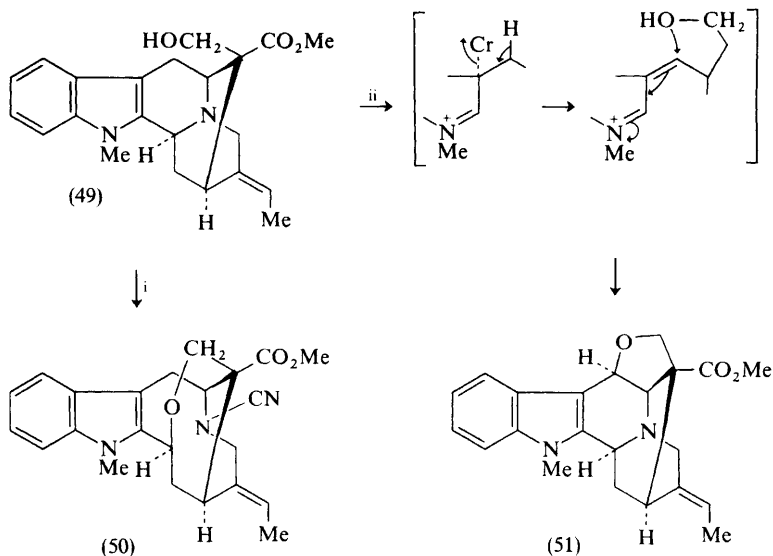
<sup>46</sup> Kh. T. Il'yasova, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 164 (*Chem. Abs.*, 1971, **75**, 49 390q).

<sup>47</sup> E. Wenkert, C.-J. Chang, D. W. Cochran, and R. Pellicciari, *Experientia*, 1972, **28**, 377.

<sup>48</sup> (a) M. Lampe-Tirions, M. Kaisin, and J. Pecher, *Bull. Soc. chim. belges*, 1971, **80**, 27;

(b) J.-C. Braekman, M. Kaisin, and J. Pecher, *Bull. Soc. chim. belges*, 1970, **79**, 665.

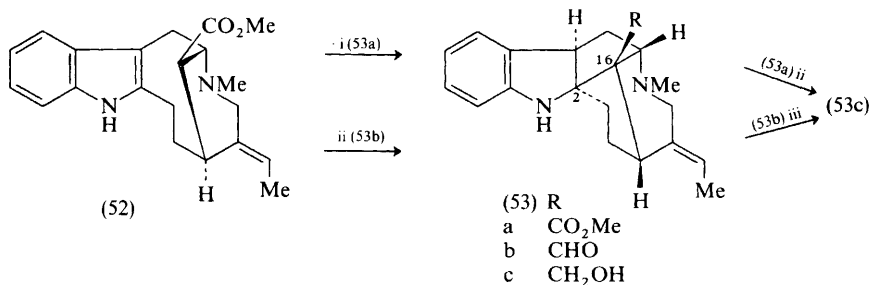
potassium dichromate parallels, in part, analogous reactions of gardnerine summarized previously.<sup>9k</sup> In the present case, oxidation in aqueous solution gave as the main product the cyclic ether (51). In aqueous acetic acid further oxidation occurred to give oxindole and indoxyl rearrangement products. Scheme 14 shows the mechanism considered to operate in the formation of (51).



Reagents: i,  $\text{CNBr}$ ; ii,  $20\% \text{ aq. K}_2\text{Cr}_2\text{O}_7$ , heat

**Scheme 14**

An unprecedented cyclization (Scheme 15), by C-16—C-2 bonding, is observed<sup>49</sup> when deoxyvobasine (52) is treated with phosphoric acid giving (53a), or with lithium aluminium hydride giving (53b).

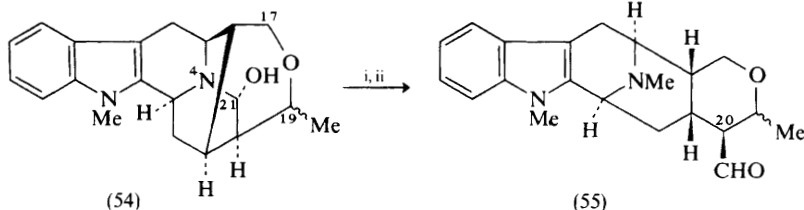


Reagents: i,  $\text{H}_3\text{PO}_4$ ,  $90^\circ\text{C}$ ; ii,  $\text{LiAlH}_4$ ; iii,  $\text{NaBH}_4$

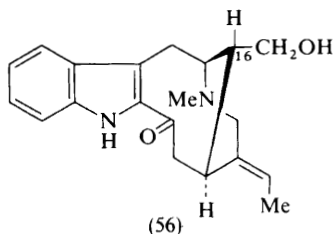
**Scheme 15**

<sup>49</sup> K. A. Jaeggi and U. Renner, *Helv. Chim. Acta*, 1972, **55**, 446.

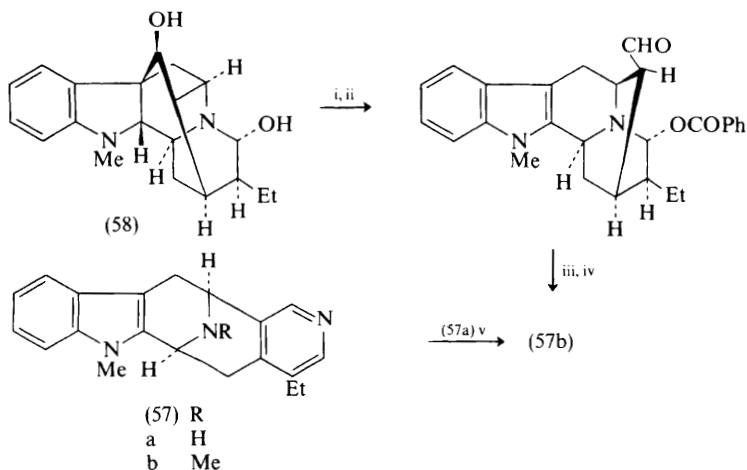
Three more alkaloids from *Pleiocarpa talbotii* have been examined<sup>50</sup> and assigned structures (54)–(56). Talpinine (54) contains the ether linkage



Reagents: i, MeI–PhH; ii, heat (epimerization at C-20)



C-17–O–C-19 first encountered in one half of the bisindole alkaloid villalstonine.<sup>51</sup> Quaternization, cleavage of C-21–N-4, and epimerization at C-20 gave talcarpine (55). 16-Epiaffinine (56) was chemically correlated with vobasine.



Reagents: i, PhCOCl–PhH; ii, Pb(OAc)<sub>4</sub>; iii, MeI; iv, NH<sub>3</sub> (? + O<sub>2</sub>); v, CH<sub>2</sub>O–trace AcOH–NaBH<sub>4</sub>–MeOH

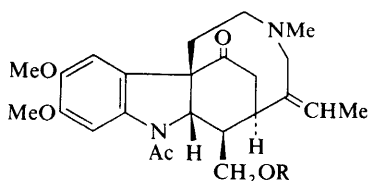
### Scheme 16

<sup>50</sup> J. Naranjo, M. Pinar, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1972, **55**, 752.

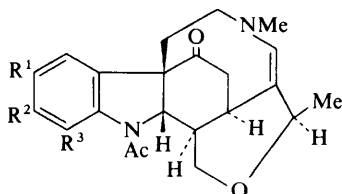
<sup>51</sup> A. A. Gorman, M. Hesse, H. Schmid, P. G. Waser, and W. H. Hopff, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1, p. 265.

Suaveoline (57a)<sup>52</sup> from *Rauwolfia suaveolens* was chemically interrelated with ajmaline (58), as shown in Scheme 16. It is considered not to be an artefact.

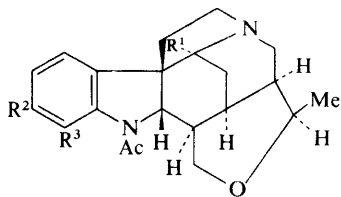
**Strychnine-Akuammicine-Uleine Group.** Studies have recently been carried out on *Strychnos paramensis*,<sup>53</sup> *S. romeu belenii*,<sup>54</sup> *S. tabascana*,<sup>55</sup> and *S. brasiliensis*.<sup>56</sup> Amongst others, *S. paramensis* contains<sup>53</sup> strychnine, brucine, and diaboline, *S. romeu belenii* has<sup>54</sup> 11-methoxy-diaboline, *S. tabascana*<sup>55</sup> has tabascanine (59a),



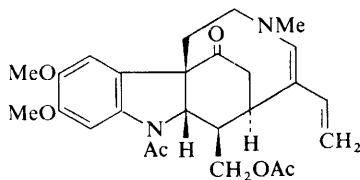
(59) R  
a H  
b Ac



(60) R<sup>1</sup> R<sup>2</sup> R<sup>3</sup>  
a H H H  
b MeO H H  
c H MeO HO  
d MeO MeO H



(61) R<sup>1</sup> R<sup>2</sup> R<sup>3</sup>  
a MeO H H  
b H H H  
c H MeO HO



(62)

strychnobrasiline (60a) and 10-methoxystrychnobrasiline (60b), and *O*-methyl-*N*-acetylstrychnosplendine (61a), and *S. brasiliensis* has,<sup>56</sup> as well as spermostrychnine (61b), 12-hydroxy-11-methoxyspermostrychnine (61c), strychnobrasiline, 12-hydroxy-11-methoxystrychnobrasiline (60c), 10,11-dimethoxystrychnobrasiline (60d), strychnosilidine (59b), the *O*-acetate of tabascanine, and strychnosiline (62).

The structure of sewarine from *Rhazya stricta* has been confirmed<sup>57</sup> as 10-hydroxyakuammicine by an *X*-ray analysis of its methiodide.

*Bleekeria vitiensis*<sup>30</sup> and *Ochrosia balansae*<sup>31a</sup> contain ellipticine types: the former is the best source yet reported for 9-methoxyellipticine.

<sup>52</sup> S. P. Majumdar, P. Potier, and J. Poisson, *Tetrahedron Letters*, 1972, 1563.

<sup>53</sup> G. B. Marini-Bettolo, M. A. Ciasca, C. Galeffi, N. G. Bisset, and B. A. Krukoff, *Phytochemistry*, 1972, 11, 381.

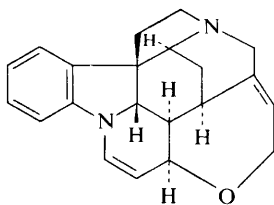
<sup>54</sup> G. B. Marini-Bettolo, E. M. delle Monache, S. A. Giuffra, and C. Galeffi, *Gazzetta*, 1971, 101, 971.

<sup>55</sup> C. Galeffi, C. M. Rendina, E. M. delle Monache, and G. B. Marini-Bettolo, *Farmaco, Ed. Sci.*, 1971, 26, 1100 (*Chem. Abs.*, 1972, 76, 59 837a).

<sup>56</sup> I. Iwataki and J. Comin, *Tetrahedron*, 1971, 27, 2541.

<sup>57</sup> J. M. Karle and P. W. Le Quesne, *J. C. S. Chem. Comm.*, 1972, 416.

Didehydrostrychnidine (63) can be produced<sup>58</sup> by partial reduction of the amide carbonyl group of strychnine with a limited amount of lithium aluminium hydride. Thiodeoxystrychnine (sulphur instead of ether oxygen) has been prepared<sup>59</sup> *via* bromodeoxystrychnine.



(63)

A modification<sup>60</sup> of a previously established route<sup>6b</sup> to the dasycarpidone system has led to an improvement in selectivity, only the dasycarpidone epimeric series being produced *via* ( $\pm$ )-*N*<sub>b</sub>-nordasycarpidone.

*Eburnamine-Aspidospermine Group.* 14,15-Dehydrovincamine and its C-16-epimer have been obtained<sup>61a</sup> from *Crioceras longiflorus*, and their 11-methoxy-analogues, the C-16 epimeric 14,15-dehydrovincines, have been obtained from *Craspidospermum verticillatum*.<sup>61b</sup> A mixture of (–)- and ( $\pm$ )-vincadine has been isolated<sup>62</sup> from *Amsonia tabernaemontana*.

5-Oxominovine, which can be synthesized from minovine by permanganate oxidation, is a minor *Vinca* base;<sup>63a</sup> 5-oxo- and 5,6-dioxo-vincadiformines (stereochemistry not defined) were obtained from *V. erecta*.<sup>63b</sup> Both of these last two reportedly gave vincadiforminol with lithium aluminium hydride.

The proton nuclear relaxation times of the hydrogen atoms in vindoline have been determined.<sup>64</sup>

In a possibly biomimetic sequence<sup>65</sup> (Scheme 17) the two-carbon side-chain of an aspidospermine derivative has been eliminated, to give the carbon skeleton of aspidodispermine.<sup>91</sup>

During biosynthetic studies<sup>66a</sup> on vindoline (64a), a lactam ether (65a) was produced by chromium trioxide oxidation. Later cathovaline, from *Catharanthus*

<sup>58</sup> G. A. Swan and J. D. Wilcock, *J. C. S., Perkin II*, 1972, 1068.

<sup>59</sup> J. Szychowski and O. Achmatowicz, *Roczniki Chem.*, 1971, **45**, 189 (*Chem. Abs.*, 1971, **75**, 64 061b).

<sup>60</sup> T. Kametani and T. Suzuki, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1424.

<sup>61</sup> (a) A. Cavé, A. Bouquet, and B. Das, *Compt. rend.*, 1971, **272**, C, 1367; (b) C. Kan-Fan, R. Besselièvre, A. Cavé, B. C. Das, and P. Potier, *ibid.*, p. 1431.

<sup>62</sup> B. Zsádon and J. Tamás, *Chem. and Ind.*, 1972, 32.

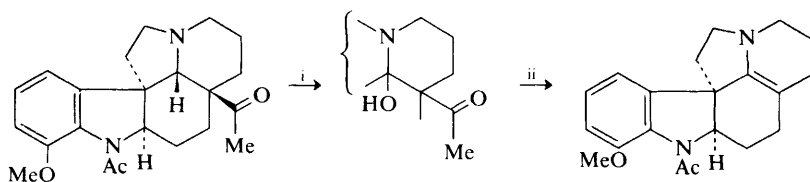
<sup>63</sup> (a) H. Meisel and W. Döpke, *Pharmazie*, 1971, **26**, 182 (*Chem. Abs.*, 1971, **75**, 20 731r); (b) V. M. Malikov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 640 (*Chem. Abs.*, 1972, **76**, 85 984n).

<sup>64</sup> R. Burton, C. W. M. Grant, and L. D. Hall, *Canad. J. Chem.*, 1972, **50**, 497.

<sup>65</sup> T. Gebreyesus and C. Djerassi, *J. C. S. Perkin I*, 1972, 849.

<sup>66</sup> (a) A. R. Battersby and K. H. Gibson, *Chem. Comm.*, 1971, 902; (b) N. Langlois and P. Potier, *Compt. rend.*, 1971, **273**, C, 954; (c) G. H. Aynilian, M. Tin-Wa, N. R. Farnsworth, and M. Gorman, *Tetrahedron Letters*, 1972, 89; (d) G. H. Aynilian, B. Robinson, and N. R. Farnsworth, *ibid.*, 1972, 391.

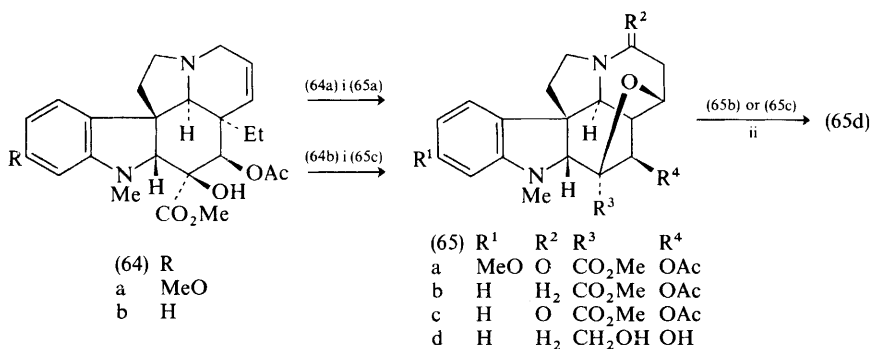




Reagents: i,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$ ; ii,  $\text{Ac}_2\text{O-H}_2\text{SO}_4$

Scheme 17

*ovalis*, was assigned,<sup>66b</sup> without stereochemistry, a structure (65b) with the same type of ether linkage. Cathanneine from *C. lanceus* has also been given<sup>66c</sup> the same structure (65b) but with stereochemistry fully defined<sup>66d</sup> by correlation with vindorosine (64b) (Scheme 18).



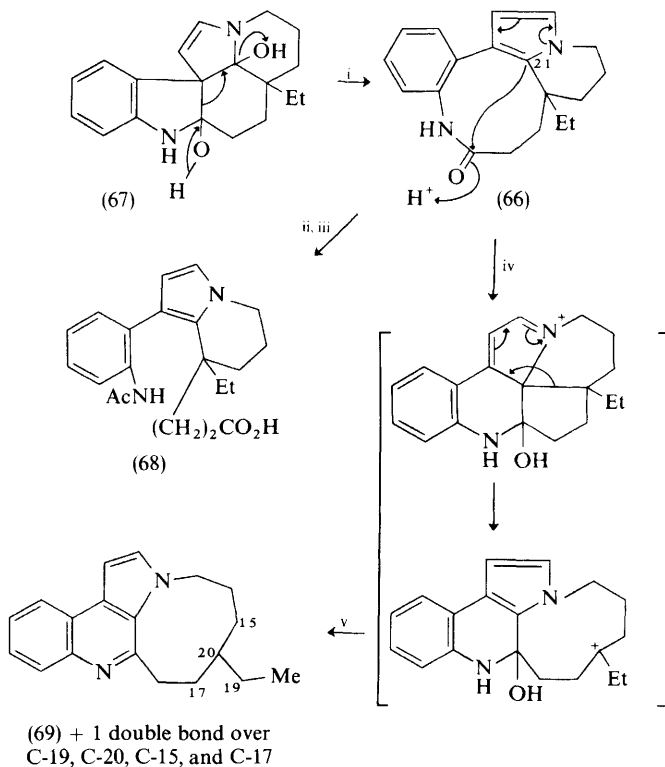
Reagents: i,  $\text{CrO}_3\text{-pyridine}$ ; ii,  $\text{LiAlH}_4$

Scheme 18

Quite the most fascinating new indole alkaloid structure this year is that of rhazinilam (66). This was deduced<sup>67a</sup> by chemical degradation and spectroscopic measurements and confirmed by *X*-ray analysis.<sup>67b</sup> Rhazinilam is a neutral compound which has been isolated from *Rhazya stricta*,<sup>67a</sup> *Aspidosperma quebracho blanco*<sup>67b</sup> and *Melodinus australis*.<sup>67c</sup> Its structural relationship to the *Aspidosperma* alkaloids can be seen from the postulated precursor (67) from which may occur, it is suggested, the observed *in vitro* build-up of the compound in basic fractions from *Rhazya stricta* (Scheme 19). The major loss of ethyl in the mass spectrum of rhazinilam, and of  $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$  in that of the  $N_\alpha$ -acetyl derivative (68) of the amino-acid obtained by alkaline hydrolysis, suggested the attachment of these two groups at a position benzylic to the pyrrole ring. Taking these data, the absence of  $N_\beta$ -hydrogen, the presence of four benzene aromatic protons, a clean AB quartet for the pyrrole  $\alpha$ - and  $\beta$ -hydrogens, the compound's

<sup>67</sup> (a) K. T. D. De Silva, A. H. Ratcliffe, G. F. Smith, and G. N. Smith, *Tetrahedron Letters*, 1972, 913; (b) D. J. Abraham, R. D. Rosenstein, R. L. Lyon, and H. H. S. Fong, *ibid.*, p. 909; (c) H. H. A. Linde, *Helv. Chim. Acta*, 1965, **48**, 1822.

neutrality, and, critically, the acid-catalysed formation of a pyrrolo[2,3-*c*]quinoline (see below) into account, the structure shown can be deduced.



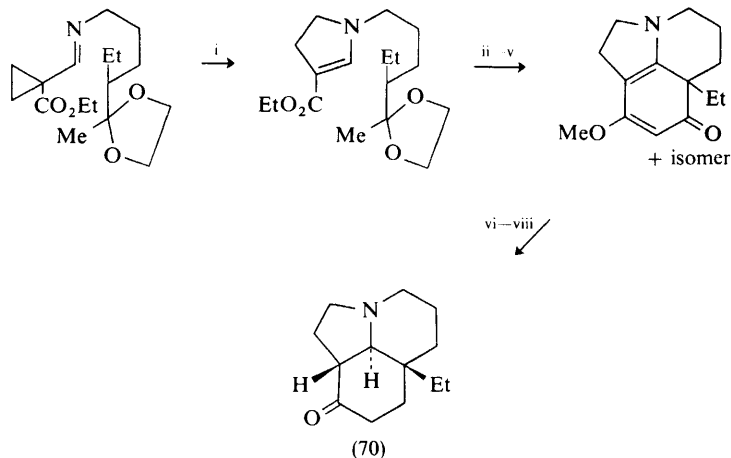
Reagents: i, *in vitro* ?; ii, NaOH; iii, Ac<sub>2</sub>O; iv, aq. H<sub>2</sub>SO<sub>4</sub>, RT; v, -H<sub>2</sub>O, -H<sup>+</sup>

**Scheme 19**

Two further interesting aspects deserve mention. In spite of the apparent presence of several conjugated chromophores, the alkaloid displays only end absorption in the u.v. This is because the ring stereochemistry allows little conjugative overlap between the various components of the apparently extended chromophore.

Crucial to the structure determination was the acid-catalysed rearrangement of rhazinilam to a mixture of compounds (69) all having the distinctive u.v. absorption of a pyrrolo[2,3-*c*]quinoline. This transformation can be seen to involve [arrows on (66) in Scheme 19] electrophilic attack by protonated amide carbonyl on the pyrrole  $\alpha$ -position, C-21, followed by a reverse alkylation of the pyrrole ring. Loss of water and proton (in one of four possible ways) then leads to the observed mixture (69) of pyrroloquinolines.

Still another different sequence has been described<sup>68</sup> which gives a hydro-lulolidine intermediate (70)<sup>6c,9m</sup> for *Aspidosperma* system synthesis. The key ring-forming steps are shown in Scheme 20.



Reagents: i,  $\text{NH}_4\text{Cl}$ -160 °C - 0.1 mmHg; ii,  $\text{HCl}(\text{gas})\text{-Et}_2\text{O}$ ; iii, aq.  $\text{HCl}$ ; iv,  $\text{MeONa-MeOH}$ ; v,  $\text{HCl}(\text{gas})$ ; vi,  $\text{LiAlH}_4$ ; vii, aq.  $\text{H}^+$ , heat; viii,  $\text{H}_2\text{-Pd-C}$

**Scheme 20**

An intermediate (71) of a type previously used<sup>9m</sup> in a synthesis of 14,15-dehydroquebrachamine, has now been prepared in a different way and taken through (Scheme 21) to ( $\pm$ )-tabersonine (72).<sup>69</sup>

In a beautiful synthesis<sup>70</sup> of ( $\pm$ )-vindorosine (64b) (Scheme 22), c and e rings are made in a one-step process which depends on the fact that indoles, even  $\beta$ -substituted indoles, react more rapidly with electrophiles at the  $\beta$ -position than at the  $\alpha$ -position. In the present context the elegant step which makes use of this concept is the formation of (74), together with some (76), from (73). The electrophilic species is generated by interaction of the enamide at the future C-20 with an acid. The success of this step depends on the possibility of trapping a rapidly formed 3,3-disubstituted-3*H*-indolium salt intermediate, (75) in the present case, by an intramolecular nucleophilic addition to the indole  $\alpha$ -carbon; here the nucleophile is the enol of the methyl ketone.

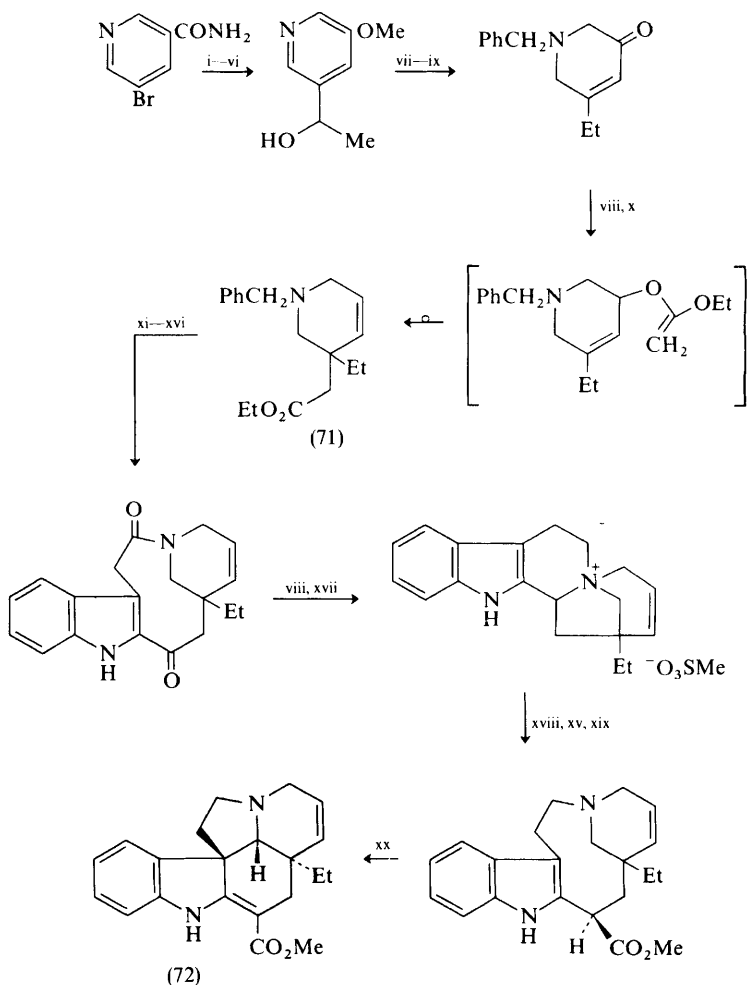
Some of the product (76) resulting from the alternative,  $\alpha$ -substitution was obtained but it was demonstrated that the desired product (74) is not formed, at least principally, by a rearrangement of (76).

<sup>68</sup> R. V. Stevens, J. M. Fitzpatrick, M. Kaplan, and R. L. Zimmerman, *Chem. Comm.*, 1971, 857.

<sup>69</sup> F. E. Ziegler and G. B. Bennett, *J. Amer. Chem. Soc.*, 1971, **93**, 5930.

<sup>70</sup> G. Büchi, K. E. Matsumoto, and H. Nishimura, *J. Amer. Chem. Soc.*, 1971, **93**, 3299.

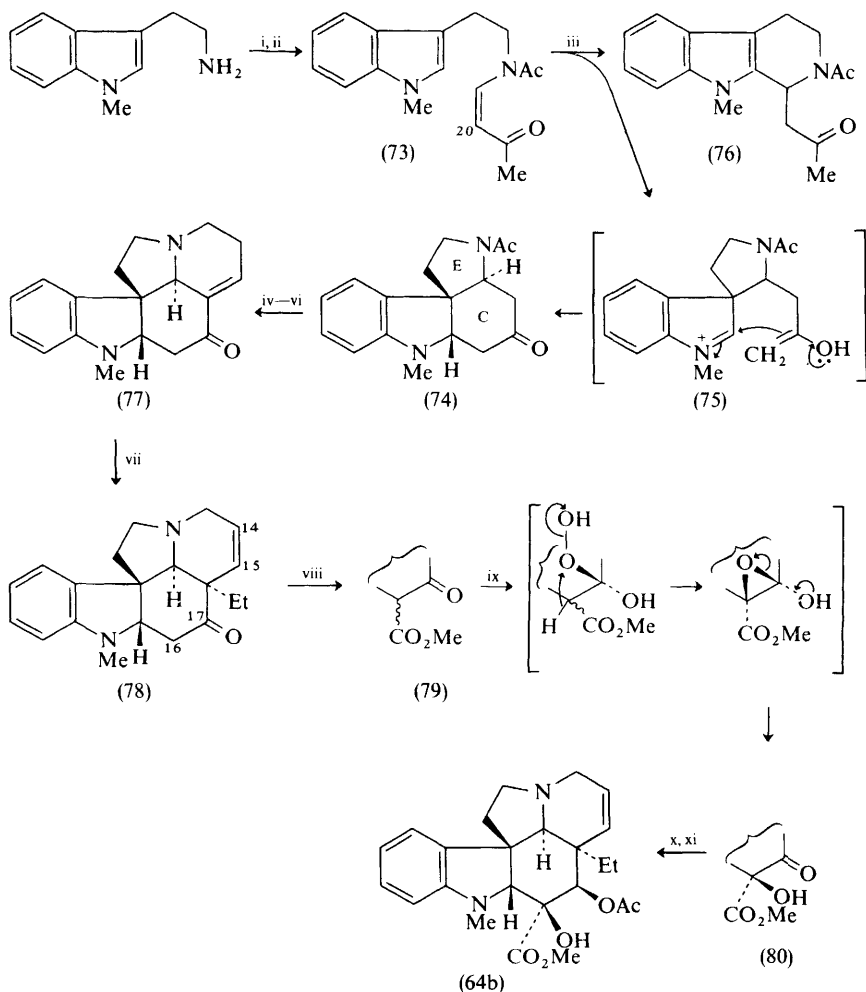
In adding the final ring, (74)  $\rightarrow$  (77), an enone grouping was inserted. This cleverly allowed not only the introduction of the ethyl substituent,  $\rightarrow$  (78), necessarily with migration of the double bond to the desired 14,15-position, but



Reagents: i, NaOBr; ii,  $\text{HNO}_2$ ; iii, aq.  $\text{H}_2\text{SO}_4$ , heat; iv,  $-15^\circ\text{C}$ ,  $\text{CH}_2\text{N}_2\text{-Et}_2\text{O-Bu}^t\text{OH}$ ; v,  $\text{Mg-EtBr}$ ; vi,  $\text{MeCHO}$ ; vii,  $\text{PhCH}_2\text{Br-Me}_2\text{CO}$ , heat; viii,  $\text{LiAlH}_4\text{-THF}$ ; ix, aq.  $\text{HCl-MeOH}$ ; x,  $\text{MeC(OEt)}_3\text{-pivalic acid}$ ,  $140^\circ\text{C}$ ; xi,  $\text{ClCO}_2\text{Et-PhH}$ , heat; xii, aq.  $\text{KOH}$ , heat; xiii,  $\text{MeOH-HCl}$ ; xiv, 3-indolyl- $\text{CH}_2\text{COCl}$ ; xv, saponify; xvi,  $\text{PPA}$ ,  $80^\circ\text{C}$ ; xvii,  $\text{MeSCl-pyridine}$ ,  $0^\circ\text{C}$ ; xviii,  $\text{KCN-DMF}$ , heat; xix,  $\text{CH}_2\text{N}_2$ ; xx,  $\text{O}_2\text{-Pt-EtOAc}$

Scheme 21

also left a C-17 carbonyl as the handle for finally forming the C-17 acetoxy-group and for activating C-16 for the insertion of *both* ester and hydroxy-groups (!).

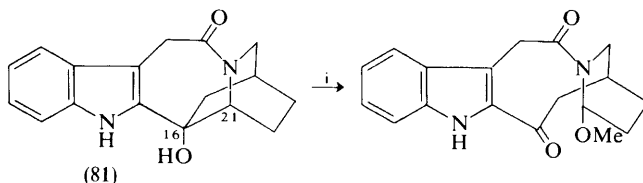


Reagents: i,  $\text{ClCH}=\text{CHCOMe}-\text{Et}_3\text{N}-\text{EtOH}$ ; ii,  $\text{Ac}_2\text{O}-\text{Et}_3\text{N}-\text{PhH}$ , heat; iii,  $\text{BF}_3-\text{Et}_2\text{O}$ ,  $90^\circ\text{C}$ ; iv, 10% aq.  $\text{HCl}$ , heat; v,  $\text{CH}_2=\text{CHCHO}-\text{MeONa}-\text{MeOH}$ ; vi,  $\text{BF}_3-\text{AcOH}$ , RT; vii,  $\text{Bu}^t\text{OK}-\text{Bu}^t\text{OH}-\text{EtI}$ ; viii,  $(\text{MeO})_2\text{CO}-\text{NaH}$ ; ix,  $\text{H}_2\text{O}_2-\text{Bu}^t\text{OK}-\text{Bu}^t\text{OH}-\text{DME}$ ; x,  $-70^\circ\text{C}$ ,  $\text{LiAlH}_4$  (limited)-THF; xi,  $\text{Ac}_2\text{O}-\text{AcONa}$

**Scheme 22**

In the final stages of the synthesis the required stereochemistry at C-16 results, it is thought, by way of the mechanism indicated,  $(79) \rightarrow (80)$ .

**Ibogamine–Cleavamine Group.** Another<sup>6d,9o</sup> synthesis of (±)-velbanamine and (±)-isovelbanamine has been reported<sup>71</sup> in which a precursor (81) having the five rings of the pentacyclic ibogamine type is cleaved between C-16 and C-21.



Reagents: i,  $\text{Pb}(\text{OAc})_4$ – $\text{MeOH}$ – $\text{THF}$ ,  $0^\circ\text{C}$

**Skeletal Rearrangements and Interconversions.** Full experimental details of the Anglo-French re-examination<sup>9p</sup> of the response of tabersonine,<sup>72d</sup> stemmadenine,<sup>72b</sup> and catharanthine<sup>72b</sup> to hot acetic acid have been given. Interestingly, in the conversion of catharanthine (82a) into  $\psi$ -catharanthine (83), 90% racemization was observed.<sup>72b</sup> The product was optically stable under the conditions used, and evidence that a 15,20-double bond must be present for the racemization to occur led to the suggestion that the operation of the equilibria represented in in Scheme 23a is responsible. Flipping of the medium-sized ring in (84a and b) before and faster than reprotonation and closure to the  $\psi$ -catharanthine system would allow for the formation of both (+) and (–)- $\psi$ -catharanthine.†

### 3 Biogenetically Related Quinoline Alkaloids

A stereoisomer of dihydroquinamine has been isolated<sup>73</sup> from *Isertia hypoleuca*. Mercuric acetate oxidation of the C-4'-epimeric 9-deoxy-1',2',3',4',10,11-hexahydrocinchonines and  $\beta$ -1',2',3',4',10,11-hexahydrocinchonine leads<sup>74a</sup> to aromatization of the tetrahydroisoquinoline hetero-ring, whereas similar treatment of the  $\alpha$ -1',2',3',4',10,11-hexahydrocinchonine isomer gave<sup>74b</sup> the cyclic ether (85).

Syntheses<sup>75</sup> of 9-epiquinine and 9-epiquinidine follow routes in which the method of making the quinuclidine unit evolves from the sequence previously described.<sup>9a</sup> The ketone (86) derived by a condensation of 6-methoxy-4-quinolyl-lithium with the piperidine ester (87) (for method of converting ethyl precursor to desired vinyl compound see p. 202) was converted (Scheme 24) into a mixture of the *erythro*-epoxides (88). Ring closure, by a mechanism analogous in principle to that in the previously devised sequence,<sup>9a</sup> using either the epoxides or the precursor *threo*-chlorohydrins, then gave 9-epiquinine (89a) and 9-epiquinidine (89b).

† See note added in proof, on p. 225.

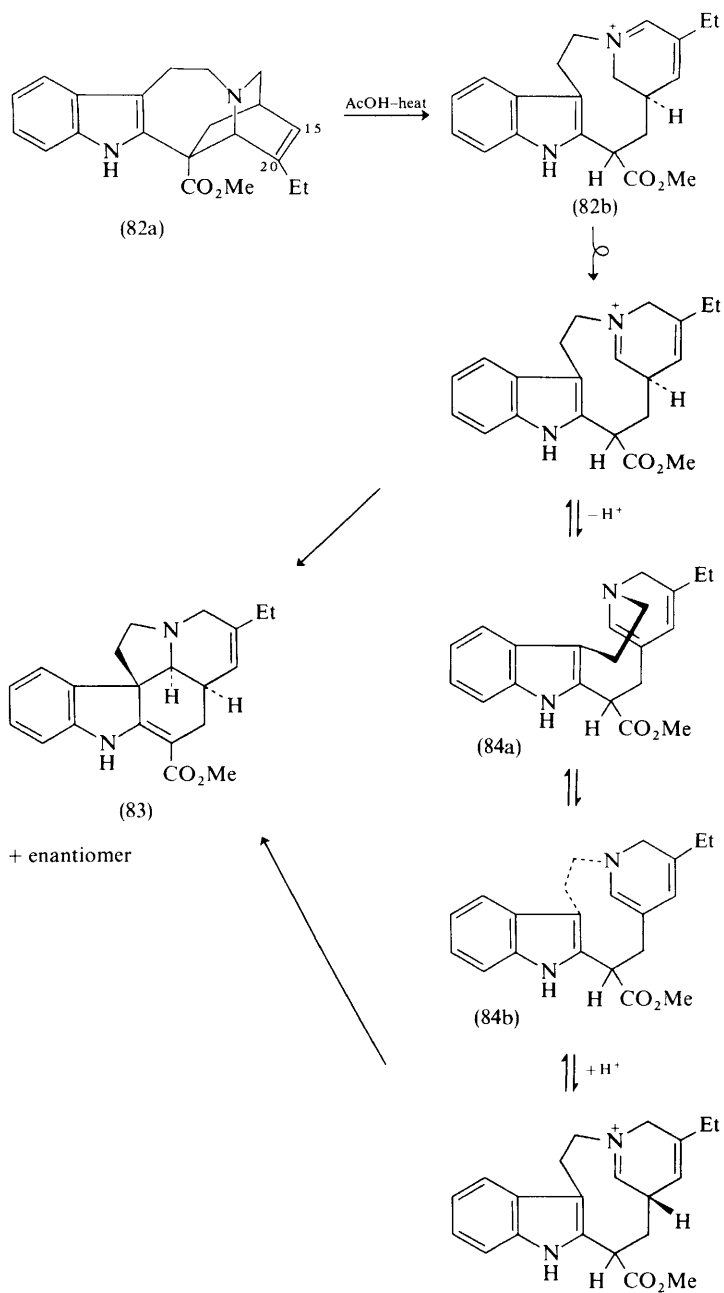
<sup>71</sup> M. Narisada, F. Watanabe, and W. Nagata, *Tetrahedron Letters*, 1971, 3681.

<sup>72</sup> (a) M. Moquet, N. Konesch, and J. Poisson, *Tetrahedron*, 1972, **28**, 1363; (b) R. T. Brown, J. S. Hill, G. F. Smith, and K. S. J. Stapleford, *ibid.*, 1971, **27**, 5217; (c) Attar-Rahman, *Pakistan J. Sci. Ind. Res.*, 1971, **14**, 487; (d) J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, and V. R. Nelson, *J. Amer. Chem. Soc.*, 1970, **92**, 1704.

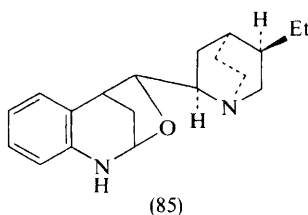
<sup>73</sup> C. A. Lau-Cam and J. Tashiro, *Phytochemistry*, 1971, **10**, 1655.

<sup>74</sup> (a) B. Golankiewicz, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1971, **19**, 685, 693 (*Chem. Abs.*, 1972, **76**, 72 690s and 72 691t); (b) B. Golankiewicz, *ibid.*, p. 7 (*Chem. Abs.*, 1971, **75**, 36 421a).

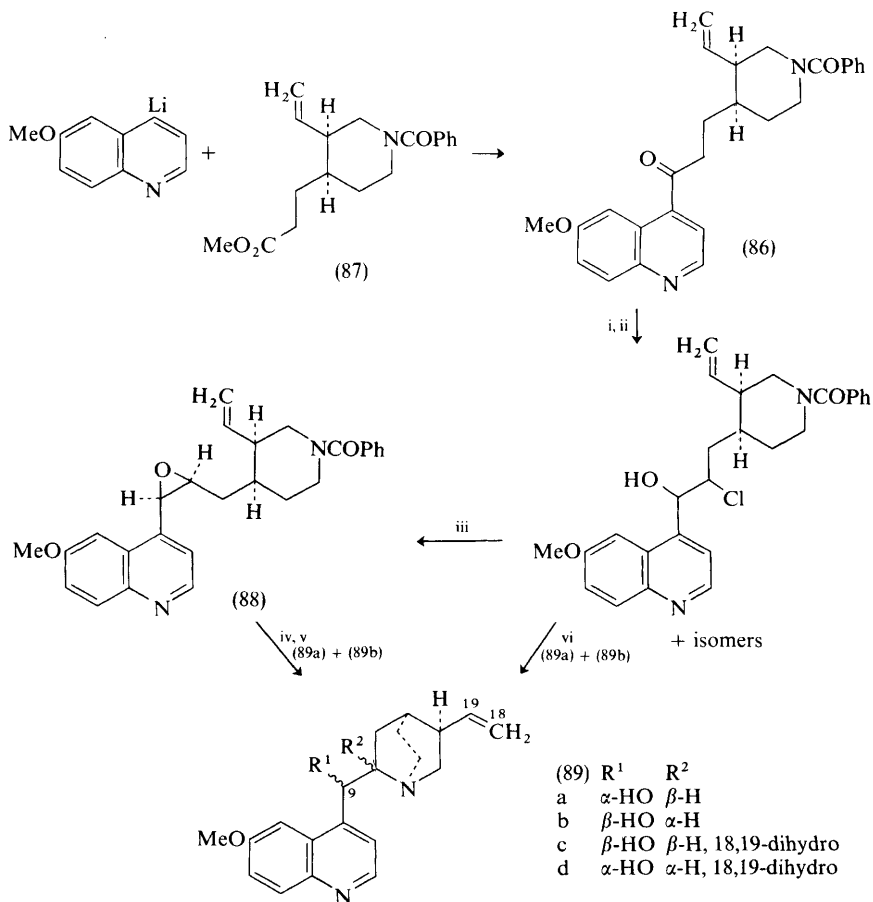
<sup>75</sup> G. Grethe, J. Gutzwiller, H. L. Lee, and M. R. Uskoković, *Helv. Chim. Acta*, 1972, **55**, 1044.



Scheme 23a



Syntheses<sup>76</sup> of quinine, quinidine, and their dihydro-analogues also make use of 6-methoxy-4-quinolyl-lithium, this time in reaction with an aldehyde, *e.g.*



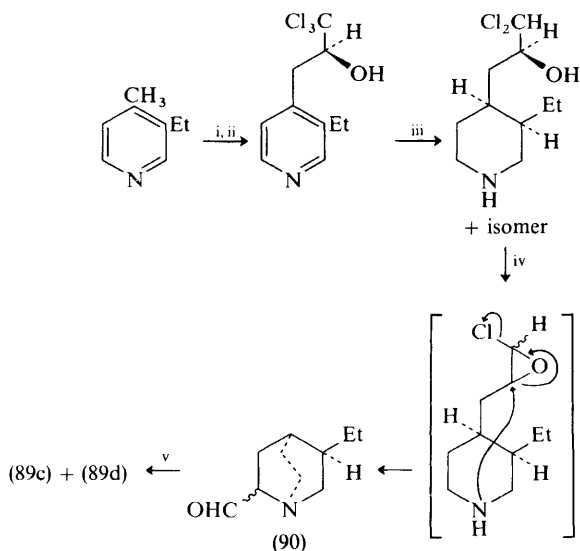
Reagents: i,  $\text{ClNPr}_2$ -100%  $\text{H}_3\text{PO}_4$ , dark; ii,  $\text{NaBH}_4$ -EtOH, 0 °C; iii, aq. KOH-PhH, RT; iv, -78 °C,  $\text{Bu}_2\text{AlH}$ -PhMe (de-acylation); v, PhMe-MeOH (100-1), heat; vi, aq. KOH-MeOH, heat

**Scheme 24**

<sup>76</sup> G. Grethe, H. L. Lee, T. Mitt, and M. R. Uskoković, *J. Amer. Chem. Soc.*, 1971, **93**, 5904.



(90), already having a completed quinuclidine ring system. The aldehydes were prepared starting from 3-ethyl- and 3-vinyl-piperidine-4-acetic esters (see p. 202) and also, in the dihydro-series, from 3-ethyl-4-methylpyridine. Scheme 25 shows the synthesis of dihydroquinine (89c) and dihydroquinidine (89d) from this pyridine.



Reagents: i,  $\text{CCl}_3\text{CHO}$ ; ii, resolve; iii,  $\text{H}_2$ -Pt-5% aq. HCl; iv, 2N-NaOH-PhH; v,  $-70^\circ\text{C}$ , 6-methoxy-4-quinolyl-lithium-Et<sub>2</sub>O-THF

**Scheme 25**

As well as further model,<sup>77a,f,g</sup> analogue,<sup>77b</sup> and prospective synthetic precursor<sup>77c-e</sup> work in the camptothecin area, four total syntheses<sup>78-81</sup> of the ( $\pm$ )-alkaloid have been announced in the year under review.

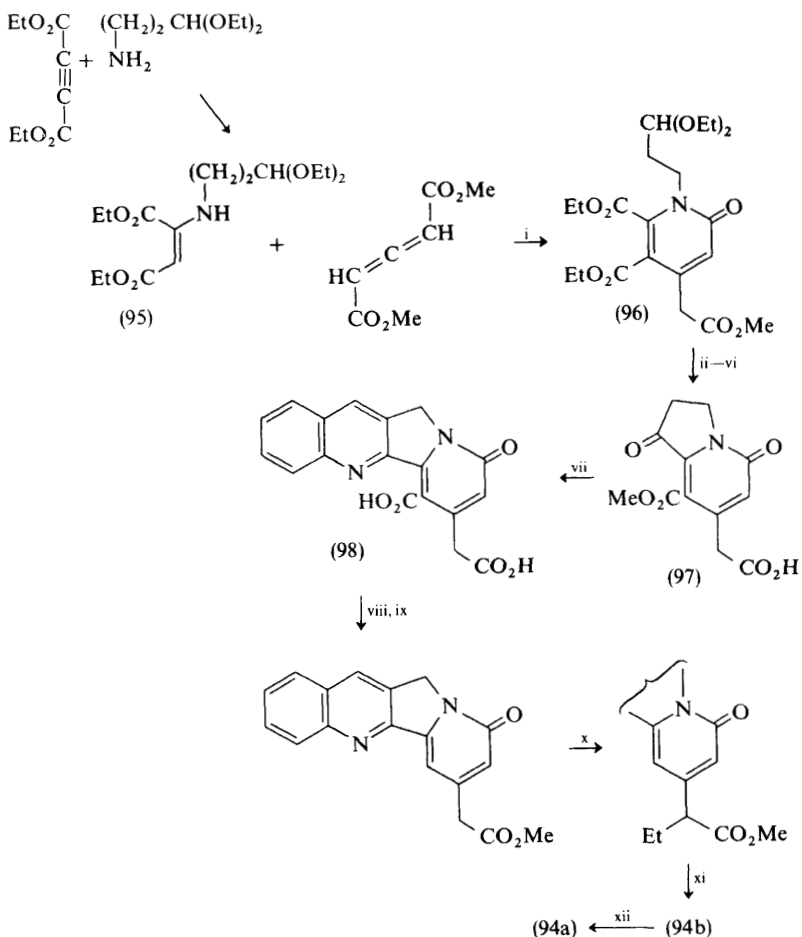
The first synthesis<sup>78</sup> (Scheme 26) to be announced employed a straightforward route<sup>77e,78</sup> to the tetracyclic piperidone intermediate (91). This was then transformed to the 5,6-dihydro-2-pyridone (92); the D-ring oxidation level was chosen in order to allow introduction, (92)  $\rightarrow$  (93), of the remaining substituent atoms of camptothecin in a single, extremely elegant and potentially general, new step, involving the addition-cyclization of the carbonate of an  $\alpha$ -hydroxy-ester to the  $\alpha\beta$ -unsaturated amide. The remaining requisite oxidation level adjustments, which led to ( $\pm$ )-camptothecin (94a), are detailed in Scheme 26.

<sup>77</sup> (a) T. Kametani, S. Takano, and H. Takeda, *Yakugaku Zasshi*, 1971, **91**, 966 (*Chem. Abs.*, 1971, **75**, 151 704g); (b) J. A. Beisler, *J. Medicin. Chem.*, 1971, **14**, 1116; (c) R. F. Borch, C. V. Grudzinckes, D. A. Peterson, and L. D. Weber, *J. Org. Chem.*, 1972, **37**, 1141; (d) L. H. Zalkow, J. B. Nabors, K. French, and S. C. Bisary, *J. Chem. Soc. (C)*, 1971, 3551; (e) T. K. Liao, W. H. Nyberg, and C. C. Cheng, *J. Heterocyclic Chem.*, 1971, **8**, 373; (f) E. Winterfeldt and H.-E. Radunz, *Chem. Comm.*, 1971, 373; (g) J. Warneke and E. Winterfeldt, *Chem. Ber.*, 1972, **105**, 2120.

<sup>78</sup> G. Stork and A. G. Schultz, *J. Amer. Chem. Soc.*, 1971, **93**, 4074.



A new pyridone synthesis<sup>79a</sup> was developed to form the basis of the second synthesis<sup>79b</sup> (Scheme 27) to be announced. This new heterocyclic method involves, in essence, the interaction of a 1,3-dialkoxycarbonyllallene with a  $\beta$ -aminocrotonate [in the present context, (95)] or mono-enamine of a 1,3-dicarbonyl



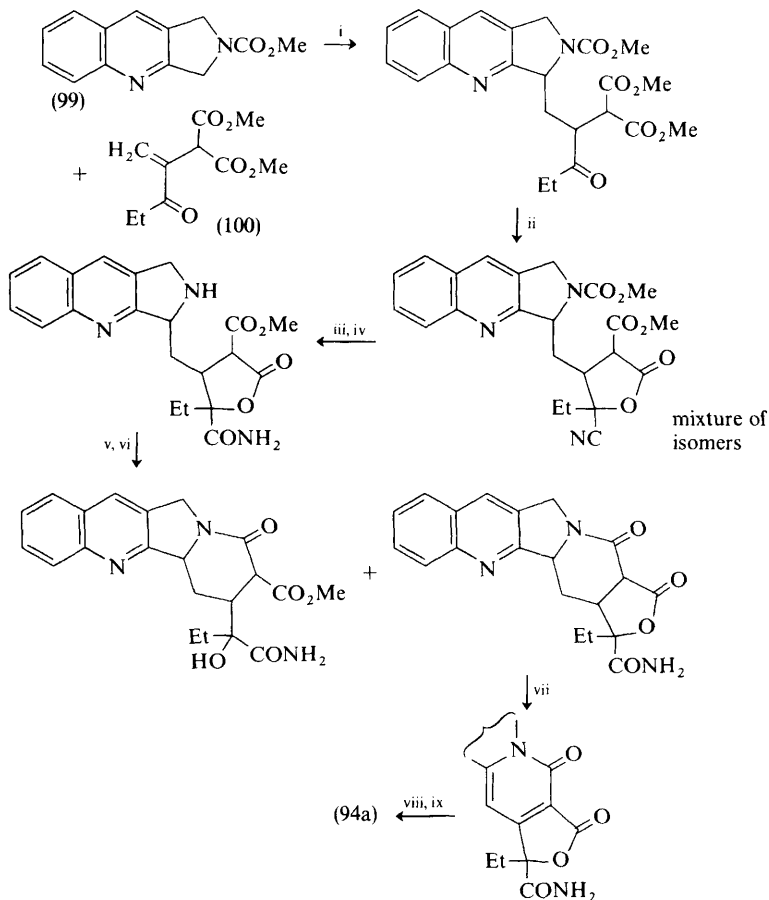
Reagents: i, MeOH-Et<sub>3</sub>N, RT; ii, aq. HCl-Me<sub>2</sub>CO; iii, CrO<sub>3</sub>-aq. H<sub>2</sub>SO<sub>4</sub>-Me<sub>2</sub>CO; iv, MeOH-HCl; v, 3MeONa-MeOH-heat; vi, hydrolysis (and -CO<sub>2</sub>); vii, 2 *o*-aminobenzaldehyde-3NaOH-H<sub>2</sub>O, heat; viii, mono-esterify; ix, 240 °C, 0.3 CuO; x, EtI-NaH, RT, DME; xi, paraformaldehyde-dioxan-trace conc. H<sub>2</sub>SO<sub>4</sub>, 100 °C; xii, 1 aq. H<sub>2</sub>O<sub>2</sub>-Bu'OK-Bu'OH-DMSO

Scheme 27

<sup>79</sup> (a) S. Danishevsky, S. J. Etheridge, R. Volkmann, J. Eggler, and J. Quick, *J. Amer. Chem. Soc.*, 1971, **93**, 5575; (b) R. Volkmann, S. Danishevsky, J. Eggler, and D. M. Solomon, *ibid.*, p. 5576.

compound. Application of this route gave intermediate (96). This was converted into a bicyclic ketone (97) and thence *via* a Friedlander synthesis into a quinoline (98), the E-ring of which was then elaborated as shown in the Scheme.

In a third synthesis,<sup>80b</sup> activation of alkyl at a quinoline  $\alpha$ -position in the tricyclic starting material (99)<sup>77d</sup> was used to introduce a moiety (100)<sup>80a</sup> which of itself provided all but one of the carbon atoms necessary for the D and E rings. The full sequence is summarized in Scheme 28.

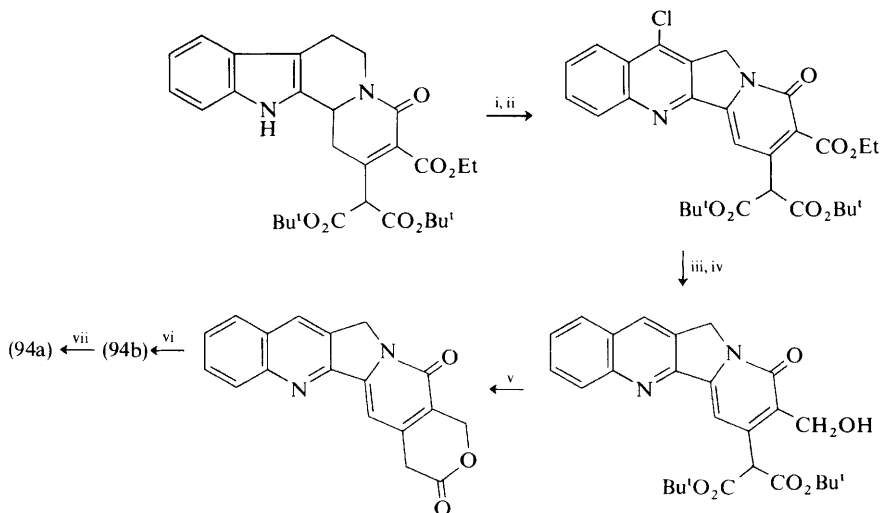


Reagents: i, 100 °C; ii,  $\text{HCN}(\text{liq.})\text{--KCN}$  (trace); iii,  $\text{MeOH--HCl}$ , RT, 2 days; iv,  $\text{HBr--AcOH}$ ; v,  $\text{MeONa--MeOH}$ , 0 °C; vi,  $\text{PhH}$ , heat; vii,  $\text{DDQ--dioxan}$ , heat; viii,  $\text{LiBH}_4\text{--THF}$ , heat; ix, dil. aq.  $\text{HCl}$

Scheme 28

<sup>80</sup> (a) M. E. Wall, H. F. Campbell, M. C. Wani, and S. G. Levine, *J. Amer. Chem. Soc.*, 1972, **94**, 3632; (b) M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Keppler, M. E. Wall, and S. G. Levine, *ibid.*, p. 3631.

The oxidative rearrangement of indoles to quinolines, described in principle in last year's Report,<sup>6e</sup> has been developed into a full synthesis<sup>77f,g,81</sup> of ( $\pm$ )-camptothecin itself (Scheme 29).

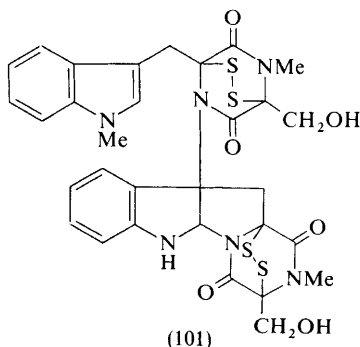


Reagents: i, O<sub>2</sub>-Bu<sup>t</sup>OK-DMSO, RT; ii, SOCl<sub>2</sub>-DMF; iii, hydrogenolysis; iv, Bu<sub>2</sub>AlH; v, CF<sub>3</sub>CO<sub>2</sub>H; vi, NaH-EtI-DMF; vii, O<sub>2</sub>-CuCl<sub>2</sub>-DMF

Scheme 29

#### 4 Bisindole Alkaloids

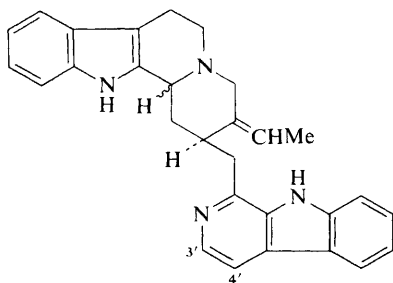
Chetomin, a toxic metabolite from *Chaetomium cochliodes* and *C. globosum*, has been assigned<sup>82</sup> the structure (101) as the most reasonable working possibility on present evidence. Analyses revealed the presence of two acylatable and



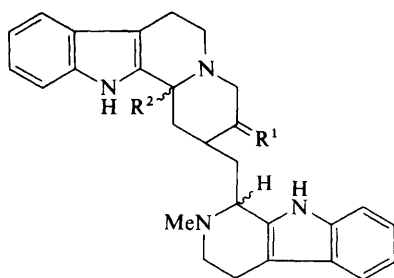
<sup>81</sup> E. Winterfeldt, T. Korth, D. Pike, and M. Boch, *Angew. Chem. Internat. Edn.*, 1972, **11**, 289; M. Boch, T. Korth, J. M. Nelke, D. Pike, H. Radunz, and E. Winterfeldt, *Chem. Ber.*, 1972, **105**, 2126.

<sup>82</sup> S. Safe and A. Taylor, *J. C. S. Perkin I*, 1972, 472.

silylatable  $\text{CH}_2\text{OH}$  groups, three *N*-methyl groups, two epidithiodioxopiperazine rings, and the system  $\text{Ar}\cdot\text{NH}\cdot\text{CH}(\text{C}, \text{C})$ . The mass spectrum of the diacetate showed no molecular ion, but did have an  $(M - S_4 - 2\text{AcOH})$  peak which in turn fragmented into two important ions at  $m/e$  281 and 265, as one would expect

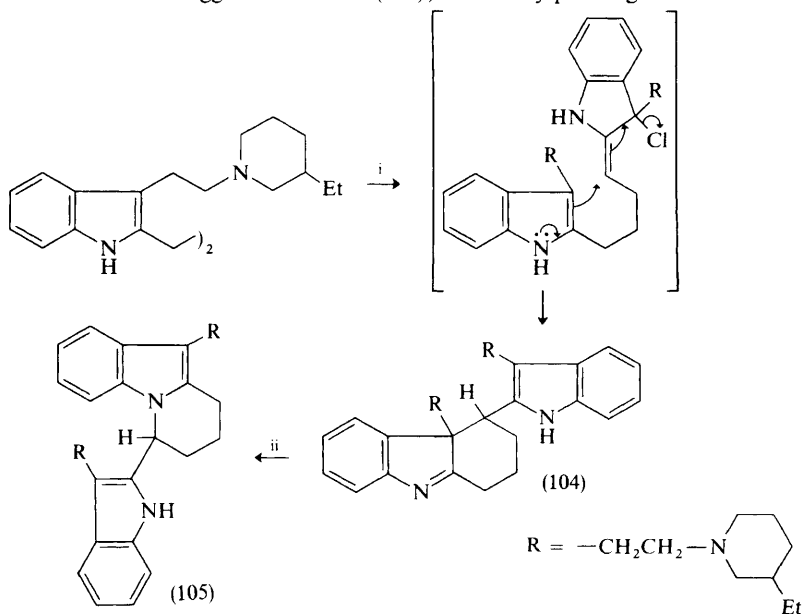


(102)



(103)  $\begin{matrix} R^1 & R^2 \\ \text{a} & \text{CHMe} & \beta\text{-H} \\ \text{b} & \text{H, Et} & \alpha\text{-H} \end{matrix}$

from the structure (101). The u.v. spectrum is reportedly very similar to that of echinulin, *i.e.* it is like that of an indole with, apparently, no hint of the second chromophore,  $\text{ArNH}$ , for which n.m.r. evidence is presented and such as is contained in the suggested structure (101); this is very puzzling.

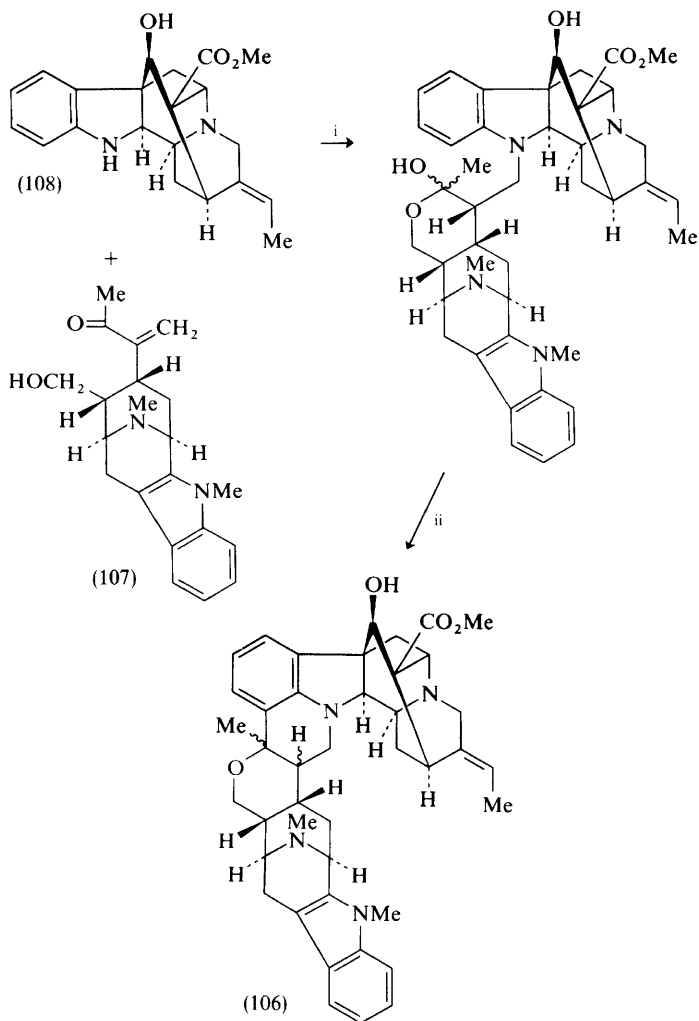


Reagents: i,  $\text{Bu}^t\text{OCl}-\text{Et}_3\text{N}-\text{CH}_2\text{Cl}_2$ ; ii,  $2\text{N}-\text{HCl}$ , RT

Scheme 30

From *Strychnos usambarensis*<sup>83</sup> have been isolated<sup>83b</sup> usambarensine (102), 3',4'-dihydro-usambarensine, and the tetrahydro-derivative<sup>83c</sup> usambarine (103a).

Ochrolifuanines A and B (103b) from *Ochrosia lifuana*<sup>84</sup> and *O. oppositifolia*<sup>31b</sup> are stereoisomers of the same structural type.



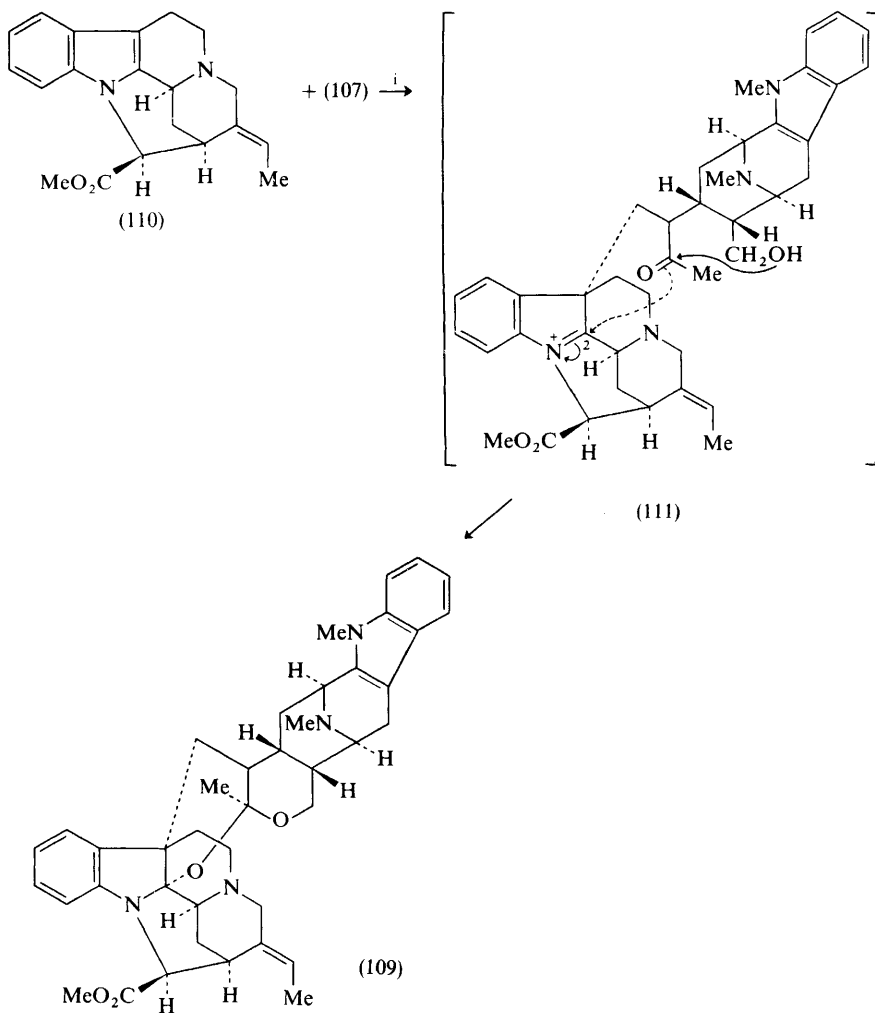
Reagents: i, 0.2N-HCl, RT, 3 days; ii, BF<sub>3</sub>-Et<sub>2</sub>O, 0 °C

**Scheme 31**

<sup>83</sup> (a) L. Angenot and A. Denoe, *Planta Med.*, 1972, **21**, 96 (*Chem. Abs.*, 1972, **76**, 138 174k); (b) L. Angenot and N. G. Bisset, *J. Pharm. Belg.* 1971, **26**, 585 (*Chem. Abs.*, 1972, **76**, 72 694w); (c) M. Koch and M. Plat, *Compt. rend.*, 1971, **273**, C, 753.

<sup>84</sup> N. Peube-Locou, M. Koch, M. Plat, and P. Potier, *Compt. rend.*, 1971, **273**, C, 905.

Tetrahydrosecamine has been isolated<sup>85</sup> from *Amsonia elliptica*. ( $\pm$ )-Didemethoxycarbonyltetrahydropresecamine (104) and ( $\pm$ )-didemethoxycarbonyltetrahydrosecamine (105) have been synthesized.<sup>85</sup> the essence of the sequence is summarized in Scheme 30.



Reagent: i, 0.2N-HCl, RT, 18 h

**Scheme 32**

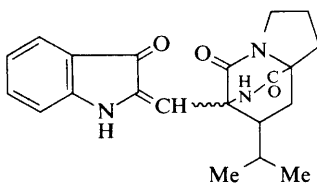
<sup>85</sup> S. Sakai, N. Aimi, K. Kato, H. Ido, and J. Haginawa, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1503.



The structure for alstonisidine<sup>6f</sup> has been revised to (106) on the basis of a possibly biomimetic partial synthesis<sup>86</sup> (Scheme 31) from the two monomeric components, macroline (107) and quebrachamine (108); the latter has now been isolated from the plant source of alstonisidine.

Villalstonine (109)<sup>51</sup> has been partially synthesized<sup>87</sup> (Scheme 32) from its two 'halves', pleiocarpamine (110) and macroline, in an analogous synthesis, a process which in this case reverses a degradation<sup>51</sup> of the alkaloid. It is interesting to note that the partial synthesis may well proceed *via* (111), in which electrophilic attack has occurred at the  $\beta$ -position of the pleiocarpamine indole nucleus. As in the example discussed earlier (see p. 211) this  $\beta$ -substitution is secured by a subsequent intramolecular nucleophilic addition to the  $\alpha$ -carbon, C-2.

*Notes added in proof:* \*More details of work on the brevianamides have been given;<sup>25b</sup> brevianamide B was shown to be a stereoisomer of brevianamide A at the spiro-carbon. Brevianamides C and D are the two geometrical isomers of (15b). In fact these two compounds are photochemical artifacts of the work-up procedure. Irradiation of brevianamide A in methanol solution, with visible light, gives a high yield of a mixture of brevianamides C and D. Brevianamide F is simply *cyclo-L*-tryptophanyl-L-proline.



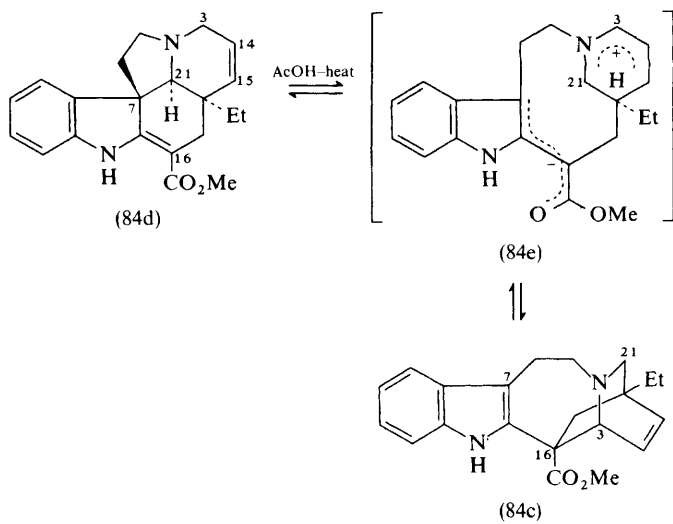
(15b)

† It is relevant to mention here that the structure (82b) has been given<sup>72a</sup> to a salt obtained from catharanthine by refluxing in aqueous acetic acid. Borohydride reduction of the salt gave a mixture of  $\alpha$ - and  $\beta$ -methoxycarbonyl-cleavamines, though these are better obtained preparatively by AcOH-NaBH<sub>4</sub> reduction of catharanthine.<sup>72c,d</sup>

In the French work<sup>72a</sup> too a piperidine-ring double-bond, C-14—C-15 in this case, was shown to be essential to the operation of a rearrangement mechanism; here the formation of allocatharanthine (84c) and related compounds,<sup>9p</sup> in optically active form, from (–)-tabersonine (84d) and the reversibility of the rearrangement, led to the postulation of a solvated 'chano-immonium ion', represented as (84e), as intermediate (Scheme 23b). Whatever the precise pathway, it is clear that the two rearrangements, Schemes 23a and 23b, are a pair of structurally analogous transformations involving the interconversion of *Iboga* and *Aspidosperma* ring skeleta without actual rearrangement of the C<sub>10</sub>-unit.

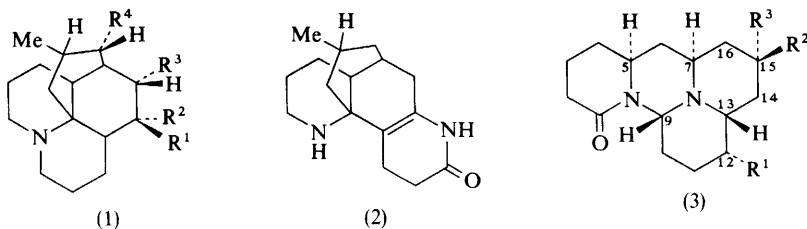
<sup>86</sup> D. E. Burke, J. A. Cook, and P. W. Le Quesne, *J. C. S. Chem. Comm.*, 1972, 697.

<sup>87</sup> D. E. Burke and P. W. Le Quesne, *J. C. S. Chem. Comm.*, 1972, 678.



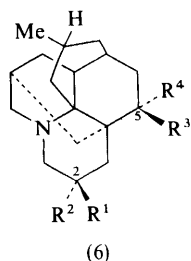
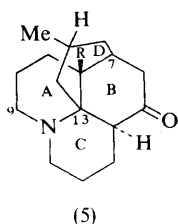
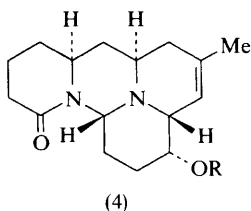
Scheme 23b

The previously uninvestigated *Lycopodium alpinum* has been shown to elaborate the known alkaloids lycopodine (1;  $R^1 + R^2 = O$ ,  $R^3 = R^4 = H$ ), lycoclavine (1;  $R^1 = OAc$ ,  $R^2 = R^4 = H$ ,  $R^3 = OH$ ), clavonine (1;  $R^1 + R^2 = O$ ,  $R^3 = H$ ,  $R^4 = OH$ ), and de-*N*-methyl- $\alpha$ -obscurne (2).<sup>1</sup> The known alkaloid lycocernuine (3;  $R^1 = OH$ ,  $R^2 = Me$ ,  $R^3 = H$ ) and two new compounds, anhydrolycocernuine (3;  $R^1 = R^3 = H$ ,  $R^2 = Me$ , 12,13-double bond) and carolinianine (4;  $R = H$ ), have been isolated from *L. carolinianum* var. *affine*.<sup>2</sup> Anhydrolycocernuine was shown to be identical with the previously known dehydration product of lycocernuine. The structure of carolinianine was deduced from spectral evidence, in particular from its n.m.r. spectrum which showed a masked absorption at  $\delta$  3.50 (1H, C-12—H), a singlet at  $\delta$  1.67 (3H, C-15—Me), and a broad singlet at  $\delta$  5.23 (1H, C-14—H). The  $\delta$  3.50 absorption was predictably shifted downfield to a quartet at  $\delta$  4.89 in the corresponding acetate (4;  $R = Ac$ ) defining the secondary nature of the hydroxyl function. The location of the double bond at C-14—C-15 rather than at C-15—C-16 was deduced by double irradiation experiments. These experiments also established configurations at C-12 and C-13 of carolinianine (4;  $R = H$ ) since irradiation of C-13—H led to the collapse of the C-12—H quartet at  $\delta$  4.89 ( $J = 2$  and 2 Hz) to a triplet ( $J = 2$  Hz). This result, together with the nature of the C-9—H absorption ( $\delta$  5.46, q,  $J = 2$  and 12 Hz) and the lack of intramolecular hydrogen-bonding from hydroxyl to basic nitrogen in the i.r. spectrum of carolinianine, was shown to fit conditions used previously to assign C-9, C-12, and C-13 configurations in lycocernuine (3;  $R^1 = OH$ ,  $R^2 = Me$ ,  $R^3 = H$ ). Furthermore, the configurations at C-5 and C-7 were assigned on the basis of comparison of n.m.r. spectra of



<sup>1</sup> N. Miller, F. Mees, and J. C. Braekman, *Phytochemistry*, 1971, **10**, 1931.

<sup>2</sup> N. Miller, C. Hootele, C. Braekman-Danheux, and J. C. Braekman, *Bull. Soc. chim. belges*, 1971, **80**, 629.



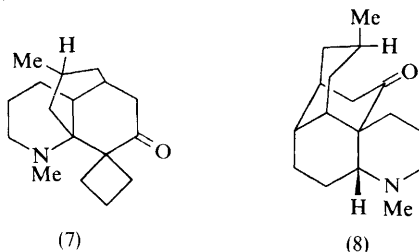
carolinianine and *O*-acetylcarolinianine with those of lycocernuine and *O*-acetyl-lycocernuine. Finally, dihydrocarolinianine was shown to be 15-epilycocernuine (3;  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{Me}$ ) on the basis of spectral and chemical evidence.

The known alkaloids lycocernuine (3;  $R^1 = \text{OH}$ ,  $R^2 = \text{Me}$ ,  $R^3 = \text{H}$ ) and cerneuine (3;  $R^1 = R^3 = \text{H}$ ,  $R^2 = \text{Me}$ ) have been isolated from *L. cernuum*.<sup>3</sup> The same group also reported the isolation of lycocernuine, anhydrolycocernuine (3;  $R^1 = R^3 = \text{H}$ ,  $R^2 = \text{Me}$ , 12,13-double bond), lycopodine (5;  $R = \text{H}$ ), and alkaloid LI Base A from *L. inundatum*.<sup>3</sup> The structure of anhydrolycocernuine was independently established. The structure of alkaloid LI Base A was not determined but it may be related to inundatine (6;  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ,  $R^3 + R^4 = \text{O}$ ), isoinundatine (6;  $R^1 + R^2 = \text{O}$ ,  $R^3, R^4 = \text{H, OH}$ ), and dehydrolycopecurine (6;  $R^1 = R^2 = \text{H}$ ,  $R^3 + R^4 = \text{O}$ ), obtained from *L. inundatum* by another group of workers.<sup>4</sup> The isolation of lycopodine (5;  $R = \text{H}$ ) and lycodoline (5;  $R = \text{OH}$ ) from *L. inundatum* was also reported in this paper.<sup>4</sup> Definite evidence for the pentacyclic framework of inundatine (6;  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ,  $R^3 + R^4 = \text{O}$ ) was secured by its Jones oxidation to dehydroinundatine which was shown to be identical with the diketone (6;  $R^1 + R^2 = R^3 + R^4 = \text{O}$ ) previously obtained from alopecurine (6;  $R^1 = \text{H}$ ,  $R^2 = \text{OCOC}_6\text{H}_5$ ,  $R^3 = \text{OH}$ ,  $R^4 = \text{H}$ ) whose structure had been established by *X*-ray analysis. Base-catalysed deuterium exchange of inundatine gave a dideuteriated derivative showing that the ketone function is located at C-5 rather than at C-2. Comparison of the physical properties of inundatine with those of debenzoyldehydroalopecurine (6;  $R^1 = \text{H}$ ,  $R^2 = \text{OH}$ ,  $R^3 + R^4 = \text{O}$ ) showed that these compounds are epimeric at C-2 and therefore established the complete stereochemistry of inundatine as written (6;  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ,  $R^3 + R^4 = \text{O}$ ). The relationship of inundatine to isoinundatine (6;  $R^1 + R^2 = \text{O}$ ,  $R^3, R^4 = \text{OH, H}$ ) was indicated by Jones oxidation of both alkaloids to the same diketone (6;  $R^1 + R^2 = R^3 + R^4 = \text{O}$ ). The location of the ketone function in isoinundatine was established by deuterium exchange studies (incorporation of four deuterium atoms) but the stereochemistry of the C-5—OH group was not determined. Finally, the structure of dehydrolycopecurine (6;  $R^1 = R^2 = \text{H}$ ,  $R^3 + R^4 = \text{O}$ ) was confirmed by its reduction

<sup>3</sup> Y. Inubushi, T. Harayama, T. Hibino, and M. Akatsu, *J. Pharm. Soc. Japan*, 1971, **91**, 980 (*Chem. Abs.*, 1971, **75**, 148 492f).

<sup>4</sup> J. C. Braekman, C. Hootele, and W. A. Ayer, *Bull. Soc. chim. belges*, 1971, **80**, 83.

with sodium borohydride to a dihydro-derivative which was shown by direct comparison to be identical with the known alkaloid, lycopocurine (6;  $R^1 = R^2 = R^4 = H$ ,  $R^3 = OH$ ).



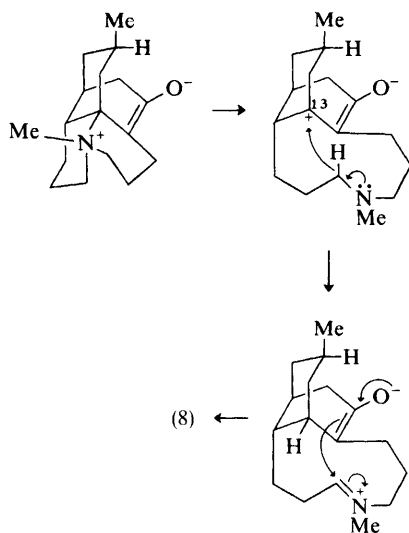
The Hofmann degradation product of lycopodine (5;  $R = H$ ) methiodide for which structure (7) had been previously proposed has now been shown to possess structure (8) by chemical, spectral, and *X*-ray analysis.<sup>5</sup> Key evidence that structure (7) is untenable was obtained from the mass spectrum which showed only a weak  $M^+ - 57$  peak. This peak is usually the observed base peak in lycopodine and its derivatives, and attributable to loss of the C-7—C-13 bridge and a hydrogen atom. The absence of this peak in the mass spectrum of the Hofmann base thus implies the absence of the N—C-13 bond. The Hofmann base showed a base peak at  $m/e$  57 ( $C_3H_7N$ ) whose origin was studied by preparing the corresponding bases from lycopodine  $N$ - $[^2H_3]$ methiodide and  $[9,9-^2H_2]$ lycopodine methiodide. The mass spectrum of the Hofmann product derived from lycopodine  $N$ - $[^2H_3]$ methiodide showed the  $m/e$  57 base peak shifted to  $m/e$  60 indicating that the NMe function is part of the  $C_3H_7N$  fragment, whereas that of the product from  $[9,9-^2H_2]$ lycopodine methiodide showed no shift of the base peak. The latter fact eliminates structure (7) from further consideration. The methiodide of the Hofmann base showed in its n.m.r. spectrum three protons at  $\delta$  4.65, 4.08, and 3.80 which were at lower fields than in the free base itself, suggesting the presence of three hydrogens on carbons adjacent to nitrogen. Furthermore, of these signals only the  $\delta$  4.65 peak is absent in the spectrum of the methiodide of the Hofmann base derived from  $[9,9-^2H_2]$ lycopodine methiodide, an observation which strongly suggests structure (8) for the Hofmann base. The structure was confirmed by *X*-ray analysis of the hydrobromide derivative. A mechanism for the unusual rearrangement was proposed involving a hydride transfer from C-9 to C-13 (Scheme 1) for which evidence could possibly be obtained from further mass spectral studies of the Hofmann base and its deuteriated derivatives.

A synthetic approach to compound (9), a tricyclic analogue of lycopodine (5;  $R = H$ ), which was originally announced in 1966 and utilized in the meantime by other workers as described in detail<sup>6</sup> has been published in full.<sup>7</sup> The approach

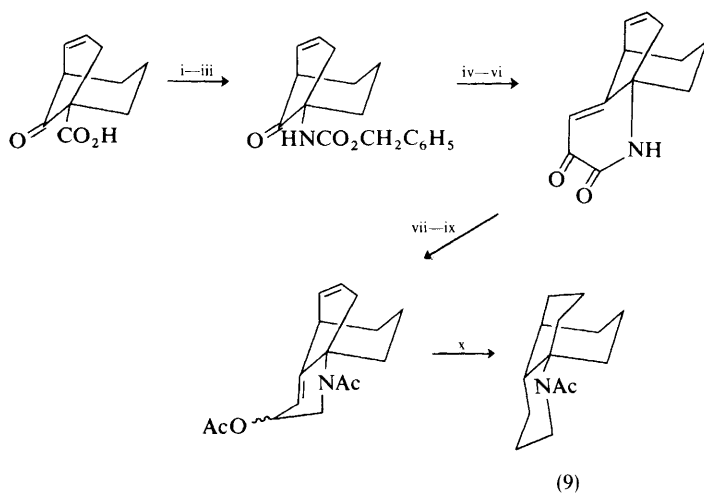
<sup>5</sup> N. Chin-You, D. B. MacLean, A. Prakash, and C. Calvo, *Canad. J. Chem.*, 1971, **49**, 3240.

<sup>6</sup> V. A. Snieckus, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1, p. 341.

<sup>7</sup> E. W. Colvin, J. Martin, W. Parker, R. A. Raphael, B. Shroot, and M. Doyle, *J. C. S. Perkin I*, 1972, 860.



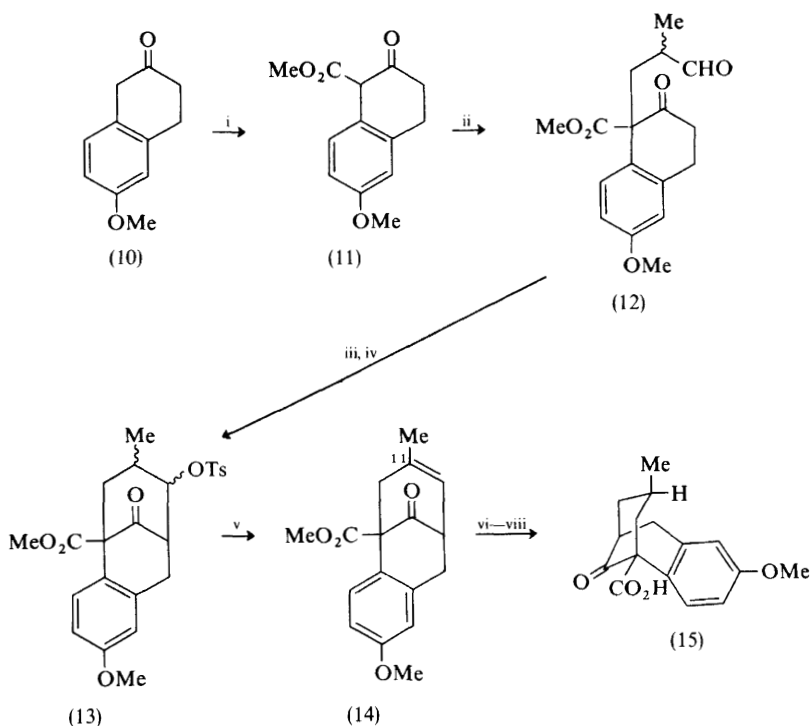
Scheme 1



Reagents: i,  $\text{ClCO}_2\text{Et}-\text{Et}_3\text{N}$ ,  $0^\circ\text{C}$ ; ii,  $\text{NaN}_3$ ; iii,  $\text{C}_6\text{H}_5\text{CH}_2\text{OH}-\text{C}_6\text{H}_5\text{Me}$ ,  $100^\circ\text{C}$ ; iv, 50%  $\text{HBr}-\text{HOAc}$ ,  $0^\circ\text{C}$ ; v,  $\text{MeCOCO}_2\text{H}-\text{POCl}_3-\text{Et}_3\text{N}-\text{THF}$ ,  $-15^\circ\text{C}$ ; vi,  $\text{NaH}-\text{THF}$ ; vii,  $\text{Et}_3\text{O}^+\text{BF}_4^--\text{CH}_2\text{Cl}_2$ ; viii,  $\text{LiAlH}_4-\text{Et}_2\text{O}$ ; ix,  $\text{Ac}_2\text{O}-\text{C}_5\text{H}_5\text{N}$ ; x,  $\text{H}_2-\text{Pd/C}-\text{EtOH}-\text{HClO}_4$ .

Scheme 2

is delineated in abbreviated form in Scheme 2. The paper is instructive reading for its unexpected results and unpredictably unsuccessful reactions. The second part of the paper describes the preparation of (15), a suitable intermediate for elaboration of lycopodine (Scheme 3). Methoxycarbonylation of the tetralone (10) gave exclusively  $\beta$ -keto-ester (11) which was subjected to the Michael reaction with methyl methacrylate to yield the aldehyde (12). Cyclization gave a mixture of all the four possible isomeric ketols which were directly converted into the corresponding isomeric tosylates (13). After considerable experimentation with the isomeric ketols, conditions were found for the conversion of the tosylate mixture (13) into the olefin (14). Control of developing stereochemistry at C-11 was possible by catalytic reduction of (14) over palladium-charcoal to give after two further steps a good yield of the desired compound (15). It is envisaged that the keto-acid function in (15) may serve for elaboration of ring A of lycopodine (5; R = H) as before (Scheme 2) and that the anisole ring may be regarded as the potential source of ring C of the alkaloid.



Reagents: i,  $\text{NaH}-(\text{MeO})_2\text{CO}$ ; ii,  $\text{NaOMe}-\text{CH}_2=\text{C}(\text{Me})\text{CHO}$ ,  $-70^\circ\text{C}$ ; iii, 6N-HCl-dioxan, room temp.; iv,  $\text{TsCl}-\text{C}_5\text{H}_5\text{N}$ ; v, anhydr.  $\text{HOAc}-\text{NaOAc}$ , reflux; vi,  $\text{H}_2-\text{Pd/C}$ ; vii, Jones oxid.; viii,  $\text{OH}^-$ .

Scheme 3

## 1 Introduction

Structural and synthetic studies of the diterpene alkaloids of the *Aconitum*, *Delphinium*, and *Garrya* species continue to provide more insight into the chemistry of these complex bases. In recent years Japanese workers have isolated a series of isoprenoid alkaloids from plants of *Daphniphyllum macropodum* Miquel. Structural work on four new alkaloids representing three new structural types has been reported during this year.

X-Ray crystallographic methods have assumed a dominant role in these structure determinations. These techniques have been especially valuable in the cases where only a small amount of the natural product is available. Crystallographic structure determinations have also been employed in some synthetic efforts to verify structure and stereochemistry.

Mass spectral studies have also been used more extensively. Soviet investigators at Tashkent in their mass spectral analyses of the *Aconitum* and *Delphinium* alkaloids have provided a mass spectral data base of great utility in the structure elucidation of new alkaloids with the lycoctonine skeleton. A study employing trimethylsilyl derivatives in a gas chromatograph-mass spectrometer system has also been reported. A brief review of mass spectral studies on diterpene alkaloids has appeared.<sup>1</sup>

Several new synthetic approaches to the atisine and veatchine alkaloids have been reported, and a detailed account of the synthesis of an optically active relay intermediate in the synthesis of delphinine has appeared.

The numbering system used for alkaloids with basic lycoctonine, atisine, or veatchine skeletons is based upon the standard skeletons aconane, atisane, and kaurane, and is fully described in the previous volume of these Reports.<sup>2</sup>

## 2 Structural and Chemical Investigations

***Aconitum* and *Delphinium* Alkaloids. C<sub>19</sub>-Skeleton.—Oxonitine.** Wiesner and Jay<sup>3</sup> have re-examined the nature of the *N*-acyl group of oxonitine, the

<sup>1</sup> S. D. Sastry, in 'Biochemical Applications of Mass Spectrometry,' ed. G. R. Waller, Wiley-Interscience, New York, 1972, p. 662.

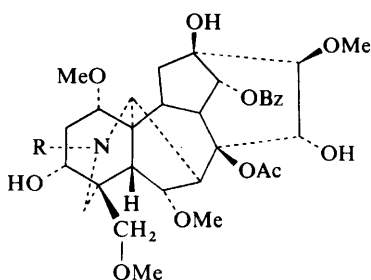
<sup>2</sup> S. W. Pelletier and L. H. Wright, 'Recent Developments in Diterpene Alkaloid Chemistry,' in 'The Alkaloids,' (Specialist Periodical Reports), ed. J. E. Saxton, The Chemical Society, London, 1972, Vol. 2, p. 247.

<sup>3</sup> K. Wiesner and L. Jay, *Experientia*, 1971, **27**, 758.

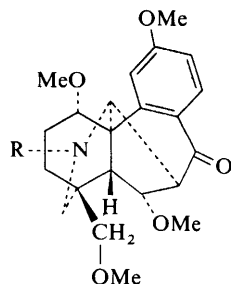


permanganate oxidation product of aconitine (1). The controversy over the structure of oxonitine has been whether this compound is an *N*-formyl or an *N*-acetyl derivative.

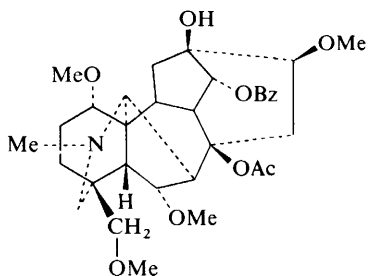
Oxonitine was converted into the *N*-acyl aromatization product (2). Although homogeneous by thin-layer chromatography, n.m.r. and mass spectral data indicated this product to be a mixture of both *N*-formyl and *N*-acetyl derivatives. These compounds were hydrolysed to the base (3) with hydrochloric acid in methanol. This tetracyclic amine was identical with samples prepared from delphinine (4) and by total synthesis. The authors noted that, since samples of aconitine are known to contain varying amounts of mesaconitine (5), the differing *N*-acyl groups could result from the oxidation of the *N*-methyl group of mesaconitine and the *N*-ethyl group of aconitine in the mixture.<sup>3</sup>



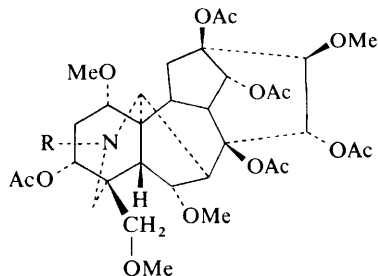
Aconitine (1) R = Et  
Mesaconitine (5) R = Me



(2) R = CHO and Ac  
(3) R = H



Delphinine (4)

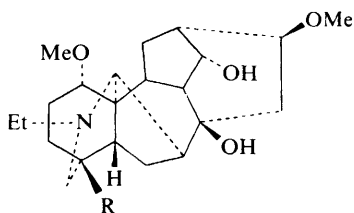


Penta-acetylaconine (6) R = <sup>14</sup>CH<sub>2</sub>Me

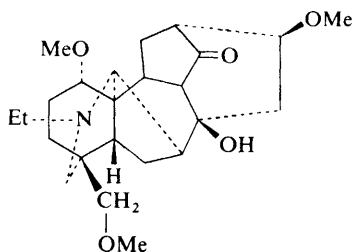
Turner and co-workers<sup>4</sup> have shown, however, that the *N*-formyl group does not arise from the direct oxidation of the *N*-alkyl group during the reaction with methanolic permanganate. The oxidation of penta-acetylaconine (6) containing an *N*-ethyl group labelled at the carbon adjacent to the nitrogen atom produces penta-acetyl-'*N*-formyloxonitine' with only 6% of the original activity. The ambiguities in the identity of the *N*-acyl group of oxonitine probably result from a combination of the mesaconitine impurities in 'aconitine', and competing oxidation reactions.

<sup>4</sup> R. B. Turner, J. P. Yeschke, and M. S. Gibson, *J. Amer. Chem. Soc.*, 1960, **82**, 5182.

*Aconosine*. Russian workers have isolated a new alkaloid, aconosine, from *Aconitum nasutum* Fisch. et Rchb.<sup>5</sup> This base,  $C_{22}H_{35}NO_4$ , m.p. 148 °C, was found in all parts of the plant. The n.m.r. and i.r. spectral analyses indicated the presence of an *N*-ethyl group, two methoxy-groups, and two hydroxy-functions. The mass spectrum of this compound is characteristic of an alkaloid with a lycotoxine skeleton. Oxidation of aconosine with chromium trioxide in acetone gave dehydroaconosine,  $C_{22}H_{33}NO_4$ , containing a carbonyl function in a five-membered ring. With these data and the mass spectral comparison of aconosine, dehydroaconosine, and their acetyl derivatives with talatizamine (7), dehydrotalatizamine (8), and their acetyl derivatives, structure (9) for aconosine has been proposed.<sup>5</sup>

Talatizamine (7) R =  $CH_2OMe$ 

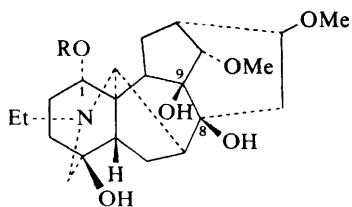
Aconosine (9) R = H



Dehydrotalatizamine (8)

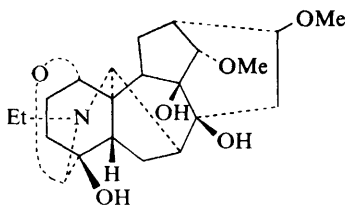
*Lapaconidine*. Additional data supporting structure (10) for lapaconidine,  $C_{22}H_{35}NO_6$ , a base isolated from *Aconitum leucostomum*, have been presented.<sup>6</sup> The previous work<sup>7</sup> had established the presence of an *N*-ethyl, two methoxy, and four acetylatable hydroxy-groups. Methylation with methyl iodide-sodium hydride afforded tetramethyl-lapaconidine, which was identical with trimethyl-lappaconine. The additional free hydroxyl in lapaconidine was assigned to C-1 on the basis of mass spectral data.

The permanganate oxidation product of lapaconidine was identified as the inner carbinolamine ether (11). This compound was converted into the original



Lapaconidine (10) R = H

Lappaconine (14) R = Me



(11)

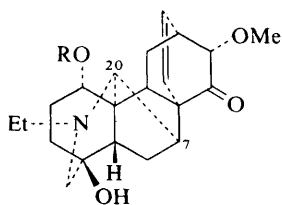
<sup>5</sup> D. A. Muravjeva, T. I. Plekhanova, and M. S. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 128 (*Chem. Abs.*, 1972, **77**, 72 562).

<sup>6</sup> V. A. Tel'nov, M. S. Yunusov, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 622 (*Chem. Abs.*, 1972, **76**, 99 877).

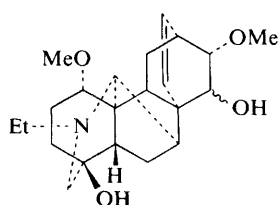
<sup>7</sup> V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 639 (*Chem. Abs.*, 1971, **74**, 76 573).

alkaloid on reduction with Adams' catalyst. The presence of a peak at  $M - 56$  (loss of a molecule of acrolein) in the mass spectrum of (11) also supported this structure (see the following section).

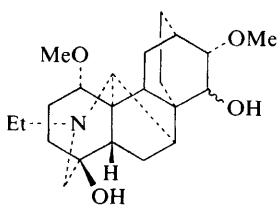
Treatment of lapaconidine with sulphuric acid yielded a compound,  $C_{21}H_{29}NO_4$ , which was assigned structure (12) from the available spectral data. An analogous product (13) had previously been obtained from lappaconine (14),<sup>8</sup> probably *via* a pinacolonic-type rearrangement. These compounds contain the basic atisine ring system with an additional C-7—C-20 bond, further suggesting a relationship between the atisine and lycoctonine skeletons.<sup>9</sup> Reduction of (13) with sodium amalgam in absolute alcohol afforded a crystalline derivative,  $C_{22}H_{33}NO_4$ , assigned structure (15), on the basis of i.r. and mass spectral data and the formation of a diacetate derivative. Hydrogenation of (13) with Adams' catalyst gave (16). Chromic anhydride–acetone oxidation of lapaconidine produced (17), providing further evidence for the diol system at C-8—C-9.



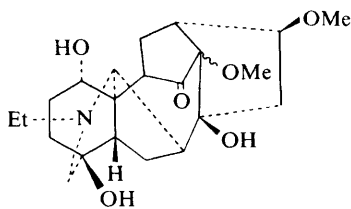
(12) R = H  
(13) R = Me



(15)



(16)



(17)

*Mass Spectral Studies of the  $C_{19}$ -Diterpene Alkaloids.* Yunusov and co-workers<sup>10,11</sup> have published further studies on the mass spectra of diterpene alkaloids possessing the lycoctonine-type skeleton.<sup>12</sup>

<sup>8</sup> V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 583 (*Chem. Abs.*, 1971, **74**, 42 527).

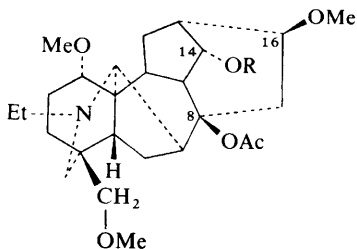
<sup>9</sup> Cf. O. E. Edwards, 'Diterpenoid Alkaloids,' in 'The Alkaloids,' (Specialist Periodical Reports), ed. J. E. Saxton, The Chemical Society, London, 1971, Vol. 1, p. 374.

<sup>10</sup> M. S. Yunusov, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 626 (*Chem. Abs.*, 1972, **76**, 72 680).

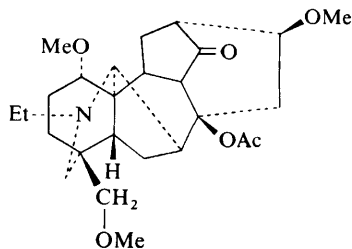
<sup>11</sup> M. S. Yunusov, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1972, **8**, 85 (*Chem. Abs.*, 1972, **77**, 62 192).

<sup>12</sup> Cf. Ref. 9, p. 369.

The pyrolyses of aconitine (1), benzoyletaltatizamine (18), diacetylaltatizamine (19), and dehydroacetylaltatizamine (20) were examined by mass spectral analyses at elevated temperatures (105–125 °C).<sup>10</sup> Assuming that steric interactions of the axial substituents at C-8, C-14, and C-16 should increase the ease of elimination of the C-8 acetoxy-group, the relative ease of pyrolysis should be (1)  $\approx$  (18)  $\geq$  (19) > (20). On the basis of the observed intensities of the peaks  $M^+ - \text{AcOH}$  and  $M^+ - \text{AcO}$ , the order of this series is correct. The increasing ease of pyrolysis from (20) to (1) was also evident from the intensities of the respective molecular ions: (20), 3.5%; (19), 2%; (18), 0.1%; and (1), absent.



Benzoylaltatizamine (18) R = Bz  
Diacetylaltatizamine (19) R = Ac

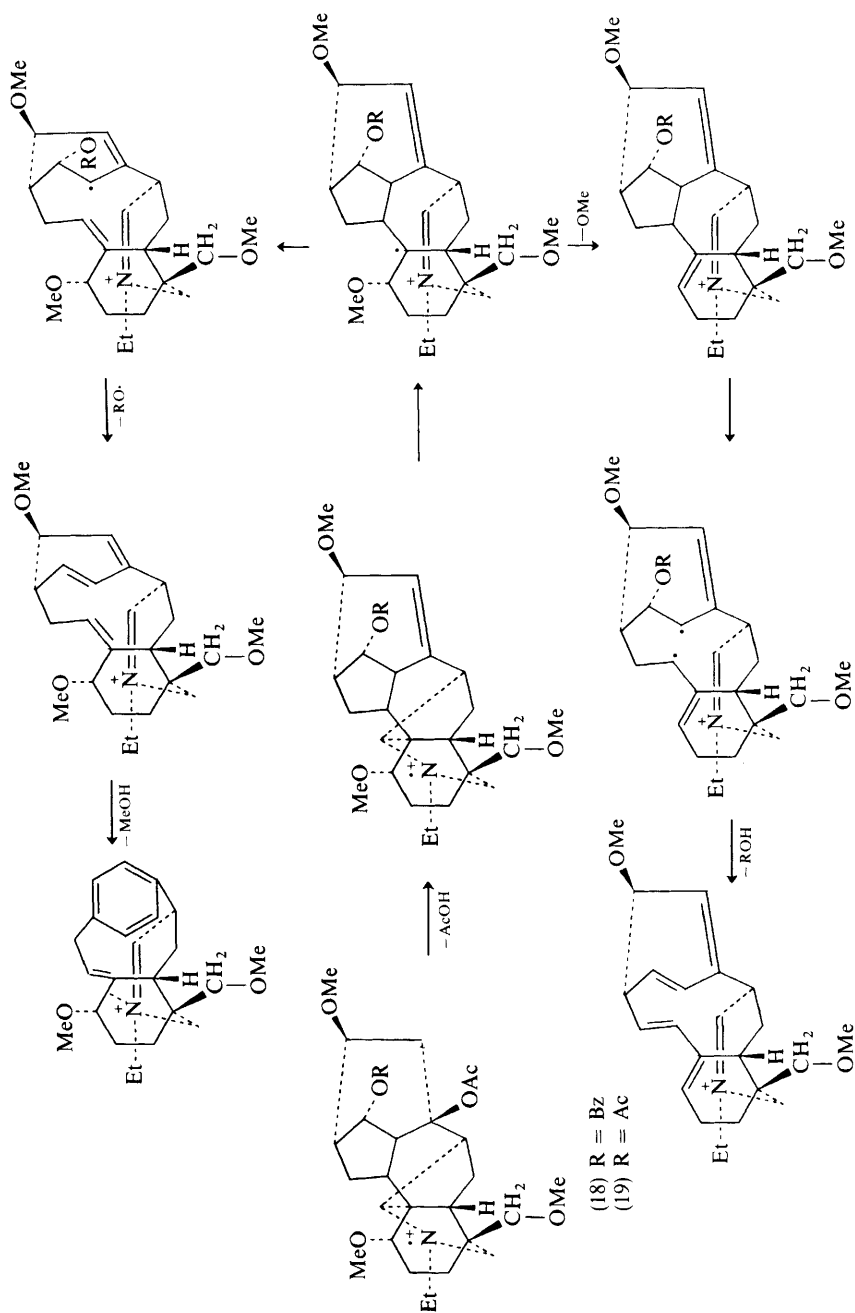


Dehydroacetylaltatizamine (20)

At lower temperatures (70–80 °C), pyrolytic decomposition was not observed, and the formation of the  $M^+ - \text{AcOH}$  ion was proposed to result from electron impact as in Scheme 1, with the formation of the acetoxy radical as in Scheme 2 competing. The authors concluded that diacetylaltatizamine (19) fragments primarily according to Scheme 1 at 125 °C, whereas at lower temperatures (70 °C), it fragments predominantly according to Scheme 2. In the case of dehydroacetylaltatizamine (20) much less temperature dependence was observed, with fragmentation occurring primarily *via* Scheme 2.

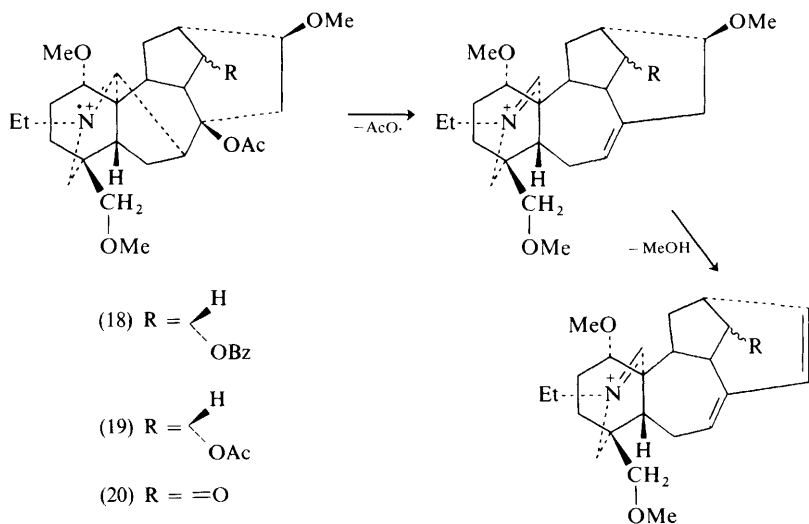
The relative ease of elimination of acetic acid from these alkaloids was also confirmed by the length of time required for the complete elimination on heating under normal conditions: compounds (1), (18), and (19) required 5 min, whereas (20) required 15 min. These reactions were monitored in part by chromatography.

Mass spectral methods for the determination of the orientation of the C-1 substituents and the nature of the C-4 substituents in the lycoctonine–aconitine alkaloids have been proposed.<sup>11</sup> In this work mass spectral data on the following alkaloids were presented: neoline (21), condelphine (22), isotalatizidine (23), talatizadine (24), talatizamine (25), aconine (26), lycoctonine (27), delphatine (28), browniine (29), acetylcondelphine (30), and diacetylaltatizamine (31). Comparison of the spectra of (21), (22), and (23) (C-1 :  $\alpha$ -OH) with that of (24) (C-1 :  $\beta$ -OH) indicated in the last compound a significant stabilization of the molecular ion, significant decrease in the intensity of the  $M^+ - 17$  peak, and a significant increase in the intensity of the  $M^+ - 15$  peak. In the case of (25) and (26) (C-1 :  $\alpha$ -OMe)

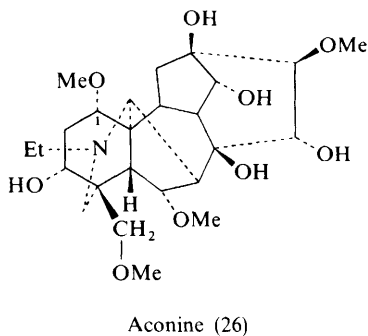
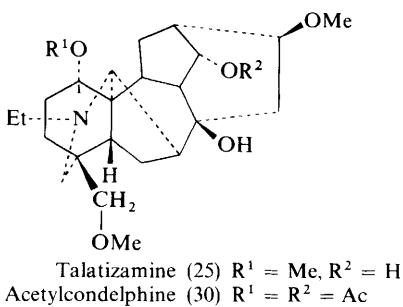
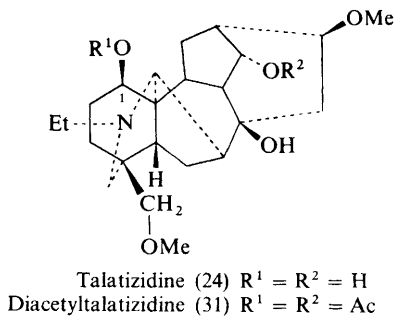
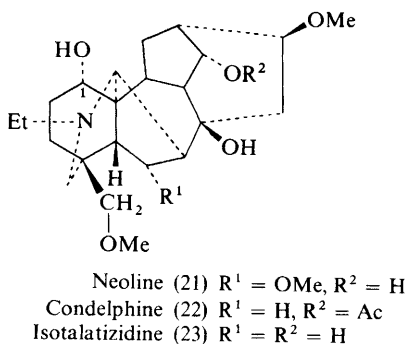


### Scheme 1

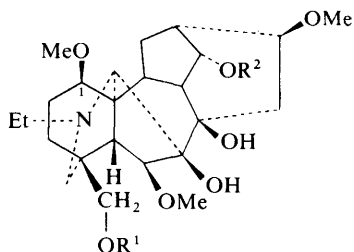
compared with (27), (28), and (29) (C-1: $\beta$ -OMe), there was no notable stabilization of the molecular ion, but the intensity of the  $M^+ - 15$  peak was sharply



Scheme 2



increased with the change from the  $\alpha$ - to the  $\beta$ -configuration. The ratios of  $M^+ - OR^2 : M^+$  and  $M^+ - OR^2 : M^+ - 15$  are in most cases significantly larger

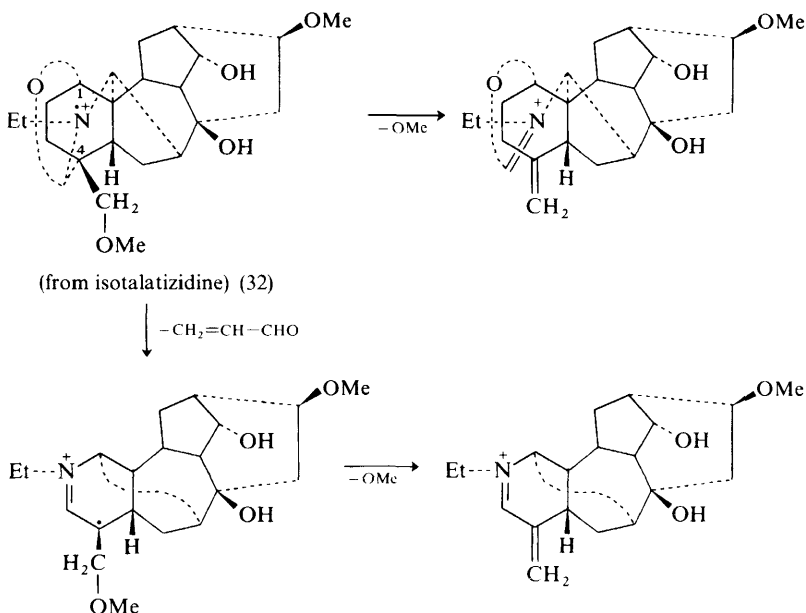


Lycoctonine (27)  $R^1 = H, R^2 = Me$

Delphatine (28)  $R^1 = R^2 = Me$

Browniine (29)  $R^1 = Me, R^2 = H$

for the C-1  $\alpha$ -configuration, the latter relationship being more definitive, particularly in the case of the methoxy-substituents. These conclusions were supported by the metastable peaks in these mass spectra.

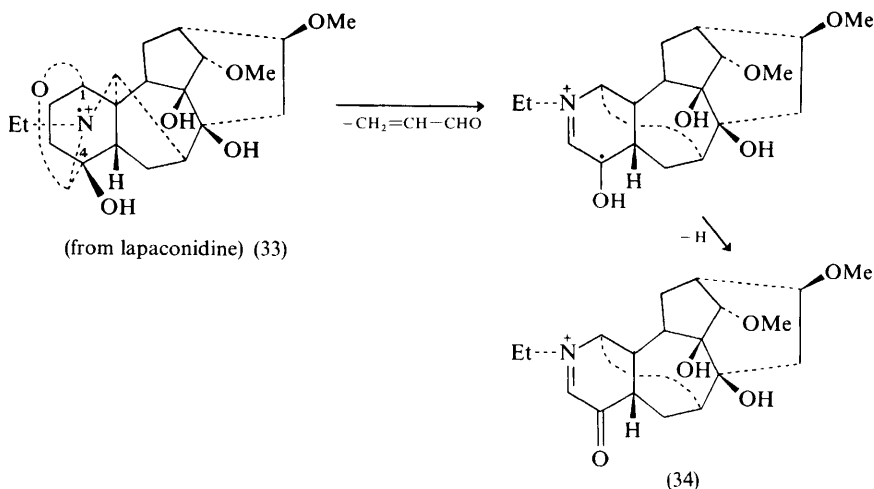


Scheme 3

The methoxymethylene group attached to C-4 does not normally take part in the fragmentation of these alkaloids.<sup>13</sup> In order to utilize mass spectral

<sup>13</sup> M. S. Yunusov, Ya. V. Rashkes, V. A. Tel'nov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, 5, 515 (*Chem. Abs.*, 1970, 73, 15 053).

methods to determine the nature of the C-4 substituents, the mass spectra of the carbinolamine ethers formed by the oxidation of alkaloids with an  $\alpha$ -hydroxy-group at C-1 were examined.<sup>11</sup> Scheme 3 illustrates the proposed fragmentation pathways. For the carbinolamine ether (33) from lapaconidine, formation of the  $\alpha\beta$ -unsaturated ketone (34) was proposed to account for the observed spectrum (Scheme 4).



Scheme 4

**Aconitum and Delphinium Alkaloids. C<sub>20</sub>-Skeleton.**—*Staphisine*. The structure of staphisine has been determined using *X*-ray crystallographic techniques.<sup>14</sup> This diterpene alkaloid dimer was first isolated from the mother liquors accumulated in the extraction of delphinine from *Delphinium staphisagria* in 1941.<sup>15</sup> Chemical studies of this compound were hindered by its instability and by the fact that attempted degradation led to complex changes involving numerous unstable products.

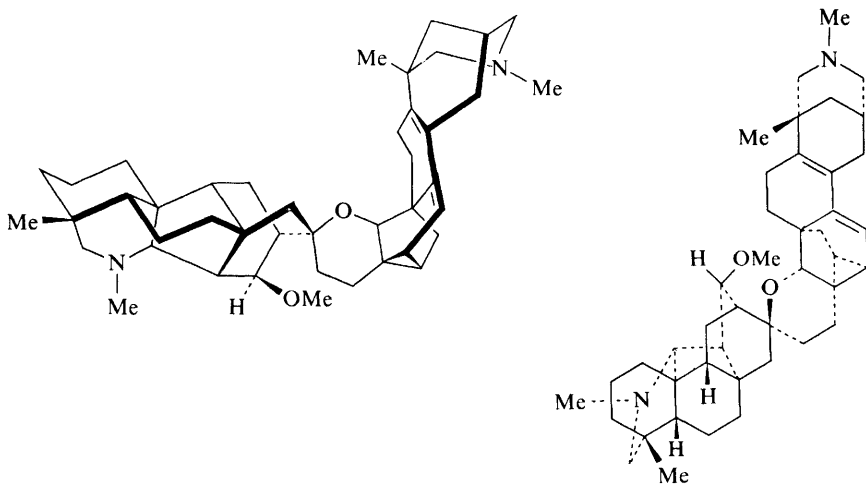
Mass spectral studies established the molecular formula of staphisine as C<sub>43</sub>H<sub>60</sub>N<sub>2</sub>O<sub>2</sub> (*m/e* 636.4648). N.m.r., i.r., and u.v. spectral examination indicated the presence of two *N*-methyl groups, a methoxy-group, a cyclopropyl ring, and a conjugated diene system [ $\lambda_{\text{max}}$  (95% EtOH) 268 nm;  $\epsilon$  17 300]. Hydrogenation experiments also supported the existence of two double bonds.<sup>14</sup> A single-crystal *X*-ray crystallographic structure determination of staphisine monomethiodide indicated the structure of the free base to be (35) with an *R* value of 0.113. This structure is consistent with the observed chemical and spectral data for staphisine. The selenium-dehydrogenation products, pimanthrene and

<sup>14</sup> S. W. Pelletier, A. H. Kapadi, L. H. Wright, S. W. Page, and M. G. Newton, *J. Amer. Chem. Soc.*, 1972, **94**, 1754.

<sup>15</sup> W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, 1941, **141**, 67.

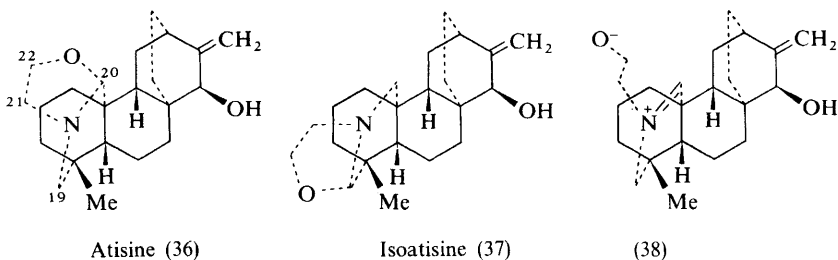


1,3-dimethyl-7-isopropylphenanthrene, may be rationalized with structure (35). Staphisine is thus established as a dimer of two diterpene alkaloid molecules of the atisine type.



Staphisine (35)

*Atisine–Isoatisine Rearrangement.* Further work has been presented by Pradhan and Girijavallabhan<sup>16</sup> on the atisine (36) to isoatisine (37) rearrangement,<sup>17</sup> which occurs on treatment with methanolic base. The n.m.r. spectrum of the reaction mixture in deuteriated solvent was examined at frequent intervals to



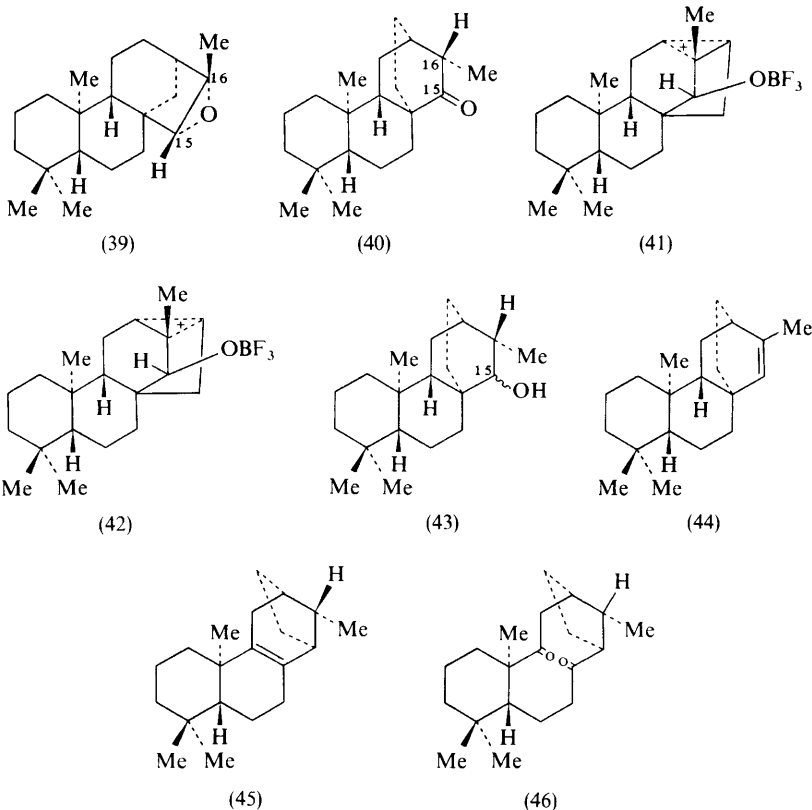
determine the extent of the deuteriation relative to isomerization. These authors reported that the initially formed isoatisine incorporated a deuterium atom at C-20 and did not undergo further deuteriation. The atisine in the mixture was deuteriated at positions C-19 and C-20, and at about 30% of the rearrangement completed, the atisine recovered was fully deuteriated at C-19 and C-20. No deuteriation was observed at C-21 or C-22. This evidence was interpreted to

<sup>16</sup> S. K. Pradhan and V. M. Girijavallabhan, Abstracts of Papers Presented at the I.U.P.A.C. Symposium on Natural Products, New Delhi, 1972, p. 72.

<sup>17</sup> S. W. Pelletier, K. W. Gopinath, and K. Kawazu, *Chem. and Ind.*, 1966, 28.

indicate the irreversible formation of isoatisine and that the proton abstraction leading to exchange and rearrangement is achieved internally by the anionic portion of the proposed zwitterion intermediate (38).<sup>18</sup>

*Rearrangement of ent-Kaurane-15 $\beta$ ,16 $\beta$ -epoxide to ent-(16R)-Atisane-15-one.* MacMillan and Walker<sup>19</sup> have reported further studies on rearrangements involving the C and D ring systems of the atisane skeleton. Treatment of *ent*-kaurane-15 $\beta$ ,16 $\beta$ -epoxide (39) with boron trifluoride-ether complex in benzene yielded a mixture of ketonic (30%) and hydrocarbon (70%) products. The major ketonic product was shown to be *ent*-(16R)-atisane-15-one (40), with a minor amount of the 16S-isomer also formed. The hydrocarbon fraction was a complex mixture of dienes. This rearrangement was postulated as occurring through the interconverting bridged ions (41) and (42).



Reduction of (40) with lithium aluminum hydride afforded a 1:1 mixture of the 15-epimeric alcohols (43). Chromatography of the tosylate derivatives of

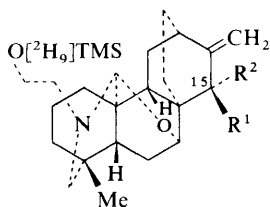
<sup>18</sup> S. K. Pradhan and V. M. Girijavallabhan, *Chem. Comm.*, 1970, 644.

<sup>19</sup> J. MacMillan and E. R. H. Walker, *J. C. S. Perkin I*, 1972, 1274.

(43) resulted in the formation of three isomeric compounds, *viz.* (44), (45), and a minor unidentified product. Oxidation of (45) with osmium tetroxide–sodium periodate gave the diketone (46).

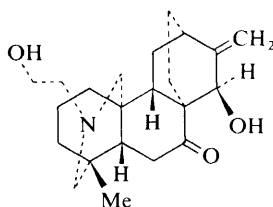
**Mass Spectral Studies of Ajaconine.** Waller and Sastry have reported utilizing a gas chromatograph–mass spectrometer in studies of ajaconine (isolated from *Delphinium ajacis*).<sup>20</sup> A sample identified as ‘pure ajaconine’ produced a mixture of five components when the [<sup>2</sup>H<sub>9</sub>]trimethylsilyl derivatives were analysed. The relative amounts of these compounds by peak-area estimation were: (i)  $M^+ 477$ , 9%; (ii)  $M^+ 521$ , 16%; (iii)  $M^+ 521$ , 27%; (iv)  $M^+ 521$ , 5%; and (v)  $M^+ 604$ , 43%.

The mass spectrum of ‘peak (iii) ajaconine’ had more intense  $M^+$  and  $M^+ - 1$  ions and a less intense  $M^+ - (\text{HO}[\text{C}^{15}\text{H}_9]\text{TMS})$  ion than the mass spectrum of ‘peak (ii) ajaconine’. The authors reasoned that the more intense molecular ion should occur in the spectrum of the less crowded equatorial epimer, whereas the axial epimer should eliminate more readily. Structures (47) and (48) were accordingly assigned ‘ajaconine peaks (iii) and (ii)’, respectively. The mass spectrum of g.l.c. peak (iv) was similar to those of peaks (ii) and (iii). The configuration of the C-15-centre of this compound was proposed as in structure (48), with a steric difference at some ring junction. On the basis of the mass spectral fragmentation and biogenetic considerations, peak (v) was assigned structure (49).<sup>1</sup> It should be noted that at the temperature prevailing on the g.l.c. column (215 °C) and the elution time required (12.7–27.8 min), ajaconine may have undergone rearrangement on the column to produce other components. The C-15-hydroxyl of ajaconine had previously been assigned a  $\beta$ -configuration [as in (48)] by chemical correlation of atidine (50) with dihydroajaconine (51).<sup>21</sup>

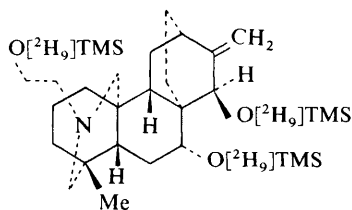


(47)  $R^1 = \text{H}$ ,  $R^2 = \text{O}[\text{C}^{15}\text{H}_9]\text{TMS}$

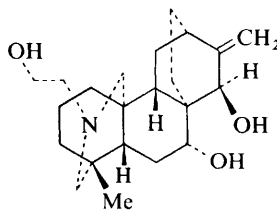
(48)  $R^1 = \text{O}[\text{C}^{15}\text{H}_9]\text{TMS}$ ,  $R^2 = \text{H}$



Atidine (50)



(49)

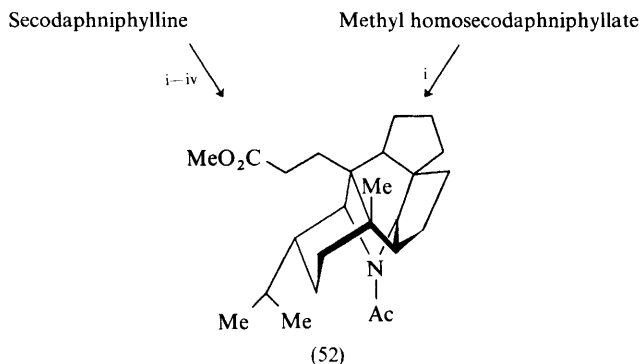


Dihydroajaconine (51)

<sup>20</sup> S. D. Sastry and G. R. Waller, *Chem. and Ind.*, 1972, 381.

<sup>21</sup> S. W. Pelletier, *J. Amer. Chem. Soc.*, 1965, **87**, 799.

**Daphniphyllum Alkaloids.**—*Secodaphniphylline* and *Methyl Homosecodaphniphyllate*. These alkaloids have been isolated from *Daphniphyllum macropodum* Miquel.<sup>22</sup> Secodaphniphylline,  $C_{30}H_{47}NO_3$ , m.p. 130 °C, has been chemically correlated with methyl homosecodaphniphyllate,  $C_{23}H_{37}NO_2$ , m.p. 103 °C, via (52) as outlined in Scheme 5.<sup>22,23</sup>

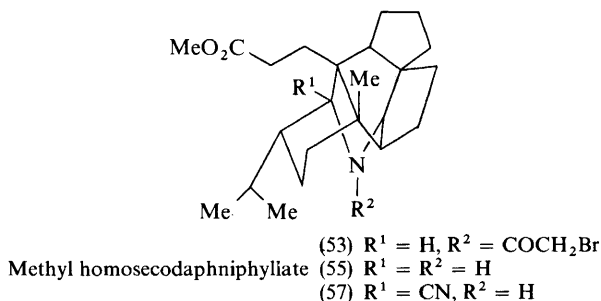


Reagents: i,  $Ac_2O$ -pyridine; ii,  $NH_2OH.HCl$ -pyridine; iii,  $MsCl$ -pyridine; iv, 6N-HCl-MeOH

**Scheme 5**

A heavy-atom X-ray crystal-structure analysis of methyl *N*-bromoacetyl-homosecodaphniphyllate (53) established the structures of secodaphniphylline and methyl homosecodaphniphyllate as (54) and (55), respectively.<sup>24</sup> The absolute configuration of this derivative was determined by anomalous dispersion procedures. These alkaloids are members of another new group of alkaloids isolated from *Daphniphyllum macropodum*.

An interesting oxidation reaction yielding an imine that violates Bredt's rule was discovered in these studies.<sup>23</sup> Methyl homosecodaphniphyllate on oxidation with lead tetra-acetate in dry benzene at room temperature afforded a product,  $C_{23}H_{35}NO_2$ , which was assigned structure (56) on the basis of chemical

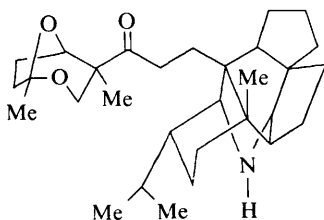


<sup>22</sup> H. Irikawa, M. Toda, S. Yamamura, and Y. Hirata, *Tetrahedron Letters*, 1969, 1821.

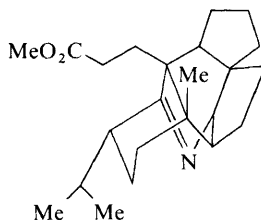
<sup>23</sup> M. Toda, Y. Hirata, and S. Yamamura, *Tetrahedron*, 1972, **28**, 1477.

<sup>24</sup> K. Sasaki and Y. Hirata, *J. Chem. Soc. (B)*, 1971, 1565.

and spectral data. Reduction of (56) with sodium borohydride or by catalytic hydrogenation yielded the starting alkaloid. Treatment of (56) with excess sodium cyanide in dimethylformamide afforded (57), but attempted acetylation in acetic anhydride-pyridine gave no reaction. The formation of the 2-azabicyclo[3,3,1]non-1-ene system in (56) was attributed to relief of steric repulsions and to the stability imparted by the boat conformation of this ring system being fixed in part by other ring junctions.



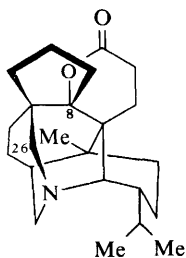
Secodaphniphylline (54)



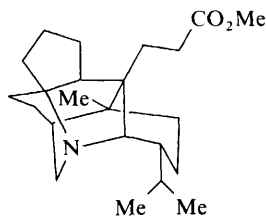
(56)

*Daphnilactone-A*. This alkaloid has been isolated from *Daphniphyllum macropodum* Miquel in very minor amounts. It was previously identified as alkaloid C from this plant.<sup>25</sup> *Daphnilactone-A*,  $C_{23}H_{35}NO_2$ , m.p. 194.5–195.5 °C, was shown by spectral evidence to contain an isopropyl group, a tertiary methyl group, and a  $\delta$ -lactone ring. The structure of daphnilactone-A was determined to be (58) by an *X*-ray crystallographic study employing direct phasing relationships.<sup>26</sup>

This alkaloid contains the 2-azabicyclo[3,3,1]nonane ring system characteristic of all the *Daphniphyllum* alkaloids. It represents a new structural type, having four rings with the C-8 atom common in a spiro-system. Its skeleton may be related to methyl homodaphniphyllate (59) by insertion of a single carbon unit (C-26) and lactonization.



Daphnilactone-A (58)



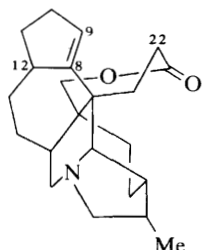
Methyl homodaphniphyllate (59)

*Daphnilactone-B*. The fruits of *Daphniphyllum macropodum* Miquel yield as a major alkaloidal component daphnilactone-B,  $C_{22}H_{31}NO_2$ , m.p. 92–94°C. Spectral data indicated the presence of a secondary methyl group, a vinyl proton, and a lactone ring. The structure of this compound was established as (60) by an

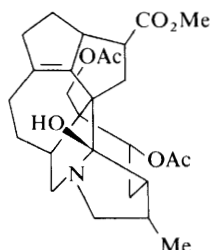
<sup>25</sup> M. Toda, H. Irikawa, S. Yamamura, and Y. Hirata, *J. Chem. Soc. Japan*, 1970, **91**, 103.

<sup>26</sup> K. Sasaki and Y. Hirata, *Tetrahedron Letters*, 1972, 1275.

X-ray crystallographic determination utilizing direct phasing methods.<sup>27</sup> Although this compound contains the 2-azabicyclo[3,3,1]nonane ring system common to all of the *Daphniphyllum* alkaloids, it represents another new structural type. It is possibly related to yuzurimine (61) by formation of a C-8—C-22 bond and double-bond migration from C-8—C-9 to C-8—C-12.



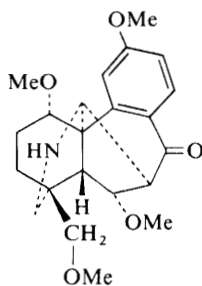
Daphnilactone-B (60)



Yuzurimine (61)

### 3 Synthetic Studies

**Aconitine-type Alkaloids: Syntheses Directed toward Delphinine.**—The New Brunswick group have published in detail their work on the stereoselective total synthesis of optically active (62), an advanced relay compound in the synthesis



(62)

of delphinine (4).<sup>28</sup> Some preliminary papers on this work have previously been reviewed in these Reports.<sup>29</sup> The synthetic route is outlined in Scheme 6.

The racemate (62) was resolved into its optical antipodes by reaction with L-camphorsulphonyl chloride in pyridine.<sup>30</sup> The reaction was stopped at 50% completion, and isolation of the unreacted free base afforded an optically active material which was identical in all respects with the natural degradation product. This synthesis represents an outstanding achievement not only because the

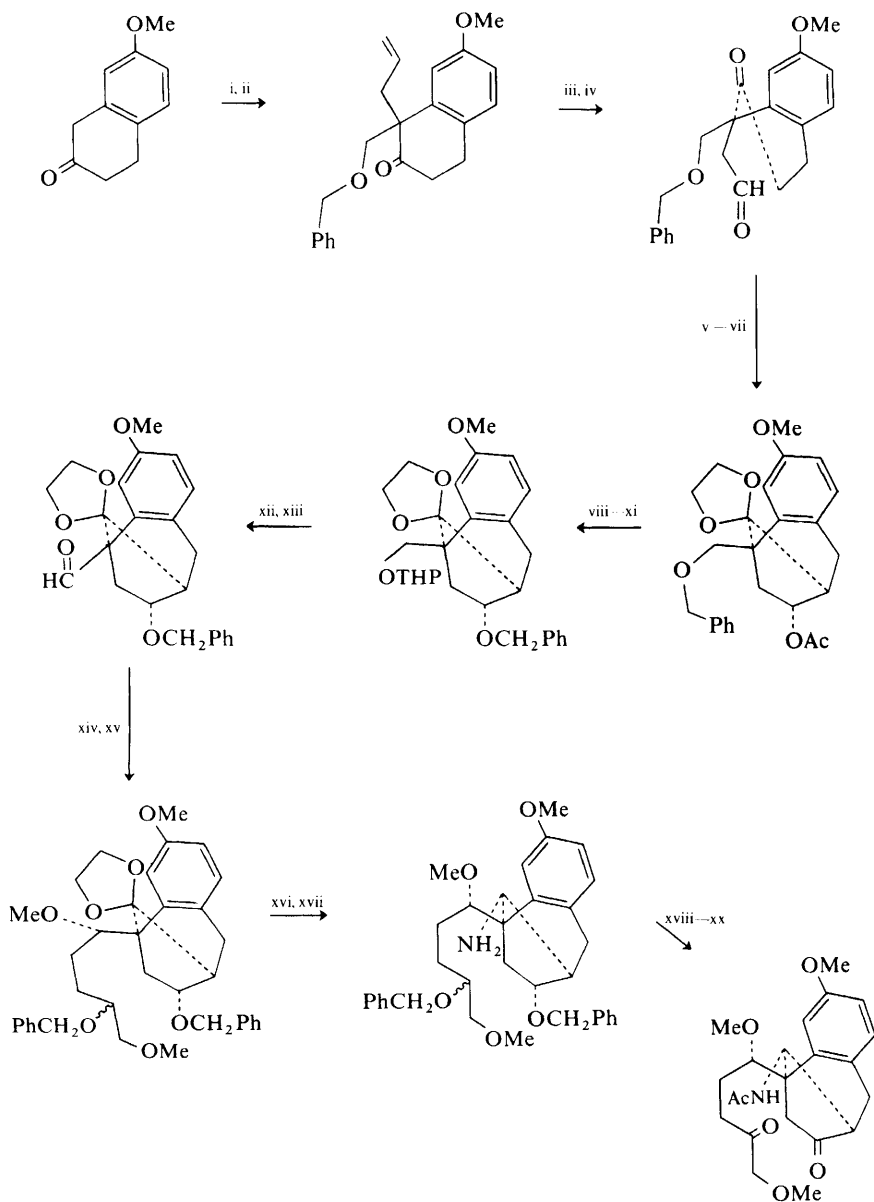
<sup>27</sup> K. Sasaki and Y. Hirata, *Tetrahedron Letters*, 1972, 1891.

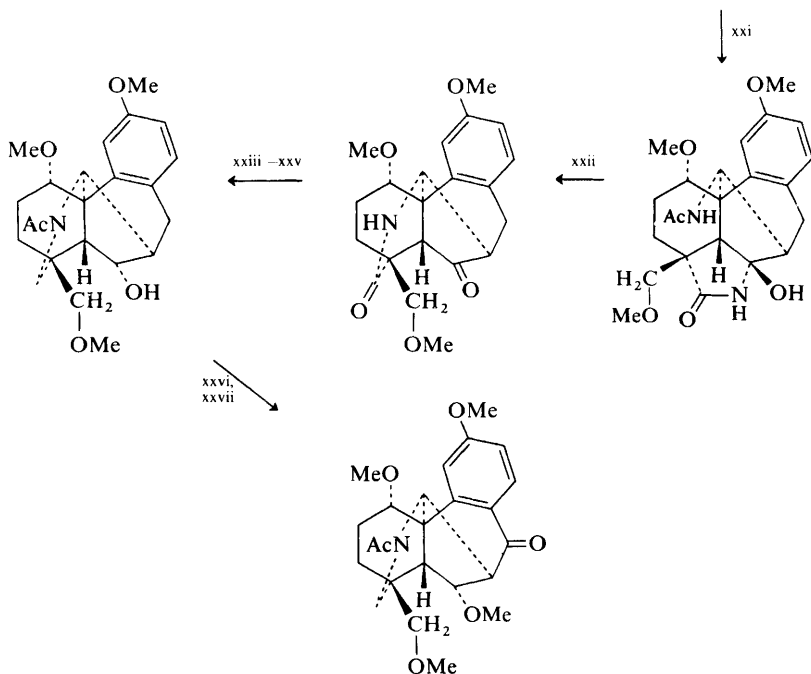
<sup>28</sup> K. Wiesner, E. W. K. Jay, T. Y. R. Tsai, C. Demerson, L. Jay, T. Kanno, J. Krepinsky, A. Vilim, and C. S. Wu, *Canad. J. Chem.*, 1972, **50**, 1925.

<sup>29</sup> Cf. ref. 9, p. 365.

<sup>30</sup> K. Wiesner, E. W. K. Jay, and L. Jay, *Experientia*, 1971, **27**, 363.

immediate synthetic objective has been achieved, but also because the synthesis provides a clarification of the structure and chemistry of delphinine and related alkaloids.

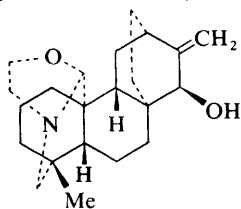




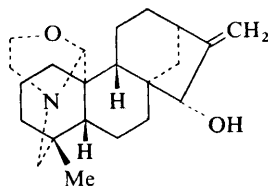
Reagents: i, pyrrolidine- $\text{CH}_2=\text{CHCH}_2\text{Br}$ ; ii,  $\text{NaH}-\text{PhCH}_2\cdot\text{O}\cdot\text{CH}_2\text{Cl}$ ; iii,  $\text{OsO}_4-\text{NaClO}_3$ ; iv,  $\text{NaIO}_4$ ; v,  $\text{NaOH}-\text{MeOH}$ ; vi,  $\text{HOCH}_2\text{CH}_2\text{OH}-\text{TsOH}$ ; vii,  $\text{Ac}_2\text{O}-\text{pyridine}$ ; viii,  $\text{Pd/C}-\text{H}_2$ ; ix, DHP; x,  $\text{LiAlH}_4$ ; xi,  $\text{NaH}-\text{PhCH}_2\text{Cl}$ ; xii, 1%  $\text{HCl}-\text{MeOH}$ ; xiii,  $\text{CrO}_3-\text{pyridine}$ ; xiv,  $\text{BrMgCH}_2\text{CH}_2\cdot\text{CH}(\text{OCH}_2\text{Ph})\cdot\text{CH}_2\text{OMe}$ ; xv, Jones' reagent,  $\text{LiAlH}_4$ ,  $\text{NaH}-\text{MeI}$ ; xvi,  $\text{AcOH}$ ; xvii, Raney Ni-liq.  $\text{NH}_3-\text{MeOH}$ ; xviii,  $\text{Ac}_2\text{O}-\text{pyridine}$ ; xix,  $\text{Pd/C}-\text{H}_2$ ; xx,  $\text{CrO}_3-\text{pyridine}$ ; xxi,  $\text{KCN}-\text{EtOH}-\text{H}_2\text{O}$ ; xxii,  $\text{HCl}-\text{MeOH}$ ; xxiii,  $\text{LiAlH}_4$ ; xxiv,  $\text{Ac}_2\text{O}-\text{pyridine}$ ; xxv,  $\text{KOH}-\text{MeOH}$ ; xxvi,  $\text{NaH}-\text{MeI}$ ; xxvii, Jones' reagent.

Scheme 6

**Veatchine- and Atisine-type Alkaloids.**—*Novel Syntheses of the Diterpenoid BCD Ring System.* The preparation of the BCD ring skeleton of the atisine (36) and veatchine (63) alkaloids by an intramolecular carbenoid addition has been reported by Beames, Halleday, and Mander.<sup>31</sup>



Atisine (36)

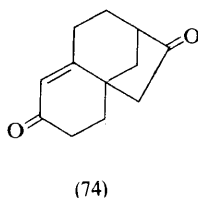
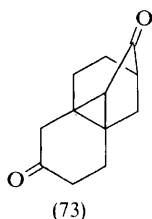
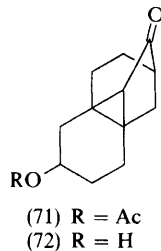
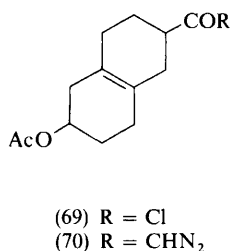
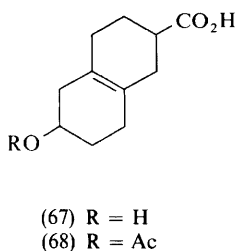
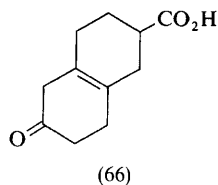
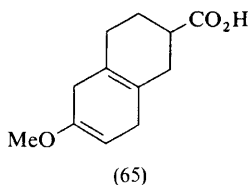
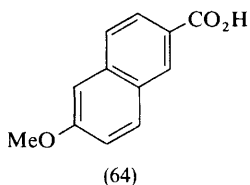


Veatchine (63)

<sup>31</sup> D. J. Beames, J. A. Halleday, and L. N. Mander, *Austral. J. Chem.*, 1972, **25**, 137.



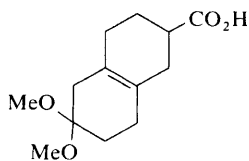
Starting from 6-methoxynaphth-2-oic acid (64), the 1,2,3,4,5,8-hexahydro-derivative (65) was prepared by reduction with excess lithium and t-butyl alcohol in liquid ammonia. Compound (65) was converted into the keto-acid (66) by hydrolysis. Reduction of (66) with lithium tri-t-butoxyaluminium hydride gave the hydroxy-acid (67). The acetate derivative (68) was converted into the acid chloride (69) by reaction with oxalyl chloride in pyridine. Treatment of this compound with diazomethane afforded the diazoketone (70). Decomposition of the latter with copper powder in cyclohexane gave the cyclopropyl ketone (71) in yields of 70—80%. The acetate function was then hydrolysed, and the resulting hydroxy-ketone (72) was oxidized to the cyclopropyl diketone (73) with Jones' reagent. Treatment of (73) with a weakly acidic acetone solution or adsorption on to basic alumina produced the enedione (74) *via* a retrograde



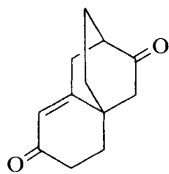
Michael reaction. The overall yield from (64) was 41 %. A similar synthetic route utilizing an acetal group (75) in place of the acetoxy-function was investigated. However, despite the fewer steps required, this sequence gave lower yields of the tricyclic ketone (74). This compound possesses the BCD ring system of the veatchine-type alkaloids.

The intermediate (76) for the atisine ring system was prepared from the naphthoic acid (77) by analogous transformations in an overall yield of 26%. These

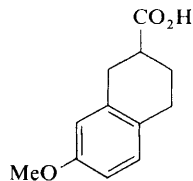
high-yield preparations render these tricyclic compounds important intermediates in the total syntheses of the atisine and veatchine alkaloids as well as other tetracyclic diterpenoids.



(75)



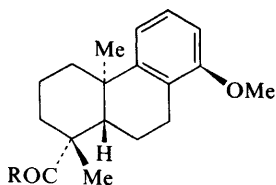
(76)



(77)

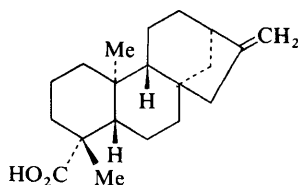
*Diterpene Alkaloid Synthesis from a Diterpene Acid Intermediate.* Mori, Saeki, and Matsui have converted an intermediate (78) in their synthesis of kaur-16-en-19-oic acid (79) into the tetracyclic lactam (83).<sup>32</sup> This lactam was an intermediate in Wiesner's total syntheses of garryine and veatchine.<sup>33</sup>

The racemic acid (78) was converted into the acid chloride (80) by reaction of its sodium salt with oxalyl chloride in benzene. Compound (80) was treated with anhydrous hydrazine to afford the hydrazide (81). Reaction with nitrous acid followed by photolysis of the resulting azide (82) gave the desired  $\delta$ -lactam (83).

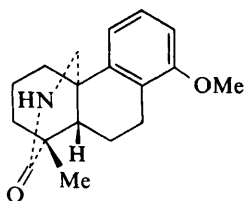


(78) R = OH

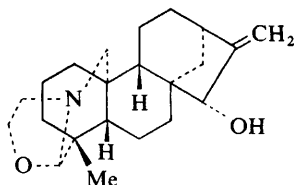
(80) R = Cl

(81) R = NHNH<sub>2</sub>(82) R = N<sub>3</sub>

(79)



(83)



Garryine (84)

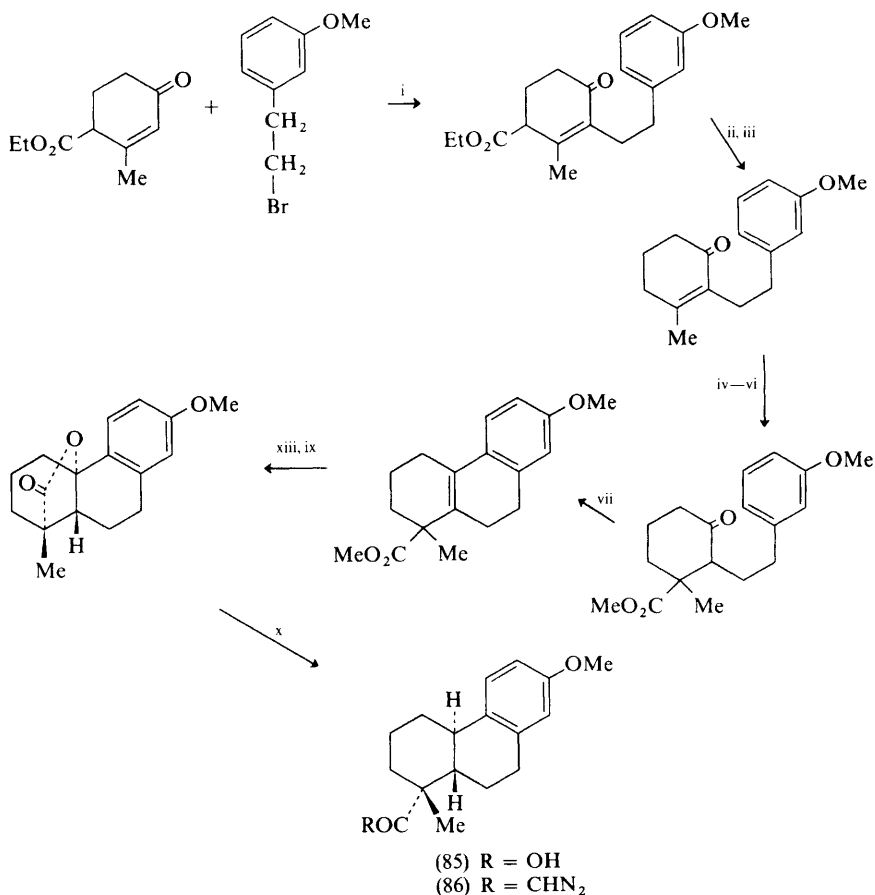
Since garryine (84) and veatchine (63) had been previously synthesized from this lactam,<sup>33</sup> and veatchine converted into atisine (36),<sup>34</sup> this work completes another formal total synthesis of these alkaloids.

<sup>32</sup> K. Mori, K. Saeki, and M. Matsui, *Agric. and Biol. Chem. (Japan)*, 1971, **35**, 956.

<sup>33</sup> R. W. Guthrie, W. A. Henry, H. Immer, C. M. Wong, Z. Valenta, and K. Wiesner, *Coll. Czech. Chem. Comm.*, 1966, **31**, 602.

<sup>34</sup> S. Masamune, *J. Amer. Chem. Soc.*, 1964, **86**, 291.

*A New Approach to the Synthesis of Ring E of the Diterpene Alkaloids.* An intramolecular carbenoid insertion as a means of introducing the C-20 functionality has been employed by Ghatak and Chakrabarty in work related to their general diterpenoid syntheses.<sup>35,36</sup>



Reagents: i, Bu<sup>1</sup>OK-Bu<sup>1</sup>OH; ii, KOH-H<sub>2</sub>O-EtOH; iii, HCl; iv, KCN-H<sub>2</sub>O-EtOH; v, KOH-H<sub>2</sub>O; vi, CH<sub>2</sub>N<sub>2</sub>; vii, PPA; viii, KOH-DEG-H<sub>2</sub>O; ix, H<sub>2</sub>SO<sub>4</sub>; x, Li-liq. NH<sub>3</sub>-NH<sub>4</sub>Cl

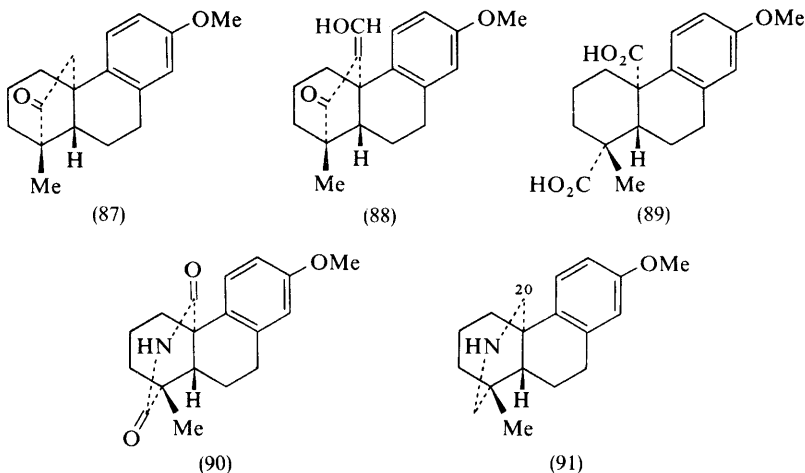
**Scheme 7**

The 20-nor-ring-C-aromatic resin acid analogue (85) was prepared as outlined in Scheme 7.<sup>35</sup> This acid was converted into the diazoketone (86). Treatment of (86) with anhydrous copper sulphate in boiling cyclohexane-tetrahydrofuran

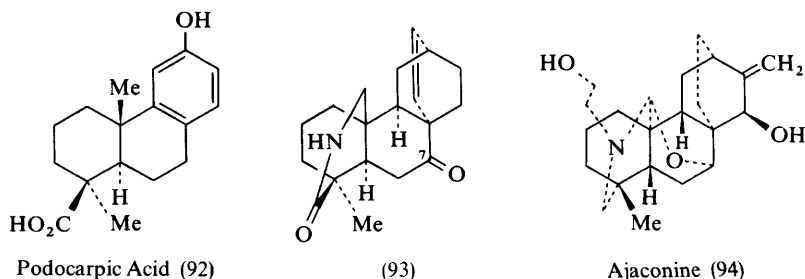
<sup>35</sup> U. R. Ghatak and N. R. Chatterjee, *Indian J. Chem.*, 1971, **9**, 804.

<sup>36</sup> U. R. Ghatak and S. Chakrabarty, *J. Amer. Chem. Soc.*, 1972, **94**, 4756.

produced the tetracyclic ketone (87) in yields of 20–25%. Condensation of (87) with ethyl formate–sodium hydride gave (88), which was oxidized to the dicarboxylic acid (89) with alkaline hydrogen peroxide. This diacid was converted into the imide (90) by treatment with boiling acetyl chloride (*via* the anhydride) followed by heating with urea. Reduction with lithium aluminium hydride in diglyme afforded (91), which had previously served as a key intermediate in the syntheses of atisine, veatchine, and garryine.<sup>37,38</sup>



*Syntheses Directed toward Ajaconine and Atidine.* The conversion of podocarpic acid (92) into a key intermediate (93) in the synthesis of the enantiomers of the diterpene alkaloids ajaconine (94) and atidine (50) has been reported by Zalkow and co-workers.<sup>39</sup> The pentacyclic unsaturated keto-lactam (93) was prepared



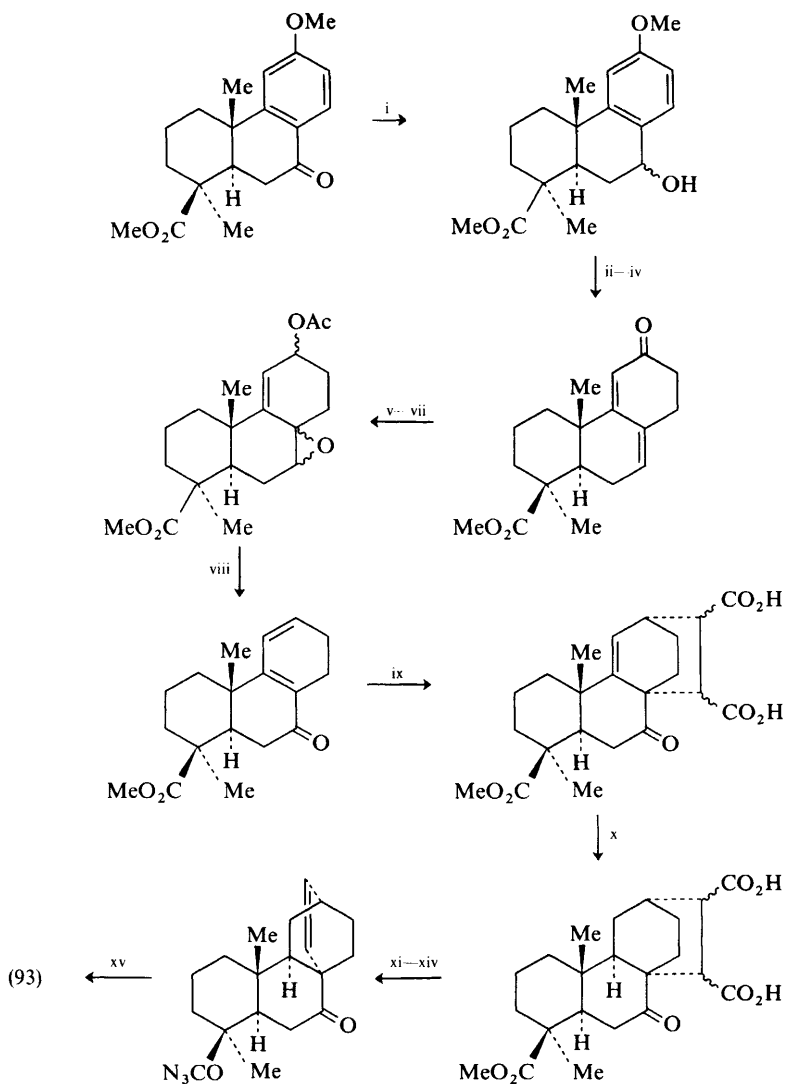
as outlined in Scheme 8. This compound contains the active functionalities necessary for conversion into these alkaloids.

<sup>37</sup> W. Nagata, T. Sugawara, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, 1967, **89**, 1483.

<sup>38</sup> W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugawara, *J. Amer. Chem. Soc.*, 1967, **89**, 1499.

<sup>39</sup> J. B. Nabors, D. H. Miles, B. Kumar, and L. H. Zalkow, *Tetrahedron*, 1971, **27**, 2385.

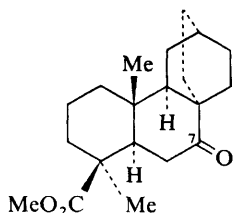
The o.r.d. curves of a number of tetracyclic compounds from this synthetic work containing a C-7 carbonyl function and a bicyclo[2,2,2]octane CD ring system have been compared.<sup>39</sup> This study gives some indication of the effects of CD ring substitution on the conformation of ring B.



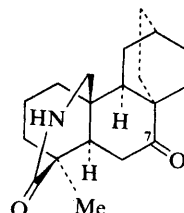
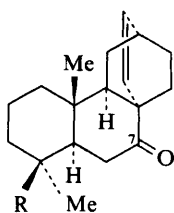
Reagents: i, NaBH<sub>4</sub>; ii, Na-EtOH-liq. NH<sub>3</sub>; iii, HCl-MeOH; iv, CH<sub>2</sub>N<sub>2</sub>; v, NaBH<sub>4</sub>; vi, Ac<sub>2</sub>O-pyridine; vii, *m*-chloroperbenzoic acid; viii, BF<sub>3</sub> etherate, alumina chromatography; ix, maleic anhydride; x, Pt/C-H<sub>2</sub>-HOAc; xi, Pb(OAc)<sub>4</sub>-pyridine; xii, KOH-DEG; xiii, SOCl<sub>2</sub>; xiv, NaN<sub>3</sub>; xv, photolysis in hexane

Scheme 8

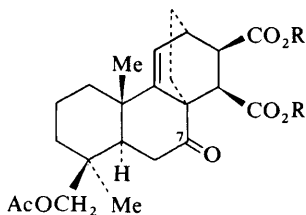
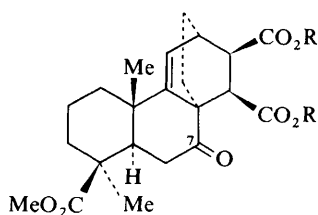
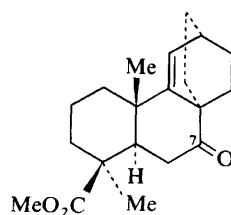
The 7-keto-compounds with a saturated ring B [(93), (95), (96), (97), and (98)] show negative Cotton effects, which are predicted by the octant rule when their B rings are in the chair conformation. Compounds in which ring B forms part of an exocyclic  $\beta\gamma$ -unsaturated cyclohexanone system exhibited both positive and negative Cotton effects experimentally. Compounds (99)–(103) show



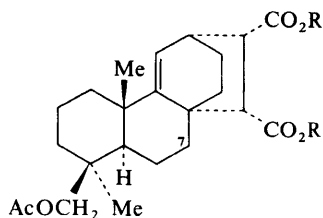
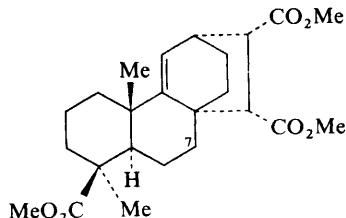
(95)



(98)

(99) R = H  
(100) R = Me(101) R = H  
(102) R = Me

(103)

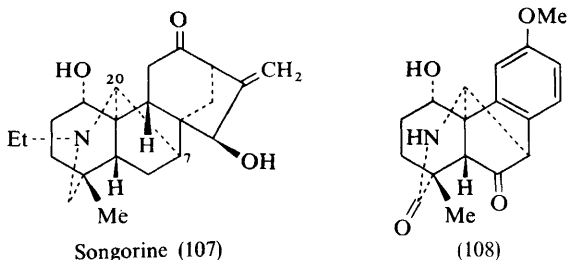
(104) R = H  
(105) R = Me

(106)

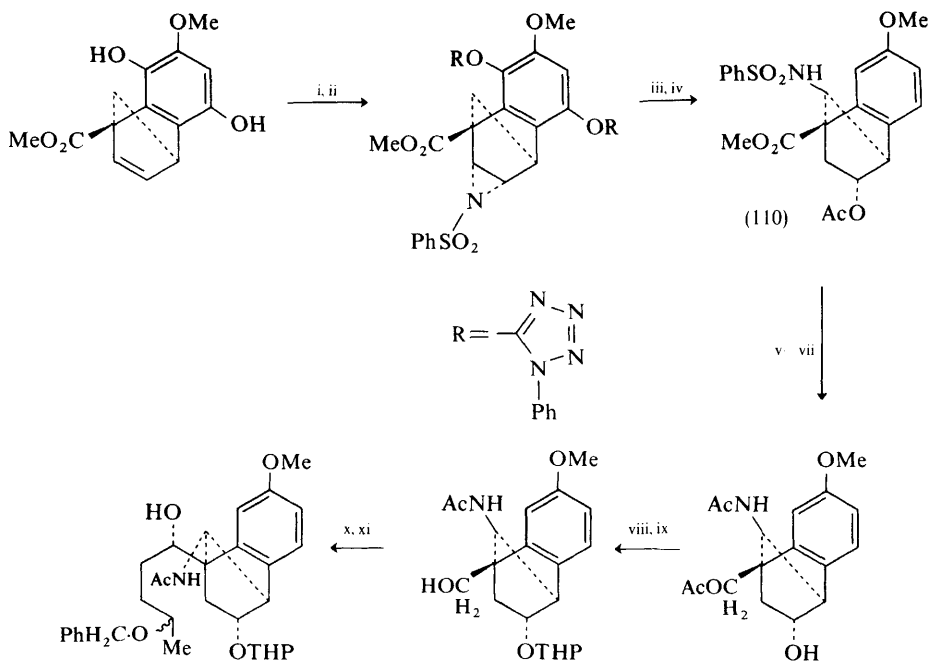
positive Cotton effects, indicative of a ring B boat conformation. Compounds (104)–(106) had negative Cotton curves, which support chair-like conformations for ring B in these compounds. This evidence shows that no change in conformation of ring B occurs on changing substituents on the bicyclic CD ring system in the saturated compounds. In the case of the unsaturated compounds, changes in conformation occur. This has been explained as reflection of the reduction of the energy barrier for the interconversion of the boat- and chair-like forms of ring B on introduction of a second  $sp^2$  carbon in this ring. The chair-like

conformations of compounds (104)–(106) were attributed to the steric interactions which would be present in the boat conformations.

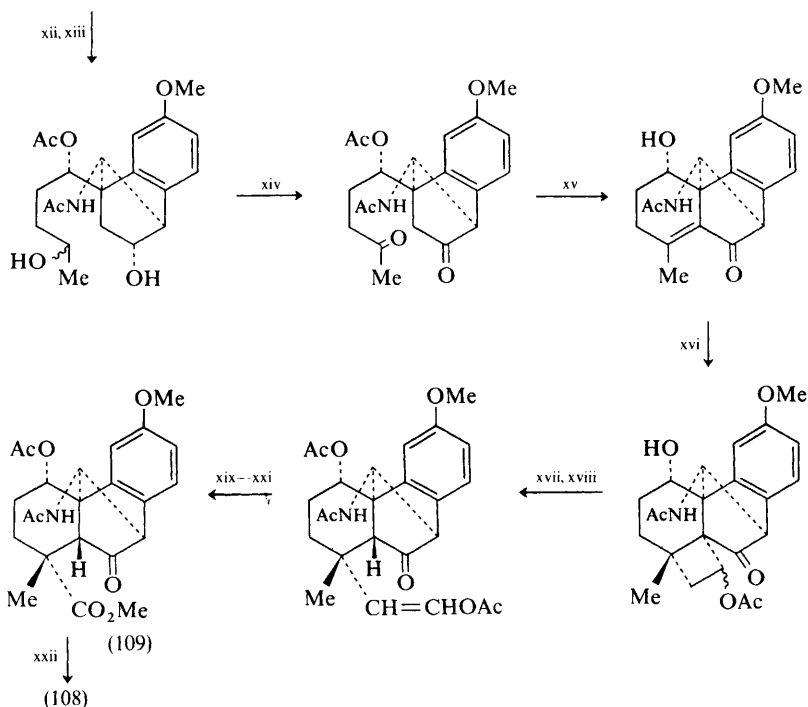
*Syntheses Directed toward Songorine.* Although songorine (107) is similar to the other  $C_{20}$ -diterpene alkaloids, the additional bond between C-7 and C-20 necessitates a synthetic approach more like that required for the  $C_{19}$ -diterpene



alkaloids of the aconitine type. Wiesner and co-workers have synthesized the pentacyclic keto-lactam (108).<sup>40</sup> Their synthetic approach is outlined in Scheme 9. The structure of (109) has been confirmed by a single-crystal X-ray structure



<sup>40</sup> K. Wiesner, Pak-tsun Ho, D. Chang, and J. F. Blount, *Experientia*, 1972, **28**, 766. We wish to thank Professor Wiesner for a pre-publication copy of this paper.

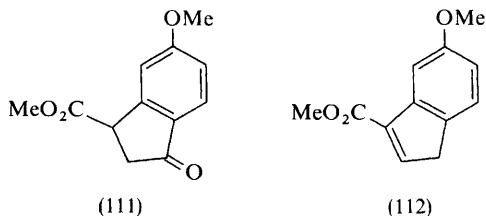


Reagents: i, RCl; ii,  $\text{PhSO}_2\text{N}_3$ ; iii, AcOH; iv,  $\text{Pd/C-H}_2$ ; v,  $\text{LiAlH}_4$ ; vi,  $\text{Ac}_2\text{O}$ -pyridine; vii,  $\text{K}_2\text{CO}_3$ -aq. MeOH; viii, DHP; ix, alkaline hydrolysis; x, DMSO-carbodiimide; xi,  $\text{BrMgCH}_2\text{-CH}_2\text{-CHMe-O-CH}_2\text{Ph}$ ; xii,  $\text{Ac}_2\text{O}$ -pyridine; xiii,  $\text{Pd/C-H}_2$ ; xiv,  $\text{CrO}_3$ -pyridine; xv,  $\text{K}_2\text{CO}_3$ -MeOH; xvi,  $\text{CH}_2=\text{CHOAc}$ -irradiation at  $-10^\circ\text{C}$ ; xvii, 1% KOH-MeOH; xviii,  $\text{Ac}_2\text{O-NaOAc}$ ; xix,  $\text{OsO}_4\text{-NaIO}_4$ ; xx,  $\text{CrO}_3$  (Jones'); xxi,  $\text{CH}_2\text{N}_2$ ; xxii, 6% KOH-8:2 MeOH:Bu'OH

Scheme 9

determination of the *N*-*m*-bromobenzoyl derivative.<sup>40</sup> The preliminary reports of this work have been previously discussed.<sup>41</sup>

A much more satisfactory synthesis of (110) has recently been reported.<sup>42</sup> The keto-ester (111) was converted into (112) on reduction with sodium borohydride

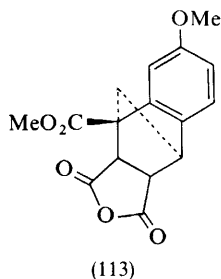


<sup>41</sup> Cf. ref. 9, p. 360.

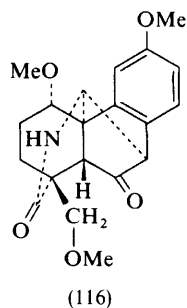
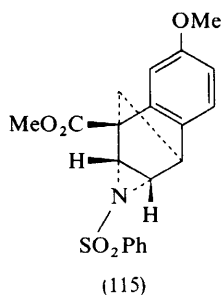
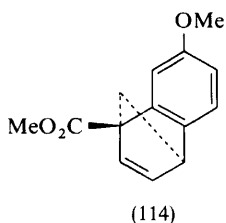
<sup>42</sup> Pak-tsun Ho, S. Oida, and K. Wiesner, *Chem. Comm.*, 1972, 883.



followed by treatment with methanolic 6% sulphuric acid. Reaction with maleic anhydride afforded the adduct (113), which was subjected to bisdecarboxylation



with dicarbonylbistriphenylphosphinenickel in diglyme to yield (114). This olefin was treated with benzenesulphonyl azide to form the aziridine (115). This



unstable compound was rearranged to (110) on treatment with acetic acid. The overall yield from (111) to (110) was 38%.

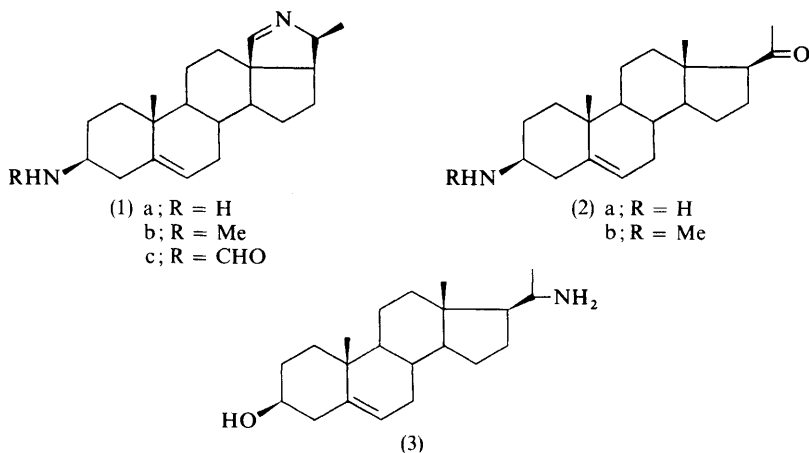
Since the required procedures for the elaboration of the CD ring system have been investigated on a model system,<sup>43</sup> the successful total synthesis of songorine is virtually at hand. Analogues of (108) [such as (116)] could serve as intermediates for synthesis of the aconitine alkaloids.

<sup>43</sup> K. Wiesner, A. Deljac, T. Y. R. Tsai, and M. Przybylska, *Tetrahedron Letters*, 1970, 1145.

## PART I: Alkaloids of the Apocynaceae

The *Holarrhena* and *Paravallis* Alkaloids

**A. Steroidal Alkaloids and Amines.**—Three conkurchine-type alkaloids, conkurchine (1a), conessidine (1b), and *N*-formylconkurchine (1c), the last being a new compound, and three amino-derivatives of pregnane, holaphyllamine (2a), holaphylline (2b), and holafèbrine (3), have been extracted from the leaves of *Holarrhena crassifolia* Pierre, an Apocynaceae species from Laos and Cambodia. The abundance of conkurchine-type alkaloids in this plant is an argument in favour of the maintenance of the species as *H. crassifolia*, since in the past it has been confused with *H. curtisii* King and Gamble. The latter species has been found to contain steroid alkaloids of a different type.<sup>1</sup>

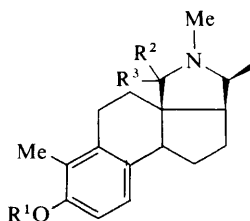
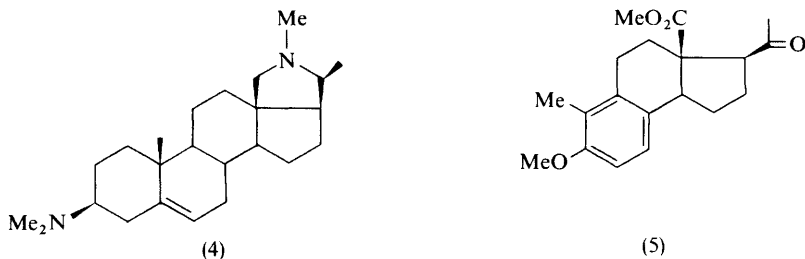


In the experiments on the synthesis of conessine (4), preparation of tetracyclic intermediates has been achieved.<sup>2</sup> Condensation of 2-(2-methyl-3-methoxyphenyl)ethyl bromide with dimethylcyclopentanone-2,3-dicarboxylate, followed by cyclodehydration, catalytic hydrogenation, and conversion of the secondary methoxycarbonyl group into a methyl ketone gave (5). This, on Leuckart reaction with MeNHCHO gave stereospecifically (6a), which on reduction and demethylation gave (6b), corresponding to the BCDE rings of conessine (4).

<sup>1</sup> J. Einhorn, Cl. Monneret, and Q. Khuong-Huu, *Phytochemistry*, 1972, **11**, 769.

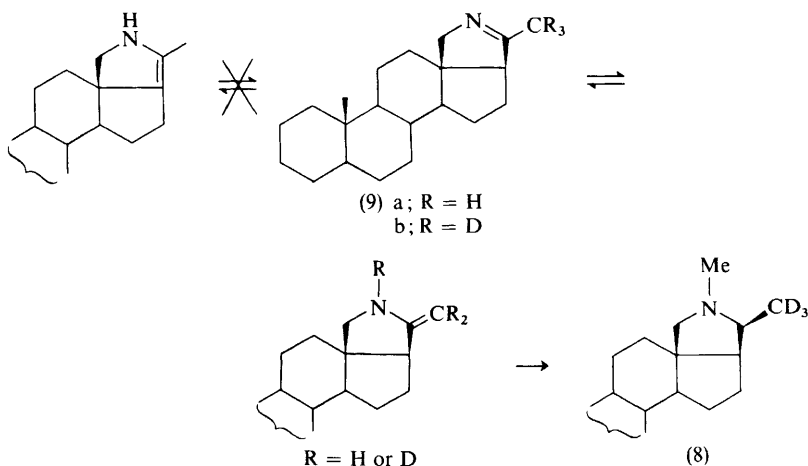
<sup>2</sup> P. C. Mukharji, J. C. Sircar, and V. V. Devasthale, *Indian J. Chem.*, 1971, **9**, 515.

Leuckart reaction of (5) with  $\text{HCONH}_2$  gave a mixture of two epimeric lactams, in contrast to the complete stereospecificity observed in the reaction with  $\text{MeNHCHO}$ .



- (6) a;  $\text{R}^1 = \text{Me}, \text{R}^2 + \text{R}^3 = \text{O}$   
 b;  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$

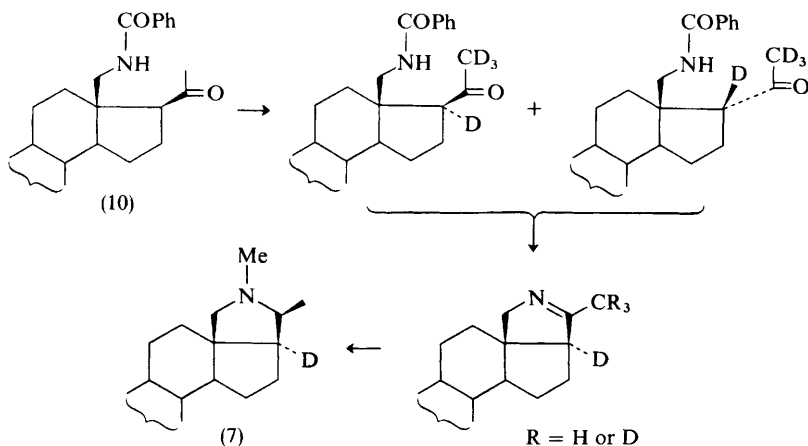
Selective deuteration of the pyrrolidine ring of conanine has been studied.<sup>3</sup> A rapid imine–enamine equilibrium following Bredt's rule permitted the preparation of  $[17\alpha\text{-}^2\text{H}]$ conanine (7) and  $[21,21,21\text{-}^2\text{H}_3]$ conanine (8) by selective deuteration. The  $5\alpha,20(\text{N})$ -conene (9a), with deuteriomethanol in alkaline medium,



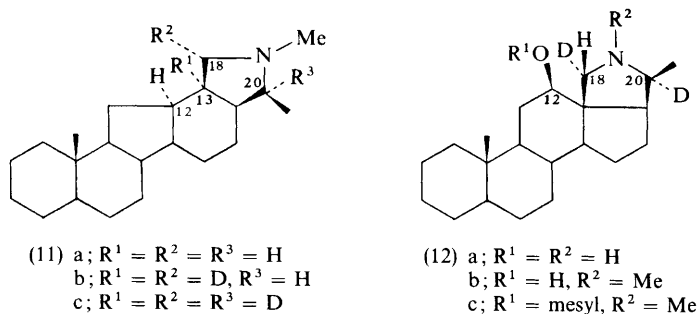
<sup>3</sup> G. Lukacs, A. Picot, L. Cloarec, A. Kornprobst, L. Alais, and X. Lusinchi, *Tetrahedron*, 1971, **27**, 3215.

afforded a deuteriated imine (9b) which, after reduction with sodium borohydride and methylation, led to [21,21,21- $^2\text{H}_3$ ]conanine (8).

By employing the procedure of Kasal,<sup>4</sup> the imine (9a) with benzoyl chloride gave the ketone (10). The hydrogen atoms at the  $\alpha$ -positions to the carbonyl group exchange with deuterium in alkaline medium, and some epimerization at position 17 also occurs. The mixture of epimeric [17 $\alpha$ - $^2\text{H}$ ]- and [17 $\beta$ - $^2\text{H}$ ]-ketones with deuteriated acid gave the tetradeuteriated imine, which led to the [17 $\alpha$ - $^2\text{H}$ ]imine after equilibration. The [17 $\alpha$ - $^2\text{H}$ ]imine led to the [17 $\alpha$ - $^2\text{H}$ ]conanine (7), after reduction and methylation.



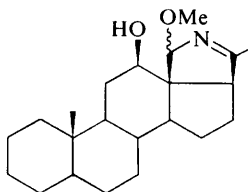
The mechanism of formation and the structure of the C-nor-D-homo-conanine (11a) have been studied and the configurations at positions 12 and 13 have been established.<sup>5</sup> 12 $\beta$ -Hydroxy-N-demethyl[18 $\alpha$ ,20 $\alpha$ - $^2\text{H}_2$ ]conanine (12a) has been prepared by reaction of lithium aluminium deuteride with the methoxylated imine (13). The stereospecific reduction which was observed in this case resulted from an intramolecular reduction by the complex alcoholate formed by reaction



<sup>4</sup> A. Kasal, V. Cerny, and F. Sorm, *Coll. Czech. Chem. Comm.*, 1960, **25**, 2849.

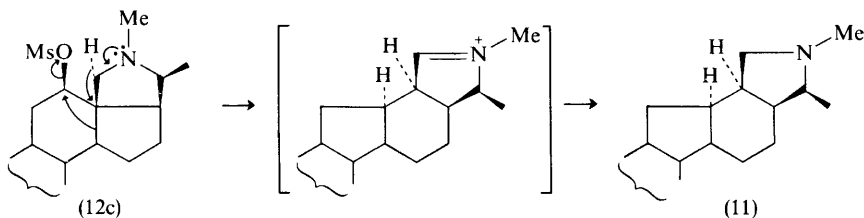
<sup>5</sup> G. Lukacs, P. Longevialle, and X. Lusinchi, *Tetrahedron*, 1971, **27**, 1891.

of lithium aluminium deuteride with the  $12\beta$ -hydroxy-group; methylation of (12a) gave (12b). Rearrangement of the mesylate (12c) with  $\text{AlHCl}_2$  led to C-nor-D-homo-[ $13\alpha, 20\alpha$ - $^2\text{H}_2$ ]conanine (11b), and rearrangement of the mesylate (12c) with  $\text{AlDCl}_2$  afforded C-nor-D-homo-[ $13\alpha, 18\alpha, 20\alpha$ - $^2\text{H}_3$ ]conanine (11c).



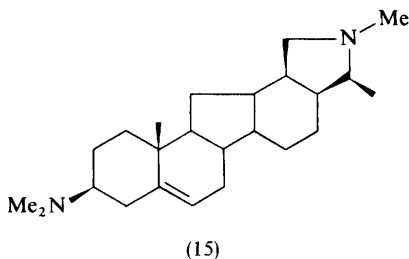
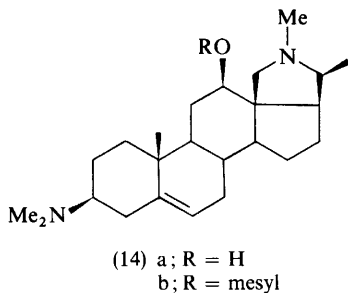
(13)

These results indicated that the Wagner–Meerwein-type rearrangement was followed by a stereospecific hydride transfer from C-18 $\alpha$  to C-13 $\alpha$  which led to an immonium ion, the latter finally being reduced to derivative (11) (Scheme 1). Inversion at position 12, as expected for a Wagner–Meerwein-type rearrangement, is in accordance with the generality of the C-nor-D-homo rearrangement.



Scheme 1

On the other hand, transformation of holarrhenine (14a) to a C-nor-D-homo-derivative (15) by a superior method to that used by Uffer<sup>6</sup> has been investigated.<sup>7</sup> The arrangement of holarrhenine mesylate (14b) leading to derivative (15) is complete in anhydrous alcohols using an excess of sodium borohydride.

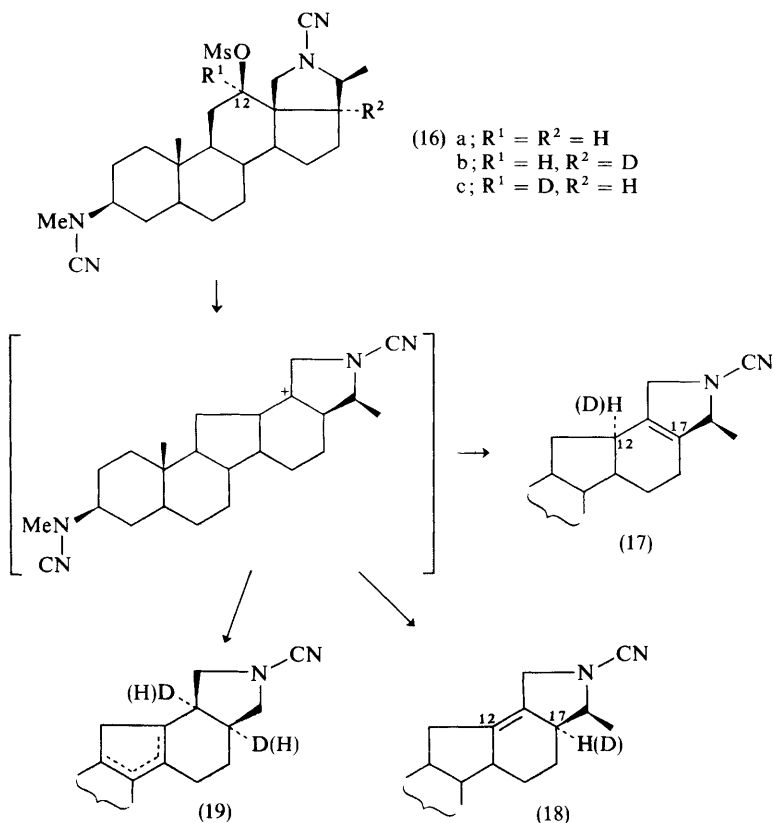


<sup>6</sup> A. Uffer, *Helv. Chim. Acta*, 1956, **39**, 1834.

<sup>7</sup> G. Van de Woude and L. Van Hove, *Tetrahedron Letters*, 1972, 1305.

Reduction of (14b) with sodium borodeuteride in *O*-deuterio- or *O*-deuterioisopropyl alcohol led to a 97% monodeuteriated rearranged product in which 80% of the deuterium was incorporated at position 18.

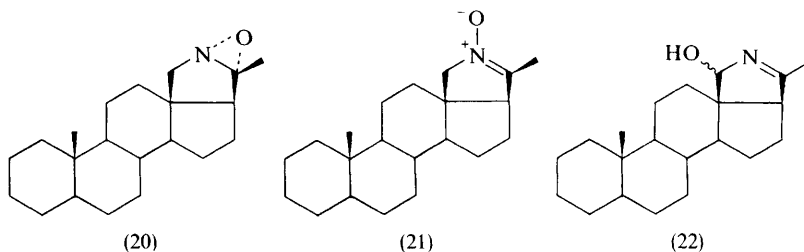
By the action of collidine, a successful C-nor-D-homo rearrangement of 12 $\beta$ -mesyloxy-*NN'*-dicyanodihydroconimine (16a) in a non-reductive medium has been reported to give a mixture of two ethylenic main products.<sup>8</sup> These have been shown to have tetrasubstituted double bonds and their possible structures are (17), (18), or (19). The presence of the derivatives (17) and (18) in the reaction



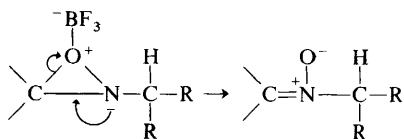
mixture has been determined by performing the reaction with derivatives deuteriated at positions 12 $\alpha$  and 17 $\alpha$ . An estimate of the extent of deuterium labelling by mass spectrometry, both before and after rearrangement, led to the identification of derivative (17) by loss of deuterium during rearrangement of 12 $\beta$ -mesyloxy-*NN'*-dicyanodihydro[17 $\alpha$ ,20 $\alpha$ ,21,21,21- $^2\text{H}_5$ ]conimine (16b) and, similarly, the identification of derivative (18) by loss of deuterium during rearrangement of 12 $\beta$ -mesyloxy-*NN'*-dicyanodihydro[12 $\alpha$ - $^2\text{H}$ ]conimine (16c).

<sup>8</sup> G. Lukacs, L. Cloarec, L. Lacombe, and X. Lusinchi, *Bull. Soc. chim. France*, 1972, 180.

The isomerization of the heterocyclic oxaziridine (20), in an acidic medium, can lead either to the nitrone (21) or to the iminocarbinal (22).<sup>9</sup> With a Lewis acid,

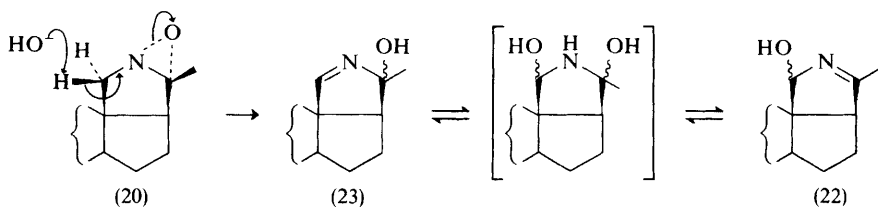


the oxaziridine (20) led to the nitrone (21) (Scheme 2). With a protonic acid, the oxaziridine (20) led to the iminocarbinal (22), which arose from the isomerization



Scheme 2

of the iminocarbinal (23) first formed (Scheme 3). These reactions are identical with the hydrolysis reactions of aliphatic oxaziridines explained by Emmons.<sup>10</sup> These arise by heterolysis of the protonated form of the oxaziridine along either



Scheme 3

the  $\text{C}=\text{O}$  bond or the  $\text{C}-\text{N}$  bond and afford a carbonium ion or a nitrenium ion which in turn leads to the formation of the products.

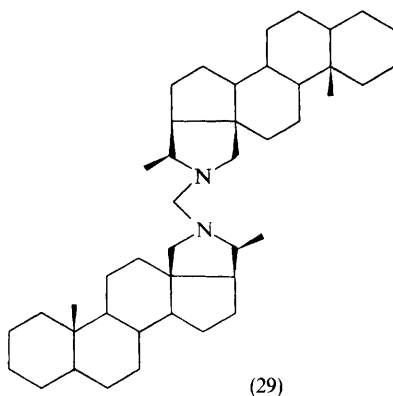
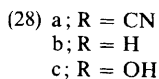
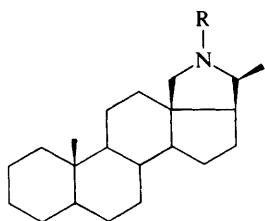
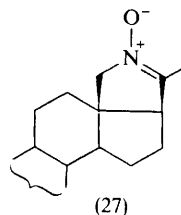
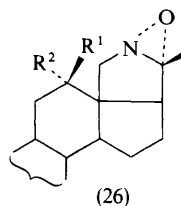
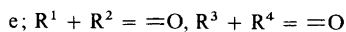
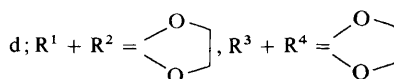
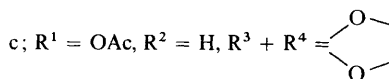
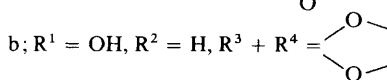
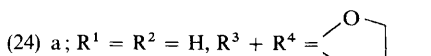
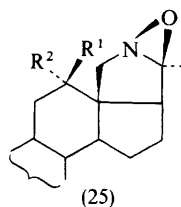
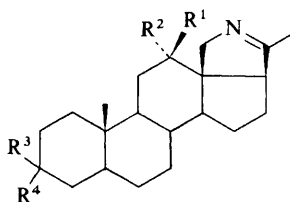
The presence and the nature of a functional group at position 12 on imine derivatives of  $5\alpha,20(\text{N})$ -conene (24) changed the reactivity of the imino-group towards peracids.<sup>11</sup> By the action of one mole of *p*-nitroperbenzoic acid on some derivatives of  $5\alpha,20(\text{N})$ -conene (24) (with various substituents at position 12), the (20*R*)-oxaziridine (25), the (20*S*)-oxaziridine (26), and the nitrone (27) were obtained

<sup>9</sup> P. Milliet and X. Lusinch, *Tetrahedron Letters*, 1972, 3763.

<sup>10</sup> W. D. Emmons, *J. Amer. Chem. Soc.*, 1957, **79**, 5739.

<sup>11</sup> G. Roblot, G. Lukacs, and X. Lusinch, *Tetrahedron Letters*, 1972, 505.

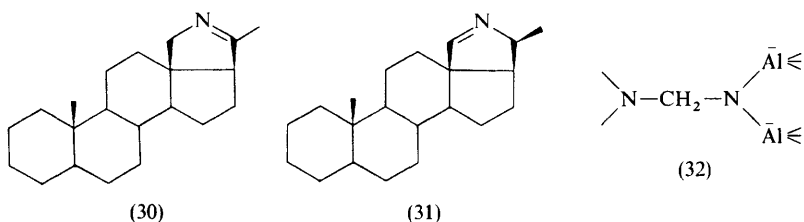
in differing amounts. Under the same conditions an imine, without substitution at position 12, led only to the (20*R*)-oxaziridine. These results have been explained by invoking a mechanism for the formation of the oxaziridines similar to the mechanism suggested for the epoxidation of alkenes.<sup>12</sup>



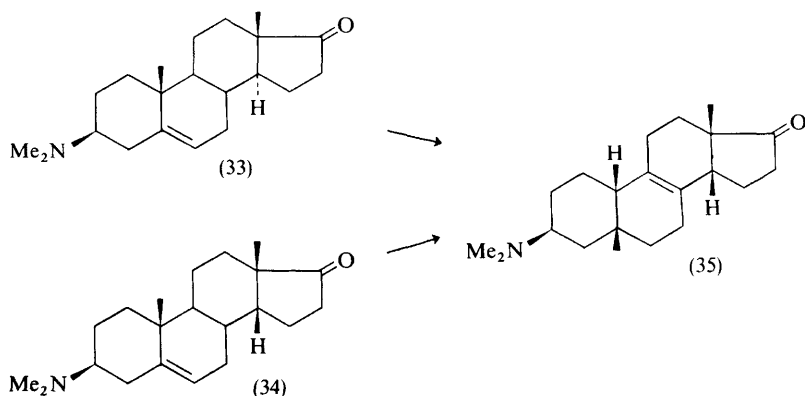
<sup>12</sup> H. Henbest, *Proc. Chem. Soc.*, 1963, 159; M. M. Mousseron-Canet and B. Labeew, *Bull. Soc. chim. France*, 1963, 4171; V. Madan and L. B. Clapp, *J. Amer. Chem. Soc.*, 1970, **92**, 4902.



Reduction of *N*-cyano-*N*-demethylconanine (28a) with lithium aluminium hydride, under nitrogen, afforded the methylenic *gem*-diamine (29) when the reaction was carried out at room temperature, and the secondary amine (28b) was formed when this reaction was carried out in a refluxing solvent (THF).<sup>13</sup> However, in presence of air, the hydroxylamine (28c) and the imines (30) and (31) were formed in small amounts as a result of oxidation reactions. The organo-metallic intermediate (32) can explain the formation of these products. The reduction of (28a) with  $\text{LiAlH}_4\text{--AlCl}_3$  led only to the secondary amine (28b).



Backbone rearrangements of various steroidal amines have been carried out in order to study the mechanism and to elucidate the stereochemistry of the rearranged products.<sup>14,15</sup> The two  $3\beta$ -dimethylamino- $\Delta^5$ -androst-17-ones epimeric at position 14, (33) and (34), when treated with concentrated sulphuric



acid at 0 °C led to the same ketone (35).<sup>14</sup> On the other hand,  $3\alpha$ -methylamino- $\Delta^5$ -androst-17-one (36) afforded, under the same conditions, the two isomeric ketones (37) and (38).<sup>15</sup> Similarly,  $3\alpha$ -methylamino- $\Delta^5$ -conanene (39) led to the two products (40) and (41).<sup>15</sup> In these acidic conditions the two groups of derivatives [(37) and (38), and (40) and (41)] are in equilibrium. The position of

<sup>13</sup> A. Picot and X. Lusinchi, *Bull. Soc. chim. France*, 1972, 1097.

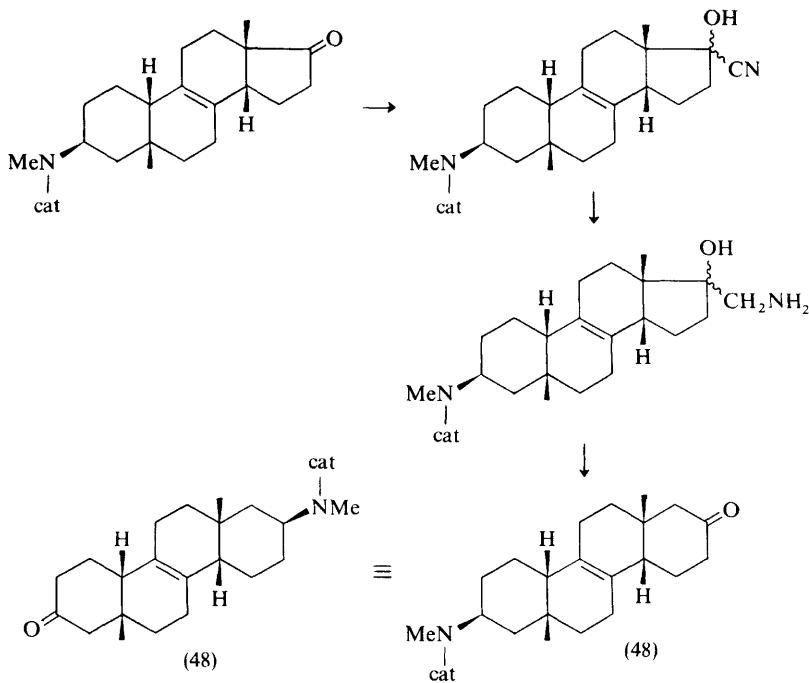
<sup>14</sup> F. Frappier, M. Pais, and F. X. Jarreau, *Bull. Soc. chim. France*, 1972, 610.

<sup>15</sup> F. Frappier, J. Thierry, and F. X. Jarreau, *Bull. Soc. chim. France*, 1972, 617; cf. preliminary paper: F. Frappier, J. Thierry, and F. X. Jarreau, *Tetrahedron Letters*, 1971, 1887.



the double bond at 8,9 in the derivatives (35), (37), (38), (40), and (41) has been determined by the method of Castells and Meakins.<sup>16</sup>

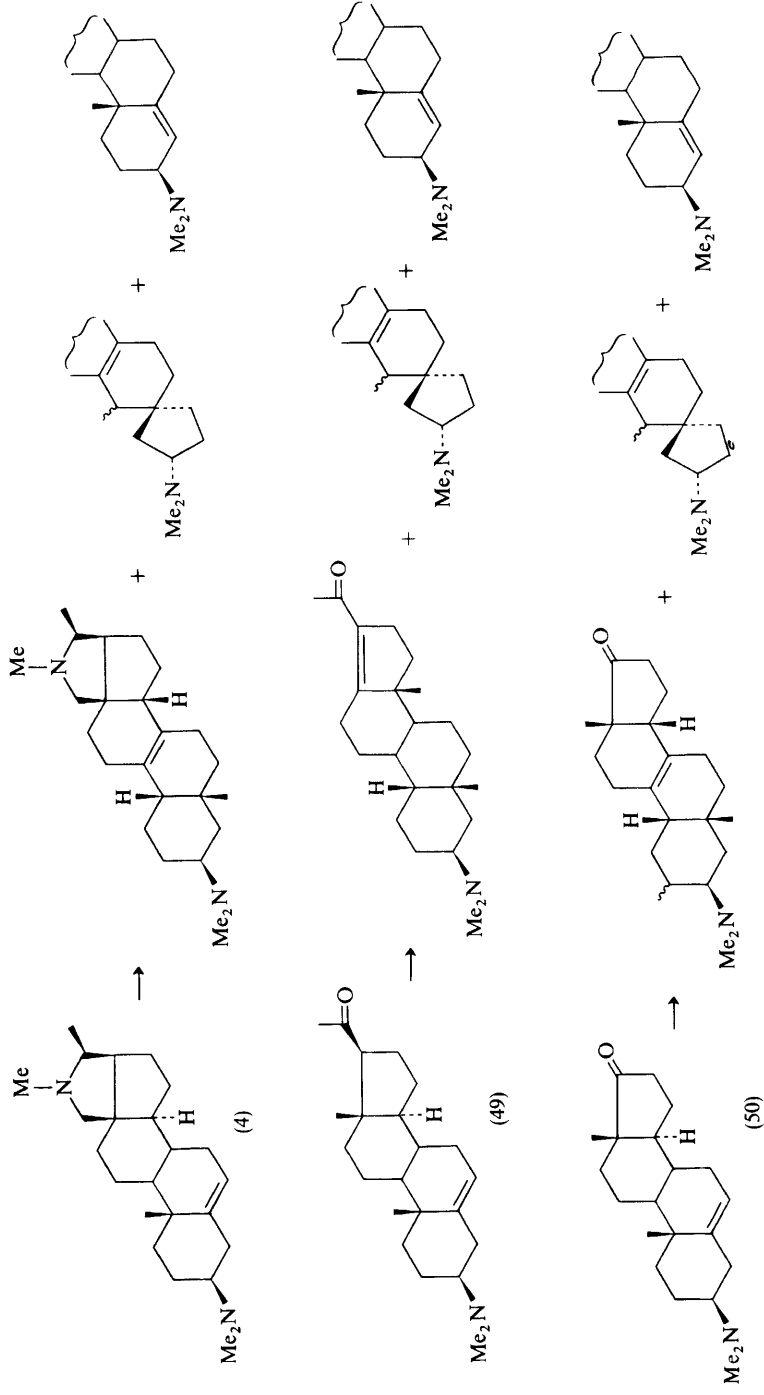
Through c.d. measurements of the ketones (42), (43), (44), (45), and (46), which were obtained from the corresponding amines, the precise stereochemistry at position 10 has been determined. Similarly, c.d. measurements of the 17-ketonic chromophore of the derivatives (35), (37), and (38) allowed a  $14\beta$ -H configuration for these products to be postulated. The same diketone (47) has been prepared starting from (35) and from (37). Finally, the  $14\beta$ -H configuration has been determined by c.d. measurements of the derived ketone (48), obtained from (35) (Scheme 4). The sign and the amplitude of the Cotton effect of ketone (48) are



**Scheme 4**

typical for a 3-ketosteroid with a A/B *cis* 'non steroid' ring junction. These results enabled the authors to claim that, with concentrated sulphuric acid, backbone rearrangements of these steroidal amines are thermodynamically controlled and proceed through a sequence of protonations and deprotonations. The double bond migrates from the 5,6-position to the positions 9,10, 8,14, and, finally, 8,9. The nature of the functional groups which are present in the starting molecule determines the structures of the products. For example, a  $3\alpha$ -amino-group is responsible for the observed equilibrium of derivatives epimeric at position 10.

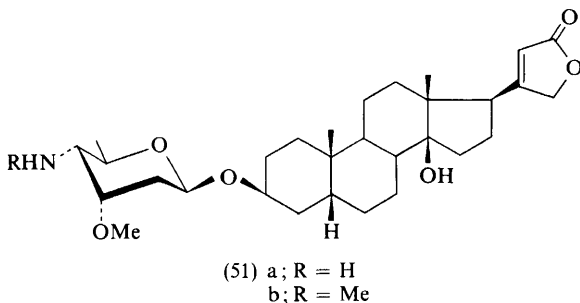
<sup>16</sup> J. Castells and G. D. Meakins, *Chem. and Ind.*, 1956, 248.



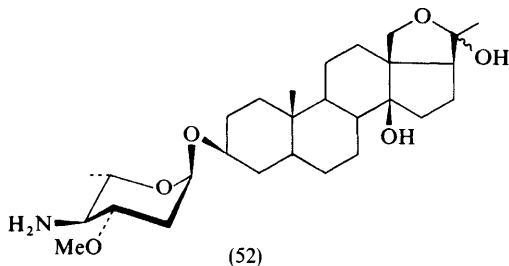
Scheme 5

The isomerization of some  $3\beta$ -dimethylaminosteroids, namely conessine (4),  $3\beta$ -dimethylamino- $\Delta^5$ -pregnen-20-one (49), and  $3\beta$ -dimethylamino- $\Delta^5$ -androsten-17-one (50), in a sulphuric acid-acetic acid medium, gave 1(10 $\rightarrow$ 5)-*abeo*-steroids and  $\Delta^4$ -steroids, as well as backbone-rearranged products (Scheme 5).<sup>17</sup> It was shown that  $\Delta^4$ -derivatives could be eventual intermediates in the formation of 1(10 $\rightarrow$ 5)-*abeo*-steroids. On the other hand,  $3\alpha$ -dimethylaminosteroids do not afford 1(10 $\rightarrow$ 5)-*abeo*-steroids under these experimental conditions; an explanation is proposed.

**B. Aminoglycosteroids.**—*N*-Demethylmitiphylline (51a), as well as mitiphylline (51b), has been extracted from the leaves of *Holarrhena mitis*.<sup>18</sup>



Three new aminoglycosteroids have been isolated from the leaves of *Holarrhena antidysenterica*, holantosines C (52) and D (53a) and holarosine A (54).<sup>19</sup> These products are  $\alpha$ -L-glycosides. The genine of holantosine C is holantogenine;<sup>20</sup> the genine of holantosine D is anhydroholantogenine;<sup>20</sup> the genine of holarosine A is allouzarigenine.<sup>21</sup> These genines are attached to a new aminodeoxy-sugar, L-holantosamine or 4-amino-4-deoxy-L-oleandrose. N.m.r. measurements of



<sup>17</sup> F. Frappier and F. X. Jarreau, *Bull. Soc. chim. France*, 1972, 625.

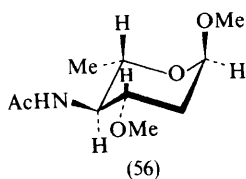
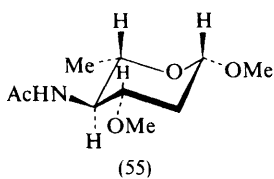
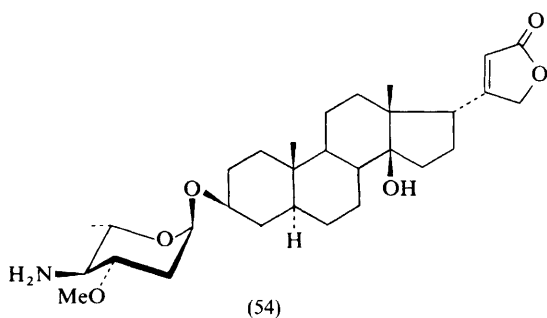
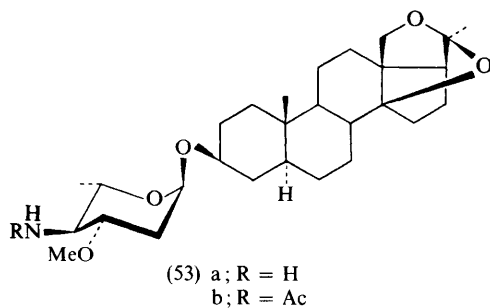
<sup>18</sup> M. Leboeuf, A. Cavé, G. P. Wannigama, and R. Goutarel, *Phytochemistry*, 1972, **11**, 843.

<sup>19</sup> Q. Khuong-Huu, Cl. Monneret, I. Kaboré, P. Choay, J. M. Tekam, and R. Goutarel, *Bull. Soc. chim. France*, 1971, 864.

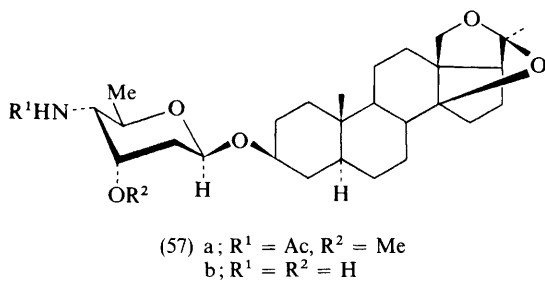
<sup>20</sup> M.-M. Janot, Q. Khuong-Huu, C. Monneret, I. Kaboré, J. Hildesheim, S. D. Géro, and R. Goutarel, *Tetrahedron*, 1970, **26**, 1695.

<sup>21</sup> Pl. A. Plattner, L. Ruzicka, H. Heussler, and E. Angliker, *Helv. Chim. Acta*, 1947, **30**, 1073; A. Kuritzkes, J. Von Euw, and T. Reichstein, *Helv. Chim. Acta*, 1959, **42**, 1502.

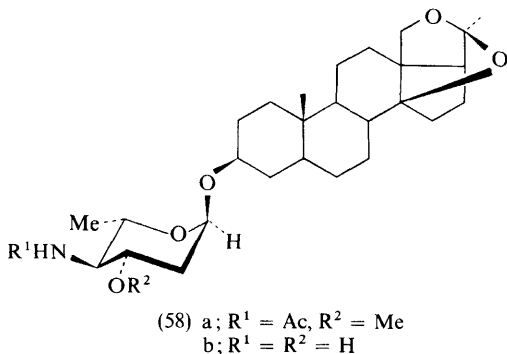
*N*-acetylholantosine D (53b) (at 220 MHz) and of methylglycosides (55) and (56) (at 60 MHz) led to structural assignment for *L*-holantosamine. Reduction of



*N*-acetylholantosines B (57a) and D (58a) with lithium in ethylamine afforded the derivatives (57b) and (58b), respectively, by reductive cleavage of the amide

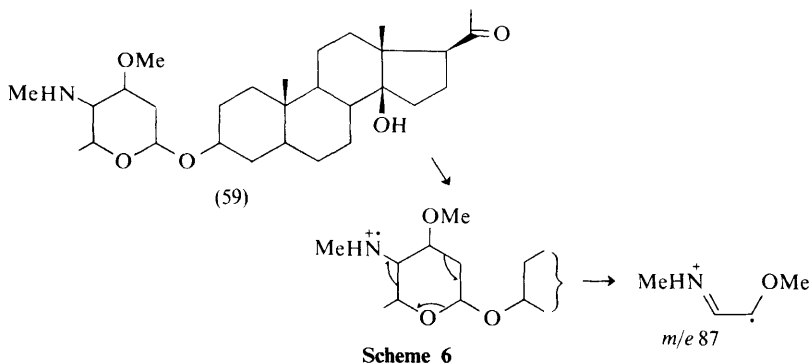


group and *O*-demethylation of the methoxy-group without cleavage of either the glycosidic bond or the hemiacetal function.<sup>22</sup>



**C. Mass and N.M.R. Spectra of Steroidal Amines.**—The fragmentation pattern in the mass spectrometer of steroidal diamines has been reported.<sup>23</sup>

A comparative study of the fragmentation pattern of holacurtine (59) by electronic impact and by chemical ionization has been carried out.<sup>24</sup> These two mass spectrometric techniques gave complementary information. By electronic impact, the base peak is *m/e* 87, indicating the close vicinity of the ether and amine



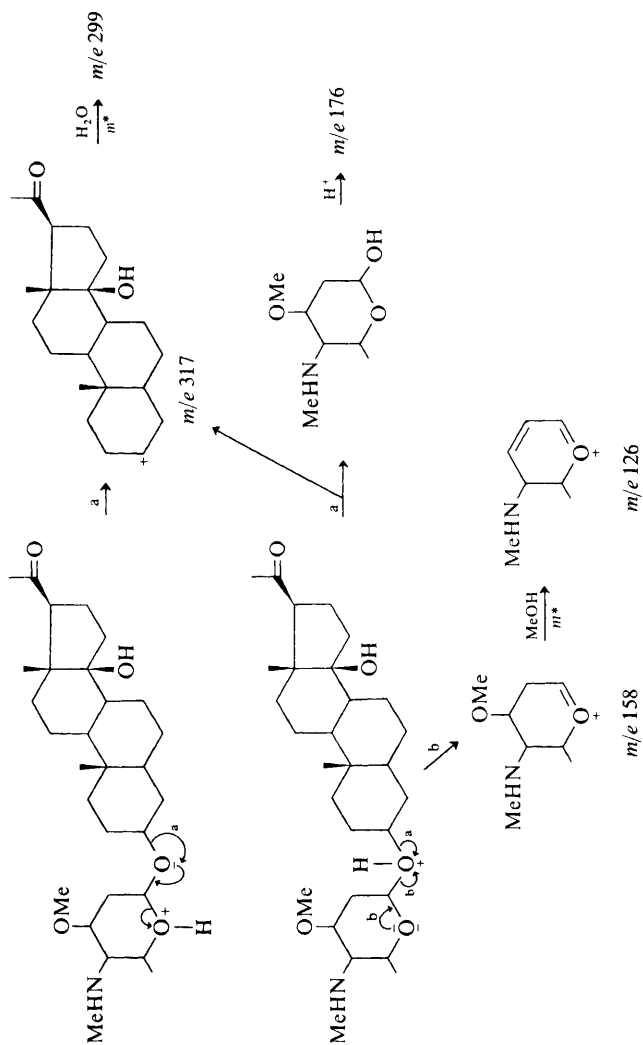
functions (Scheme 6). By chemical ionization, holacurtine (59) led to ions  $MH^+$ ,  $(MH - 18)^+$ , and the fragments which are summarized in Scheme 7.

In the <sup>1</sup>H n.m.r. spectrum of 12β-hydroxyconanine (60) the methylene at position 18 appeared as an AB system. Owing to the proximity of the hydroxy-group at position 12, the signals of this AB system have been assigned after

<sup>22</sup> Q. Khuong-Huu, Cl. Monneret, I. Kaboré, and R. Goutarel, *Tetrahedron Letters*, 1971, 1935.

<sup>23</sup> P. Longevialle, in 'Recent Developments in Mass Spectroscopy,' ed. Koreichi Ogata and Teruo Hayakawa, University of Tokyo Press, 1970.

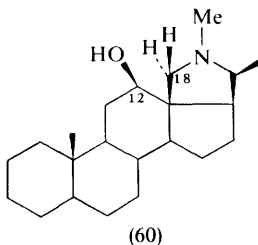
<sup>24</sup> P. Longevialle, Ph. Devissaguet, Q. Khuong-Huu, and H. M. Fales, *Compt. rend.*, 1971, 273, C, 1533.



Scheme 7



complexation with  $\text{Eu(dpm)}_3$ .<sup>25</sup> This assignment has been confirmed by a stereospecific deuteration at position 18 $\alpha$ . The effects of a gradual complexa-



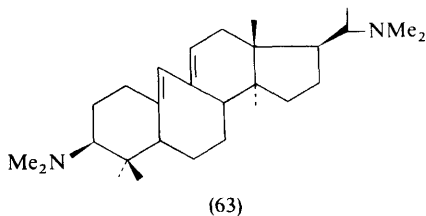
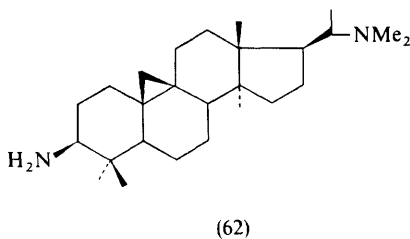
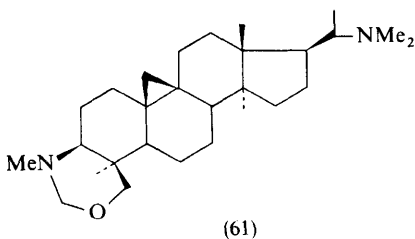
tion with  $\text{Eu(dpm)}_3$  have been investigated in order to find a general method for the differentiation of the protons of an AB system.

$^{13}\text{C}$  nuclear magnetic resonance spectra of conessine and related products have been recorded and the signals have been discussed and assigned.<sup>26</sup>

## PART II: Alkaloids of Buxaceae

### 1 *Buxus* Alkaloids

The strongly basic fraction of *Buxus sempervirens* extract yielded cycloprotobuxine C and 16-deoxycyclobuxoxazine A (61),  $\text{C}_{28}\text{H}_{48}\text{N}_2\text{O}$ ; spectral data indicated the structure for the latter.<sup>27</sup>



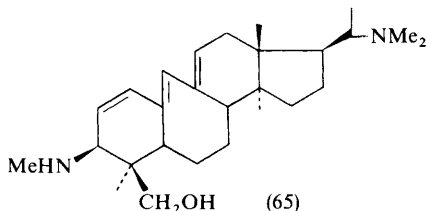
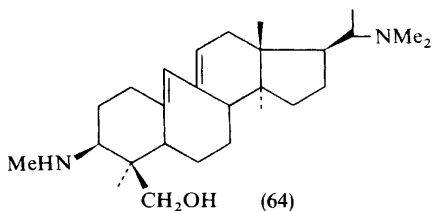
<sup>25</sup> G. Lukacs, X. Lusinchi, P. Girard, and H. Kagan, *Bull. Soc. chim. France*, 1971, 3200.

<sup>26</sup> G. Lukacs, A. Picot, X. Lusinchi, H. J. Koch, and A. S. Perlin, *Compt. rend.*, 1971, **272**, C, 2171.

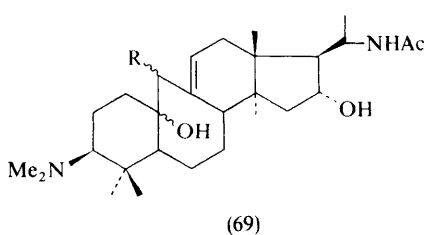
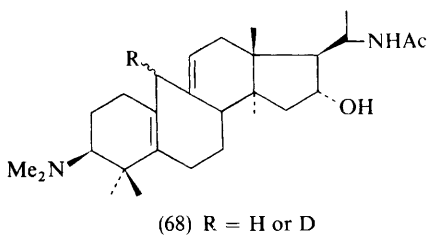
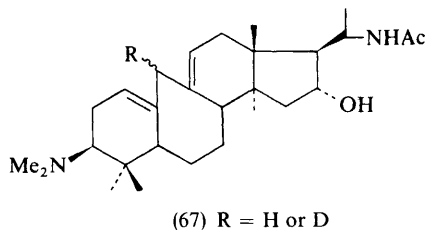
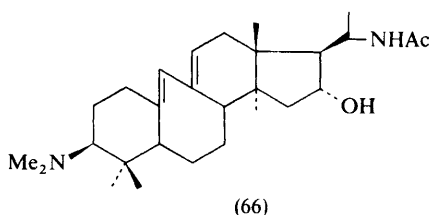
<sup>27</sup> R. Härtel, W. Döpke, E. Grundemann, and G. Lehmann, *Tetrahedron Letters*, 1971, 2743.

The alkaloids from the leaves of *Buxus wallichiana* Baill., from India, have been studied.<sup>28</sup> Cycloprotobuxine C, cyclovirobuxine D, cyclobuxine D, and buxta-  
uine have been identified by combination of elemental analysis, spectral data, and  
preparation of suitable (previously described) derivatives.

Five alkaloids have been extracted from stem bark and roots of *Buxus mada-  
gascariensis* Baill. subsp. *Xerophila forma salicicola*;<sup>29</sup> these are cycloprotobuxine  
C, cycloprotobuxine F (62), buxamine A (63), 16-deoxybuxidienine C (64), and  
buxitrienine C. Physico-chemical properties and preparation of suitable deriva-  
tives led to their structural assignments. Buxitrienine C (65) is a new type of  
*Buxus* alkaloid.



The direct irradiation of *N*-acetylbuxaminol (66) has been carried out in acetic  
acid solution, giving the two isomeric dienes (67) and (68) and the two epimeric  
alcohols (69).<sup>30</sup> Synthesis of the derivative (70) starting from (67) and from



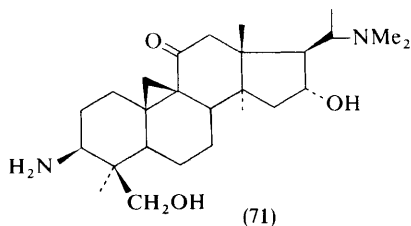
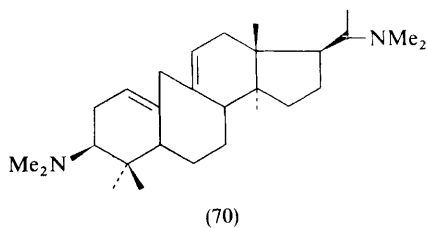
cyclobuxine F (71) established the structure (67) for one product. Chemical  
correlations between (67), (68), and (69) led to the structural assignments of  
derivatives (68) and (69). An irradiation in a deuteriated medium clearly showed

<sup>28</sup> R. H. Burnell and M. Soucy, *Phytochemistry*, 1972, **11**, 1853.

<sup>29</sup> F. Khuong-Huu, R. Paris, R. Razafindrambao, A. Cavé, and R. Goutarel, *Compt. rend.*, 1971, **273**, C, 558.

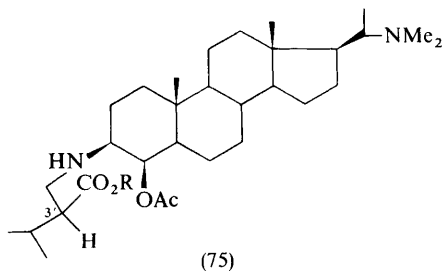
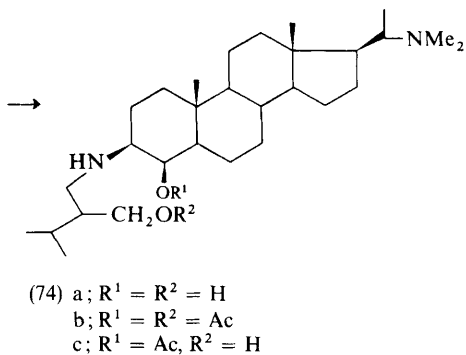
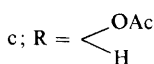
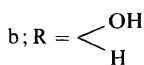
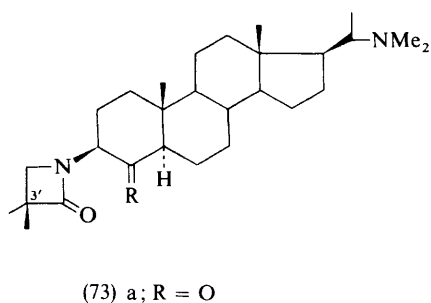
<sup>30</sup> F. Khuong-Huu, D. Herlem, and M. Bénéchie, *Bull. Soc. chim. France*, 1972, 1092.

that there had been a stereospecific introduction of a deuterium at position 19. An ionic species has been suggested as an intermediate.



## 2 *Pachysandra* Alkaloids

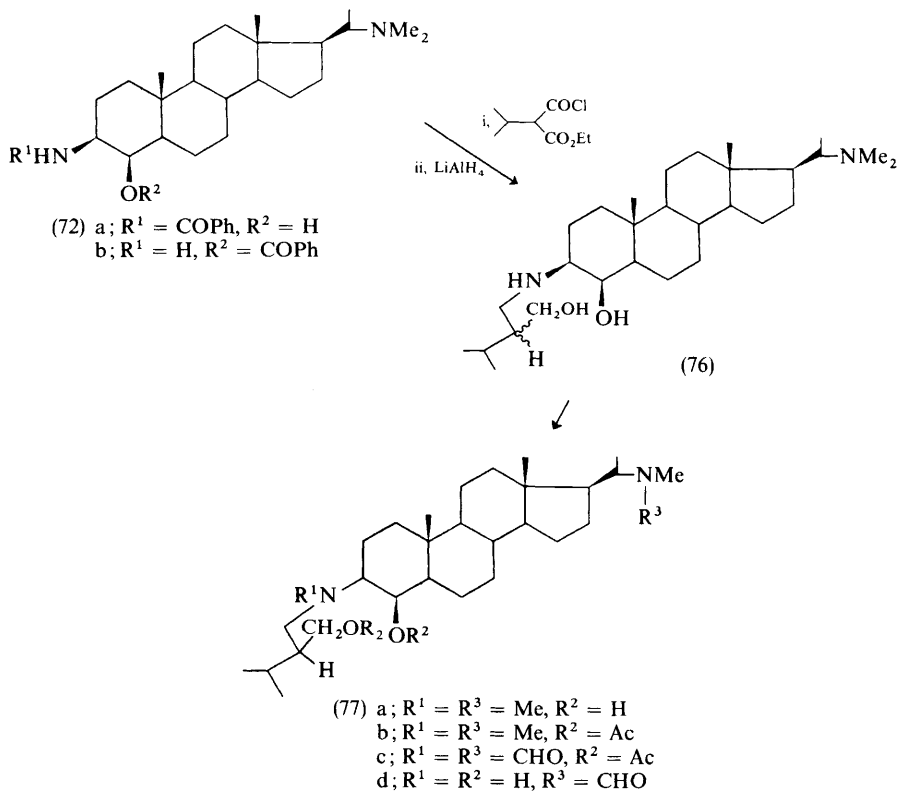
A full paper on the synthesis of pachysandrines and epipachysandrines A from ergosterol has been published.<sup>31</sup> A preliminary account<sup>32</sup> of this work was reviewed in Volume 1 of this series.



<sup>31</sup> T. Kikuchi, T. Nishinaga, and Y. Yoshimura, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1886.

<sup>32</sup> R. Goutarel, in 'The Alkaloids', (Specialist Periodical Reports), ed. J. E. Saxton, The Chemical Society, London, 1970, Vol. 1, p. 382.

The chemical transformation of epipachysandrine A (72a) into pachystermines A (73a) and B (73b) has been carried out.<sup>33</sup> The diol (74a), obtained after reduction of pachystermine A (73a) with lithium aluminium hydride, gave a diacetyl derivative (74b). Partial saponification gave the monoacetyl derivative (74c), which was oxidized to the amino-acid (75).



In a similar way, pachystermine B (73b) afforded the amino-acid (75) with retention of configuration at position-3'.

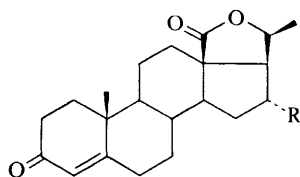
The crude amino-acid (75) when treated with dicyclohexylcarbodi-imide gave a  $\beta$ -lactam identical with acetyl pachystermine B (73c). Reduction of the latter with lithium aluminium hydride gave pachystermine B (73b), which in turn was oxidized to pachystermine A (73a). On the other hand, the product (72b), an acyl-migration product of epipachysandrine A (72a), when treated with the acyl chloride of ethyl isopropylmalonate gave a condensation product which, when reduced with lithium aluminium hydride, afforded a mixture of 3'-epimeric diols (76).

<sup>33</sup> T. Kikuchi, T. Nishinaga, S. Uyeo, O. Yamashiro, and K. Minami, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1893 (cf. *Tetrahedron Letters*, 1968, 909).

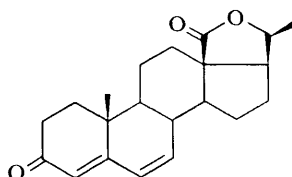
Methylation of (76) gave methylated products. *N*-Methylpachystermine diol (77a) was obtained after chromatographic separation. Oxidation of (77b) gave the diformate (77c) which was partially hydrolysed to the monoamide (77d). This product, when reduced with lithium aluminium hydride, gave pachystermine diol (74).

### PART III: Biological and Biogenetic Notes

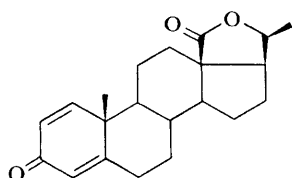
Six steroidal ketones have been isolated from the leaves of *Paravallaris microphylla*.<sup>34</sup> These ketones [(78)–(82)] have a 18 → (20S) lactone function, characteristic of the alkaloids found in this plant, namely paravallarine and paravallardine. The co-occurrence of both steroidal ketones and steroidal amines



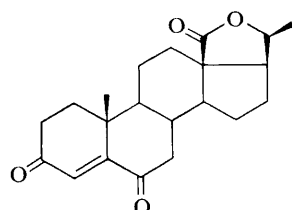
(78) a; R = H  
b; R = OH



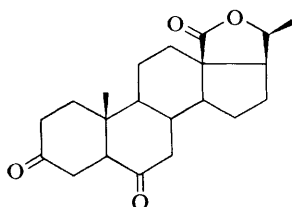
(79)



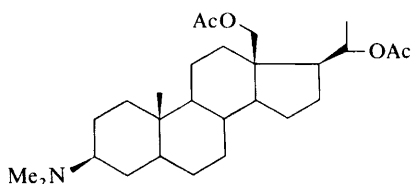
(80)



(81)



(82)



(83)

further augments the suggestion of a biogenetic relationship between these two groups of compounds.

<sup>34</sup> H.-P. Husson, L. Fernandès, C. Kan-Fan, P. Potier, and J. Le Men, *Bull. Soc. chim. France*, 1971, 1686.

A comparative study of the pharmacological, biochemical, and physico-chemical properties of various salts of the semisynthetic derivative (83), obtained starting from paravallarine, has been carried out.<sup>35</sup>

The preparation and curarizing activity of some semisynthetic paravallaridine derivatives have been reported.<sup>36</sup> Relationships were discussed between activity and the following chemical structures: saturated or unsaturated substituents at positions 16 $\alpha$  and 16 $\beta$ , (20*R*) or (20*S*) configuration, substitution at positions 18 and 20, mono- and di-quaternary ammonium derivatives.

Irehdiamine A has been found to have a potentializing activity on the hepatocarcinogenesis induced by DAB, in the rat.<sup>37</sup>

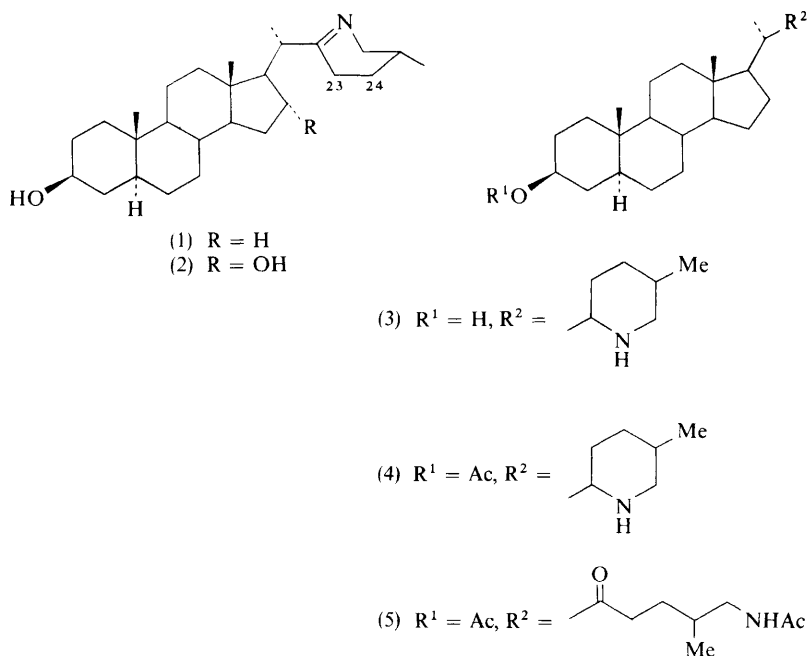
<sup>35</sup> G. Gerfaux, P. Forgacs, H. Eyraud, and M. Aurousseau, *Chim. Ther.*, 1971, **6**, 384.

<sup>36</sup> J. Le Men, J. F. Desclonclois, R. Tiberghien, and P. Forgacs, *Chim. Ther.*, 1971, **6**, 502.

<sup>37</sup> A. Lacassagne, L. Hurst, Nguyen-Dat-Xuong, Q. Khuong-Huu, and R. Goutarel, *Compt. rend.*, 1972, **274**, D, 2830.

The period covered by this review is from January 1969 to the end of June 1972. A thorough survey has been carried out *via Chemical Abstracts* (volumes 74–76) and *Chemical Titles* for the period January 1971 to June 1972 but only the more important papers of the preceding period have been included.

The *Solanum* and *Veratrum* steroidal alkaloids have been reviewed quite recently, both comprehensively<sup>1,2</sup> and briefly.<sup>3,4</sup>



<sup>1</sup> K. Schreiber, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1968, p. 1.

<sup>2</sup> S. M. Kupchan and A. W. By, in ref. 1, p. 193.

<sup>3</sup> Y. Sato, in 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand-Reinhold, New York, 1970, p. 591.

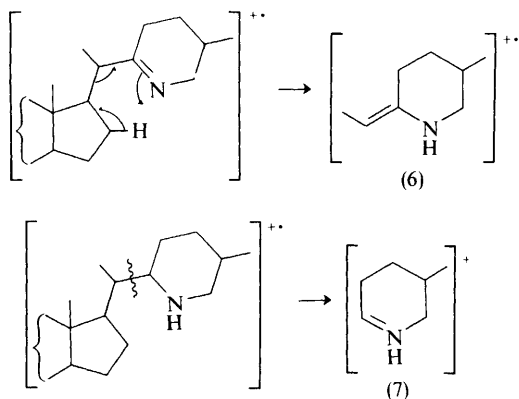
<sup>4</sup> K. S. Brown, jun., in ref. 3, p. 631.

# 1 *Solanum* Alkaloids

Acid hydrolysis of an extract of *Solanum congestiflorum* has afforded four new alkaloids: solacongestidine (1), solafloridine (2), and 23-oxo- and 24-oxo-solacongestidine.<sup>5</sup>

Solacongestidine,  $C_{27}H_{45}NO$ , gave an n.m.r. spectrum whose methyl resonances were typical of a *Solanum*-type steroidal alkaloid. A single, secondary, hydroxy-group was present (i.r., *O*-monoacetate, chromic acid oxidation), which was located at C-3 on the basis of the shift differences observed for the methyl resonances at C-18 and C-19 in the n.m.r. spectrum of the derived ketone. A  $C=N$  moiety was apparent (i.r. and n.m.r. of the derived enamine acetate). Solacongestidine gave a dihydro-derivative whose melting point and that of its *O*-monoacetate corresponded to those of (3) and (4), respectively.<sup>6</sup> Structure (1) may thus be assigned to solacongestidine.

Confirmation of the site of saturation as being in the piperidine ring came from (a) the mass spectrum of solacongestidine, which showed a prominent peak at  $m/e$  125 corresponding to the ion (6), whereas the spectrum of dihydrosolacongestidine showed instead an ion (7) at  $m/e$  98, and (b) acid hydrolysis of



*O,N*-diacetylsolacongestidine, which led to piperidine-ring cleavage to give (5), a reaction characteristic of a  $\Delta^2$ -tetrahydropyridine function.<sup>7</sup> Finally, it was shown<sup>5</sup> that solacongestidine was identical with a synthetic specimen<sup>6</sup> of (1).

Solafloridine differed from solacongestidine only in possessing an additional hydroxy-group, which was shown to be located at C-16 by conversion of solafloridine into (2*S*,25*R*)-solanidan-3-one (8). The  $\alpha$ -configuration was assigned to the C-16 hydroxy-group because the physical constants of dihydrosolafloridine were different from those of the known 16 $\beta$ -isomer<sup>8</sup> and treatment of solafloridine with alcoholic base failed to give a spirosolane. Finally, the struc-

<sup>5</sup> Y. Sato, Y. Sato, H. Kaneko, E. Bianchi, and H. Kataoka, *J. Org. Chem.*, 1969, **34**, 1577.

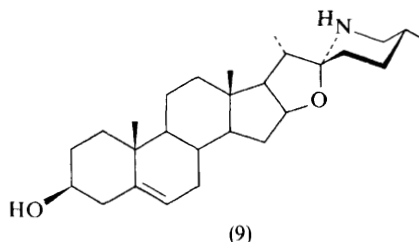
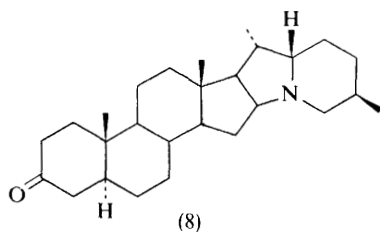
<sup>6</sup> K. Schreiber and G. Adam, *Tetrahedron*, 1964, **20**, 1707.

<sup>7</sup> Y. Sato and N. Ikekawa, *J. Org. Chem.*, 1960, **25**, 786, and papers cited therein.

<sup>8</sup> Y. Sato, H. G. Latham, jun., and E. Mosettig, *J. Org. Chem.*, 1957, **22**, 1496.

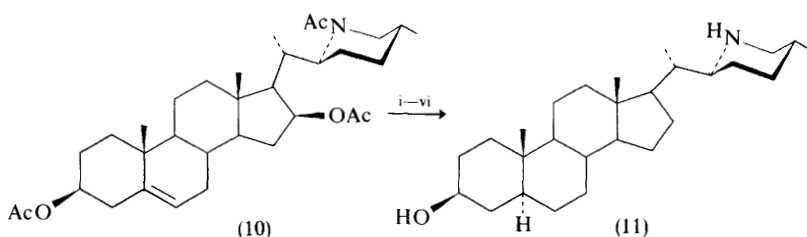


ture (2) for solafloridine was confirmed by comparison<sup>5</sup> of the i.r. spectra of solafloridine and its dihydro-derivative with those of synthetic specimens.<sup>9</sup>



23-Oxo- and 24-oxo-solacongestidine are minor constituents of *S. congestiflorum*, and although they appeared to exist in the plant *per se*, they were also formed, during isolation, from solacongestidine. Their structures were deduced principally from spectral data.

Solacongestidine, as we have seen above, has been shown to be identical with the synthetic material (1). An alternative synthesis of this alkaloid from readily available solasodine (9) has been described.<sup>10</sup> Sodium borohydride reduction<sup>11</sup> of solasodine and acetylation gave the triacetate (10),<sup>12</sup> which was converted in unexceptional steps, illustrated in Scheme 1, into (11). This base was then



Reagents: i, KOH; ii, 1 eq.  $\text{CrO}_3$ , NaOAc buffer iii, ethane-dithiol, HCl; iv, Raney Ni; v, Pt,  $\text{H}_2$ , HOAc; vi, KOH, ethylene glycol.

**Scheme 1**

<sup>9</sup> K. Schreiber and G. Adam, *Annalen*, 1963, **666**, 176.

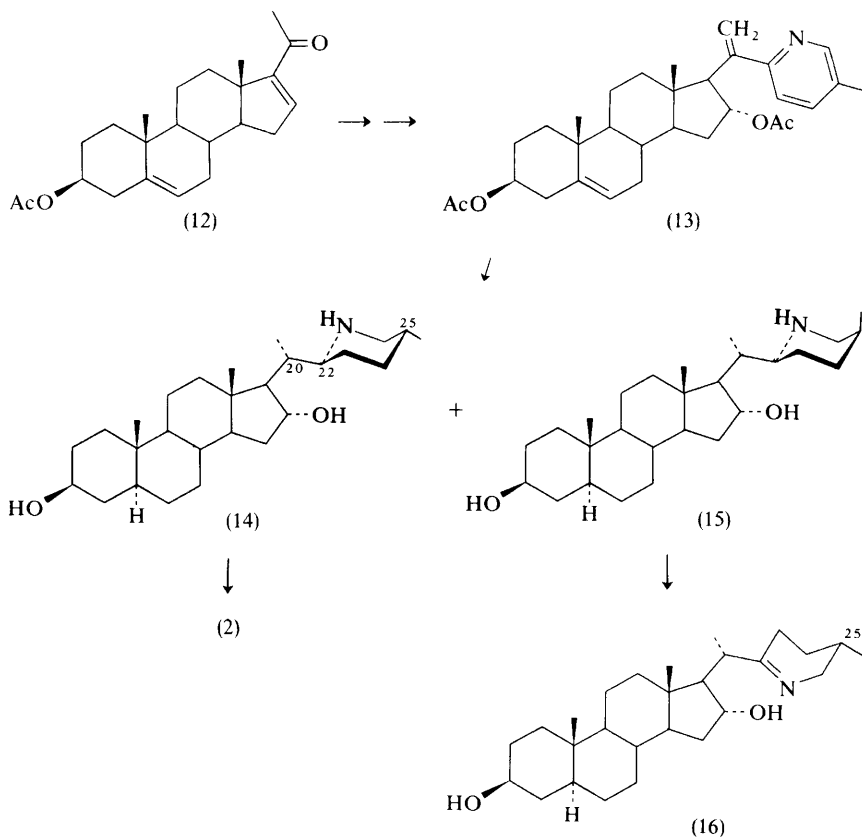
<sup>10</sup> G. Adam, D. Voigt, and K. Schreiber, *J. prakt. Chem.*, 1971, **313**, 45.

<sup>11</sup> G. Adam and K. Schreiber, *Z. Chem.*, 1969, **9**, 227.

<sup>12</sup> L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 1950, 3020.

transformed, in known steps<sup>6</sup> of chlorination and dehydrochlorination, into solacongestidine (1).

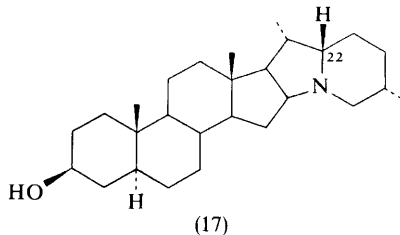
3 $\beta$ ,16 $\alpha$ -Diacetoxy-20-(5-methyl-2-pyridyl)pregna-5,20-diene (13), available from 3 $\beta$ -acetoxypregna-5,16-dien-20-one (12),<sup>1</sup> has been used in a synthesis of solafloridine (2) and 25-isosolafloridine (16).<sup>13</sup> The compound (13) was hydrogenated (H<sub>2</sub>, Pt, HOAc) and two piperidinyl derivatives that were produced



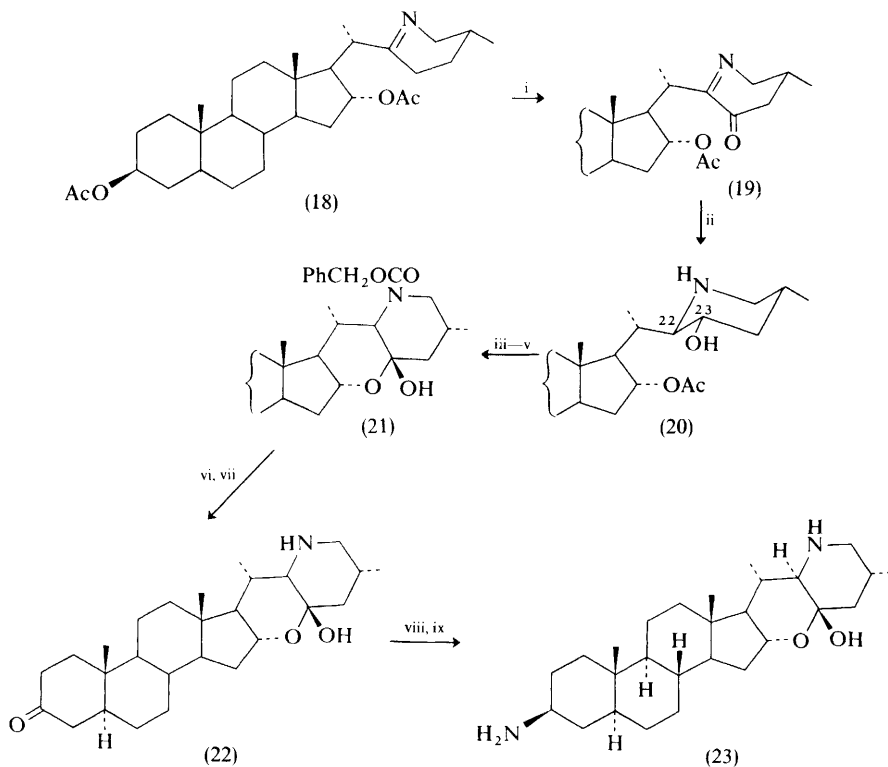
were isolated and deacetylated. One, (14), was identical with material from another source which was known to be of 20*S*,22*S*,25*R*-configuration,<sup>1,9</sup> whilst the configurations of the other, (15), at C-22 and C-25 were both established as *S* on the basis of molecular rotation and o.r.d. measurements, which also confirmed the configuration assigned to (14). The configuration of (15) at C-20 was established as *S* by conversion of (15) into 22-isodemissidine (17) identical with material obtained from dihydrotomatidine A.<sup>1</sup>

<sup>13</sup> H. Ripperger, F.-J. Sych, and K. Schreiber, *Tetrahedron*, 1972, **28**, 1619.

*N*-Chlorination and dehydrochlorination of (14) and (15) gave solafloridine (2) and isosolafloridine (16), respectively. A sequence involving photolysis of the



*N*-nitroso-*OO*-diacetyl derivative of (14) under acid conditions was attempted as an alternative method of synthesizing solafloridine (2), but although this and attendant reactions could be carried out, the overall yield was low.



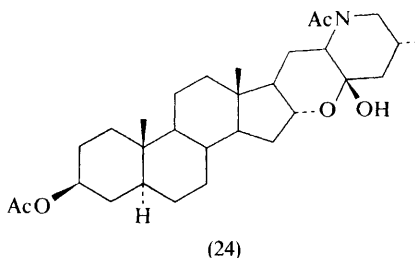
Reagents: i,  $\text{MnO}_2$ ; ii,  $\text{NaBH}_4$ ; iii,  $\text{PhCH}_2\text{OCOCl}$ ,  $\text{NaOH}$ ; iv,  $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ ; v, 2.5%  $\text{KOH}$ ,  $\text{MeOH}$ , R.T.; vi,  $\text{CrO}_3$ , pyridine; vii,  $\text{HBr}$ ,  $\text{HOAc}$ ; viii,  $\text{NH}_2\text{OH}$ ; ix,  $\text{H}_2$ ,  $\text{Pt}$ ,  $\text{HOAc}$

**Scheme 2**

The diacetates of both alkaloids were prepared and characterized.

Solanocapsine has been assigned the structure (23) on the basis of degradative<sup>1</sup> and synthetic work,<sup>14,15</sup> n.m.r. analysis,<sup>14</sup> and an *X*-ray analysis of its *N*-(2-bromobenzylidene) derivative.<sup>16</sup> The diacetate (18) of solafioridine (2), whose synthesis was described above, provided a convenient starting point for the synthesis of solanocapsine. The salient steps of the successful synthesis<sup>17</sup> are shown in Scheme 2. The manganese dioxide oxidation of (18) gave two products apart from (19), one of which was the 24-ketone. The other resulted from aromatization of the piperidine ring. In contrast to work with C(16)-unsubstituted analogues, selenium dioxide oxidation (18) gave no (19). The structure for (20) follows from its physical constants; the stereochemistry at C-22 and C-23 was deduced from the n.m.r. spectrum. Reduction of the oxime of (22) afforded solanocapsine and 3-isolanocapsine.

The synthetic work which supported the structure assigned to solanocapsine involved (a) the synthesis<sup>15</sup> of the degradation product (24) from solafioridine



diacetate in steps similar to those used for the synthesis of solanocapsine described above, and (b) the synthesis from solasodine (9) of the 16 $\beta$ -isomer of (23), which was shown to be different from solanocapsine.<sup>14</sup> The structure of the 16 $\beta$ -isomer was confirmed as the result of a study of the position of hydroxyl absorption in the i.r. spectra of this compound and of solanocapsine.<sup>18</sup>

Solanidine (33) has been the subject of an elegant total synthesis<sup>19</sup> (Scheme 3), beginning with (25), by adaptation of a synthetic route to sapogenins.<sup>20</sup> The nitro-ester (28) was obtained from (*S*)-2-allylpropionic acid (27).<sup>21</sup> This was then added to (26)<sup>22</sup> in a Michael reaction to give the key compound (29) together with its C(22)-isomer (30). The former isomer was then converted into solanidine (33).

<sup>14</sup> H. Ripperger and K. Schreiber, *Annalen*, 1969, **723**, 159.

<sup>15</sup> N. Nagai and Y. Sato, *Tetrahedron Letters*, 1970, 2911.

<sup>16</sup> E. Höhne, H. Ripperger, and K. Schreiber, *Tetrahedron*, 1970, **26**, 3569.

<sup>17</sup> H. Ripperger, F.-J. Sych, and K. Schreiber, *Tetrahedron*, 1972, **28**, 1629; *Tetrahedron Letters*, 1970, 5251.

<sup>18</sup> F.-J. Sych, H. Ripperger, and K. Schreiber, *Tetrahedron*, 1972, **28**, 1645.

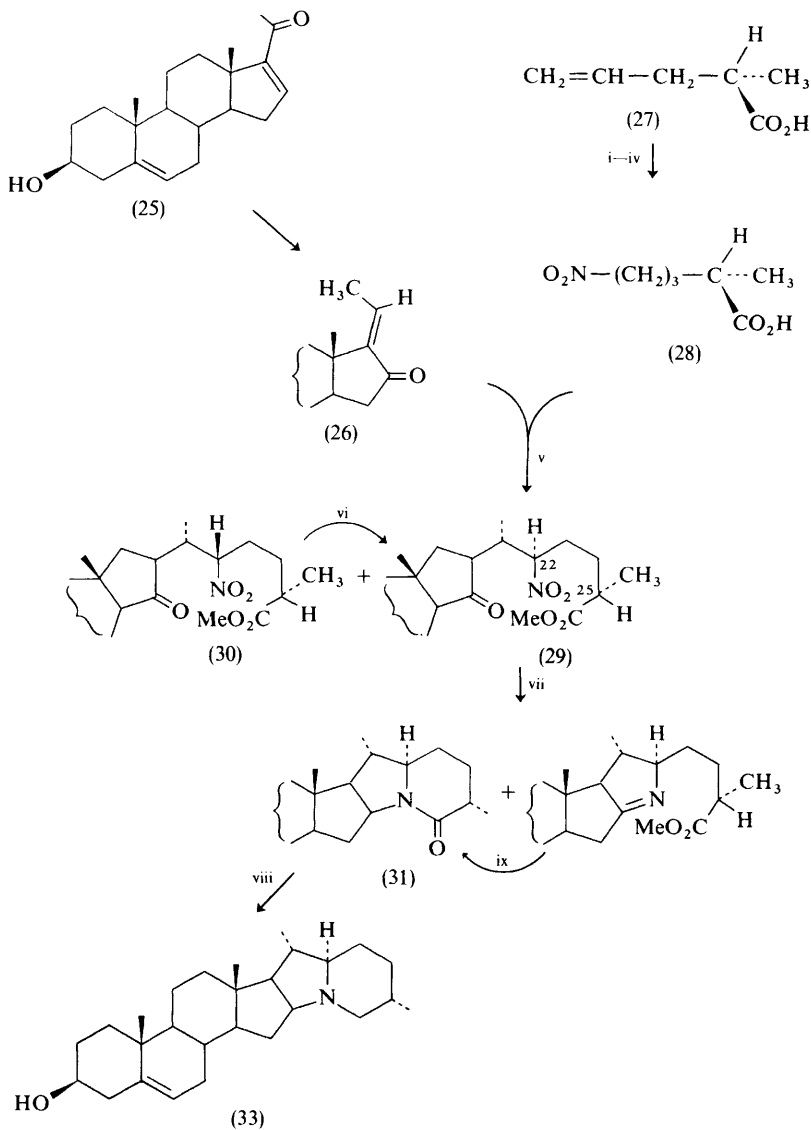
<sup>19</sup> S. V. Kessar, A. L. Rampal, S. S. Gandhi, and R. K. Mahajan, *Tetrahedron*, 1971, **27**, 2153.

<sup>20</sup> S. V. Kessar, Y. P. Gupta, R. K. Mahajan, G. S. Joshi, and A. L. Rampal, *Tetrahedron*, 1968, **24**, 899.

<sup>21</sup> G. I. Fray and N. Polgar, *J. Chem. Soc.*, 1956, 2036; G. Stållberg, *Acta Chem. Scand.*, 1957, **11**, 1430.

<sup>22</sup> S. V. Kessar and A. L. Rampal, *Tetrahedron*, 1968, **24**, 887.

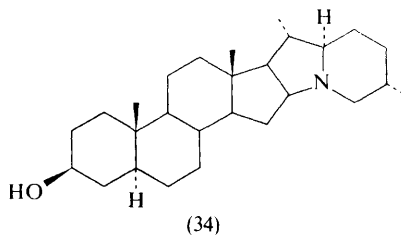
The isomer (30) was converted similarly into a tertiary base, which should have been 22-isolanidine if the two Michael products were isomeric only at



Reagents: i,  $\text{HBr}$ ,  $(\text{PhCO}_2)_2$ ; ii,  $\text{CH}_2\text{N}_2$ ; iii,  $\text{NaI}$ ; iv,  $\text{AgNO}_2$ ,  $0^\circ\text{C}-\text{R.T.}$ ; v,  $\text{K}$ ,  $\text{Bu}^t\text{OH}$ ; vi, pyridine; vii,  $\text{Zn}$ ,  $\text{HOAc}$ ; viii,  $\text{LiAlH}_4$ ; ix,  $\text{NaBH}_4$ ,  $\text{HCl}$ ,  $0^\circ\text{C}$

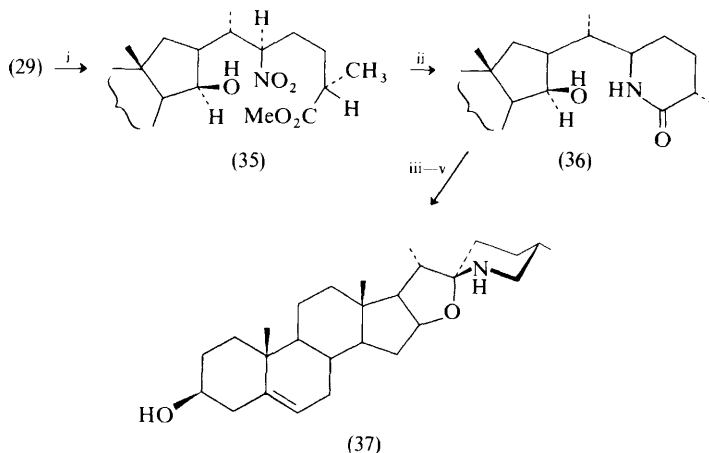
Scheme 3

C-22 as expected. This base was identical with material derived from tomatid-5-en-3 $\beta$ -ol<sup>23</sup> on comparison by i.r., chromatography, and melting point, but the mixed melting point was depressed. The base was, however, epimerized at C-22 and reduced (platinum and hydrogen in methanol) to give a product identical with



natural demissidine (34),<sup>1</sup> which indicated that the structural assignment of the compound obtained from (30) as 22-isosolanidine is correct.

The Michael adducts (29) and (30) have also been used in a stereospecific synthesis of tomatid-5-en-3 $\beta$ -ol (37),<sup>24</sup> illustrated in Scheme 4 for the isomer



Reagents: i, NaBH<sub>4</sub>, <30 °C, pH 3—7; ii, Zn, HOAc; iii, LiAlH<sub>4</sub>; iv, *N*-chlorosuccinimide; v, NaOMe, MeOH

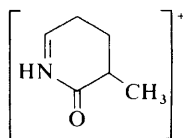
**Scheme 4**

(29); the same reaction sequence with (30) also gave tomatid-5-en-3 $\beta$ -ol, which confirms, incidentally, that (29) and (30) are isomeric at C(22) only. It can be noted that sodium borohydride reduction of (29) even under mild conditions causes some destruction of the nitro-group, but under acid conditions reduction to (35) proceeds smoothly. The amide (36) and its C(22)-epimer were characterized in part by mass spectrometry, and the base peak at *m/e* 112 corresponding

<sup>23</sup> K. Schreiber and H. Ronsch, *Tetrahedron*, 1965, **21**, 645.

<sup>24</sup> S. V. Kessar, Y. P. Gupta, M. Singh, and R. K. Mahajan, *Tetrahedron*, 1971, **27**, 2869.

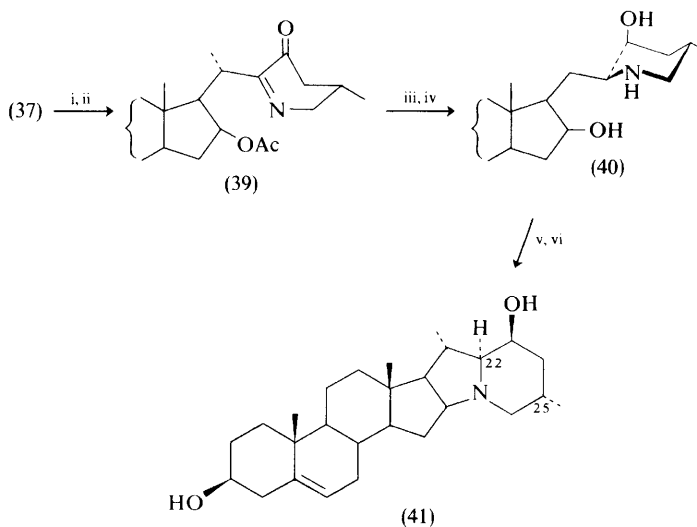
to (38), which arises by C-20—C-22 bond fission, was suggested as being of excellent diagnostic value for ring F amides.



(38)

A stereospecific synthesis of solasodine (9) was similarly achieved by replacing (*S*)-2-allylpropionic acid in the above synthetic route to tomatid-5-en-3 $\beta$ -ol by its enantiomer and using exactly similar reactions.<sup>24</sup>

Leptinidine (41)<sup>1</sup> has been synthesized from tomatidenol (37).<sup>25</sup> The synthetic route is illustrated in Scheme 5. The catalytic reduction of (39) gave, in addition



Reagents: i,  $\text{Ac}_2\text{O}$ ,  $\text{ZnCl}_2$ ,  $\text{HOAc}$ ; ii,  $\text{SeO}_2$ ; iii,  $\text{Pt}$ ,  $\text{H}_2$ ,  $\text{HOAc}$ ; iv,  $\text{KOH}$ ,  $\text{MeOH}$  (removal of both acetyl groups); v,  $\text{CrO}_3$ ,  $\text{HOAc}$ ,  $\text{NaOAc}$ ; vi,  $\text{NaBH}_4$

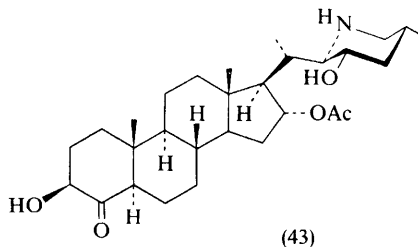
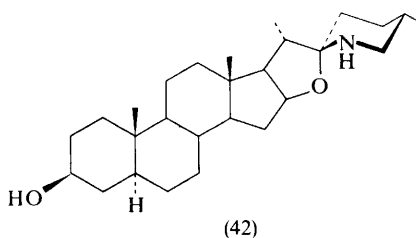
Scheme 5

to (40), three other stereoisomeric piperidine derivatives. Use of these products, as well as those obtained in similar manner from solasodine (9) and tomatidine (42), allowed the synthesis of other 23 $\beta$ -hydroxysolanidanes, stereoisomeric at C-22 and C-25.

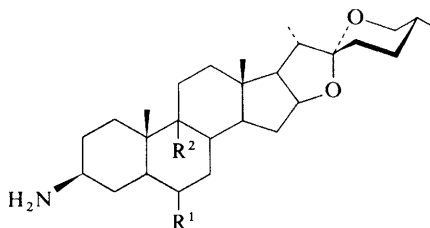
The unusual structure (43) has been assigned to solaphyllidine, the most abundant alkaloid found in *Solanum hypomalacophyllum* Bitter, on the basis of

<sup>25</sup> H. Ripperger and K. Schreiber, *Chem. Ber.*, 1969, **102**, 4080.

an *X*-ray analysis and supporting chemical and spectroscopic data, of unexceptional character.<sup>26</sup> The *X*-ray results did not allow assignment of absolute configuration; this was assumed to be the same as cholesterol.



Three new alkaloids have been isolated from the roots of *Solanum paniculatum* and characterized as isojuripidine (44), isojuribidine (45), and isopaniculidine (46). In addition, five glycosides were isolated, four of which gave (45) on hydrolysis whilst the fifth gave (44).<sup>27</sup>



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

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

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

Solasurine, solamargine, and salsonine have been isolated from the ripe berries of *S. khasianum* var. *chatterjeenum* Sengupta.<sup>28</sup> Solasurine was also isolated from *S. eleagnifolium* berries.<sup>28</sup> It was originally isolated from *S. surattense* and identified as solasodino-L-rhamnosyl- $\beta$ -D-glucose.<sup>29</sup> Solasonine and solamargine have been identified in extracts of all seven members of the subgenus *Archaeosolanum* (*Solanum* genus), and the concentration in immature fruits was found to be generally higher than in the leaves.<sup>30</sup> These two glyco-alkaloids have been identified in *S. palinacanthum* and *S. lycocarpum* fruits,<sup>31</sup> and in the above-ground parts of *S. kieseritzkii*, together with tomatine and solasodine. Solasodine

<sup>26</sup> A. Usubilliga, C. Seelkopf, I. L. Karle, J. W. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, 1970, **92**, 700.

<sup>27</sup> S. Cambiaghi, E. Dradi, and R. Longo, *Ann. Chim. (Italy)*, 1971, **61**, 99.

<sup>28</sup> D. K. Seth, *J. Inst. Chem. Calcutta*, 1971, **43**, 116 (*Chem. Abs.*, 1972, **76**, 1802).

<sup>29</sup> D. K. Seth and R. Chatterjee, *J. Inst. Chem. Calcutta*, 1968, **41**, 194 (*Chem. Abs.*, 1970, **72**, 79 405).

<sup>30</sup> D. C. Lewis and D. R. Liljgren, *Phytochemistry*, 1970, **9**, 2193.

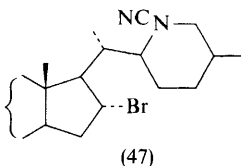
<sup>31</sup> M. Motidome, M. E. Leekning, and O. R. Gottlieb, *Anal. Acad. brasil Cienc.*, 1970, **42** (Suppl.), 375 (*Chem. Abs.*, 1971, **75**, 95 366).



and probably solasodiene have been found in the acid hydrolysate of an extract of the dried fruits and stems of *S. indicum*.<sup>32</sup> Solasodiene has been isolated from *S. eleagnifolium*.<sup>33</sup> Solasonine, solamargine, a trace of  $\beta$ -solamargine, and an unidentified glyco-alkaloid have been isolated from *S. nigrum*.<sup>34</sup> The aerial parts of *S. dulcamara* have yielded the glyco-alkaloids  $\alpha$ - and  $\beta$ -soladulcine.<sup>35</sup> Hydrolysis of extracts of *S. dulcamara* from 22 European sites has given in each case mainly soladulcidine or tomatid-5-en-3 $\beta$ -ol.<sup>36</sup> *S. marginatum* has been the subject of a systematic phytochemical and pharmacological examination.<sup>37</sup> Five different alkaloids of the solanocapsine type have been identified in the fruit of *S. pseudoquina* and two of these bases corresponded to alkaloids in *S. pseudo-capsicum*.<sup>38</sup>

One of the partial hydrolysis products of the sugar moiety of  $\alpha$ -solanine, 2-*O*- $\alpha$ -L-rhamnopyranosyl-D-galactose, has been synthesized.<sup>39</sup>

Contrary to an earlier report,<sup>40</sup> solanidine (33) and demissidine (34) have been found to react smoothly with cyanogen bromide with opening of ring E to give (47), a reaction which may be of synthetic utility.<sup>41</sup> Lithium aluminium hydride



reduction resulted in the expected loss of bromine, but considerable reclosure of the ring also occurred. Hydrolysis of the demissidine derivative gave exclusive ring-closure, under very mild conditions.

The Beckmann rearrangement of solasod-4-en-3-one, 5 $\beta$ -solasodan-3-one, and their *N,O*-diacetyl derivatives has been studied, and was successfully achieved only with thionyl chloride (dioxan at 40 °C).<sup>42</sup>

<sup>32</sup> I. P. Varshney and A. A. Khan, *Indian J. Pharm.*, 1971, **33**, 49 (*Chem. Abs.*, 1972, **76**, 1795).

<sup>33</sup> E. Guerreiro, O. S. Giordano, J. Karka, and A. T. D'Arcangelo, *Anales de Quim.*, 1971, **67**, 789 (*Chem. Abs.*, 1972, **76**, 70 133).

<sup>34</sup> S. M. Aslanov, *Khim. prirod. Soedinenii*, 1971, **7**, 674 (*Chem. Abs.*, 1972, **76**, 83 530).

<sup>35</sup> E. A. Tukalo and B. T. Ivanchenko, *Khim. prirod. Soedinenii*, 1971, **7**, 207 (*Chem. Abs.*, 1971, **75**, 31 316).

<sup>36</sup> I. Mathe jun., *Herba Polonica*, 1970, **16**, 278 (*Chem. Abs.*, 1971, **75**, 59 820).

<sup>37</sup> A. A. Herrera and G. M. Kegan, *Rev. Colomb. Cienc. Quim.-Farm.*, 1970, **1**, 41 (*Chem. Abs.*, 1971, **74**, 84 024).

<sup>38</sup> S. Cevallos and P. Martinod, *Politecnica*, 1969, **1**, 133 (*Chem. Abs.*, 1971, **75**, 137 527).

<sup>39</sup> D. M. van Niekerk and B. H. Koeppen, *Experientia*, 1972, **28**, 123.

<sup>40</sup> C. Schöpf and R. Hermann, *Chem. Ber.*, 1933, **66**, 298.

<sup>41</sup> J. A. Beisler and Y. Sato, *J. Chem. Soc. (C)*, 1971, 149; *Chem. Comm.*, 1968, 963.

<sup>42</sup> G. A. Tolstikov, V. P. Yur'ev, G. N. Romachenko, and M. I. Goryaev, *Izvest. Akad. Nauk. Kazakh. S.S.R., Ser. khim.*, 1971, **21**, 42 (*Chem. Abs.*, 1972, **76**, 59 857).

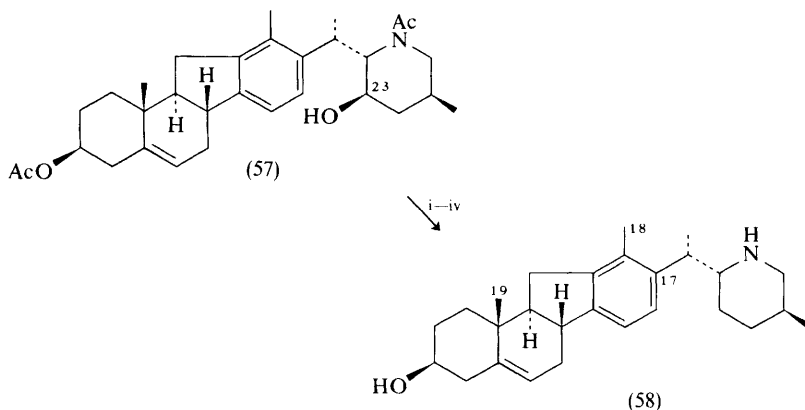


## 2 Veratrum Alkaloids

The total synthesis<sup>43</sup> of veratramine (56) was achieved some years ago *via* (51).<sup>44</sup> This same intermediate was used for the synthesis of jervine.<sup>45</sup> A recent synthesis<sup>46</sup> of veratramine (Scheme 6) also involved (51) and part of the synthetic route to jervine.

The keto-acetate (50) was obtained fortuitously as a result of the attempted epoxidation of (48), which gave instead (49). This compound was then converted into (50). The mixture of epimeric bromides (52), obtained in three steps from (51), was unstable, in practice particularly towards chromatography, but could be condensed with the pyrrolidine enamine of (50) to give the C-22 epimer of (53). The final steps to veratramine (56) involved introduction of a C-5—C-6 double bond, which meant initial conversion into (54) by oxidation of the 23-O,*N*-diacetyl derivative of (53).

Verarine has been formulated as 22-desoxyveratramine (58) on chemical and spectral evidence,<sup>2,47</sup> confirmed by the conversion<sup>45,48,49</sup> of veratramine (56) into (58). This conversion began with the formation of the diacetate (57); the remaining steps are illustrated in Scheme 7.



Reagents: i,  $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ ; ii, ethanedithiol,  $\text{HCl}$ ,  $0^\circ\text{C}$ ; iii, Raney Ni; iv, Na, ethylene glycol,  $\text{N}_2\text{H}_4$

Scheme 7

<sup>43</sup> W. S. Johnson, H. A. P. de Jongh, C. E. Coverdale, J. W. Scott, and U. Burckhart, *J. Amer. Chem. Soc.*, 1967, **89**, 4523.

<sup>44</sup> W. S. Johnson, J. M. Cox, D. W. Graham, and H. W. Whitlock, jun., *J. Amer. Chem. Soc.*, 1967, **89**, 4524; W. S. Johnson, N. Cohen, E. R. Habicht, jun., D. P. G. Hamon, G. P. Rizzi, and D. J. Faulkner, *Tetrahedron Letters*, 1968, 2829.

<sup>45</sup> T. Masamune, M. Takasugi, A. Murai, and K. Kobayashi, *J. Amer. Chem. Soc.*, 1967, **89**, 4521.

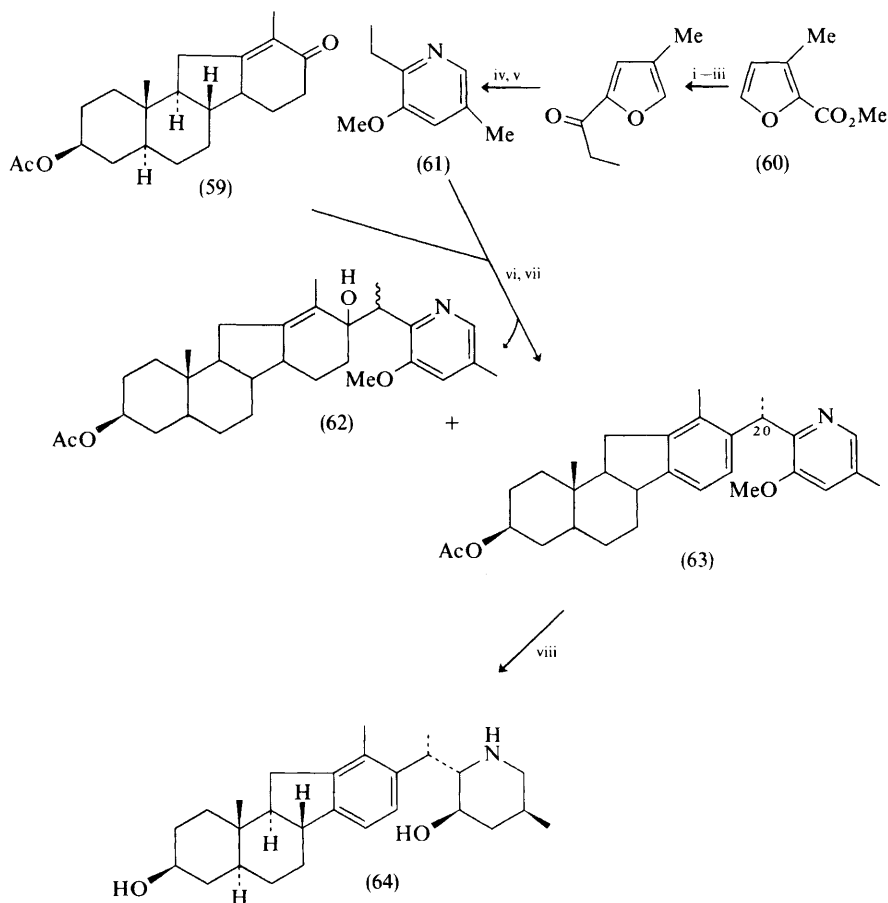
<sup>46</sup> T. Masamune, M. Takasugi, and A. Murai, *Tetrahedron*, 1971, **27**, 3369.

<sup>47</sup> J. Tomko and S. Bauer, *Coll. Czech. Chem. Comm.*, 1964, **29**, 2570; J. Tomko and A. Vassova, *Chem. Zvesti*, 1964, **18**, 266.

<sup>48</sup> T. Masamune, I. Yamazaki, and M. Takasugi, *Bull. Chem. Soc. Japan*, 1966, **39**, 1090.

<sup>49</sup> T. Masamune, I. Yamazaki, K. Orito, and M. Takasugi, *Tetrahedron*, 1971, **27**, 3387.

An alternative, total, synthesis of verarine has been reported by other workers,<sup>50</sup> which involved, as a key step, the coupling of (59) with the lithio derivative of 2-ethyl-5-methylpyridine. The use instead of the lithio derivative of 2-ethyl-3-methoxy-5-methylpyridine (61) led to 5 $\alpha$ ,6-dihydroveratramine (64).<sup>51</sup> This synthesis is illustrated in Scheme 8, where, of two routes to (61), the better one,



Reagents: i,  $(\text{CH}_3\text{CH}_2\text{CO})_2\text{O}$ ,  $\text{H}_3\text{PO}_4$ ; ii,  $\text{OH}^-$ ; iii, Cu, quinoline,  $200^\circ\text{C}$ ; iv,  $\text{NH}_3$ ; v,  $\text{CH}_2\text{N}_2$ ; vi, lithio derivative of (61) (MeLi, THF); vii, acetylation; viii,  $\text{H}_2$ , Pt, acid

Scheme 8

<sup>50</sup> J. P. Kutney, J. Cable, W. A. F. Gladstone, H. W. Hanssen, E. J. Torupka, and W. D. C. Warnock, *J. Amer. Chem. Soc.*, 1968, **90**, 5332.

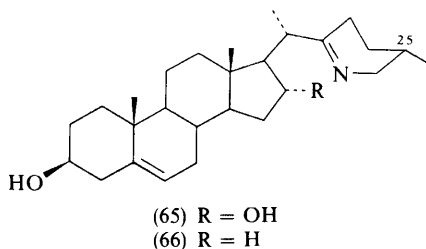
<sup>51</sup> J. P. Kutney, J. Cable, G. V. Nair, and W. D. C. Warnock, *Intra-Sci. Chem. Reports*, 1970, **4**, 265.

which began with (60),<sup>52</sup> is shown. The coupling reaction gave two products which could be separated as their acetates (62) and (63). Palladium dehydrogenation of (62) gave the C-20 epimer of (63).

In connection with work on verarine (58), the n.m.r. spectra of etiojerva-12,14,16-trienes with an aromatic ring D as well as a *trans*-fused B/C ring junction have been collated.<sup>49</sup> It was observed that (a) for the C-19 methyl group the observed chemical shifts were in good agreement with those calculated, and (b) substituents at C-17 have little effect on chemical shift. In most of the *N*-acetylated derivatives of verarine and related compounds and in all the *N*- and 23-*O*-acetyl derivatives, the 18-methyl, *N*-acetyl, and *O*-acetyl protons appears as two or three lines, suggesting the presence of at least two conformers.

The natural-abundance <sup>13</sup>C n.m.r. spectra of jervine and veratramine have been analysed. Correlation of the chemical shifts of these two alkaloids and jervine degradation products, together with proton-decoupling techniques, allowed unambiguous assignments of most of the resonances.<sup>53</sup>

Two new glycosidic alkaloids have been isolated from the leaves of budding *Veratrum grandiflorum*. They were of interest since their concentration was observed to decrease on etiolation as the concentration of solanidine (33) increased, thus appearing to be precursors for (33).<sup>54</sup> After hydrolysis of the plant extract and chromatography, a major component, named etioline, was obtained and its structure assigned as (65) on the following evidence: (a) biological relationship with solanidine, (b) a molecular formula of C<sub>27</sub>H<sub>43</sub>NO<sub>2</sub>,



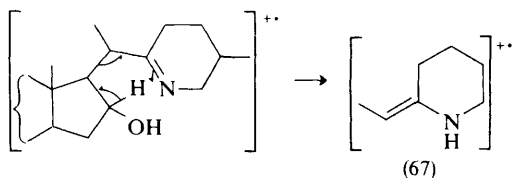
(c) an i.r. spectrum indicating the presence of C=N and hydroxy-groups, (d) a single olefinic proton in the n.m.r. spectrum, (e) formation of an *O,O,N*-triacetate with one new olefinic proton (enamine acetate) in the n.m.r., (f) Oppenauer oxidation, which gave an  $\alpha\beta$ -unsaturated ketone, (g) chromic acid oxidation, which gave a product with i.r. absorption characteristic of a five-membered-ring ketone plus a six-membered-ring ketone; a hydroxy-group at C(16) of a normal steroid nucleus was thus likely for etioline, and it appeared to be  $\alpha$  because a spiro-solane was not formed on refluxing etioline in alcoholic potassium hydroxide, (h) a mass spectrum which showed fragment ions at *m/e* 125 (base peak),

<sup>52</sup> D. M. Burness, in 'Organic Syntheses', ed. M. Tishler, J. Wiley and Sons, New York, 1959, Vol. 39, p. 49.

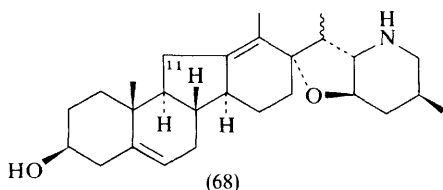
<sup>53</sup> P. W. Sprague, D. Doddrell, and J. D. Roberts, *Tetrahedron*, 1971, 27, 4857.

<sup>54</sup> K. Kaneko, M. Watanabe, Y. Kawakoshi, and H. Mitsuhashi, *Tetrahedron Letters*, 1971, 4251.

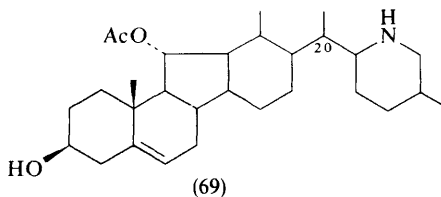
124, and 98; the base peak in the spectrum was assigned to (67), being found also in the spectrum of verazine (66)<sup>55</sup> and solacongestidine (1).<sup>56</sup> The configuration at C-25 was assumed to be *S* by analogy with the configuration of other *Veratrum* alkaloids.



Three steroidal alkaloids have been isolated from *V. californicum*.<sup>57</sup> One of these, cyclopamine, which is the constituent of this plant responsible for malformation of the central nervous system in sheep,<sup>57,58</sup> has been shown to be 11-deoxyjervine (68).<sup>59</sup> The other alkaloids are veratramine and muldamine.



Muldamine was deduced<sup>60</sup> to be the veratramine derivative (69), principally from the following evidence: (a) molecular formula:  $C_{29}H_{47}O_3N$ ; (b) i.r. spectrum: saturated ester, no ether bands; (c) mass spectra of the alkaloid and its



deacetyl derivative: principal ion at  $m/e$  98, in accord with a methylpiperidine substituent (at C-20); (d) n.m.r. spectra of the alkaloid and its deacetyl derivative, which were compared with those of jervine and jervane derivatives.

Veracintine, an alkaloid isolated from *V. album* subsp. *lobelianum*, has been shown<sup>61</sup> to have the structure (70) with the unusual feature of a five-membered heterocyclic ring and  $C_{26}$  skeleton. The mass spectrum showed a base peak at

<sup>55</sup> G. Adam, K. Schreiber, J. Tomko, and A. Vassova, *Tetrahedron*, 1967, **23**, 167.

<sup>56</sup> Y. Sato, Y. Sato, H. Kaneko, E. Bianchi, and H. Kataoka, ref. 5; see discussion above.

<sup>57</sup> R. F. Keeler, *Phytochemistry*, 1968, **7**, 303.

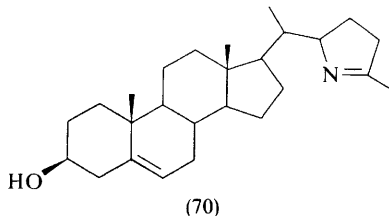
<sup>58</sup> R. F. Keeler and W. Binns, *Phytochemistry*, 1971, **10**, 1765.

<sup>59</sup> R. F. Keeler, *Phytochemistry*, 1969, **8**, 223.

<sup>60</sup> R. F. Keeler, *Steroids*, 1971, **18**, 741.

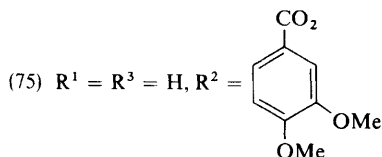
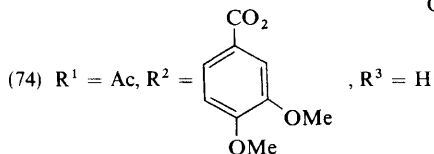
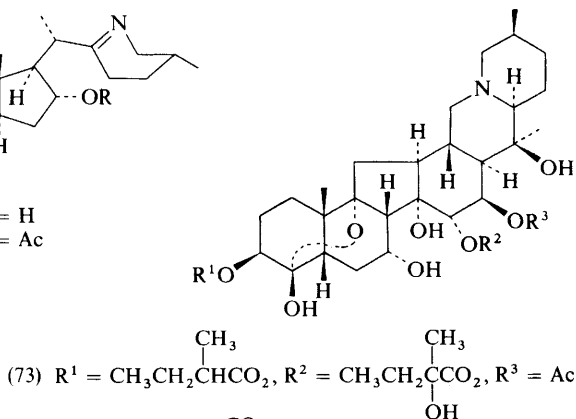
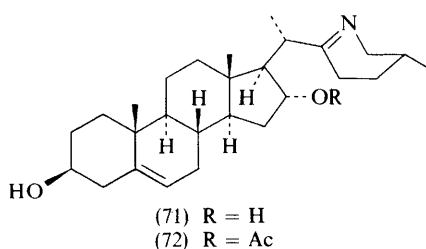
<sup>61</sup> J. Tomko, V. Brázdová, and Z. Votický, *Tetrahedron Letters*, 1971, 3041.

*m/e* 82 which could be associated with the pyrroline ring, arising by normal C-20—C-22 cleavage. The n.m.r. spectrum showed the methyl resonances expected of a normal steroid nucleus together with a signal for a single vinyl proton,



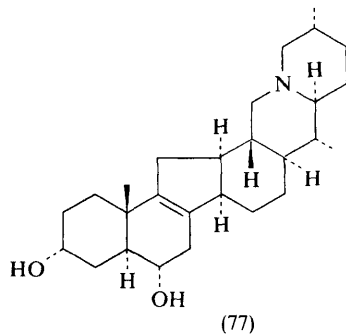
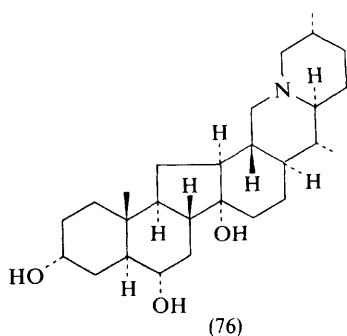
whilst a C=N group was apparent in the i.r. spectrum. The alkaloid gave both a dihydro- and a tetrahydro-derivative, and a diacetate; these derivatives showed differences in their n.m.r. and i.r. spectra which, taken together with the physical data on veracintine itself, allowed the structure to be assigned as (70).

Two minor alkaloids, veralosidine and veralosinine, have been isolated from the aerial parts of *V. album* subsp. *lobelianum*. Veralosidine and veralosinine were identified as (71) and (72), respectively.<sup>62</sup> Germinaline, a further minor

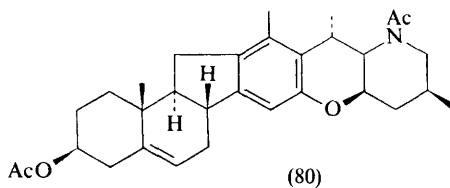
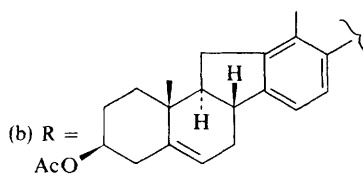
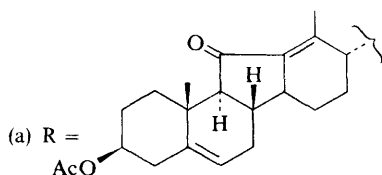
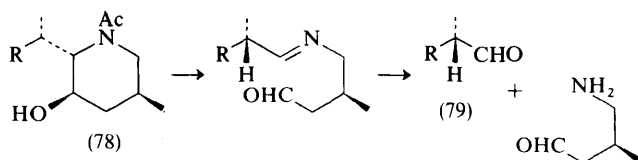


<sup>62</sup> A. M. Kashimov, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, 7, 779 (*Chem. Abs.*, 1972, **76**, 141 109).

alkaloid of the aerial parts of *V. album* subsp. *lobelianum*, has been identified as (73),<sup>63</sup> a positional isomer of germitrine;<sup>2</sup> saponification gave germine.<sup>2</sup> The



novel veratroyl derivatives of germine, (74) and (75), have been identified in this plant.<sup>64</sup> The following alkaloids have also been isolated from *V. album* subsp.



*lobelianum*: protoveratrine A, ervine, veramine (stalks and leaves);<sup>65</sup> deacetylprotoveratrine A, rubijervine, isorubijervine, germerine, veratroylzygadenine,

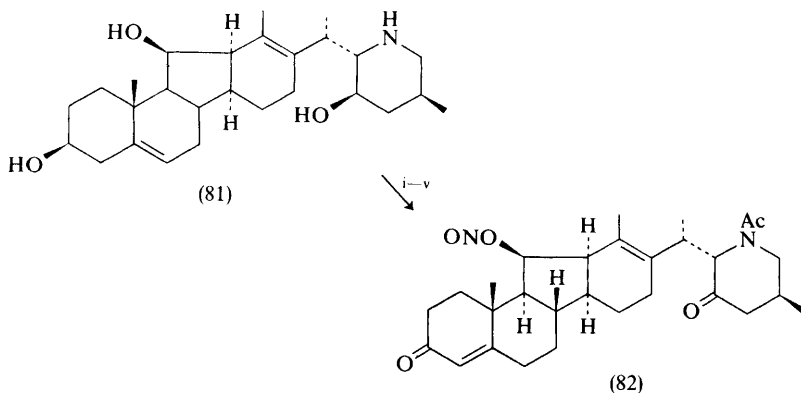
<sup>63</sup> K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, 7, 790 (*Chem. Abs.*, 1972, 76, 141 099).

<sup>64</sup> J. Tomko and A. Vassová, *Chem. Zvesti*, 1971, 25, 69.

<sup>65</sup> M. P. Gruk, N. V. Bondarenko, and G. I. Gerashchenko, *Tr. Vitebsk. Tekhnol. Inst. Legk. Prom.*, 1970, 1, 119 (*Chem. Abs.*, 1972, 76, 1834).



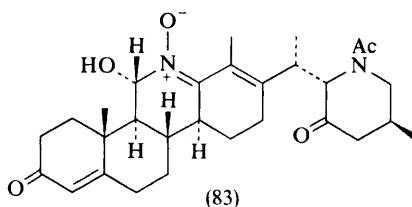
jervine, pseudojervine, and three unidentified alkaloids (roots).<sup>66</sup> Two minor alkaloids from the aerial parts of *Korolkowia sewerzowi* (*Fritillaria sewerzowi*), korseveramine and korseverinine, have been deduced to be (76)<sup>67</sup> and (77),<sup>68</sup>



Reagents: i, Al isopropoxide; ii,  $\text{Ac}_2\text{O}$ , pyridine; iii, 5% KOH, MeOH, R.T.; iv,  $\text{CrO}_3$ , pyridine; v, NOCl, pyridine,  $-20$  to  $-30^\circ\text{C}$

**Scheme 9**

respectively. Imperialine, edpetiline, petiline, and petilidine have been separated from an extract of *Petilium radiana*.<sup>69</sup>



An interesting method<sup>70</sup> for removing the piperidine ring from *Veratrum* alkaloids under mild conditions has been reported. It involved either treatment of (78) with lead tetra-acetate and iodine or photolysis in the presence of mercuric oxide and iodine; an improved yield of (79b) was observed when (78b) was photolysed, but (80) was also obtained. The reactions appear to proceed by a radical mechanism.

<sup>66</sup> N. V. Bondarenko, A. L. Shinkarenko, and G. I. Gerashchenko, *Khim. prirod. Soedinenii*, 1971, 7, 854 (*Chem. Abs.*, 1972, 76, 124 139); R. Shakirov and S. Yu. Yunusov, *ibid.*, p. 852 (*Chem. Abs.*, 1972, 76, 124 140); T. A. Tsulikyan, L. A. Musaelyan, and V. A. Mnatsakanyan, *Armenian. khim. Zhur.*, 1971, 24, 928 (*Chem. Abs.*, 1972, 76, 72 683).

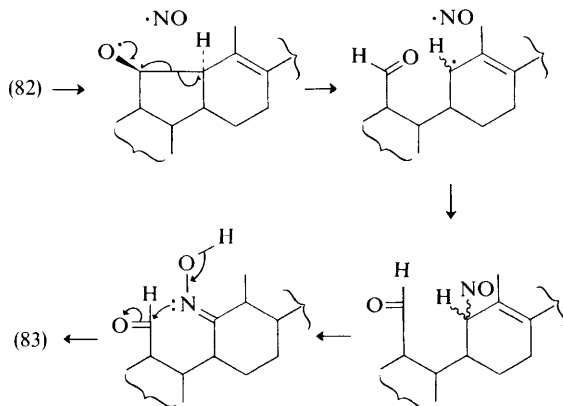
<sup>67</sup> R. N. Nuriddinov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, 7, 773 (*Chem. Abs.*, 1972, 76, 141 112).

<sup>68</sup> R. N. Nuriddinov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, 7, 767 (*Chem. Abs.*, 1972, 76, 141 110).

<sup>69</sup> B. Barbaev, Kh. N. Aripov, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1970, 6, 776 (*Chem. Abs.*, 1971, 74, 108 117).

<sup>70</sup> H. Sugimoto, H. Umeda, and T. Masamune, *Tetrahedron Letters*, 1970, 4571.

The nitrite (82), prepared<sup>71</sup> from the jervine derivative (81)<sup>72</sup> (Scheme 9), has been photolysed under the conditions of the Barton reaction to give, unexpectedly, the cyclic nitrone (83); the reaction may proceed by the mechanism shown in Scheme 10. *O*-Acetyljervine has been photolysed and the major constituents of the complex mixture of products that was obtained have been characterized.<sup>73</sup>



Scheme 10

The sodium-alcohol reduction of imperialine<sup>2,74</sup> has been re-examined. In addition to isodihydroimperialine,<sup>74</sup> dihydroimperialine was obtained, and it was shown on the basis of n.m.r. and i.r. evidence that the hydroxy-group introduced at C-6 was axial in the former compound and equatorial in the latter.<sup>75</sup>

Preparation of germine-3,16-diacetate and germine-3-acetate has been reported.<sup>76</sup>

<sup>71</sup> H. Suginome, N. Sato, and T. Masamune, *Tetrahedron*, 1971, **27**, 4863.

<sup>72</sup> T. Masamune, K. Kobayashi, M. Takasugi, Y. Mori, and A. Murai, *Tetrahedron*, 1968, **24**, 3461.

<sup>73</sup> E. Baggidini, H. G. Berscheid, G. Bozzato, E. Cavaliere, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, 1971, **54**, 429.

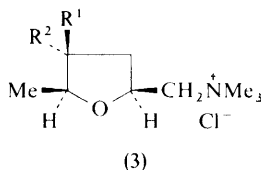
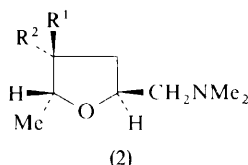
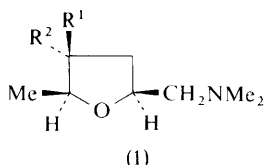
<sup>74</sup> H. G. Boit, *Chem. Ber.*, 1954, **87**, 472.

<sup>75</sup> R. N. Nuriddinov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 458 (*Chem. Abs.*, 1971, **75**, 12 998).

<sup>76</sup> A. E. Erickson, U.S.P. 3 632 811/1972.

## 1 Muscarine Alkaloids

*Inocybe geophylla* has been shown to contain normuscarine (1;  $R^1 = H$ ,  $R^2 = OH$ ), epi-normuscarine (1;  $R^1 = OH$ ,  $R^2 = H$ ), and allo-normuscarine (2;  $R^1 = OH$ ,  $R^2 = H$ ).<sup>1</sup> G.c. analysis of the (*S*)- $\alpha$ -methoxypropionates of ( $\pm$ )-epi-normuscarine and (–)-epi-normuscarine showed that the naturally occurring muscarine derivative is the (+)-isomer,



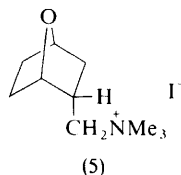
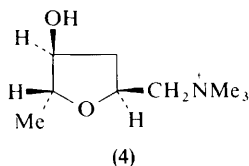
The chiralities of all the stereoisomeric muscarines have been determined by chemical modification of (–)-muscarine chloride (3;  $R^1 = H$ ,  $R^2 = OH$ ).<sup>2</sup> Compound (3;  $R^1 = H$ ,  $R^2 = OH$ ) was converted into (+)-normuscarone (1;  $R^1 + R^2 = O$ ), which when subjected to acid gave an epimeric mixture of (1;  $R^1 + R^2 = O$ ) and (2;  $R^1 + R^2 = O$ ). Lithium aluminium hydride reduction of this mixture gave the expected optically active stereoisomeric noralcohols. It was established that the naturally occurring muscarines possess the following configurations: (+)-(2*S*,3*R*,5*S*)-muscarine (3;  $R^1 = H$ ,  $R^2 = OH$ ), (–)-(2*S*,3*R*,5*R*)-allo-muscarine (4), and (+)-(2*S*,3*S*,5*S*)-epi-muscarine (3;  $R^1 = OH$ ,  $R^2 = H$ ). Cotton effects of optically active muscarone (3;  $R^1 + R^2 = O$ ) and normuscarone (1;  $R^1 + R^2 = O$ ) were used to assign absolute configurations by

<sup>1</sup> H. Bollinger and C. H. Eugster, *Helv. Chim. Acta*, 1971, **54**, 1332.

<sup>2</sup> H. Bollinger and C. H. Eugster, *Helv. Chim. Acta*, 1971, **54**, 2704.

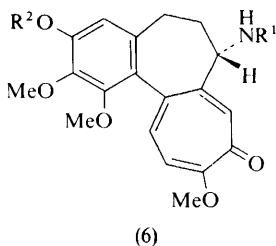
reference to optically active substituted cyclopentanone derivatives. Normuscarone was shown to be thermodynamically more stable than allo-normuscarone (2;  $R^1 + R^2 = O$ ).

Rigid deoxymuscarine analogues, e.g. (5), have been synthesized and shown to possess muscarinic activity.<sup>3</sup>



## 2 Colchicine Alkaloids

Colchicine (6;  $R^1 = \text{Ac}$ ,  $R^2 = \text{Me}$ ), *N*-deacetyl-*N*-formylcolchicine (6;  $R^1 = \text{CHO}$ ,  $R^2 = \text{Me}$ ), and 3-demethylcolchicine (6;  $R^1 = \text{Ac}$ ,  $R^2 = \text{H}$ ) were isolated from *Bulbocodium vernum*.<sup>4</sup> A number of minor alkaloids, including 2-demethylcolchicine,  $\beta$ - and  $\gamma$ -lumicolchicine, and demecolcine, were also detected by t.l.c. A new base, merenderine, was isolated together with a large number of known colchicine alkaloids from *Merendera raddeana*.<sup>5</sup> The structure of merenderine [ $\text{C}_{21}\text{H}_{25-27}\text{O}_5\text{N}$ , mol. wt. 374, u.v. (max) 260 nm] has not been determined. *M. robusta* was shown to contain colchicine and minor amounts of *N*-deacetyl-*N*-formylcolchicine and  $\beta$ - and  $\gamma$ -lumicolchicines by t.l.c.<sup>6</sup> The seeds of the related species *M. sobolifera* (*Colchicum soboliferum*) yielded 0.45% of pure colchicine.<sup>7</sup>



Quantitative determination of colchicine (6;  $R^1 = \text{Ac}$ ,  $R^2 = \text{Me}$ ) by acidimetric titration has been used for some time. It has now been shown that this reaction involves cleavage of the methyl ether in the troponone and does not

<sup>3</sup> W. L. Nelson, D. R. Allen, and F. F. Vincenzi, *J. Medicin. Chem.*, 1971, **14**, 698.

<sup>4</sup> F. Santavy, P. Sedmera, G. Snatzke, and T. Reichstein, *Helv. Chim. Acta*, 1971, **54**, 1084.

<sup>5</sup> A. A. Trozyan, M. K. Yusupov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1971, **7**, 541 (*Chem. Abs.*, 1972, **76**, 1819e).

<sup>6</sup> A. S. Sadykov, M. K. Yusupov, B. Chommadov, and Kh. Turdikulov, *Khim.-Farm. Zhur.*, 1971, **5**, 29 (*Chem. Abs.*, 1971, **75**, 80 216 m).

<sup>7</sup> M. Micevska and B. Podolesov, *God. Zb., Prir.-Mat. Fak. Univ., Skopje, Mat., Fiz. Hem.*, 1969 (publ. 1971), **19**, 95 (*Chem. Abs.*, 1971, **75**, 112 821y).

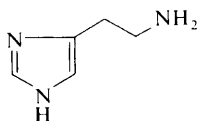
affect the *N*-acetyl function or cause rearrangement of the tropolone ring.<sup>8</sup> Thin-layer electrophoresis of colchicine-containing pharmaceutical preparations appears to be a useful method for the separation of the alkaloid.<sup>9</sup>

The potential use of colchicine in cancer chemotherapy has been reported.<sup>10</sup>

### 3 Imidazole Alkaloids

A review on phosphorylated derivatives of natural products containing the imidazole ring has appeared.<sup>11</sup>

Histamine (7) and two other unidentified alkaloids have been isolated from *Capsella bursapastoris* (shepherd's purse).<sup>12</sup>



(7)

Pilocarpine (13) has been synthesized by a new and improved procedure (Scheme 1).<sup>13</sup> Furfural (8) was air-oxidized in sunlight to give the dihydrofuran (9) in 44% yield, which upon Michael condensation with diethyl ethylmalonate afforded the lactone (10) in almost quantitative yield. Two conventional steps then led to (±)-homopilopie acid (11). Treatment of the acid chloride of (11) with sodio di-*t*-butyl acetamidomalonate followed by acidic hydrolysis and decarboxylation gave the α-aminoketone (12) without isolation of intermediates. The latter compound yielded (±)-pilocarpine (13) using previously reported but not experimentally described steps.

An α-D-glucopyranoside derivative (14) has been converted into (+)-(*R*)-2,3-bisacetoxymethylpentyl acetate (15) by conventional carbohydrate reactions.<sup>14</sup> Compound (15) has also been previously obtained by lithium aluminium hydride reduction of (+)-isopilopie acid (16) followed by acetylation. Furthermore, it has been established that the configurations at C-4 in (16) and in pilocarpine (13) are the same, but that the configuration at C-3 differs in the two compounds. Thus since compound (15) was shown to possess the (*R*)-configuration, the configurational assignment (3*S*,4*R*) for pilocarpine (13) is confirmed.

A series of quaternary ammonium salts of pilocarpine (13) have been shown to possess acetylcholine antagonist properties.<sup>15</sup>

<sup>8</sup> B. Muchlenbruch and H. J. Roth, *Deut. Apoth.-Ztg.*, 1971, **111**, 1851 (*Chem. Abs.*, 1972, **76**, 76 443m).

<sup>9</sup> A. S. C. Wan, *J. Chromatog.*, 1971, **60**, 371.

<sup>10</sup> S. Banerjee and L. Margulis, *Cancer Chemotherapy Reports, Part 1*, 1971, **55**, 531 (*Chem. Abs.* 1972, **77**, 234u).

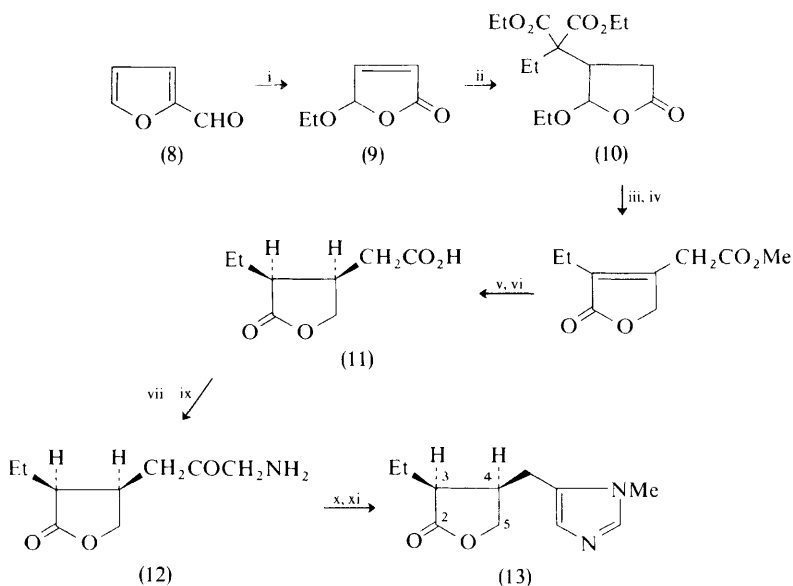
<sup>11</sup> R. A. Zavalishina and E. I. Koroleva, *Uspekhi Biol. Khim.*, 1971, **12**, 220 (*Chem. Abs.*, 1972, **76**, 153 631a).

<sup>12</sup> S. Jurisson, *Tarta Riikliku Ulikooli Toim.*, 1971, 71 (*Chem. Abs.*, 1972, **76**, 23 018v).

<sup>13</sup> J. I. DeGraw, *Tetrahedron*, 1972, **28**, 967.

<sup>14</sup> T. D. Inch and G. J. Lewis, *Carbohydrate Res.*, 1972, **22**, 91.

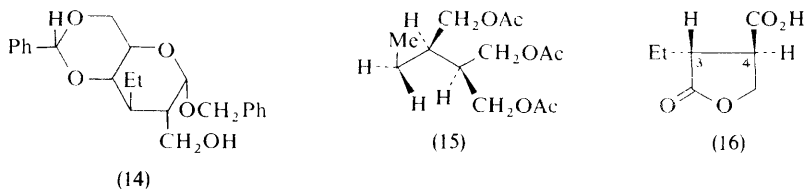
<sup>15</sup> A. Ben Bassat, D. Lavie, H. Edery, and G. Porath, *J. Medicin Chem.*, 1971, **14**, 1066.



Reagents: i,  $\text{EtOH}$ ,  $h\nu$ , eosin,  $\text{O}_2$ ; ii,  $\text{NaC(Et)(CO}_2\text{Et)}_2$ ; iii, 30%  $\text{HBr}$ ,  $\text{HOAc}$ ; iv,  $\text{CH}_2\text{N}_2$ ; v,  $\text{H}_2$ , 5%  $\text{Rh-C}$ ,  $\text{EtOH}$ ; vi,  $\text{4N-HCl}$ ; vii,  $\text{SOCl}_2$ ; viii,  $\text{NaC(NHAc)(CO}_2\text{Bu}^t)_2$ ; ix, 3N- $\text{HCl}$ ; x,  $\text{K}_2\text{CO}_3$ ,  $\text{MeN=C=S}$ ,  $\text{THF-H}_2\text{O}$ , 20 °C; xi, Raney  $\text{Ni}$ ,  $\text{MeOCH}_2\text{CH}_2\text{OH}$ , 100 °C.

Scheme 1

A thin-layer electrophoretic method for separation of pilocarpine from drug sources has been developed.<sup>9</sup> Other recent analytical methods used for the determination of pilocarpine include t.l.c.,<sup>16</sup> potentiometry with ion-selective membrane electrodes,<sup>17</sup> and photodensitometry.<sup>18</sup> Histamine (7) has been found not to be active at the water-air interface by electric-potential and surface-tension measurements of aqueous solutions of the alkaloid.<sup>19</sup>



<sup>16</sup> S. Ebel, W. D. Mikulla, and K. H. Weisel, *Deut. Apoth.-Ztg.*, 1971, **111**, 931 (*Chem. Abs.*, 1971, **75**, 80 317v).

<sup>17</sup> J. Kalman, K. Toth, and D. Kuttel, *Acta Pharm. Hung.*, 1971, **41**, 267 (*Chem. Abs.*, 1972, **76**, 50 003t).

<sup>18</sup> V. Massa, F. Gal, P. Susplugas, and G. Maestre, *Trav. Soc. Pharm. Montpellier*, 1970, **30**, 267 (*Chem. Abs.*, 1971, **75**, 25 455p).

<sup>19</sup> J. Kurk, *Zesz. Nauk. Uniw. Jagiellon, Pr. Chem.*, 1971, 101 (*Chem. Abs.*, 1971, **75**, 122 269p).

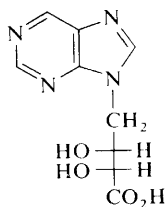
## 4 Purine Alkaloids

A book dealing with alkaloids in foods contains an account on caffeine and related compounds.<sup>20</sup> The synthesis of caffeine, the conversion of uric acid into xanthine, and various syntheses of related heterocyclic compounds form subject matters in a review of broad scope.<sup>21</sup> The role of purine alkaloids in trace-metal metabolism, disease resistance, mutagenesis, and chemotaxonomic considerations in plants has been reviewed.<sup>22</sup>

Triacanthine (17)\* has been isolated from *Holarrhena mitis*.<sup>23</sup> Details on the structure and total synthesis of eritadenine (18), a hypocholesterolemic alkaloid from *Lentinus edodes*, have been reported.<sup>24</sup> An unsuccessful attempt to improve the imidazole ring-closure reaction in a total synthesis of eritadenine, which has been previously discussed,<sup>25</sup> was also reported in this study. Concentrations of both caffeine and theobromine in the cocoa bean were shown to increase most markedly in the time period from flowering to harvest.<sup>26</sup>



(17)



(18)

A tremendous upsurge in synthetic activity in this field is evident. A stereoselective synthesis of *cis*-zeatin (22), whose geometrical isomer was first isolated from *Zea mays* and shown to be a stimulant of cell division in plant tissue cultures, has been reported (Scheme 2).<sup>27</sup> The Diels-Alder reaction of 1-chloro-1-nitrosocyclohexane (19) with isoprene gave the dihydro-1,2-oxazine hydrochloride (20) in moderate yield. Liberation of the base of (20) followed by zinc-acetic acid reduction gave the required amino-alcohol (21), which upon treatment with 6-chloropurine provided a separable mixture of *cis*-zeatin (22) and *trans*-zeatin. Standard tobacco callus bioassay for cytokinin activity showed that the natural *trans*-zeatin is at least 50 times more active than the synthetic *cis*-isomer (22).

\* For an alternative structure proposal, see ref. 25.

<sup>20</sup> J. Schormueller, 'Handbook of Food Chemistry, Vol. 6: Alkaloid-Containing Food Substances, Spices, Salt,' Springer-Verlag, Berlin, 1970.

<sup>21</sup> H. Bredereck, *Pharm. Ztg.*, 1971, **116**, 780 (*Chem. Abs.*, 1971, **75**, 88 511z).

<sup>22</sup> J. A. Williams, *W. African J. Biol. Appl. Chem.*, 1971, **14**, 10 (*Chem. Abs.*, 1971, **75**, 137 592n).

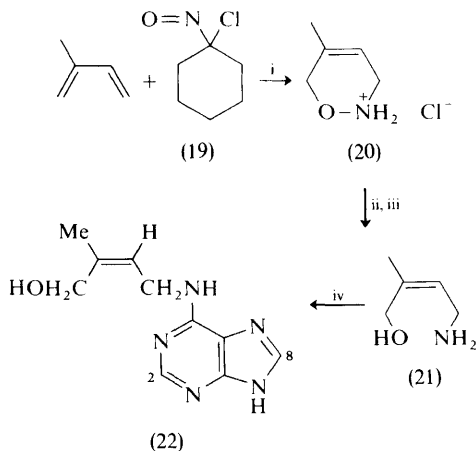
<sup>23</sup> M. Leboeuf, A. Cave, G. P. Wannigama, and R. Goutarel, *Phytochemistry*, 1972, **11**, 843.

<sup>24</sup> T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *Tetrahedron*, 1972, **28**, 899.

<sup>25</sup> V. A. Snieckus, in 'The Alkaloids,' ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, vol. 2, chap. 15.

<sup>26</sup> U. M. Senanayake and R. O. B. Wijesekera, *J. Sci. Food Agric.*, 1971, **22**, 262.

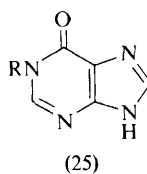
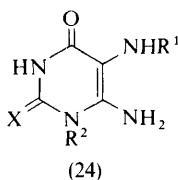
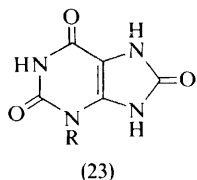
<sup>27</sup> N. J. Leonard, A. J. Playtis, F. Skoog, and R. Y. Schmitz, *J. Amer. Chem. Soc.*, 1971, **93**, 3056.



Reagents: i, EtOH-C<sub>6</sub>H<sub>6</sub>; ii, KOH; iii, Zn-HOAc; iv, 6-Cl-purine-Bu<sup>o</sup>OH.

**Scheme 2**

3-Hydroxyuric acid (23; R = OH) is believed to be a chemical oncogen which is produced by the metabolism of 3-hydroxyxanthine. A facile synthesis of (23; R = OH) involving a new imidazole ring-closure has been reported.<sup>28</sup> Since conventional methods to form the imidazole ring in (24; X = O, R<sup>1</sup> = H, R<sup>2</sup> = OCH<sub>2</sub>Ph) failed, the ethoxycarbonyl derivative (24; X = O, R<sup>1</sup> = CO<sub>2</sub>Et, R<sup>2</sup> = OCH<sub>2</sub>Ph) was prepared and catalytically debenzylated to (24; X = O, R<sup>1</sup> = CO<sub>2</sub>Et, R<sup>2</sup> = OH). When this compound was treated with an excess of sodium ethoxide in refluxing ethanol, a 34% yield of 3-hydroxyuric acid (23; R = OH) was obtained. On the other hand, extensive experimentation led to the discovery of new conditions for the imidazole ring closure.<sup>29</sup> Treatment of the pyrimidine derivative (24; X = S, R<sup>1</sup> = R<sup>2</sup> = H) with a special desulphurizing agent (Raney alloy containing a catalytic amount of nickel) in formic acid produced hypoxanthine (25; R = H) in high yield. A different synthesis of hypoxanthine (25; R = H) and its derivatives (25; R = Me or CH<sub>2</sub>Ph) by catalytic



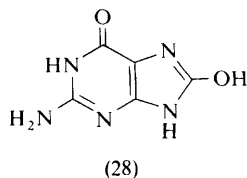
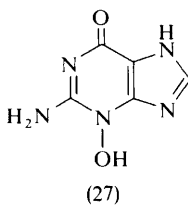
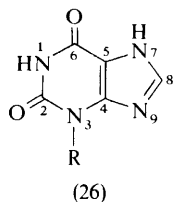
<sup>28</sup> T.-C. Lee, G. Stoehrer, M. N. Teller, A. Myles, and G. B. Brown, *Biochemistry*, 1971, **10**, 4463.

<sup>29</sup> N. Nakamizo, K. Shiozaki, S. Hirai, and S. Kudo, *Bull. Chem. Soc. Japan*, 1971, **44**, 2192.



reduction over Raney nickel of 2-cyano-2-phenylazo-*N*-allylacetamides in ammonia-formamide solution has been described.<sup>30</sup>

Details concerning the scope of the acetic anhydride promoted rearrangement of 3-hydroxyxanthine (26; R = OH) to uric acid (23; R = H) and of 3-hydroxyguanine (27) to 8-hydroxyguanine (28) have been published.<sup>31</sup> This method may be applied to the conversion of a variety of 3-acyloxy-purine derivatives into 8-substituted xanthines and guanines. For example, 8-chloro-, -bromo-, -nitro-, and -azido-derivatives were prepared from the reaction of (26; R = OAc) with the corresponding nucleophiles. Apparently the rearrangement requires the presence of a C-2 substituent. The preparation of the 3-hydroxy-guanine and -xanthine<sup>32</sup> and the corresponding 3-acyloxy-derivatives<sup>33</sup> has been separately reported. A series of different 8-substituted hypoxanthines (25) was prepared from the 8-chloro-derivatives by nucleophilic displacement reactions.<sup>34</sup> Compounds prepared include the 8-CO<sub>2</sub>Et, -NEt<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>Cl)<sub>2</sub>, and -CH(NH<sub>2</sub>)-CO<sub>2</sub>H derivatives.



1-Methoxyadenine (29; R = Me) was shown to undergo the Dimroth rearrangement to yield *N*-methoxyadenine (30; R = OMe) in 59% yield.<sup>35a</sup> Similar treatment of the 1-benzyloxy-analogue (29; R = CH<sub>2</sub>Ph) gave the proposed intermediate in the rearrangement, (31), which upon further treatment under the conditions of the reaction yielded compound (30; R = OCH<sub>2</sub>Ph). The synthesis of compounds of the type (29) was separately reported.<sup>35b</sup> Ureido-derivatives (30; R = CONHalk) were readily prepared from adenine (30; R = H) and shown to promote growth of tobacco callus cultures.<sup>36</sup>

A number of investigators have been concerned with structural modification of purine systems. For example, alkylation at the 7-position of xanthine (26;

<sup>30</sup> M. Sekiya and J. Suzuki, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 209.

<sup>31</sup> N. J. M. Birdsall, U. Woelcke, T.-C. Lee, and G. B. Brown, *Tetrahedron*, 1971, **27**, 5969.

<sup>32</sup> J. C. Parham, N. J. M. Birdsall, T.-C. Lee, and T. J. Delia, *J. Org. Chem.*, 1971, **36**, 2635.

<sup>33</sup> N. J. M. Birdsall, T.-C. Lee, and U. Woelcke, *Tetrahedron*, 1971, **27**, 5961.

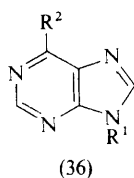
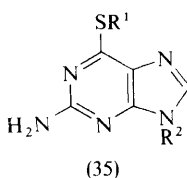
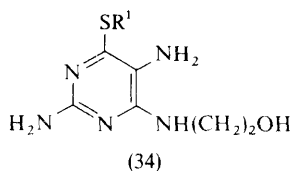
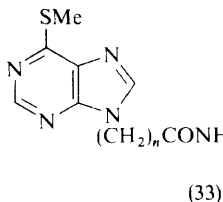
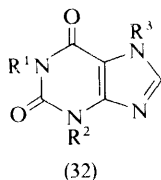
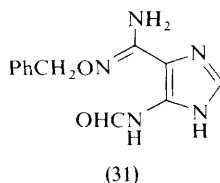
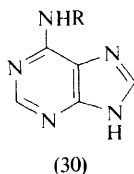
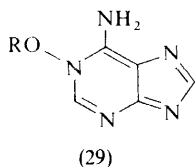
<sup>34</sup> L. A. Gutorov and E. S. Golovchinskaya, *Khim.-Farm. Zhur.*, 1971, **5**, 13 (*Chem. Abs.*, 1971, **75**, 140 793j).

<sup>35a</sup> T. Fujii, T. Sato, and T. Itaya, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1731.

<sup>35b</sup> T. Fujii, C. C. Wu, and T. Itaya, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1368.

<sup>36</sup> J. J. McDonald, N. J. Leonard, R. Y. Schmitz, and F. Skoog, *Phytochemistry*, 1971, **10**, 1429.

$R = \text{Me}$ )<sup>37</sup> and theophylline (32;  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{H}$ )<sup>38</sup> derivatives has been reported. The xanthine derivatives exhibited coronary vasodilator properties. The preparation of the nicotinamidylalkylamidoalkyl derivative (33) using conventional chemical transformations deserves special mention.<sup>39</sup> Reduction of (33) with sodium dithionite provided the corresponding 1,4-dihydropyridine derivative. Other 9-substituted-6-alkylthiopurines have been synthesized.<sup>40,41</sup> The general route involved the preparation of N-substituted pyrimidines and their cyclization to the purines, e.g. (34)  $\rightarrow$  (35;  $R^1 = \text{alkyl}$ ,  $R^2 = \text{CH}_2\text{CH}_2\text{OH}$ ).<sup>41</sup>



A general method developed by Carroll and Phillip which utilizes a 6-diphenyl-methylthio-substituent for regioselective alkylation at the 9-position has been extended to the preparation of 2,6-disubstituted 9-ethylpurine derivatives.<sup>42</sup> For example, treatment of (35;  $R^1 = \text{CHPh}_2$ ,  $R^2 = \text{H}$ ) with ethyl iodide and

<sup>37</sup> D. S. Bariana and M. Savic, *Chim. Therap.*, 1971, **6**, 101 (*Chem. Abs.*, 1971, **75**, 129 988f).

<sup>38</sup> A. F. Pozharskii, E. A. Zvezdina, I. S. Kashparov, Yu. P. Andreichikov, V. M. Mar'yakovskii, and A. M. Simonov, *Khim. geterotsikl. Soedinenii*, 1971, 1230 (*Chem. Abs.*, 1972, **76**, 25 126c).

<sup>39</sup> I. N. Gracheva, A. Ya. Veinberg, and G. I. Samokhvalov, *Zhur. obshchei Khim.*, 1971, **41**, 1376 (*Chem. Abs.*, 1971, **75**, 88 579c).

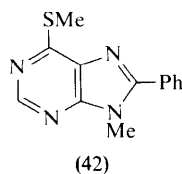
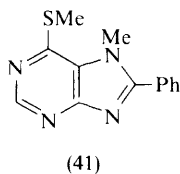
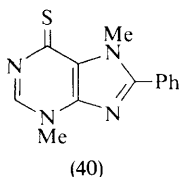
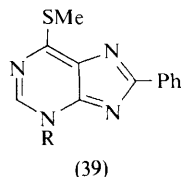
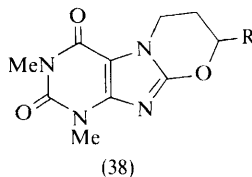
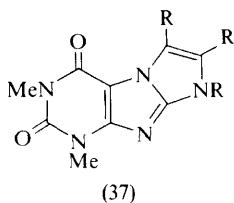
<sup>40</sup> M. Lidaks, J. Sluke, B. Zarina, and S. Poritere, *Khim. geterotsikl. Soedinenii*, 1971, 262 (*Chem. Abs.*, 1971, **75**, 35 945n).

<sup>41</sup> E. I. Abramova, A. V. Kuteliya, and E. S. Karavaeva, *Puti Sin. Izyskaniya Protivoopuk-holevykh Prep.*, 1968 (publ. 1970), no. 3, p. 105 (*Chem. Abs.*, 1971, **75**, 35 947q).

<sup>42</sup> M. Israel, N. Muhammad, and E. J. Modest, *J. Heterocyclic Chem.*, 1971, **8**, 1019.

potassium carbonate in DMF yielded the *N*-ethyl derivative (35;  $R^1 = \text{CHPh}_2$ ,  $R^2 = \text{Et}$ ) which could be converted into the thiol (35;  $R^1 = \text{H}$ ,  $R^2 = \text{Et}$ ) with a mixture of trifluoroacetic acid and phenol. Compound (35;  $R^1 = \text{H}$ ,  $R^2 = \text{Et}$ ) was used for the preparation of novel derivatives, e.g. [35,  $R^1 = 5$ -(1-methyl-4-nitro)imidazolyl,  $R^2 = \text{Et}$ ]. Other 6-substituted purine derivatives, e.g. [36;  $R^1 = \text{Et}$ ,  $R^2 = \text{NH}(\text{CH}_2)_3\text{Me}$ ] were prepared by effecting nucleophilic displacement reactions on the thiomethylguanine, (35;  $R^1 = \text{Me}$ ,  $R^2 = \text{Et}$ ). The same reaction was applied to the synthesis of 6-substituted 9-vinylpurine systems, e.g. (36;  $R^1 = \text{CH}=\text{CH}_2$ ,  $R^2 = \text{N}(\text{Et})_2$ ).<sup>43</sup> Finally, 6-substituted purine *N*-oxides have been obtained by treatment of 6-chloropurine *N*-oxides with nucleophilic agents in a reaction which is mechanistically analogous.<sup>44</sup>

As part of programmes directed towards the synthesis of new potential biologically active compounds, a variety of cyclic xanthine derivatives, e.g., (37) and (38), have been prepared by Russian workers.<sup>45</sup> During a detailed study aimed at elucidating modes of alkylation of purines, treatment of 6-methylthio-8-phenylpurine (39;  $R = \text{H}$ ) with methyl iodide in DMF was shown to yield a single methiodide, which upon hydrolysis gave exclusively the 3-methyl derivative (40).<sup>46</sup> Similarly, the 7-methyl and 7-methyl analogues, (41) and (42), yielded 3-methyl



derivatives, (43) and (44), respectively. The 3-methyl isomer (39;  $R = \text{Me}$ ) also gave the 7-methyl derivative (43) and the 1-methyl analogue (45) provided the 9-methyl derivative (46) under comparable conditions. On the other hand, an

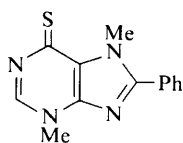
<sup>43</sup> K. Takemoto, F. Kawakubo, and K. Kondo, *Bull. Chem. Soc. Japan*, 1971, **44**, 1718.

<sup>44</sup> A. Giner-Sorolla, *J. Heterocyclic Chem.*, 1971, **8**, 651.

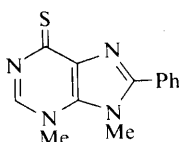
<sup>45</sup> J. Zajackowska and M. Eckstein, *Diss. Pharm. Pharmacol.*, 1971, **23**, 209 (*Chem. Abs.*, 1971, **75**, 151 760x); V. I. Nosachenko and A. A. Tkachenko, *Khim. Issled. Farm.*, 1970, 45 (*Chem. Abs.*, 1971, **75**, 151 761y); A. A. Tkachenko, P. M. Kochergin, and G. F. Panchenko, *Khim. geterotsikl. Soedinenii*, 1971, 686 (*Chem. Abs.*, 1972, **76**, 126 931s); A. A. Tkachenko, P. M. Kochergin, and F. A. Zubkov, *ibid.*, p. 682 (*Chem. Abs.*, 1972, **76**, 126 932t).

<sup>46</sup> F. Bergmann, Z. Neiman, D. Lichtenberg, and J. Deutsch, *J. Chem. Soc. (C)*, 1971, 1822.

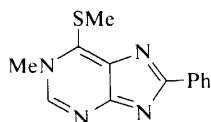
8-unsubstituted 9-methylthiopurine yielded the cation (47), which is presumably precluded in the 8-phenyl thiopurine derivatives owing to steric hindrance from the 8-substituent. The 1-alkylated xanthine derivatives [48; R = (CH<sub>2</sub>)<sub>4</sub>COMe]<sup>47</sup> and [48; R = (CH<sub>2</sub>)<sub>2</sub>NHNH<sub>2</sub>,HCl]<sup>48</sup> have been prepared. Treatment of theobromine (32; R<sup>1</sup> = R<sup>3</sup> = Me, R<sup>2</sup> = H) with phosphorus oxychloride has been reported to yield an intermediate salt which was converted into 2,6,8-trichloro-2,3-dihydro-3,7-dimethylpurine hydrochloride.<sup>49</sup>



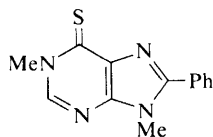
(43)



(44)



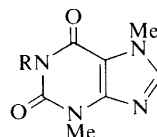
(45)



(46)



(47)



(48)

Two groups of workers have independently reported on the photochemical and radiochemical alkylation of caffeine (32; R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = Me) as model studies for radiation damage to DNA in living organisms.<sup>50-52</sup> U.v. light or  $\gamma$ -ray irradiation of caffeine in aqueous solution of a primary or secondary aliphatic amine yielded the corresponding 8-alkyl derivative in 5–10% yield.<sup>50</sup> If the irradiation of this mixture was carried out in the presence of di-*t*-butyl peroxide, the corresponding 8- $\alpha$ -aminoalkylcaffeine derivatives were obtained in up to 65% yield.<sup>51</sup>

[8-<sup>14</sup>C]Zeatin and [2,8-<sup>3</sup>H<sub>2</sub>]zeatin (22) have been prepared for biosynthetic studies.<sup>53</sup> The syntheses of [2-<sup>14</sup>C]- and [8-<sup>14</sup>C]-caffeine have been reported.<sup>54,55</sup>

<sup>47</sup> W. Mohler and A. Soeder, *Arzneim.-Forsch.*, 1971, **21**, 1159 (*Chem. Abs.*, 1971, **75**, 118 288b).

<sup>48</sup> M. Gorczyca, *Diss. Pharm. Pharmacol.*, 1971, **23**, 157 (*Chem. Abs.*, 1971, **75**, 35 948r).

<sup>49</sup> L. A. Gutorov and E. S. Golovchinskaya, *Khim.-Farm. Zhur.*, 1971, **5**, 14 (*Chem. Abs.*, 1971, **75**, 118 286z); L. A. Gutorov, L. A. Nikolaeva, and E. S. Golovchinskaya, *ibid.*, p. 17 (*Chem. Abs.*, 1972, **76**, 126 935w).

<sup>50</sup> A. Stankunas, I. Rosenthal, and J. N. Pitts, jun., *Tetrahedron Letters*, 1971, 4779.

<sup>51</sup> D. Elad and J. Salomon, *Tetrahedron Letters*, 1971, 4783.

<sup>52</sup> N.-C. Yang, L. S. Gorelic, and B. Kim, *Photochem. and Photobiol.*, 1971, **13**, 275.

<sup>53</sup> D. S. Letham and H. Young, *Phytochemistry*, 1971, **10**, 2077.

<sup>54</sup> E. Heftmann, *J. Labelled Compounds*, 1971, **7**, 463.

<sup>55</sup> G. Czok, R. Schmidt, and K. Lang, *Gazz. med. Ital.*, 1971, **130**, 157 (*Chem. Abs.*, 1971, **75**, 108 224p).

Photodensitometric<sup>56</sup> and u.v. spectrophotometric<sup>57</sup> methods for analysis of purine alkaloids have been published. The electrophoretic behaviour of purine bases has been investigated.<sup>58</sup>

### 5 *Securinega* Alkaloids

No new chemical investigations of this group have appeared. The content of securinine, the major alkaloid from *Securinega suffruticosa*, has been shown to vary with soil type, growth stage, and genotype of this species.<sup>59</sup> Application of securinine on to an active strain of rhizobia of sainfoin, peas, and soybeans has been reported to cause plant growth.<sup>60</sup>

The biosynthesis of this group is unknown. One report which has slight bearing on this problem deals with the effects of amino-acids on *S. suffruticosa* plants grown in a sterile agar nutrient medium.<sup>61</sup> Arginine, lysine, and nicotinic acid were administered and the amino-acid and securinine content of roots, stems, and leaves was determined. Securinine content was found to be highest in the leaves when arginine was administered; in the roots when lysine was used; and in the stems when nicotinic acid was added.

New potentiometric titration,<sup>62</sup> polarimetric,<sup>63</sup> and spectrophotometric<sup>64</sup> methods for quantitative determination of securinine nitrate in pharmaceutical preparations have been described. One of these allows for the detection of biologically inactive racemic securinine.<sup>63</sup> A paper-electrophoresis method for determination of securine has also been developed.<sup>65</sup>

### 6 *Galbulimima* Alkaloids

This small but fascinating group of alkaloids [e.g. himgaline (49)] has been vividly reviewed by the Australian chemists responsible for all of the associated structural elucidation work.<sup>66</sup>

<sup>56</sup> V. Massa, F. Gal, P. Susplugas, and G. Maestre, *Trav. Soc. Pharm. Montpellier*, 1971, **31**, 167 (*Chem. Abs.*, 1971, **75**, 121 455j).

<sup>57</sup> G. Lehmann, H. G. Hahn, and M. Moran, *Gordian*, 1971, **71**, 217 (*Chem. Abs.*, 1971, **75**, 150 396w).

<sup>58</sup> L. Lepri, P. G. Desideri, and V. Coas, *J. Chromatog.*, 1972, **64**, 271.

<sup>59</sup> Ch. Younos, F. Mortier, and J. M. Pelt, *Plant. Med. Phytotherap.*, 1971, **5**, 289 (*Chem. Abs.*, 1972, **76**, 138 162e).

<sup>60</sup> D. Karaguisheva, R. Z. Levina, and Sh. Alibekova, *Izvest. Akad. Nauk. Kaz. S.S.R., Ser. biol.*, 1971, **9**, 8 (*Chem. Abs.*, 1971, **75**, 16 572x).

<sup>61</sup> N. A. Trofimova, *Mater. Gor. Nauch. Konf. Molodykh Uch.-Med.*, 1st, 1967, 475 (*Chem. Abs.*, 1972, **76**, 12 037z).

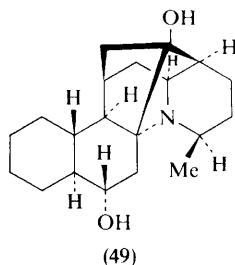
<sup>62</sup> A. P. Kreshkov, T. V. Maksimova, and V. A. Drozdov, *Farmatsiya (Moscow)*, 1972, **21**, 56 (*Chem. Abs.*, 1972, **76**, 158 410n).

<sup>63</sup> B. A. Krivot and B. K. Rostotskii, *Farmatsiya (Moscow)*, 1972, **21**, 53 (*Chem. Abs.*, 1972, **76**, 158 411p).

<sup>64</sup> B. I. Shvydkii, R. M. Pinyazhko, and I. V. Borys, *Khim. i khim. Tekhnol.*, 1969, 88 (*Chem. Abs.*, 1971, **75**, 121 447h).

<sup>65</sup> V. Mikhno and G. K. Levitskaya, *Farm. Zhur. (Kiev)*, 1971, **26**, 26 (*Chem. Abs.*, 1972, **76**, 122 476z).

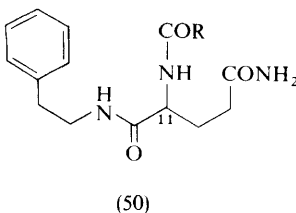
<sup>66</sup> E. Ritchie and W. C. Taylor, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1971, Vol. 13, p. 227.



## 7 Peptide Alkaloids

This group has been lucidly and comprehensively reviewed by the original Reporter for this group in the Specialist Periodical Reports series.<sup>67</sup>

The *N*-glutaminoyl-2-phenethylamine derivatives [50; R = CH(Me)Et] and [50; R = CH(Me)Me], have been isolated from *Croton humilis*.<sup>68</sup> Interpretation of all the high-resolution mass spectral peaks exceeding 4% (including the assignment of all metastables) together with a complete analysis of the 100 MHz n.m.r.

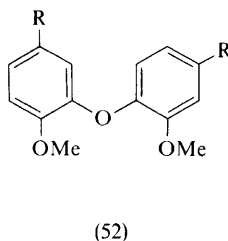
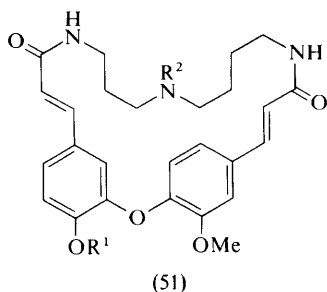


spectra of both compounds led to the structural assignment shown. Chemical confirmation was obtained by acidic hydrolysis of the mixture of the two alkaloids followed by automatic amino-acid analysis, which yielded one equivalent each of glutamic acid and ammonia. The presence of glutamic acid and 2-phenethylamine was confirmed by their isolation (preparative t.l.c.) and identification. Unfortunately, complete characterization of 2-methylbutanoic and 2-methylpropionic acids as well as the determination of the configuration at C-11 and the R side-chain was precluded by lack of material. The  $\beta$ -glutamoyl linkage of (50) is unique within the class of  $\gamma$ -glutamoyl oligopeptides. These compounds may be biogenetically derived from 2-methylbut-2-enoic acid, phenylalanine, and glutamic acid, all of which have been isolated from *C. humilis*. In addition, this constitutes the first report of peptidyl compounds isolated from the *Croton* species which is better known for the proaporphine and morphinandienone alkaloids that it elaborates.<sup>68</sup>

<sup>67</sup> E. W. Warnhoff, *Fortschr. Chem. org. Naturstoffe*, 1970, **28**, 162.

<sup>68</sup> J. P. Kutney, F. K. Klein, G. Knowles, and K. L. Stuart, *Tetrahedron Letters*, 1971, 3263.

The bark of *Codonocarpus australis* (Phytolaccaceae) has yielded a *Lunaria*-type alkaloid (see below), codonocarpine (51;  $R^1 = R^2 = H$ ).<sup>69</sup> The first indication of the relationship of codonocarpine to the *Lunaria* alkaloids was surmised from its acidic hydrolysis to spermidine,  $H_2N(CH_2)_3NH(CH_2)_4NH_2$ . The presence of a *trans*-cinnamamide structure was indicated by the u.v. [312 nm ( $\log \epsilon$  4.33), 283 (4.44), and 218 (4.42)] and n.m.r. [two AB quartets at  $\delta$  7.58, 7.42, 6.50, and 5.90, 1H each,  $J$  15 Hz in the diacetate (51;  $R^1 = R^2 = Ac$ )] spectra. The u.v. spectrum in strong alkali showed a bathochromic shift [363 nm ( $\log \epsilon$  4.33), 309 (4.32)] typical of a phenol and the n.m.r. spectrum exhibited a singlet at  $\delta$  3.84 (3H) assignable to an aromatic methoxy-group. The formation of codonocarpine *ON*-diacetate [(51;  $R^1 = R^2 = Ac$ ), n.m.r.  $\delta$  2.40 and 2.08] provided confirmatory evidence for the secondary amine and phenolic hydroxy-functions. The nature and location of the remaining oxygen atom was determined by potassium permanganate oxidation of methylated ( $Me_2SO_4$ -NaOH) codonocarpine. The oxidation product was esterified with diazomethane to yield the

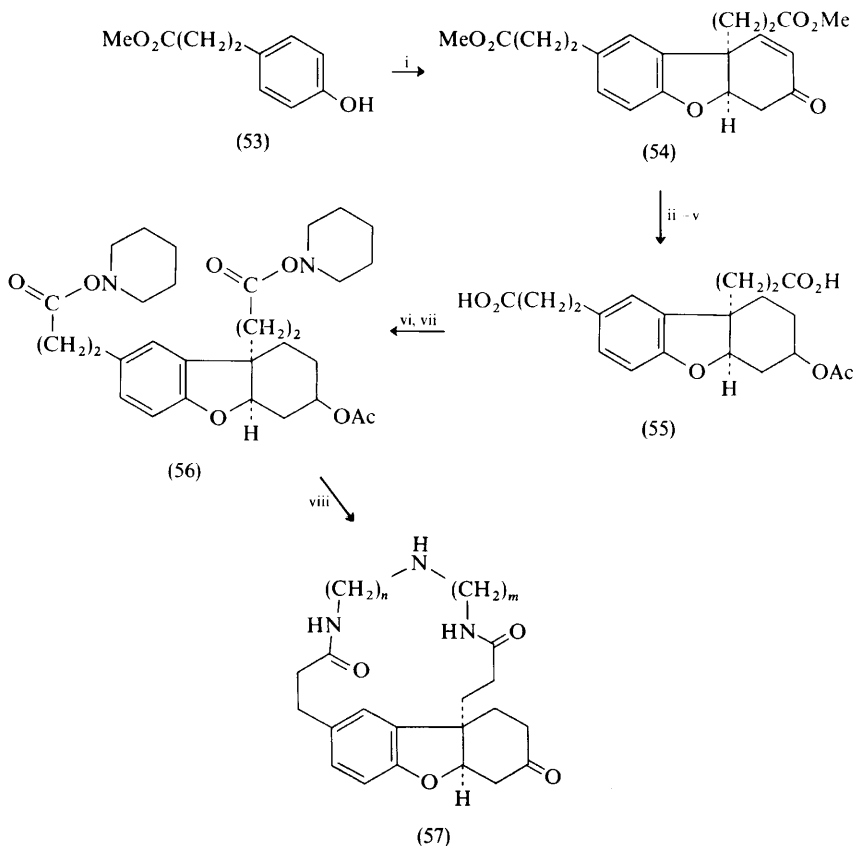


diphenyl ether (52;  $R = CO_2Me$ ) which was found to be identical with a synthetic sample. Furthermore, catalytic hydrogenation of codonocarpine *ON*-diacetate gave a tetrahydro-derivative which, upon acidic hydrolysis followed by esterification, gave the diester (52;  $R = CH_2CH_2CO_2Me$ ). These results are consistent with the presence of the intact dimeric phenylpropide unit linked *via* an ether function. The placement of the phenolic hydroxy-group in codonocarpine was based only on a negative Gibbs test (no *p*-substituent to the phenolic OH). The accumulated data support structure (51;  $R^1 = R^2 = H$ ) for codonocarpine but do not exclude one in which the spermidine bridge is reversed. It is interesting to note that previous to this report all alkaloids characterized by a diamine unit and a dicarboxylic acid resulting from oxidative coupling (see below) of two phenylpropide fragments have been isolated from *Lunaria* species belonging to the Cruciferae family. Firm evidence which establishes that the biosynthesis of the *Lunaria* alkaloids occurs *via* phenol oxidative coupling of two *p*-hydroxycinnamic acid units has now been provided<sup>70</sup> and, on the basis of these results, a biogenetic-type synthesis of ( $\pm$ )-tetrahydrolunaridine (57;  $n = 4$ ,  $m = 3$ ) has

<sup>69</sup> R. W. Doskotch, A. B. Ray, and J. L. Beal, *Chem. Comm.*, 1971, 300.

<sup>70</sup> C. Poupat and G. Kunesch, *Compt. rend.*, 1971, 273, C, 433.

been accomplished (Scheme 3).<sup>71</sup> Oxidation of (53) gave the dimeric product (54) in 14% yield, which was reduced, hydrolysed, and acetylated to the diacid acetate (55). Condensation of (55) as its diacid chloride or mixed dianhydride with spermidine gave a complex mixture which did not contain any of the desired macrocyclic ring compound (57;  $n = 4$ ,  $m = 3$ ). However, exploratory work on the reaction of primary and secondary amines with 1-benzoyloxypiperidine in acidic solution to give the corresponding amides showed a significantly faster rate of reaction for primary amines, presumably due to a steric factor. These results pointed to a possible means by which any undesirable reaction of the



Reagents: i,  $K_3Fe(CN)_6$ ; ii,  $H_2-Pd/C$ ; iii,  $NaBH_4$ ; iv,  $OH^-$ ; v,  $Ac_2O$ ; vi,  $ClCO_2Me$ ; vii,  $HONC_5H_{10}$ ; viii,  $H_2N(CH_2)_3NH(CH_2)_4NH_2$  (spermidine)-THF.

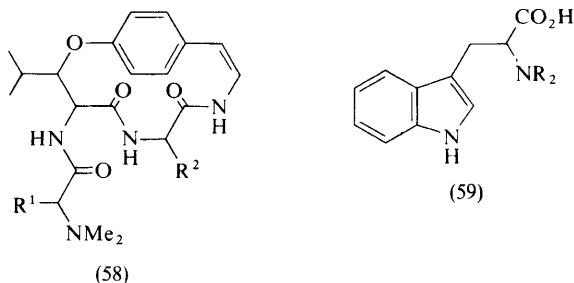
**Scheme 3**

<sup>71</sup> H. P. Husson, C. Poupat, B. Rodriguez, and P. Potier, *Tetrahedron Letters*, 1971, 2697.



secondary amine function in spermidine could be avoided. In the event, condensation of the *NN*-diacyloxypiperidine derivative (56) with spermidine under high dilution conditions furnished a 12% yield of product which, upon mild deacetylation and oxidation, gave ( $\pm$ )-tetrahydrolunaridine (57;  $n = 4$ ,  $m = 3$ ), shown to be identical with the natural product. It is interesting to note that the product in which the spermidine bridge is reversed, (57;  $n = 3$ ,  $m = 4$ ), was not found in the reaction mixture, possibly indicating a greater reactivity of one of the acyloxypiperidine groups in (56) and a greater nucleophilicity of one of the primary amine functions in spermidine.

The known<sup>67</sup> frangulanine [58;  $R^1 = \text{CH}(\text{Me})\text{Et}$ ,  $R^2 = \text{CH}_2\text{CHMe}_2$ ] and the new alkaloids, discarine A [58;  $R^1 = \beta\text{-indolyl-CH}_2$ ,  $R^2 = \text{CH}(\text{Me})\text{Et}$ ] and B [58;  $R^1 = \text{CH}(\text{Me})\text{Et}$ ,  $R^2 = \beta\text{-indolyl-CH}_2$ ] have been isolated from the root of *Discaria longispina*.<sup>72</sup> Acidic hydrolysis of discarine A gave isoleucine, whereas treatment with base provided  $N_bN_b$ -dimethyltryptophan (59;  $R = \text{Me}$ ). After several attempts to prepare (59;  $R = \text{Me}$ ) by literature methods, it was finally synthesized as follows: treatment of tryptophan with methyl iodide gave the  $N_b$ -quaternary iodide, which after iodide exchange by chloride and demethylation with sodium thiophenoxide yielded compound (59;  $R = \text{Me}$ ). Hydrogenation of discarine A followed by acidic hydrolysis provided *p*-tyramine and  $\beta$ -hydroxyleucine. These chemical facts hinted that discarine A possesses a frangulanine-type structure and this suspicion was fully confirmed by analysis of its characteristic<sup>67</sup> high-resolution mass spectrum, which provided essentially the complete structure [58;  $R^1 = \beta\text{-indolyl-CH}_2$ ,  $R^2 = \text{CH}(\text{Me})\text{Et}$ ] for discarine A. The 220 MHz n.m.r. spectrum provided additional evidence in that it showed a typical pair of doublets at  $\delta$  0.86 and 1.08 ( $J$  7 Hz) for the isopropyl group of the  $\beta$ -hydroxyleucine unit. A singlet at  $\delta$  2.66 ( $\text{NMe}_2$ ) and an asymmetric doublet (overlapping doublet and triplet?) at  $\delta$  0.61 ( $\text{C-Me}$  groups of the isoleucine residues) could also be assigned. The isomeric discarine B yielded tryptophan (59;  $R = \text{H}$ ) upon alkaline hydrolysis whereas acidic treatment of its dihydro-product gave *NN*-dimethylisoleucine,  $\beta$ -hydroxyleucine, and *p*-tyramine. Reference to its high-resolution mass spectrum led to the assignment of structure [58;  $R^1 = \text{CH}(\text{Me})\text{Et}$ ,  $R^2 = \beta\text{-indolyl-CH}_2$ ] for discarine B. Like

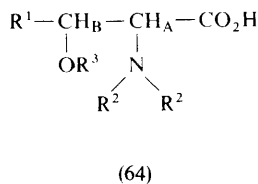
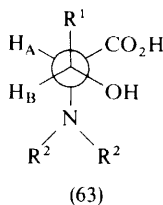
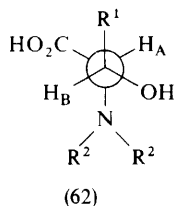
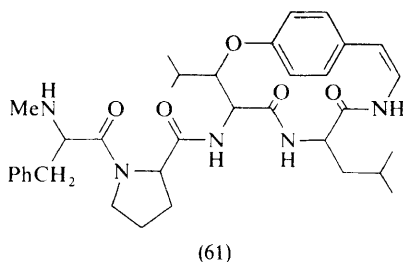
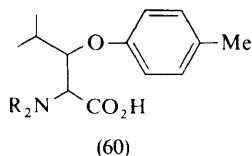


<sup>72</sup> O. A. Mascaretti, V. M. Merkuza, G. E. Ferraro, E. A. Ruveda, C.-J. Chang, and E. Wenkert, *Phytochemistry*, 1972, **11**, 1133.

discarine A, the 220 MHz n.m.r. spectrum of discarine B showed a pair of doublets for the isopropyl group of the  $\beta$ -hydroxyleucine moiety at  $\delta$  0.89 and 1.07 ( $J$  7 Hz). A singlet at  $\delta$  2.13, a triplet at  $\delta$  0.70 ( $J$  7 Hz), and a doublet at  $\delta$  0.44 ( $J$  7 Hz) were assigned to the  $\text{NMe}_2$  and the two  $\text{C-Me}$  groups of the  $\text{NN}$ -dimethylaminoisoleucine units, respectively. Two other alkaloids of unknown structure were also isolated from *D. longispina*.<sup>72</sup>

An additional 14-membered ring peptide alkaloid, scutianine-B (58;  $\text{R}^1 = \text{R}^2 = \text{CH}_2\text{Ph}$ ), has been isolated from *Scutia buxifolia*.<sup>73</sup> Its structure rests on the typical<sup>67</sup> mass and other spectral data and on the identification of the usual amino-acid fragments obtained by acidic hydrolysis. Amphibine-A, an alkaloid isolated from *Ziziphus amphibia*, appears to be identical with discarine A [58;  $\text{R}^1 = \beta$ -indolyl- $\text{CH}_2$ ,  $\text{R}^2 = \text{CH}(\text{Me})\text{Et}$ ]<sup>72</sup> on the basis of comparison with the reported physical, spectral, and chemical properties.<sup>74</sup>

An n.m.r. analysis of the preferred conformations of the *threo* and *erythro* diastereomers of  $\beta$ -hydroxyleucine, threonine, and  $\beta$ -phenylserine and their  $\text{NN}$ -dimethyl derivatives has been carried out and the results have been used to assign the relative configuration of  $\beta$ -(*p*-tolyl-oxy)leucine (60;  $\text{R} = \text{H}$ ) obtained by degradation of lasiodine B (61).<sup>75</sup> The combined effect of the bulky  $\text{NMe}_2$  group and intramolecular  $-\text{NMe}_2 \cdots \text{H}-\text{O}-$  hydrogen-bonding greatly favours conformations (62;  $\text{R}^2 = \text{Me}$ ) and (63;  $\text{R}^2 = \text{Me}$ ) for the *threo* and *erythro* diastereomers of the dimethylamino-compounds (64;  $\text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{H}$ ), whereas this is not the case in the corresponding amino-derivatives (64;  $\text{R}^2 = \text{R}^3 = \text{H}$ ) ( $\text{R}^1 = \text{alkyl or aryl in all cases}$ ). These effects manifest themselves in the observed coupling constants,  $J_{\text{AB}}$  8.5 Hz and 2.5 Hz, respectively, for the *threo*



<sup>73</sup> R. Tschesche, E. Ammermann, and H. W. Fehlaber, *Tetrahedron Letters*, 1971, 4405.

<sup>74</sup> R. Tschesche, E. U. Kaussmann, and H. W. Fehlaber, *Tetrahedron Letters*, 1972, 865.

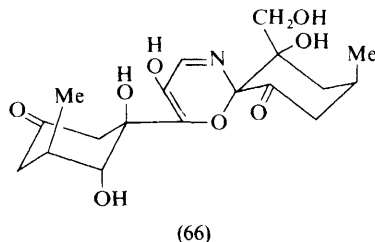
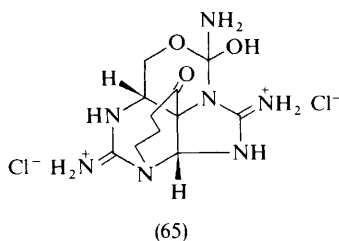
(synthetic) and *erythro* (natural) diastereomers of the hydrochlorides of (60; R = Me) and can thus be used to assign the relative configurations. That the change of a  $\beta$ -OH to a  $\beta$ -OMe function does not alter these conclusions was checked in model compounds, e.g. *NN*-dimethyl- $\beta$ -methoxyisoleucine (64; R<sup>1</sup> = CHMe<sub>2</sub>, R<sup>2</sup> = R<sup>3</sup> = Me) hydrochloride showed  $J_{AB}$  8.5 Hz and 3 Hz for the *threo* and *erythro* isomers, respectively. It is likely that this analysis will be applicable to the determination of relative configuration of  $\beta$ -hydroxyaminoacids in other peptide alkaloids.

Several of the toxic cyclopeptides of the toadstool *Amanita phalloides*<sup>25</sup> have been shown to inhibit mammalian RNA-polymerase.<sup>76</sup>

## 8 Unclassified Alkaloids and Alkaloid-containing Plants

The format adopted in the previous volumes of these Reports is followed.

Nitrogen-containing compounds which have been isolated during the past year from sources other than plants and therefore not truly defined as alkaloids are not reviewed. These are saxitoxin (65) from the dinoflagellate *Gonyaulax catenella*,<sup>77</sup> and leucogenenol (66), a metabolite of *Penicillium gilmanii*.<sup>78</sup>



Plants from the families Amaranthaceae, Dipsacaceae, and Orobanchaceae have been screened and the following species have shown positive tests for alkaloids: *Amaranthus blitoides*, *A. gracilis*, *A. graecizans*, *A. hybridus*, *A. hybridus* var. *erythrostachys*, *A. retroflexus*, *Cephalaria joppica*, *C. salicifolia*, *C. syriaca*, *Morina persica*, *Pterocephalus involucratus*, *Scabiosa argentea*, *S. palaestina*, *S. prolifera*, *Orobanche crenata*, *O. griesbachii*, *O. ramosa*, and *O. versicolor*.<sup>79</sup> Over 1300 species representing 469 genera and 102 plant families native to Western Australia have been screened for alkaloid content.<sup>80</sup> Approximately 8% of these species show strong positive tests for alkaloids. A review concerned with alkaloid-containing plants of Central Asia and the Southern Kazakhstan region

<sup>75</sup> J. Marchand, M. Pais, and F. X. Jarreau, *Bull. Soc. chim. France*, 1971, 3742.

<sup>76</sup> A. Buku, G. Campadelli-Fiume, L. Fiume, and T. Wieland, *F.E.B.S. Letters*, 1971, **14**, 42.

<sup>77</sup> J. L. Wong, R. Oesterlin, and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, **93**, 7344.

<sup>78</sup> F. A. H. Rice, *J. Chem. Soc. (C)*, 1971, 2599.

<sup>79</sup> G. H. Aynilian, C. I. Abou-Chaar, and W. Edgcombe, *Planta Med.*, 1971, **19**, 306 (*Chem. Abs.*, 1971, **75**, 31 329s).

<sup>80</sup> T. E. H. Aplin and J. R. Cannon, *Econ. Bot.*, 1971, **25**, 366.

has appeared.<sup>81</sup> Approximately 70 Costa Rican plants have been tested for alkaloids.<sup>82</sup> Continuation of a phytochemical screening programme of Indian plants for alkaloid content has been reported.<sup>83</sup> Other single species in which alkaloids have been detected but not fully characterized are summarized in the Table.

**Table** Alkaloid-containing Plants

| Species   | Comment   | Ref. |
|---|---|------|
| <i>Baccharis linearis</i>   | Three alkaloids, m.p. 157, 150, and 153 °C, respectively; possess pharmacological activity  | 84   |
| <i>Bryonia alba</i>   | Five alkaloids one of which (m.p. 84—86 °C) appears to possess N-containing ring and a Me group.  | 85   |
| <i>Clerodendron inerme</i>  | Six alkaloids (?)   | 86   |
| <i>Cytisus scoparius</i>  | T.l.c. analysis   | 87   |
| <i>Duranta repens</i>   | Two alkaloids (?) by t.l.c.   | 88   |
| <i>Empetrum nigrum</i>  | 0.074% Alkaloid content of leaves   | 89   |
| <i>Franseria artemisioides</i>  | Two alkaloids purified by t.l.c. and examined by X-ray; possess fungicidal but not insecticidal activity  | 90   |
| <i>Holarrhena antidysenterica</i>   | Total alkaloid hydrochloride and bismuth iodide derivatives isolated; hydrochlorides used in treatment of amoebic dysentery   | 91   |
| <i>Lantana camara</i>   | Crude extract from leaves shown to be toxic to albino rats  | 92   |
| <i>Leonurus sibiricus</i> , <i>L. glaucescens</i> , and <i>L. deminutus</i> | 2.0—6.5% Alkaloid content   | 93   |
| <i>Linum chamissonis</i>  | Alkaloid, antagonizes histamine and serotonin in isolated guinea-pig intestine  | 94   |
| Maize flower stigmas  | Four alkaloids by t.l.c.  | 95   |
| <i>Malacocarpus crithmifolius</i>   | Anabasine D; physical and chemical properties given   | 96   |
| <i>Nitraria komarovii</i>   | Two alkaloids (?)   | 97   |
| <i>Paeonia peregrina</i>  | Six alkaloids + benzamide from root   | 98   |
| <i>Parnassia palustris</i>  | Five alkaloids (?) from root; no phenolic alkaloids   | 99   |
| <i>Peripterygia marginata</i>   | Periphylline and isoperiphylline, both $C_{25}H_{29}O_2N_3$ ; both possess cinnamoyl and another aromatic nucleus, a secondary amine function, two amide functions one of which is linked to the cinnamoyl group, and a double bond; they may be isomeric with respect to the position of the double bond | 100  |
| <i>Scabiosa bipinnata</i>   | Root extract  | 101  |
| <i>Teucrium</i> sp.   | Several species investigated, each one of which contained one alkaloid by paper chromatography  | 102  |
| <i>Valeriana stolonifera</i>  | Root extract  | 103  |
| <i>Verbascum nobile</i>   | Verbasine, $C_{25}H_{42}N_4O_4$ , m.p. 74—75 °C, mol. wt. 462; verbascine, $C_{27}H_{44}N_4O_4$ , m.p. 125—126 °C, mol. wt. 488; another compound, m.p. 100 °C, i.r. and u.v. spectra reported  | 104  |
| <i>Xanthium strumarium</i>  | Crude extract showed pharmacological activity   | 105  |

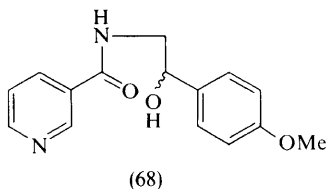
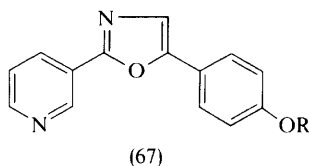
Books on t.l.c.<sup>106</sup> and high-speed liquid chromatography<sup>107</sup> as they apply to alkaloid isolation and characterization work have been published.

- <sup>81</sup> I. A. Gubanov and A. I. Ban'kovskii, *Trudy Vses. Nauch.-Issled. Inst. Lek. Aromat. Rast.*, 1969, **15**, 393 (*Chem. Abs.*, 1971, **75**, 40 266w).
- <sup>82</sup> J. A. Saenz R. and M. Nassar C., *Rev. Biol. Trop.*, 1970, **18**, 129 (*Chem. Abs.*, 1972, **76**, 138 176n).
- <sup>83</sup> L. D. Kapoor, S. L. Kapoor, S. N. Srivastava, A. Singh, and P. C. Sharma, *Lloydia*, 1971, **34**, 94.
- <sup>84</sup> M. Montes G., T. Wilkomirski F., L. Valenzuela R., and R. Neira M., *Rev. Real Acad. Cienc. Exactas. Fis. Natur. Madrid*, 1971, **65**, 499 (*Chem. Abs.*, 1971, **75**, 115 887k).
- <sup>85</sup> A. Z. Gulubov and A. P. Venkov, *Nauch. Trudy Vissh. Pedagog. Inst., Plovdiv, Mat., Fiz., Khim., Biol.*, 1970, **8**, 137 (*Chem. Abs.*, 1971, **75**, 16 118d).
- <sup>86</sup> M. A. Abdul-Alim, *Planta Med.*, 1971, **19**, 318 (*Chem. Abs.*, 1971, **75**, 16 123b).
- <sup>87</sup> S. Gill, W. Dembinska, and M. Zielinska, *Gdansk. Tow. Nauk., Rozpr. Wydz.*, 1970, **3**, 211 (*Chem. Abs.*, 1971, **75**, 112 824b).
- <sup>88</sup> M. A. Rocca, *Rev. Fac. Farm. Odontol. Araraquara*, 1970, **4**, 345 (*Chem. Abs.*, 1972, **76**, 70 153v).
- <sup>89</sup> E. E. Strel'nikova, *Uch. Zap., Kemerov. Gos. Pedagog. Inst.*, 1969, 66 (*Chem. Abs.*, 1971, **75**, 85 153y).
- <sup>90</sup> V. C. Leon and R. A. Munoz, *Politecnica*, 1969, **1**, 21 (*Chem. Abs.*, 1971, **75**, 95 419d).
- <sup>91</sup> P. Than, T. T. Nu, T. T. Ohn, P. Po, and Y. Y. Khaing, *Union Burma J. Sci. Technol.*, 1969, **2**, 423 (*Chem. Abs.*, 1972, **76**, 4055p).
- <sup>92</sup> R. P. Uppal and B. S. Paul, *Haryana Agric. Univ. J. Res.*, 1971, **1**, 98 (*Chem. Abs.*, 1972, **77**, 1545h).
- <sup>93</sup> M. Chultemsuren and V. V. Petrenko, *Farm. Zhur. (Kiev)*, 1971, **26**, 60 (*Chem. Abs.*, 1971, **75**, 106 125h).
- <sup>94</sup> M. Montes G., T. Wilkomirski F., L. Valenzuela R., and G. Ibanez S., *Rev. Real Acad. Cienc. Exactas. Fis. Natur. Madrid*, 1971, **65**, 641 (*Chem. Abs.*, 1972, **76**, 138 163f).
- <sup>95</sup> P. E. Granda and M. G.-Serranillos, *Galenica Acta*, 1968, (publ. 1971), **21**, 135 (*Chem. Abs.*, 1971, **75**, 67 377v).
- <sup>96</sup> B. Kh. Zharekeev, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 538 (*Chem. Abs.*, 1971, **75**, 126 561a).
- <sup>97</sup> G. A. Pashaeva, *Uch. Zap., Azerb. Gos. Med. Inst.*, 1969, **30**, 109 (*Chem. Abs.*, 1971, **75**, 45 657j).
- <sup>98</sup> A. Gulubov, V. B. Chervenkova, and A. Venkov, *Natura (Plovdiv)*, 1970, **3**, 83 (*Chem. Abs.*, 1971, **75**, 31 351t).
- <sup>99</sup> N. P. Kharitonova and A. F. Gammerman, *Trudy Perm. Farm. Inst.*, 1969, 179 (*Chem. Abs.*, 1971, **75**, 45 642a).
- <sup>100</sup> M. Leboeuf, A. Cave, and R. R. Paris, *Plant. Med. Phytotherap.*, 1971, **5**, 126 (*Chem. Abs.*, 1971, **75**, 95 371g).
- <sup>101</sup> V. A. Kuril'chenko, G. N. Zemtsova, and V. Ya. Bandyukova, *Khim. prirod. Soedinenii*, 1971, **7**, 534 (*Chem. Abs.*, 1972, **76**, 1823b).
- <sup>102</sup> I. A. Damirov, *Trudy Vses. S'ezda Farm., Ist*, 1967 (publ. 1970), 285 (*Chem. Abs.*, 1971, **75**, 126 575h).
- <sup>103</sup> Yu. I. Kornievskii and K. E. Koreschchuk, *Farm. Zhur. (Kiev)*, 1971, **26**, 67 (*Chem. Abs.*, 1971, **75**, 31 300a).
- <sup>104</sup> P. Ninova, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 540 (*Chem. Abs.*, 1972, **76**, 1812x).
- <sup>105</sup> V. I. Sila and L. V. Lysenko, *Farm. Zhur. (Kiev)*, 1971, **26**, 71 (*Chem. Abs.* 1971, **75**, 33 686e).
- <sup>106</sup> E. Tiyhak and D. Vagujfalvi, in 'Progress in Thin-Layer Chromatography and Related Methods', ed. A. Niederwieser, Ann Arbor Sci. Publ., Ann Arbor, Michigan, 1972, vol. 3, p. 71 (*Chem. Abs.*, 1972, **76**, 141 095r).
- <sup>107</sup> J. A. Schmit, in 'Modern Practice of Liquid Chromatography', ed. J. J. Kirkland, Interscience, New York, 1971, p. 375 (*Chem. Abs.*, 1971, **75**, 83 936g).

Reviews dealing with pharmacology of alkaloids<sup>108</sup> and alkaloid *N*-oxides<sup>109</sup> may be perused for general interest.

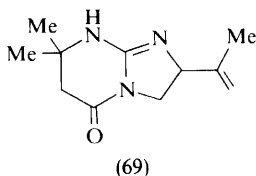
*Aegle marmelos* Correa (Rutaceae) (cf. *Halfordia scleroxyla*, Vol. 1, p. 459)

Aegelenine has been isolated and shown to be identical with halfordinol (67; R = H), previously isolated from *Halfordia scleroxyla*, on the basis of spectral and degradative evidence.<sup>110</sup> Furthermore, the synthesis of its *O*-methyl ether (67; R = Me) was effected along biogenetic lines: condensation of  $\beta$ -hydroxy- $\beta$ -(*p*-methoxyphenyl)ethylamine with nicotinic acid chloride gave the amino-alcohol (68) which, without characterization, was transformed into (67; R = OMe) by successive treatment with manganese dioxide and phosphorus oxychloride (cf. also *H. scleroxyla*).



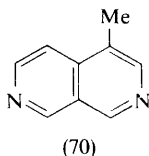
*Alchornea floribunda* and *A. hirtella* (Vol. 1, p. 458, Vol. 2, p. 279)

The *X*-ray crystal structure of the methobromide of alchornine (69) has been determined.<sup>111</sup>



*Antirrhinum majus* L. (Vol. 2, p. 281)

Besides 4-methyl-2,6-naphthyridine (70) and choline, three other tertiary alkaloids were isolated but their structures were not determined.<sup>112</sup>



<sup>108</sup> G. B. Marini-Bettolo, 1st International Congress on Pharmacognosy and Phytochemistry, 1970, ed. H. Wagner and L. Hoerhammer, Springer, Berlin, 1971, p. 201 (*Chem. Abs.*, 1971, **75**, 89 968m).

<sup>109</sup> J. D. Phillipson, *Xenobiotica*, 1971, **1**, 419 (*Chem. Abs.*, 1971, **75**, 148 657j).

<sup>110</sup> A. Chatterjee and R. Majumder, *Indian J. Chem.*, 1971, **9**, 763.

<sup>111</sup> M. Cesario and J. Guilhem, *Acta Cryst.*, 1972, **B28**, 151.

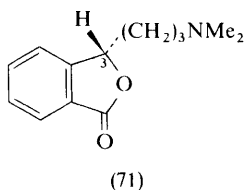
<sup>112</sup> K. J. Harkiss, *Planta Med.*, 1971, **20**, 108.

*Antirrhinum orontium* L. (*Misopates orontium* Raf.) (Vol. 2, p. 281)

4-Methyl-2,6-naphthyridine (70) and choline were isolated and identified by comparison with authentic samples.<sup>113</sup> Two other alkaloids, Base B (C<sub>15</sub>H<sub>9</sub>N<sub>3</sub>O) and Base C, were obtained in sufficient quantity only for i.r., u.v., and mass spectral determination.

*Dendrobium pierardii* Roxb. (*D. aphyllum* Roxb.) (Orchidaceae) (Vol. 1, p. 459)

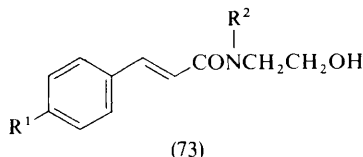
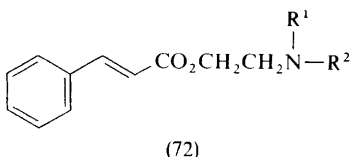
Pierardine (71) has now been synthesized and shown to possess the (S) configuration.<sup>114</sup> Condensation of the lithium salt of phthalaldehydic acid with 3-dimethylaminopropylmagnesium chloride followed by lactonization with acid gave (±)-pierardine, which was resolved by recrystallization of its di-O-benzoyl-L-tartrate. The (−)-enantiomer was shown to be identical with an authentic sample of the alkaloid. The absolute configuration of pierardine as (3S)-(3-dimethylaminopropyl)phthalide (71) was determined by comparison of



the c.d. curve of 3-propylphthalide, a degradation product of the alkaloid, with that of (3S)-butylphthalide.

*Erythrophleum chlorostachys* (F. Muell.) Bail. (Leguminosae)

The cinnamic acid derivatives (72; R<sup>1</sup> = R<sup>2</sup> = Me), (73; R<sup>1</sup> = H, R<sup>2</sup> = Me), (73; R<sup>1</sup> = OH, R<sup>2</sup> = Me), and (73; R<sup>1</sup> = R<sup>2</sup> = H) have been isolated from this extremely toxic species growing in North Queensland, Australia, and their structures have been confirmed by synthesis.<sup>115</sup> Since the synthetic esters (72; R<sup>1</sup> = H, R<sup>2</sup> = Me) and (72; R<sup>1</sup> = R<sup>2</sup> = H) readily isomerized in solution (half-life ~ 1–3 days) into the corresponding amides (73; R<sup>1</sup> = H, R<sup>2</sup> = Me) and (73; R<sup>1</sup> = R<sup>2</sup> = H), it is likely that the isolated cinnamamides (73) are artifacts.



A point of phytochemical interest is that a species recognized also as *E. chlorostachys* growing in another region of Australia was shown to contain only diterpenoid ester alkaloids and no cinnamate derivatives.

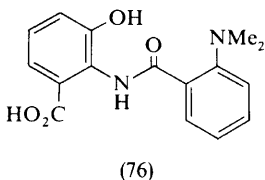
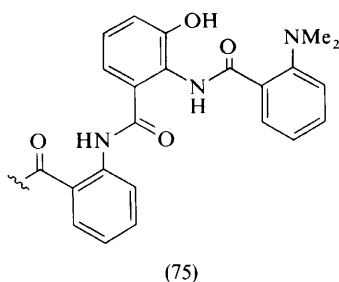
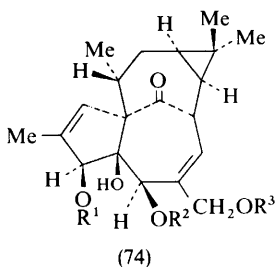
<sup>113</sup> K. J. Harkiss, *Phytochemistry*, 1971, **10**, 2849.

<sup>114</sup> M. Elander, L. Gawell, and K. Leander, *Acta Chem. Scand.*, 1971, **25**, 721.

<sup>115</sup> W. J. Griffin, J. H. Phippard, C. C. J. Culvenor, J. W. Loder, and R. Nearn, *Phytochemistry*, 1971, **10**, 2793.

*Euphorbia millii* Ch. des Moulins (Euphorbiaceae)

The unusual diterpenoid alkaloids, milliamine A [74;  $R^1 = (75)$ ,  $R^2 = H$ ,  $R^3 = Ac$ ] and milliamine B [74;  $R^1 = R^2 = H$ ,  $R^3 = (75)$ ] have been isolated.<sup>116</sup> The structure of milliamine A rests on spectral evidence and hydrolysis with sodium methoxide in methanol to the diterpene (74;  $R^1 = R^2 = R^3 = H$ ) and the methyl ester corresponding to part structure (75). The structure of the diterpene tetraol, (74;  $R^1 = R^2 = R^3 = H$ ) had been previously determined by X-ray crystallographic analysis; the structure of the alkaloidal portion was established by further degradation with hydrochloric acid to methyl anthranilate and compound (76), which was found to be identical with an authentic sample



synthesized by condensation of *NN*-dimethylantranilic acid with 3-hydroxyantranilic acid in the presence of *NN'*-carbonyl-di-imidazole followed by esterification with diazomethane.

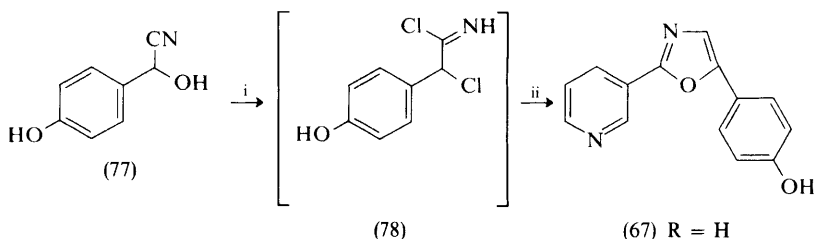
*Halfordia scleroxyla* F. Muell. (Rutaceae) (Vol. 1, p. 459)

A refreshing one-step preparation of halfordinol (67;  $R = H$ ) has been achieved by a modification of the Fischer oxazole synthesis (Scheme 4).<sup>117</sup> It was reasoned that in the reaction of *p*-hydroxymandelonitrile (77) with nicotinaldehyde, some equilibration of (77) with *p*-hydroxybenzaldehyde and hydrogen cyanide could give rise to undesirable formation of nicotinaldehyde cyanohydrin. This problem was overcome by carrying out the reaction in the presence of thionyl chloride. Under these conditions, the cyanohydrin (77) is presumably converted into the imino chloride (78), which then undergoes acid-catalysed condensation with nicotinaldehyde to form halfordinol (67;  $R = H$ ) (16.5% yield). The other

<sup>116</sup> D. Uemura and Y. Hirata, *Tetrahedron Letters*, 1971, 3673.

<sup>117</sup> T. Onaka, *Tetrahedron Letters*, 1971, 4393.





Reagents: i, dry  $\text{HCl-SOCl}_2\text{-Et}_2\text{O}$ ; ii, dry  $\text{HCl-pyridine-3-aldehyde}$ .

**Scheme 4**

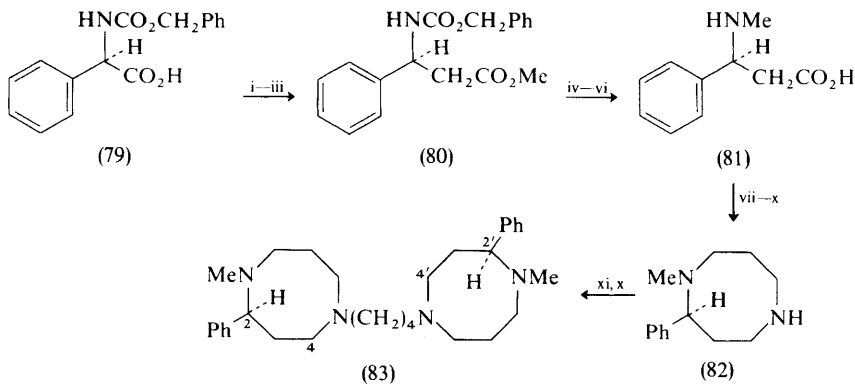
oxazole alkaloids [67;  $\text{R} = \text{CH}_2\text{CH}(\text{OH})\text{C}(\text{OH})\text{Me}_2$ ] and (67;  $\text{R} = \text{CH}_2\text{CH}=\text{CMe}_2$ ) can obviously be readily prepared using this route.

#### *Heimia salicifolia* Link and Otto

The major alkaloid cryogenine\* has been shown not to possess ganglionic activity in the rat.<sup>118</sup>

#### *Homalium* sp. (Homaliaceae)

The tentative structure (83; 4,4'-dioxo), previously proposed for homaline, has been confirmed by stereospecific synthesis of its degradation product, bis-dihydrodesoxohomaline (83) (Scheme 5).<sup>119</sup> Arndt-Eistert homologation of *N*-benzyloxycarbonyl-D-phenylglycine (79) gave the ester (80), which upon *N*-methylation, removal of the benzyloxycarbonyl protective group, and hydrolysis



Reagents: i,  $\text{Me}_2\text{CHCH}_2\text{OCOCN-Methylmorpholine}$ ; ii,  $\text{CH}_2\text{N}_2$ ; iii,  $\text{MeOH-Et}_3\text{N-PhCO}_2\text{Ag}$ ; iv,  $\text{MeI-DMF-Ag}_2\text{O}$ ; v,  $\text{H}_2\text{-Pd}$ ; vi, base; vii,  $\text{CH}_2=\text{CHCN-KOH}$ ; viii,  $\text{H}_2\text{-PtO}_2\text{-HCl}$ ; ix,  $\text{ClCO}_2\text{Et-C}_5\text{H}_5\text{N-Et}_3\text{N-DMF}$ ; x,  $\text{LiAlH}_4\text{-THF}$ ; xi,  $\text{ClCOCH}_2\text{CH}_2\text{COCl-base}$ .

**Scheme 5**

<sup>118</sup> D. S. Kosersky and M. H. Malone, *J. Pharm. Sci.*, 1971, **60**, 952.

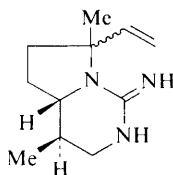
<sup>119</sup> M. Pais, R. Sarfati, F. X. Jarreau, and R. Goutarel, *Compt. rend.*, 1971, **272**, C, 1728.

\* See Note Added in Proof at the end of this chapter.

provided (*S*)-*N*-methyl- $\beta$ -phenyl- $\beta$ -alanine (81). Conversion of (81) into the diaza-1,5-cyclo-octane derivative (82) was based on previous model studies. Condensation of the latter with succinoyl chloride followed by metal hydride reduction yielded compound (83), which was shown to be identical by i.r., n.m.r., mass spectral, and optical rotation determinations with natural bis-dihydro-desoxohomaline. Thus homaline is represented by structure (83; 4,4'-dioxo) and possesses the (2*S*,2'*S*) configuration.

*Plantago arenaria* Waldst and Kit.

The structure of arenaine (84) was revealed from the interpretation of its n.m.r. ( $^1\text{H}$  and  $^{13}\text{C}$ ) spectra.<sup>120</sup> Examination of the  $^{13}\text{C}$  noise resonance decoupled and single frequency decoupled spectra showed the presence of three non-protonated carbons (carbonyl, guanidine, and  $\alpha$ -amino-tetrahedral types), three methine (olefinic methine, aminomethine, and one other) carbons, three methylenes (one olefinic and two saturated ones which appear at highly shielded and deshielded positions, thus implying that they are part of a  $\text{R}_3\text{CCH}_2\text{CH}_2$  unit), and two methyl groups. This information alone allows formulation of the

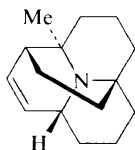


(84)

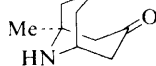
skeletal structure (84). The *trans* stereochemistry as shown was deduced from the  $^1\text{H}$  n.m.r. spectrum which exhibited signals at  $\delta$  2.10 (dd, *J* 6.5 and 13 Hz,  $\alpha$ -ketomethine H) and  $\delta$  3.51 (ddd, *J* 5.5, 11, and 13 Hz,  $\alpha$ -aminomethine H).

*Poranthera corymbosa* Brogn. (Euphorbiaceae)

The intriguing structure (85) has been established for the major alkaloid porantherine on the basis of an *X*-ray crystallographic analysis on its hydrobromide.<sup>121</sup> The postulated biogenesis of porantherine by the condensation of a  $\text{C}_{16}$ -polyketide chain with ammonia will no doubt stimulate the relevant biosynthetic experiments. The structurally related alkaloid (86) had been isolated



(85)

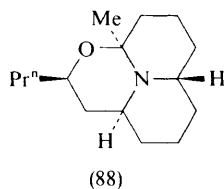
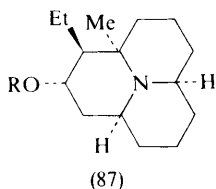


(86)

<sup>120</sup> A. Rabaron, M. Koch, M. Plat, J. Peyroux, E. Wenkert, and D. W. Cochran, *J. Amer. Chem. Soc.*, 1971, **93**, 6270.

<sup>121</sup> W. A. Denne, S. R. Johns, J. A. Lamberton, and A. McL. Mathieson, *Tetrahedron Letters*, 1971, 3107.

some years ago from *Euphorbia atoto*, a species which belongs to the same family as *Poranthera corymbosa*.<sup>121</sup> Three other alkaloids, poranthericine (87; R = H), *O*-acetylporanthericine (87; R = Ac) and porantheridine (88) were also isolated and their structures and absolute configurations were deduced by *X*-ray analysis



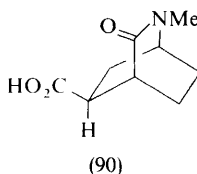
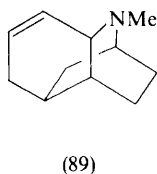
of the hydrobromides of (87; R = H) and (88) using the technique based on the anomalous scattering of the bromine atom.<sup>122</sup> The isolation of these alkaloids lends some support to the postulated biogenetic scheme.<sup>121</sup>

*Pterogyne nitens* Tul. (Leguminosae) (Vol. 1, p. 460, Vol. 2, p. 283)

Details of the isolation, structural determination, and synthesis of pterogynine  $[\text{HN}=\text{C}(\text{NH}_2)\text{N}(\text{CH}_2\text{CH}=\text{CH}_2)_2]$  and pterogynidine  $[\text{HN}=\text{C}(\text{NHCH}_2\text{CH}=\text{CMe}_2)_2]$  have been published.<sup>123</sup>

#### *Vaccinium oxycoccus*

Cannivonine, isolated from the leaves of cranberries native to New Brunswick, Canada, has been shown to possess the rare isoquinuclidine structure (89).<sup>124</sup> The molecular formula ( $\text{C}_{11}\text{H}_{17}\text{N}$ ) indicated a tricyclic structure with one double bond. The i.r. spectrum showed the absence of NH absorption and confirmed the presence of a double bond, and the n.m.r. spectrum exhibited peaks for two vinyl protons at  $\delta$  5.3, five protons  $\alpha$  to the nitrogen at  $\delta$  2.3—3.7, three allylic protons at  $\delta$  2.0—2.3, and an *N*-methyl function at  $\delta$  3.3. Hofmann degradation of cannivonine gave a product which possessed a conjugated diene system [u.v. (max) 278 nm] and thus eliminated the presence of a seven-membered ring in the alkaloid. Catalytic dehydrogenation over palladium on carbon gave 2- and 8-methylquinolines. Oxidative degradation produced the known isoquinuclidone carboxylic acid (90). These results, coupled with the interpretation of mass

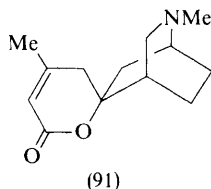


<sup>122</sup> W. A. Denne, S. R. Johns, J. A. Lamberton, A. McL. Mathieson, and H. Soares, *Tetrahedron Letters*, 1972, 1767.

<sup>123</sup> R. A. Corral, O. O. Orazi, and M. F. De Petruccelli, *Rev. Latinoamer. Quim.*, 1972, 2, 178 (*Chem. Abs.*, 1972, 76, 141 122x).

<sup>124</sup> K. Jankowski and I. Jankowska, *Experientia*, 1971, 27, 1383.

spectral data, established structure (89) for cannivonine. At least six other bases have been detected by t.l.c. in the extract from *V. oxycoccus*. Speculation concerning the biogenesis of cannivonine is premature, although its structural similarities to dioscorine (91), which is biosynthesized from piperidine and four acetate units,<sup>125</sup> are apparent.



*Verbascum songaricum*

Acetamide and an unidentified base, m.p. 195—196 °C, have been isolated from the leaves and buds.<sup>126</sup>

*Note Added in Proof:* The alkaloid cryogenine ( $\equiv$  vertine) is the quinolizidine alkaloid of *H. salicifolia* (for structure see, *inter alia*, J. P. Ferris, C. B. Boyce, R. C. Briner, B. Douglas, J. L. Kirkpatrick, and J. A. Weisbach, *Tetrahedron Letters*, 1966, 3641). It is not phenylsemicarbazide (which is also occasionally called cryogenine), as stated in the Abstract of ref. 118 (*Chem. Abs.*, 1971, **75**, 61 860).

<sup>125</sup> E. Leete and A. R. Pinder, *Chem. Comm.*, 1971, 1499.

<sup>126</sup> R. Ziyaev, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1971, **7**, 853 (*Chem. Abs.*, 1972, **76**, 124 154s).

# Errata

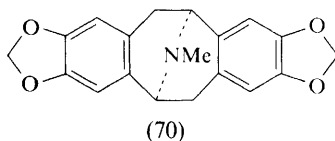
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## Vol. 1, 1971

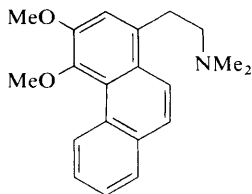
Page 460, line 18. *For* 'The latter compound' *read* 'The former compound'.

## Vol. 2, 1972

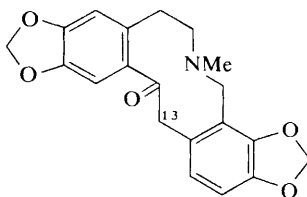
Page 114. Eschscholtzine should have appeared as



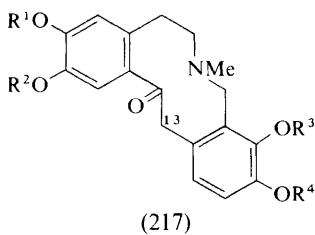
Page 116/117. Atherosperminine should have appeared as



Page 156/157. Protopine should have appeared as



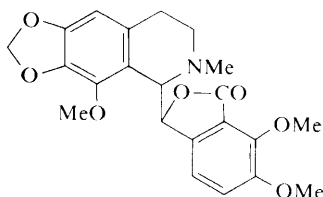
and formula (217) should have appeared as



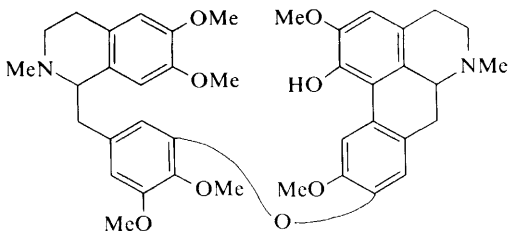
Page 157, Table 5, lines 14 and 15. For 'Salutaridine . . . etc.,' read 'Salutaridine (122:  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{OMe}$ ,  $R^4 = \text{OH}$ ), and 13-oxocryptopine (217:  $R^1 = R^2 = \text{Me}$ ,  $R^3 + R^4 = \text{CH}_2$ ; 13-oxo)

Table 5, line 17. For '13-Oxocryptopine (Salutaridine)' read '13-oxoprotopine'.

Page 158. Narcotine should have appeared as



Page 170. The structure assigned to fetidine (284) in ref. 257 is



The incorrect structure shown on p. 170 is that given in *Chem. Abs.*, 1971, **73**, 35 590. The correct structure of fetidine has now been established (M. P. Cava and K. Wakisaka, *Tetrahedron Letters*, 1972, 2309; see pp. 140, 141 of this volume).

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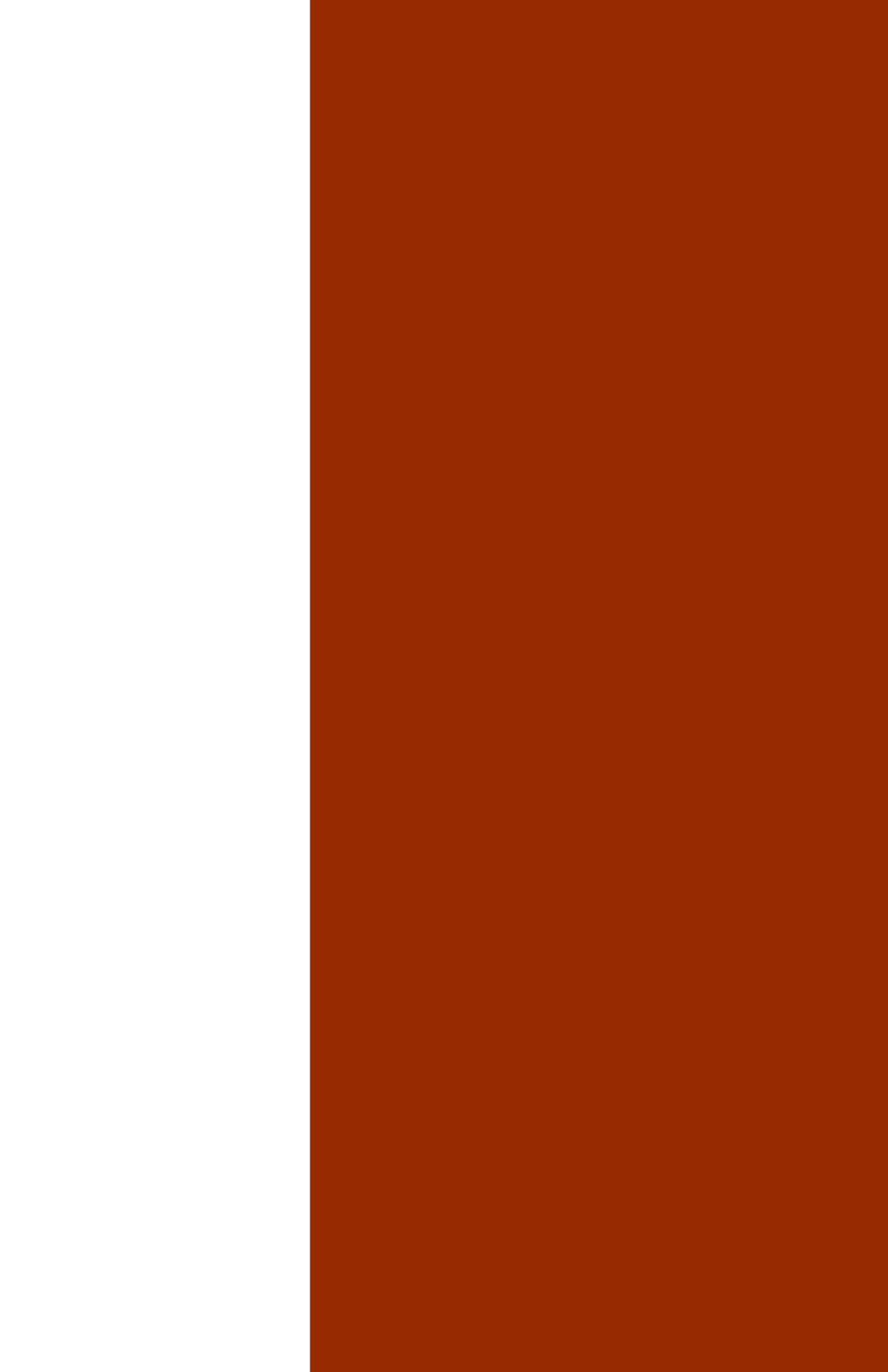
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